THE UNIVERSITY OF CALGARY

Epidemiology of Severe Acute Renal Failure and Prognosis for Renal Recovery in Critically Ill Patients

by

Sean Michael Bagshaw

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE

DEGREE OF

MASTER OF SCIENCE

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

JULY, 2005

THE UNIVERSITY OF CALGARY

THE UNIVERSITY OF CALGARY

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled “Epidemiology of Severe Acute Renal Failure and Prognosis for Renal Recovery in Critically Ill Patients”, submitted by Dr. Sean Michael Bagshaw in partial fulfillment of the requirements for the degree of Master of Science.

_____
Co-Supervisor: Dr. K. B. Laupland
Assistant Professor, Departments of Medicine, Critical Care Medicine and Community Health Sciences.

_____
Co-Supervisor: Dr. C. J. Doig
Associate Professor, Departments of Medicine, Critical Care Medicine and Community Health Sciences.

_____
Dr. G. H. Fick, Examiner
Department of Community Health Sciences.

_____
Dr. T. Godinez-Luna, Examiner
Departments of Medicine and Critical Care Medicine.

_____
Dr. G. Mortis, Examiner
Department of Medicine.

_____
Dr. P. Easton, Examiner
Departments of Medicine and Critical Care Medicine.

_____
Date

ABSTRACT

Severe acute renal failure (sARF) in the critically ill requiring dialysis is associated with considerable morbidity, mortality and health care costs. The current objective of this study was to describe the epidemiology of sARF and factors influencing long-term mortality and prognosis for renal recovery. This was a population-based surveillance cohort study. Adult residents of the Calgary Health Region (population 1 million) admitted to any multidisciplinary intensive care unit (ICU) and a cardiovascular surgery ICU from May 1, 1999 to April 30, 2002 were eligible for inclusion. Severe acute renal failure was diagnosed in 240 patients for an annual incidence of 11.0 (Exact 95% CI 9.6-12.5) per 100,000 population. The rates were highest in males and patients older than 65 years. Population risk factors for development of sARF included previous heart disease, stroke, chronic pulmonary disease, cancer, connective tissue disease, chronic renal dysfunction, diabetes mellitus and alcoholism. The annual mortality rate for sARF was 7.0 (Exact 95% CI, 5.9-8.2) deaths per 100,000 population with rates higher in males and patients older than 65 years**.** The 28-day, 90-day, and 1-year case-fatality rates were 51%, 60%, and 64%, respectively. By stratified analysis, several factors demonstrated association with death at 1-year for patients with sARF including: age $\geq$ 65 years, increased APACHE II score, Charlson co-morbidity index $\geq$ 4 points, pre-existing cancer or liver disease, a diagnosis of septic shock, use of any continuous renal replacement therapy and a low pre-dialysis serum creatinine level. Interestingly, pre-existing diabetes

mellitus was associated with a decreased risk of death at 1-year. Renal recovery occurred in 78% (68/87) of survivors at 1-year after a median duration of renal replacement therapy of 11 days. By stratified analysis, renal recovery was associated with the several factors including: male sex, age < 65 years, lower Charlson co-morbidity index score, an intra-renal etiology of sARF, a diagnosis of septic shock and use of continuous renal replacement therapy as the modality of renal replacement. In conclusion, the occurrence of sARF was common enough to be clinical important. Those at greatest risk for sARF are males, older patients, and those with pre-existing co-morbidities. Although the majority of patients with sARF will die, most survivors will become independent from renal replacement therapy within a year.

ACKNOWLEDGEMENTS

Thank you to Melissa Mucenski for patient chart reviews, Kaye Holt and Stephanie Hui for their help with data entry and database management, Dr. Lawrence Svenson for providing mortality outcome data, and Reza Shahpori for providing data from the ICU Tracer database.

Thank you to Drs. Kevin Laupland, Christopher Doig, Garth Mortis, Gordon Fick and Tomas Godinez for feedback and guidance during this project.

This study was funded by a grant from the Canadian Intensive Care Foundation (CICF).

Dr. Bagshaw was supported by a Canadian Institutes for Health Research (CIHR) Canada Graduate Scholarship Masters Award and Deans Research Excellence Award from the Faculty of Graduate Studies at The University of Calgary.

.

DEDICATION

To Heather

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

Page

A. INTRODUCTION

Acute renal failure (ARF) requiring renal replacement therapy (RRT), referred to henceforth as severe acute renal failure (sARF), in critically ill patients is associated with an excessive risk of morbidity, mortality and increased utilization of health care resources.[1-4] Recent trends suggest that the mortality rate from sARF in critically ill patients is increasing, in part due to a predominant shift from single-organ sARF to multi-organ dysfunction syndrome with associated sARF.[5-10] Despite the commonly cited poor outcome for sARF in critically ill patients, the population-based epidemiology and the long-term outcomes have not been well described, in particular in a Canadian or North American setting.

B. LITERATURE REVIEW

1. Incidence of acute renal failure in the critically ill

The estimated incidence of ARF in critically ill patients is highly variable across several hospital-based studies ranging from 1.8% to 24.7%. [3, 6, 11-18] This broad range in reported incidence likely reflects the use of differing arbitrary biochemical definitions of ARF, variation in patient selection criteria and sampling from differing patient populations.[11]

de Mendonça *et al* reported that ARF, defined as a serum creatinine > 300 μmol/L or urine output < 500 mL/day, developed in 24.7% among selected critically ill patients admitted to 40 intensive care units (ICUs) in 16 countries. [16] By virtue of exclusion of patients admitted to the ICU for < 48 hours following uncomplicated elective surgery, this incidence rate may be considerable higher than that reported in other studies. In another, large observational study of 28 multidisciplinary ICUs in France, Guerin *et al* reported that 7.7% of patients were admitted to ICU with ARF (or developed within 48 hours of admission).[12] Acute renal failure was defined as serum creatinine > 300 μmol/L, oliguria (urine output < 500 mL/day) or need for RRT. The need for RRT was the primary diagnostic criteria in 37% of the overall cohort and was more common in those patients with delayed (>7 days) rather than early onset ARF (<48 hours). In a similar study, Brivet *et al* reported a 7% incidence of ARF in critically ill patients admitted to 20 multidisciplinary ICUs.[13] ARF was defined as a serum creatinine > 310 μmol/L or an increase in serum creatinine > 100% above baseline in patients with pre-

existing chronic kidney disease (serum creatinine > 150 μmol/L). In this cohort of 360 patients diagnosed with ARF, 11% had pre-existing chronic renal disease, and overall 48% required the institution of RRT.

More clinically important than knowing the precise incidence of ARF defined by arbitrary biochemical definitions is an understanding of the epidemiology of ARF severe enough to warrant intervention with RRT. Defining severe acute renal failure (sARF) as the requirement for RRT in the presence of renal dysfunction provides a more objective outcome measure, may reflect greater severity of illness, and may allow for better comparison or generalization across studies and critically ill patient populations.[11] However, few studies have focused on the epidemiology of sARF in the critically ill.[1, 3, 6, 11, 12, 14-20] In the study by Guerin *et al*, the incidence of sARF can be estimated at 2.8% by considering only the patients with ARF defined by need for hemodialysis.[12] Schaefer *et al* reported a 3.2% incidence of sARF in a single medical ICU observational cohort study.[14] In this study, all patients received intermittent hemodialysis despite 58% having hemodynamic instability (mean arterial pressure < 70 mmHg) and 47% being diagnosed with sepsis syndrome within 24 hours of admission. The most common cited indications for institution of RRT were an elevated serum creatinine and volume overload. In the study by Brivet *et al,* although not explicitly specified, the incidence of sARF could be estimated at 3.4%.[13]

Schwilk *et al* reported a 4.3% overall incidence of sARF treated with CRRT only [specifically continuous venovenous hemodiafiltration (CVVHDF)] in a single center surgical and trauma ICU.[6] There are several limitations of this small study that raises question whether the results can be generalized to broader ICU populations. First, the authors have used a broad definition for ARF that included: any combination of oligo-anuria (not defined); multiple organ dysfunction syndrome (MODS); hemodynamic instability and decreasing urine output; and an increasing serum creatinine to greater than 250 μmol/L. Further, they have included within their cohort patients receiving CVVHDF for "insufficient water clearance or increasing tissue edema or increasing central venous pressure" and "insufficient and unacceptable electrolyte clearance" not otherwise defined in the absence of evidence of renal dysfunction.[6] They also included patients with chronic renal disease without specifying exclusion of those already receiving chronic renal replacement therapy prior to admission to ICU. Finally, these authors analyzed their data with no a priori hypothesis and provide outcome data at ICU discharge only from a single surgical ICU.

In a large observational study of 30 multidisciplinary ICUs, Metnitz *et al* reported an incidence rate of 4.9% of sARF. However, this study is limited by exclusion of approximately 3.6% of patient admissions due to incomplete ascertainment of hospital outcome status and further exclusion of patients with any chronic renal disease (not defined) totaling approximately 1.5%. Finally,

Groeneveld *et al* reported an incidence of sARF as high as 10% of all admissions to a single medical ICU in a small cohort study.[21]

Unfortunately, several studies have failed to report either the incidence rates or provide sufficient data for their calculation.[4, 15, 17-19, 22-25]

Most studies of sARF are limited in generalizability across critically ill populations due to selection bias by inclusion of patients from either medical or surgical ICUs, a single tertiary referral center or restricted by clinical criteria such as evidence of sepsis and observation bias due to ascertainment of outcome at only ICU or hospital discharge. Population-based studies where all persons within a defined population or geographic region are identified by fulfilling a case definition are best in order to minimize or eliminate selection bias and improve generalizability.[26]

All population-based studies were searched for using the following criteria: 1) population-based study design; 2) a priori definition of acute renal failure; and 3) inclusion of patients admitted to an ICU. The search identified 12 potential studies that attempted to include all patients with ARF in a well-defined population.[3, 7, 11, 20, 27-35] Four studies were excluded from further review because two were published in abstract form only and unavailable[27, 30], and two were published in non-English medical journals[29, 33]; therefore, eight studies were reviewed. The first study by Abraham *et al* prospectively identified all cases (n=77) of ARF at a single, tertiary care hospital in Kuwait over a 2-year period for a reported incidence of 9.5 per 100,000 population; however, this study did not

only include patients admitted to an ICU, did not focus on sARF and is likely prone to selection bias due to failure to report the residency status of their base population.[28] The second study by Feest *et al* prospectively identified all adult community-based episodes (n=125) of ARF (defined as serum creatinine ≥ 500 μmol/L) over a 2-year period in two regions of Devon, England.[31] The authors reported an annual incidence of 14 per 100,000 population with 1.8 per 100,000 requiring initiation of RRT. Interestingly, a large proportion of these cases were post-renal in etiology caused by prostatic disease (25%). This study was not primarily focused on sARF or admission to an ICU; thus has limited generalizability to a critically ill population.

The third study, by Liano *et al* was a large community-based cohort study of all episodes of ARF in adult patients (age > 14 years) in 13 tertiary care hospitals in Madrid, Spain over a 9- month period.[7, 32] The case definition for ARF was defined as a sudden rise in serum creatinine ≥ 177 μmol/L in subjects with prior normal kidney function or ≥ 50% increase in patients with pre-existing chronic kidney disease (serum creatinine ≤ 265 μmol/L).[32] In this study, cases were identified by voluntary completion of questionnaires by physicians at the participating tertiary care hospitals. The authors identified 253 cases (34%) of ARF associated with admission to an ICU for an annual incidence of 6.6 per 100,000 population. Although this study did not explicitly focus on sARF, 71% (n=179/253) required the institution of RRT, predominantly CRRT (72%), for an incidence of sARF of 4.2 per 100,000 population per year.[7] There are important

limitations to this study that deserve discussion. First, this study is potentially prone to selection bias as only tertiary care hospitals were sampled for cases and the determination and reporting of cases was dependent on completion of questionnaires by treating physicians. Second, the case definition used in this study is based on an arbitrary increase in serum creatinine; therefore, cases may have been excluded with a serum creatinine < 177 μmol/L despite a patient exhibiting a severe reduction in kidney function.

The fourth study by Korkeila *et al* was a small, single center, observational study that identified 41 critically ill patients with sARF over a 1-year period for reported annual incidence of 8 per 100,000 population or approximately 1-2% of all ICU admissions for the duration of the study.[3] Although this study focused on sARF in critically ill patients, the reported mortality and renal recovery outcomes are in fact not population-based as the descriptive statistics and analysis provided is based on a cohort of all patients with sARF (n=69) admitted to the study ICU during the surveillance period; whereas the authors describe only 41 patients being drawn from the primary referral or source population. Overall, this study is relatively small with few sARF events recorded, thus having limited statistically power to assess for potential factors contributing to long-term mortality and renal recovery outcomes.

The fifth study by Metcalfe *et al* was a community-based cohort study that identified all new cases of sARF in 3 health regions in Scotland over an 11-week period.[34] The authors reported an annual incidence of sARF of 2.0 per 100,000

population; however, again there was a lower overall event rate for sARF (n=48) and these cases were not solely identified in critically ill patients. Furthermore, the incidence from this study may be biased due to institution of RRT in the ICU in some centers simply due limited access to specialized units for provision of hemodialysis. Thus, many of the patients included in this study would not have been considered critically ill. Finally, this study was small, with cases identified over only 11-weeks and therefore could fail to account for any seasonal variation in the incidence of sARF. In another single-centre observational cohort study of sARF over a 7-year period in Scotland, Robertson *et al* reported an annual incidence of 18.7 per 100,000 population.[35] This study is potentially limited in generalizability as sARF was discriminated as the need for RRT for < 90 days from presentation; of which only a small proportion were considered critically ill and admitted to an ICU. Furthermore, the authors potentially introduce bias by assuming a static or fixed source population for the duration of the 7-year study upon which the population incidence rates are based.

The final study by Cole *et al* was an observational surveillance for sARF in 24 ICUs across Victoria, Australia over a 3-month period.[11] In this study, sARF was defined as any degree of ARF, which, in the opinion of the treating physician, required initiation of RRT. The authors reported an annual incidence rate of 13.4 cases per 100,000 population. However, this estimate may be prone to selection bias due to the authors not reporting the residency status of their

source population and due to inclusion of only “closed” ICUs; therefore, potentially introducing tertiary center referral bias.[26] In addition, these investigators have also reported another study with similar methodology that encompasses the entire country of Australia.[20] It remains unclear whether the two studies included overlapping data or actually capture all episodes of sARF from all “closed” ICUs.[11, 20] However, this study reported an incidence of sARF of 8 per 100,000 population per year from 81 ICUs across Australia that perform RRT.[20] To date, no data from Canada or North America has been reported on the population-based incidence of sARF in critically ill patients.

2. Risk factors for acute renal failure in the critically ill

Few studies, predominantly hospital-based, have proposed risk factors specifically for the development of ARF or sARF in critically ill patients upon admission to the ICU. Mukau *et al* reported that evidence of hypotension, exposure to know nephrotoxins (i.e. radiocontrast media) and bloodstream-infection associated sepsis were associated with development of sARF in a small cohort of surgical ICU patients.[22] Another cohort study of 437 patients with severe trauma suggested that ARF was more likely to occur in those with pre-existing co-morbid illness including chronic renal disease, malnutrition, higher injury severity scores (ISS), sepsis syndrome and concomitant non-renal organ dysfunction; however, it remains unclear what proportion of patients in this cohort ultimately required institution of RRT.[36] In a similar cohort study conducted at a

single surgical-trauma ICU, ARF was more common in patients with higher American Society of Anaesthiologists (ASA) and APACHE II scores.[6]

Groeneveld *et al* reported in a single center cohort study of medical ICU patients that advanced age, prior chronic disease, sepsis syndrome and cardiovascular and pulmonary organ dysfunction were associated with risk for ARF.[21] In a small comparative retrospective cohort study, McCarthy suggested that most patients had $\geq$ 2 identifiable factors contributing to the development of sARF with exposure to radiocontrast media and low cardiac output being more common.[24] de Mendonça *et al* reported that age > 65 years, presence of infection, documented congestive heart failure or cirrhosis, hematologic malignancy and acute circulatory or pulmonary organ dysfunction were the most important predictors of ARF at ICU admission. [16]

Two studies have assessed the epidemiology and outcomes of ARF in a population of critically ill patients diagnosed with sepsis syndrome.[37, 38] Hoste *et al* reported an incidence of ARF of 16.2% in a cohort of critically ill patients diagnosed with sepsis syndrome with 70% requiring RRT.[38] In these septic patients, a baseline serum creatinine > 88.4 μmol/L and pH < 7.3 were associated with development of ARF. Mortality was independently associated with older age, need for vasopressor therapy, mechanical ventilation and need for RRT. Neveu *et al* reported the outcomes of 345 critically ill patients with ARF, of which 157 (45%) were attributed to sepsis syndrome, in a prospective cohort study of 20 multidisciplinary ICU in France.[37] Septic critically ill patients with ARF

were significantly older (mean age 62 vs. 58 years), had greater burden of disease (SAPS 19.3 vs. 16.1; APACHE II 29.6 vs. 24.3) and organ system failure scores (OSF 2.1 vs. 1.5 organs failing) than patients with non-septic ARF. Furthermore, a higher proportion of septic critically ill patients required mechanical ventilation (69% vs. 49%). Septic ARF developed later during ICU stay than was present at admission compared with non-septic ARF (48% vs. 32%).

In summary, although several hospital-based cohort studies have suggested that a number of factors including increasing age, pre-existing co-morbid disease, exposure to nephrotoxins, sepsis syndrome, and cardiovascular, pulmonary or multi-system organ failure increase the risk for developing ARF or sARF, these studies potentially suffer from variable definitions of ARF/sARF and from selection bias which greatly limits their generalizability. Furthermore, no study to date has been adequately designed to determine actual general population risk factors for development of sARF.

3. Impact of acute renal failure on ICU and hospital outcomes

A diagnosis of ARF in the ICU is associated with a significant increased risk of prolonged hospitalization, mortality and health care costs. Estimates of ICU and in-hospital case-fatality rates range from 23-60% and 47-90%, respectively.[1, 3, 4, 8, 9, 11, 13-17, 19-22, 24, 31, 32, 34-36, 39-44] The mortality outcome across population-based studies was also highly variable with 34-72% dead in ICU[3, 11, 20]; 45-50% dead in

hospital[3, 7, 11, 20]; 46-50% dead at 3 months[31, 34, 35]; 55% dead at 6 months[3]; 66% dead at 2-years[31]; and 65% dead at 5-years[3].

Chertow *et al* reported a 1.1 % incidence of sARF in post-cardiac surgery patients, defined as the need for RRT in the 30 days following cardiac surgery. The overall operative mortality at 30 days was 63.7% for sARF following cardiac surgery. In this study, the crude odds ratio (OR) for death was 39 (95% CI, 32-48), 27 (95% CI, 22-34) following adjustment for co-morbidities and remarkably 7.9 (95% CI, 6-10) with adjustment for both co-morbidities and post-operative complications suggesting that sARF is independent associated with death following cardiac surgery.[41]

Several risk factors for death in critically ill patients with sARF have been identified, again predominantly by hospital-based studies. Some commonly identified factors include advanced age, prior chronic illness, oliguria, cardiovascular or any other organ dysfunction or requirement for vasoactive medications, need for mechanical ventilation, sepsis, illness severity as estimated by APACHE II score, and need for RRT. [1, 6, 9, 11, 13, 15, 16, 18, 20, 21, 23, 24, 27, 29, 30, 47] Interesting, in one small cohort study, the presence of ventilatory failure exactly predicted death among patients with sARF; however, this complete separation of data is unlikely applicable to larger critically ill populations.[15] Neveu *et al* reported significantly greater hospital case-fatality rates for critically ill patients with sARF rather than patients with ARF not requiring RRT.[37]

Less commonly identified risk factors for death include malignancy, increased bilirubin or cirrhosis, complicated metabolic acidosis or alkalosis, delayed occurrence of ARF or institution of RRT, hospitalization prior to ICU admission, cardiopulmonary resuscitation, massive transfusion and etiology of ARF other than acute tubular necrosis. [1, 6, 9, 13-16, 24, 30, 41] Metnitz *et al* reported that sARF represents an independent risk for hospital death in excess of expected after controlling for severity of illness.[1] In this large, multi-centre case-control study of 30 medical, surgical and multidisciplinary ICUs, five therapeutic interventions were found by multivariate analysis to predict hospital death in patients with sARF. The need for mechanical ventilation, use of a single and use of $\geq$ 2 vasoactive medications, cardiopulmonary arrest and need for treatment of metabolic acidosis/alkalosis was associated with an increased odds of hospital death; whereas, use of enteral nutrition was predictive of favorable outcome. There are several concerns with this study as previously mentioned. Specifically, this study is biased due to exclusion of approximately 3.6% of ICU admissions because of incomplete ascertainment of hospital outcome status. Further, there are concerns with the analysis and multivariate logistic model in this study, specifically concerns for co-linearity between variables in the final model not addressed by the authors.

In addition to the impact on patient mortality, the development of ARF is associated with an increased length of ICU and hospital stay and health care costs. de Mendonça *et al* reported that a diagnosis of ARF resulted in a

prolonged ICU stay by three days (median ICU stay 7 versus 4 days in non-ARF patients, p<0.01). [16] Sural *et al* reported ARF resulting in death was associated with a prolonged ICU length of stay in a small cohort study of critically ill patients from India.[8]

In a cost-effectiveness analysis, Hamel *et al* estimated that institution of RRT and continuation of aggressive care in critically ill patients with ARF resulted in an overall cost per quality-adjusted life-year saved of USD$128,200 rather than withdrawal of care and allowing death to occur.[2] However, the investigators further demonstrated that the cost-effectiveness of initiating RRT and aggressive care was dependent on initial survival prognosis. Patients with the best prognosis resulted in greater cost-effectiveness, with a cost per quality-adjusted life year of USD$61,900. In the study by Korkeila *et al*, the total cost of treatment for 62 patients with sARF consumed 7.3% of total ICU expenses during the study period.[3] The estimated average cost per patient for sARF was $36,141 and the cost per 6-month survivor was $80,026.

Although a number of predictive indexes for death have been developed in hospital-based studies they have performed relatively poorly when applied to other study populations.[19, 38, 45, 46] This may be as a result of the inherently biased selection of patients into hospital-based studies. Although population-based studies minimize this selection bias, none of the published population-based studies have evaluated independent factors associated with long-term 1-year mortality among patients with sARF.

4. Prognosis for renal recovery following sARF

The prognosis for long-term recovery of renal function in critically ill patients developing sARF has not been well described. Estimates of dialysis dependence at hospital discharge for survivors of sARF vary ranging from 5-33%.[3, 4, 11, 16, 17, 20, 34, 35, 40, 47, 48] Korkeila *et al* reported that 18% of critically ill patients with sARF were dialysis dependent at the time of discharge from hospital.[3] Further, the investigators reported overall mortality rates of 55% and 65% at 6 months and 5-years, respectively. In a small cohort study of 26 sARF survivors requiring >4 weeks of RRT, Spurney *et al* reported that 12% of patients failed to recover renal function and required dialysis at the time of hospital discharge.[40] Similarly, the two population-based studies from Australia reported that 8.3% and 9.5% of patients were dialysis dependent at hospital discharge.[11, 20]

A few studies suggest a poorer prognosis in critically ill patients following the diagnosis of sARF. One observational cohort study reported that 16.2% of patients were dialysis dependent at 90 days following initial diagnosis of sARF.[49] Manns *et al* reported dialysis dependence in 28.6% of critically ill patients surviving sARF at the time of hospital discharge.[4] Another small observational cohort study reported that 33% failed to recover kidney function and remained dialysis dependent at hospital discharge.[17]

Speigel *et al* in a cohort study of 43 consecutive critically ill patients with sARF reported that the presence of concomitant acute respiratory distress syndrome (ARDS), mechanical ventilation and need for antibiotic therapy by

univariate analysis were associated with reduced likelihood for recovery of kidney function and independence from dialysis.[15] Of note, this requires cautious interpretation, as this study was small with only five patients surviving, four of whom ultimately recovering kidney function by the time of hospital discharge.

Overall, available data from hospital-based cohort studies suggests that renal recovery and dialysis independence tends to occur in the majority of survivors of sARF by hospital discharge; however, the long-term prognosis for renal recovery remains poorly defined partly due to inadequate duration or consistency of follow-up. Importantly, none of the population-based studies published to date have assessed long-term renal recovery of critically ill patients with sARF.

Knowledge of the outcomes of sARF with respect to both mortality and renal recovery is important to aid clinicians, patients, and their families in decision-making regarding patient management choices in the ICU. Furthermore, recovery of renal function in critically ill patients remains clinically important due to the reduced health-related quality of life and increased health care costs associated with chronic outpatient dialysis therapy.[50-53] At present, the long-term mortality and renal recovery outcomes for sARF in a well-defined population are currently unknown.

C. OBJECTIVES

1. Primary Question

What is the incidence of severe acute renal failure (sARF) in a population-based cohort?

2. Secondary Questions

What are the risk factors for acquisition of severe acute renal failure (sARF) in a population-based cohort?

What is the mortality outcome at 1-year and what factors are associated with death at 1-year in critically ill patients with severe acute renal failure (sARF)?

What is the mortality outcome at 1-yr in critically ill patients by severity of renal dysfunction, including patients with end-stage renal disease (ESRD)?

What is the rate of recovery of kidney function and what factors are associated with recovery of kidney function in critically ill patients with severe acute renal failure (sARF)?

D. METHODS

1. Study Design

Population-based surveillance cohort.

2. Patients and Setting

The Calgary Health Region (CHR) provides virtually all hospital care to the residents of the cities of Calgary and Airdrie and approximately 20 nearby towns and villages.[54] A map demonstrating the geographic boundaries of hospital care provided by the CHR during the study period is displayed in Appendix 1. Adult critically ill patients in the CHR are managed in closed intensive care units (ICUs) by dedicated intensivists under the direction of the Department of Critical Care Medicine, University of Calgary and the CHR. All tertiary care services are provided within the CHR with the exception of cardiac, liver and lung transplantation, where patients undergoing these procedures are referred to provincial programs in the Capital Health Region in Edmonton.

The study population included of all adult (age $\geq$ 18 years) residents of the CHR admitted to any of the three multidisciplinary ICUs or the cardiovascular surgery ICU (CVICU). Ascertainment of CHR residency status was confirmed by review of patient postal code status. Those patients with postal codes not included within the boundary of the CHR were excluded from the study. The proportion of patients admitted to a CHR ICU or the CVICU that are non-

residents of the CHR is approximately 35% of the total population admitted.[26] The study was conducted from May 1, 1999 to April 30, 2002.

3. Operational Definitions

Severe acute renal failure (sARF) was defined as the new requirement for renal replacement therapy (RRT) with evidence of renal dysfunction (serum creatinine $\geq$150 μmol/L) at the time of or during ICU admission.[11, 20] In this study for the case-definition of sARF, evidence of renal dysfunction was defined as a serum creatinine level $\geq$150 μmol/L principally due to a serum creatinine at this value being outside the upper limit of the normal physiologic range for serum creatinine, essentially ensuring all patients included had evidence of renal dysfunction and simply for study feasibility. Although one limitation to this definition could include the potential exclusion of patients having received RRT despite a serum creatinine < 150 μmol/L, in particular elderly patients and women who generally have a lower value of serum creatinine for a given level of renal function.

Patients that received RRT for any indication in the absence of renal dysfunction suggested by a serum creatinine <150 μmol/L (i.e. toxin ingestion/overdose) and patients with end-stage renal disease (ESRD) already receiving chronic RRT or patients having their first RRT >48 hours prior to ICU admission were excluded.

Severity of renal dysfunction was defined using values of serum creatinine alone and was stratified by: no evidence of renal dysfunction (no renal failure or serum creatinine < 150 μmol/L), mild dysfunction (serum creatinine 150-299 μmol/L), moderate dysfunction (serum creatinine ≥ 300 μmol/L), sARF, and the presence of pre-existing end-stage renal disease (ESRD) requiring long-term RRT prior to ICU admission. Similar to the definition for sARF, there are limitations to defining severity of renal dysfunction solely on the basis of changes in serum creatinine, despite this being the most common method for defining acute renal failure in the literature.[7, 32, 55] Specifically, changes in serum creatinine may not accurately reflect the exact degree of decline in kidney function, but rather may also be dependent on factors such as age, sex, nutritional status, and the catabolic state of the patients.[56, 57] Although glomerular filtration rate (GFR) may represent a more accurate measure of renal function, the calculation of GFR in this study was not possible given the data available.

Renal replacement therapy encompassed continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD). No patient received peritoneal dialysis preceding or during admission to ICU. The decision for initiation of RRT was made at the discretion of the attending intensivist.

For the purposes of this study, chronic renal dysfunction was defined as a pre-existing serum creatinine ≥ 150 μmol/L for at least six months prior to ICU admission as determined upon review of data from the patient medical record.

Oliguria was defined as the production of <500 mL of urine in the 24 hours preceding assessment.[7]

The definitions used by Liano *et al* and clinical sensibility were used for classification of diagnoses of sARF.[32] For this study, the etiology of sARF was differentiated into pre-renal, post-renal and intra-renal etiologies (Table 1). Clinical sensibility was used for characterization of the indications of RRT based on data available from the patient medical record. The indications for RRT were characterized as diuretic-resistant fluid overload; uremia; metabolic acidosis; hyperkalemia or toxin removal in the setting of evidence of renal dysfunction (a priori defined as a serum creatinine ≥ 150 μmol/L).

Severity of illness at ICU admission was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score.[58]

Table 1. Study definitions for etiology and classification of sARF[7]

Term	Definition
Pre-renal failure	When treatment (i.e. volume repletion and/or increased cardiac output) was successful in restoring renal function
Post-renal (obstructive) failure	Documentation of acute obstruction of urinary tract
Intra-renal failure	Diagnosis was determined after exclusion of pre-renal and post renal failure etiologies.

The presence and evaluation of selected pre-existing co-morbidities was assessed using the Charlson Co-morbidity Index (CCI).[59] The scoring system

used for the CCI is based on the presence of selected underlying co-morbidities and is displayed in Table 2.

Table 2. Charlson Co-morbidity Index Scoring

Weight	Co-morbid Conditions
1	Myocardial infarction; Congestive heart failure; Peripheral vascular disease; Dementia; Chronic pulmonary disease; Connective tissue disease; Peptic ulcer disease; Mild liver disease; Diabetes
2	Hemiplegia; Moderate or severe renal disease; Diabetes with end organ damage; any tumor (solid tumour without metastases, diagnosed in past 5 years); Leukemia (acute and chronic and polycythemia ruba vera); lymphoma (including Hodgkin's; Waldenstrom's; myeloma; lymphosarcoma)
3	Moderate or severe liver disease (cirrhosis, portal hypertension, varices)
6	Metastatic solid tumour; HIV/AIDS
1	Age (per each 10 year increase above 40)

Hypotension was defined as a systolic blood pressure < 90 mmHg for > 30 minutes. Shock was defined as mean arterial pressure <70 mmHg and need for vasopressor therapy. The presence of sepsis, septic shock, and acute respiratory distress syndrome (ARDS) were defined according to consensus guidelines.[60, 61]

4. Data Sources

The size and demographic profile of the mid-year CHR adult population-at-risk during the three year period of surveillance was obtained by using population data from the Alberta Health Registry (Appendix 2).[62]

The prevalence of selected underlying chronic illnesses was estimated based on Canadian and United States (US) survey data.[63-67] The prevalence of chronic kidney disease (CKD) was estimated to be 4.5% from the United States Third National Health and Nutrition Examination Survey (NHANES III).[67, 68] The NHANES III is a nationwide survey conducted in the US from 1988-1994 that sampled 34,000 civilian, non-institutionalized persons over a 2 month period, of which approximately 20,000 were adult, and collected a wide range of representative information on general health and nutritional practices through interviews, conduct of clinical examinations and laboratory tests.[67] This is a comprehensive survey of the general US population; however, there are limitations to the use of the estimated prevalence of CKD from this US data sample. First, the survey may be prone to sampling error, thus providing a biased estimate of the prevalence. Second, perhaps more importantly, the prevalence may not be directly generalizable to a Canadian population such as the CHR due to fundamental differences between the US population sampled and the CHR. For example, the distribution of race (i.e. White, Black and Hispanic) likely differs in the US sample compared with the CHR and race, perhaps confounded by the higher prevalence of diabetes mellitus in some

growing ethnic groups, has been suggested as an important risk factor for CKD.[69-71] The prevalence of heart disease in the adult Canadian population was estimated at 4% based on results from the 1996/97 National Population Health Survey.[72] The prevalence of diabetes mellitus in the adult Canadian population was estimated at 4.5% from the 2000/01 Canadian Community Health Survey[73] The prevalence of ethanol abuse in the Canadian population aged > 15 years was estimated at 2.6% from the 2002 Canadian Community Health Survey. [74] The prevalence of arthritis or rheumatism in the CHR population was estimated at 13.7% by the 2003 Canadian Community Health Survey.[66] The definition includes all person age > 12 years who self-report the diagnosis of arthritis or rheumatism by a health professional, that includes rheumatoid and osteoporosis but excludes fibromyalgia. This was a conservative estimate and would be higher than expected for patients with a diagnosis of rheumatoid arthritis or a connective tissue disease only. Therefore, the prevalence of connective tissue disease including rheumatoid arthritis was based on a US population sample and estimated at 1%.[75] The estimated prevalence of chronic obstructive lung disease in the Canadian population was 1-3% based on the 1994/95 National Population Health Survey; however, the prevalence rates are confounded by sex, age and smoking status (i.e. non-smoker, ex-smoker and active smoker). Therefore, for the purposes of this study given that we are uncertain of the smoking status of CHR residents admitted to an ICU or the CVICU, we used a conservative crude estimate of the prevalence based on the data provided by Chen et al of 3%.[76]

The target population of the National Population Health Surveys (NPHS) (1994/95 and 1996/97) were household residents in all provinces of Canada with exclusion of selected populations on Native reserves, Military bases and some remote regions of Ontario and Quebec. This cross-sectional survey used a stratified two-stage design with a projected longitudinal follow-up of 10 cycles over 18 years. For the first stage, homogenous geographic and/or socioeconomic strata were formed from which independent samples of clusters were drawn from each stratum with probability proportional to size. For the second stage, dwelling lists were generated for each cluster to form the study population. Respondents of dwellings (households) were contacted in person, most interviews were conducted over the telephone, and limited information was collected on all members residing in a particular household, often by a single household member (i.e. proxy reporting) after which one household member aged ≥ 12 years was randomly selected for an in-depth interview. The NPHS sampled approximately 18,000 households, a minimum 1,200 from each province and cycles approximately every 2 years with the same respondents. The survey inquires about a broad range of health determinants including alcohol consumption, smoking, chronic conditions, health care utilization, self-perceived health status, height, weight, restriction of activities and stress. Further, the survey also collects information on the basis of age, sex, household composition, income and the labour force.

The target population of the Canadian Community Health Survey (CCHS) (2000/01 and 2003) is persons aged ≥ 12 years living in private dwellings across 10 provinces and 3 territories with the exclusion of persons living on Native reserves, Military bases and some remote regions of the country. The CCHS is estimated to represent 98% of the Canadian population. The CCHS is a cross-sectional survey of approximately 136 Health Regions in Canada with a voluntary sampling of approximately 130,000 household persons; however, unlike the NPHS is not a longitudinal survey, but subsequent 2-year cycles of the CCHS results in random sampling of different households. The sampling follows a similar stratified method as the NPHS. The primary method of response for household members for this survey was by using computer-assisted interviewing that was proposed to have several data quality advantages over direct interviewing such as: customized automated question text for simplicity and efficiency that incorporated factors such as the age and sex of the respondent, the date of the interview and answers to previous questions; automated edits to check for inconsistent answers or out-of-range responses; and questions that are not applicable to the household person are skipped automatically. The CCHS collects similar information to that reported for the NPHS. There are several limitations to the use of data generated by the NPHS and CCHS. First, the quality of the data provided was dependent on representative sampling of the entire Canadian population. Both surveys employ complex and rigorous methods of sampling; however, several select populations

have been excluded from the study (i.e. Natives, non-civilians, prison inmates etc.) and therefore may introduce selection bias by differential sampling in subsequent studies estimating prevalence rates. Second, participation in the surveys was voluntary and therefore could introduce selection bias by differential surveillance; however, both surveys have high participation rates (>90%) that likely minimize significant effects on the data generated. Third, the quality of data was also dependent on self-reporting of accurate health information and was potentially prone to observation bias, specifically recall bias; however, both surveys have employed rigorous methods of questionnaire development with pilot testing that likely will act to minimize any significant effects on the data. Fourth, the quality of data was dependent on the assumption that the medical conditions upon which the survey collects data have already been diagnosed by a health professional; therefore, could potentially miss conditions that have yet to be diagnosed or with long induction or latency periods such as several forms of cancer. Finally, the national prevalence rates for some conditions may not be directly generalizable to the population of the CHR. The estimated prevalence of a cancer diagnosis in the Canadian population is 2%.[77] The estimated prevalence of stroke in the CHR is 1% based primarily on hospital admission rates.[78]

Chronic RRT dependence status was determined from the Southern Alberta Renal Program (SARP) database that maintains information on all patients in southern Alberta receiving chronic RRT.[79]

The long-term mortality outcome information was obtained through deterministic linkage strategies with the Death Registration Database maintained by Alberta Vital Statistics and the Alberta Health and Wellness registry of insured persons.[80] Alberta Health and Wellness maintain information on all residents of Alberta eligible for publicly funded healthcare coverage (>99% of the population is included in this registry). Variables used for this linkage included the Alberta personal health number (a unique lifetime identifier), surname, given name, and date of birth. Linkage was first performed using name and date of birth information with the Vital Statistics database, which is the most up-to-date registry of deaths in Alberta. Subsequent linkage was performed using the personal health number linking to the Alberta Health and Wellness registry, which maintains a death flag. The use of both information systems ensured completeness of the linkage process. This linkage process was performed using SAS® version 8.2 (SAS Institute Inc, Cary, NC).

Data was exported from the source databases and linked using Access 2000 (Microsoft Corp., Redmond WA).

5. Study Protocol

An electronic patient information system [Quantitative Sentinel (QS), GE-Marquette Medical Systems Inc., Milwaukee, WI] interfaced to all bedside devices prospectively collects patient clinical and physiologic data that was downloaded into the ICU Tracer database. The ICU Tracer database was searched initially to identify all patient admissions to the study ICUs. Basic ICU admission data including demographic data such as age, sex, dates of hospital and ICU admission and discharge and clinical information including admission APACHE II score, vital signs, basic laboratory results including creatinine level, presence of absence of oliguria, primary diagnosis, and diagnostic category was recorded.[58, 81] The ICU Tracer database was also used to identify those patients with sARF during their ICU admission.

Hospital medical records were reviewed in detail using standardized data collection forms for all patients identified with sARF (Appendix 4). Renal replacement therapy information obtained included the date of first RRT, total duration of RRT and the specific modalities of RRT used (i.e. CRRT and/or IHD). The etiology of renal failure (pre-renal, renal, or post-renal) and the potential precipitants (i.e. nephrotoxins including aminoglycosides, radiocontrast media or amphotericin B therapy, ischemia secondary to cardiogenic, distributive, or hypovolemic shock) were determined. Further, the immediate indications for RRT (i.e. uremia, acidosis, hyperkalemia, diuretic-resistant fluid overload or other specified) were ascertained.

Data on selected pre-existing co-morbidities that could be associated with the survival status at 1-year were ascertained.[82, 83] Specific co-morbidities recorded included prior myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic pulmonary disease, liver disease, diabetes mellitus with and without end-organ damage, solid organ or hematologic malignancy and immunodeficiency such as with HIV infection or chronic alcohol abuse. Similarly, the presence of systemic inflammatory response syndrome (SIRS), sepsis syndrome, septic shock or objective evidence of infection was ascertained using consensus criteria.[84]

A trained research nurse and physician (SMB) reviewed hospital medical records to obtain clinical information for all patients identified with sARF. A study physician (SMB) reviewed all abstracted data forms prior to entry into the study database in order to ensure consistency of application of study definitions and diagnoses.

6. Data Management

Data was exported from the ICU Tracer, SARP and the Death Registration Database and the Alberta Health and Wellness registry databases into Access 2000 (Microsoft Corp., Redmond, WA). Data from medical record reviews was manually entered into Access 2000, merged with the other data sources and subsequently exported into Excel 2000.

7. Data Analysis

Analysis was performed using Stata version 8.2 (Stata Corp, College Station, TX). To avoid assessment of multiple outcomes for a single patient, only the first ICU presentation associated with sARF was analyzed for patients with multiple ICU admissions. In the event of missing data for a particular variable that was not available after review of the patient's medical record or the ICU Tracer database, the data was not replaced.

Prior to analysis, all variables were assessed for underlying distribution qualitatively using histograms or box plots. Normally or near normally distributed variables were reported as means with standard deviations (SD) and were compared using the appropriate Student's t test. Non-normally distributed continuous data were reported as medians with inter-quartile ranges (IQR) and were compared using the Mann Whitney U test. Categorical data were reported as proportions and compared using Fisher's Exact Test. Levels of significance

were not adjusted for multiple testing and a two-sided p-values of < 0.05 were considered statistically significant for all comparisons unless otherwise stated.

Primary Outcome

The primary outcome was the annual incidence of sARF in the well-defined population of the CHR. This was determined by the total number of critically ill patients diagnosed with sARF divided by the total adult (age > 18 years) population of the CHR at-risk during the three years from May 1, 1999 through April 30, 2002. The annual incidence rate of sARF was further stratified to determine age and sex-specific rates.

Secondary outcomes

General population risk factors for acquisition of sARF were determined by comparing the incidence rate of sARF in those critically ill patients with and without several selected underlying co-morbid conditions. For determination of incidence rates, denominator data from the Alberta Health Registry was used.[62] The comparison in incidence among groups were assessed through use of a Poisson distribution and presented as incidence rate ratios (IRR) with exact 95% confidence intervals.[85]

The annual mortality rate of sARF in the population of the CHR was calculated. The annual mortality rate was further stratified to calculate age and

sex-specific rates. A comprehensive stratified analysis was performed in order to assess for risk factors along with potential confounders and/or effect modifiers of the association of these risk factors and death at 1-year for patients with a diagnosis of sARF. Confounding is defined as the mixing of effects between a potential risk factor and the outcome of interest, in this example death at 1-year, due to the influence of a third factor. When this third factor, termed a confounder, is present, the resulting association between the risk factor and outcome is distorted because of the associations between the confounder and the risk factor and the confounder and the outcome. As a result of a confounder, the estimate of association between the risk factor and outcome may be altered in terms of both magnitude and direction and provide a misleading estimate of the relationship. Effect modification is defined as differences in the strength of the association between the risk factor and outcome across levels of a third factor resulting in stratum specific estimates of the relationship between the risk factor and outcome.

To determine the mortality outcome at 1-year stratified by severity of renal dysfunction, a comprehensive stratified analysis was performed in order to assess for risk factors along with potential confounders and/or effect modifiers of the association of these risk factors and death at 1-year stratified by severity of renal dysfunction. Severity of renal dysfunction was stratified by: no renal dysfunction (serum creatinine < 150 μmol/L); mild dysfunction (serum creatinine 150-299 μmol/L); moderate dysfunction (serum creatinine $\geq$ 300 μmol/L); sARF;

and pre-existing ESRD. Factors assessed included patient age; patient sex; APACHE II score as a measure of severity of illness; and admission type stratified as medical, non-cardiac surgical or cardiac surgical.

To simply describe the long-term survival experience of critically ill patients by sARF and by severity of renal dysfunction, crude Kaplan-Meier survival estimate curves were generated and truncated at 100 days. Survival function curves for patients with a diagnosis of sARF were further stratified by age $\geq$ 65, sex, age $\geq$ 65 and sex, admission type, and APACHE II score and displayed graphically. The assumption of proportional hazards was assessed graphically by use of log-log plots. Equality in the estimated survival function curves across groups was assessed by the Wilcoxon-rank test due to concern of the large proportion of failures occurring at an earlier time.

To determine the rate of renal recovery among patients with a diagnosis of sARF surviving an episode of critical illness, the proportion surviving and independent of RRT was calculated at 1-year. A further comprehensive, stratified analysis was performed in order to assess for factors that may influence the association of renal recovery at 1-year for patients with a diagnosis of sARF.

E. ETHICAL CONCERNS

This study involved the review of existing data from clinical and administrative databases and review of patient medical records. No patient or next of kin was contacted and no patient interventions were performed. Patients were assigned anonymous identifiers and actual identities remained confidential and secured under the supervision of the principal investigators. Data was password protected at all times. Data was stored in a locked cabinet in a locked office. No information was reported publicly that could be linked or recognized to belong to any given patient in the study. Prior to data acquisition, ethical review and approval was attained from the Research Ethics Board of the University of Calgary and Calgary Health Region (Appendix 3).

F. RESULTS

A total of 367 (6.4%) patients received RRT at least once during an ICU admission of which 118 (2.2%) were initially excluded from the primary analysis: 92 (1.6%) for outpatient chronic RRT or ESRD; 15 (0.3%) due to being determined as non-residents of the CHR; 8 (0.1%) having initiated RRT > 48hrs prior to admission to ICU; 6 (0.1%) for RRT in an ICU without critical illness; 4 (0.1%) received RRT for toxin removal in the absence of renal dysfunction; and 1 patients (0.01%) due to age < 18 years.

1. Incidence of sARF

Incidence is defined as the occurrence of new cases of disease fulfilling a case-definition (i.e. sARF) that develop in a defined population determined to be at risk (i.e. CHR) over a specified period of time (i.e. 3 years). Therefore, for the purposes of this study, incidence will be determined by new cases of sARF developing in the adult CHR population-at-risk during the 3-year of surveillance.

A total of 240 patients were diagnosed with sARF, representing 4.2% of total ICU cohort admitted during the study surveillance. These 240 patients represent the numerator for calculation of incidence for sARF in the CHR during the period of study surveillance. The accuracy of this numerator was dependent on several factors.

First, it was necessary for these patients to be residents of the source population (i.e. CHR). These patients were confirmed residents of the CHR and

all patients determined to be non-residents of the CHR were excluded from the study, based on the initial database review of each patient's CHR postal code status. The proportion of all patients admitted to CHR ICUs excluded based on residency status was approximately 35%.[26] Further, as a secondary quality assurance of the data, the residency status of all patients with sARF was confirmed during patient medical record review, after which an additional 15 (0.3%) patients were discovered to be non-residents of the CHR and were excluded.

Second, the accuracy of the numerator was dependent on having ascertained all cases fulfilling the a priori definition of sARF. It is plausible that residents of the CHR who were traveling abroad and developed critical illness and sARF would have been missed; however, this is likely to be a small source of potential bias. This is due to the fact that for a critically ill patient to be transferred back their own health region, the transfer would generally occur from ICU to ICU to ensure patient safety, thus minimizing the probability of missing any sARF cases that occurred as a result of travel abroad. In addition, cases of sARF could have been missed in the context of a CHR resident having received medical services not available in the CHR such as cardiac, liver or lung transplantation. This is unlikely to represent a significant source of selection bias given that these procedures occur infrequently and for similar aforementioned reasons, these critically ill patients would likely be transferred back to the CHR to an intensive care environment thus allowing capture if fulfilling the case-definition

for sARF. In addition, we may not have captured patients admitted to the cardiac intensive care unit (CCU) at the Foothills Hospital fulfilling the case-definition for sARF during admission to that unit who may have been considered critically ill. This is not likely to represent a significant source of selection bias given that those patients deemed critically ill, receiving mechanical ventilation and with evidence of considerable organ dysfunction in the CCU who proceed to fulfill the case-definition for sARF are generally transferred to the multidisciplinary ICU or the CVICU at Foothills Hospital for initiation of RRT, specifically CRRT which is not available in the CCU. Finally, one further consideration would be patients who fulfill the case-definition for sARF and perhaps have evidence of organ dysfunction and critically illness that would otherwise warrant admission to an ICU are managed instead in the emergency department or on a general medical or surgical ward, perhaps due circumstances such as bed availability or advance directives. Although, we would have missed these cases, this is unlikely to represent a significant source of selection bias. In general, patients requiring ICU admission are admitted, though may be transferred to an ICU at another hospital in the CHR, in which case they would have been captured by this study. Further, in the circumstance where patients with advanced directives requesting not to be admitted to an ICU for advanced life support, these patients are likely to die due to withdrawal of care and therefore, if included, could potentially introduce selection bias and information bias by effecting the association of sARF and the case-fatality rate at 1-year.

Third, the accuracy of the numerator was also dependent on having only captured new cases of sARF and excluding patients admitted to the ICU that were either already receiving long-term RRT (i.e. ESRD) or those patients recently having RRT initiated while outside of an ICU environment and not directly associated with or contributing to admission to an ICU. Specifically, this is important in order to discriminate between the prevalence and incidence of sARF. Prevalence is defined as the frequency of existing disease or simply as the total proportion of the population that has the disease (i.e. sARF). Therefore, it would be important to exclude that proportion of patients that had pre-existing sARF at the initiation of the study surveillance period. The consistency in application of the study case-definition for sARF and exclusion criteria were assured by patient medical record review for all patients identified initially as having sARF. By this process, patients were excluded if they had evidence of ESRD or had received RRT > 48 hours prior to admission to ICU, resulting in the exclusion of 92 (1.6%) and 8 patients (0.1%), respectively. Furthermore, a single study physician (SMB) reviewed all standardized patient data forms to ensure consistency in application of case-definitions for sARF; therefore minimizing observation bias by misclassification of sARF cases. Therefore, the 240 patients fulfilling the definition of sARF during the three years of surveillance in the CHR represent an accurate count and therefore valid measure of the numerator.

The denominator data for this study was represented by the mid-year population counts for the years of study surveillance for the CHR provided by the

Alberta Health Registry and the CHR.[62] The accuracy of the denominator data was dependent on several factors. First, the accuracy was dependent on the precision of the counts for the population of the CHR for the years 2000 and 2001 based on information provided by Alberta Health Registry database. The population of the CHR is dynamic with significant evidence of growth in the adult population during the years of surveillance as demonstrated by the adult CHR population-at-risk column in Table 3. Second, the mid-year population for 2002 was estimated by the 3-year fertility rate for the CHR and an approximated net migration of 12,000 persons per year. Third, the accuracy of the denominator was dependent on the counts of the CHR being representative of all persons in the CHR in fact being residents of the CHR. Further, it was unclear whether these counts incorporate populations of patients that reside in the CHR such as Natives on reserves, Military employees, elderly institutionalized patients, and prison inmates. Therefore, the population counts and demographic profile for the CHR are potentially prone to some error resulting in the introduction of bias into the calculation of population-based incidence of sARF. Therefore, although the counts and projections for the population of the CHR, thus the denominator for the incidence calculation, are presumed to be relatively accurate, the incidence rates are reported with exact 95% confidence intervals to account for any potential error.

The calculated crude annual incidence of sARF was 11.0 (Exact 95% CI, 9.6-12.5) per 100,000 population. The age and sex-specific population statistics

for the CHR during the study period are detailed in Appendix 2. The annual incidence of sARF was relatively stable over the three years of surveillance (Table 3). The incidence rate difference from May 2000 - April 2001 to May 1999 - April 2000 (year 2 to year 1) increased by 3.45 (95% CI, 0.4 to 6.9, p=0.048) per 100,000 population. The incidence rate from May 2001 - April 2002 to May 2000 - April 2001 (year 3 to year 2) did not change significantly and decreased by -0.9 (95% CI, -4.5 to -2.6, p=0.6) per 100,000 population. Finally the incidence rate difference from the final year of the study (May 2001 - April 2002) to the first year of the study (May 1999 - April 2000) was not significantly different and increased by 2.0 (95% CI, -1.3 to 5.2, p=0.25) per 100,000 population.

Table 3. Crude annual population-based incidence of sARF among adult residents of the CHR.

Year	No. Patients with sARF (%)	Adult CHR Population at-risk	Crude Incidence (per 100,000 population) Exact 95% CI
May 1999 - April 2000	65 (27)	708,077	9.2 (7.1-11.7)
May 2000 - April 2001	92 (38)	728,207	12.6 (10.2-15.5)
May 2001 - April 2002	83 (35)	745,749	11.1 (8.9-13.8)
Overall	240 (100)	2,182,033	11.0 (9.6-12.5)

A sensitivity analysis was performed to determine the effect of potential error in the denominator data for the CHR. The mid-year population counts for 2000, mid-year projections for 2002 and the mid-year projections for 2004 were

used to estimate the crude annual incidence rates for sARF during the period of surveillance (Table 4). The sensitivity analysis demonstrated that the crude annual incidence rates remain stable with no significant differences when comparing the weighted crude incidence rate of 11.0 (Exact 95% CI, 9.6-12.5) per 100,000 population incorporating the individual CHR population counts/projections for each year of surveillance and the crude incidence rate of 11.3 (Exact 95% CI, 9.9-12.8) per 100,000 population using only mid-year population counts for 2000, the crude incidence rate of 10.7 (Exact 95% CI, 9.4-12.2) per 100,000 population using only mid-year population projections for 2002, and the crude incidence rate of 10.2 (Exact 95% CI, 9.0-11.6) per 100,000 population using only the mid-year population projections for 2004. Therefore, results of this sensitivity analysis would suggest that the crude incidence rates for sARF remain relatively robust to changes or small sources of error in the denominator data based on data from the Alberta Health Registry used for the primary incidence calculations.

Table 4. Sensitivity analysis of crude annual population-based incidence of sARF among adult residents admitted to a CHR ICU based on: A) the mid-year population counts for 2000; and B) the mid-year population projections for 2002; C) the mid-year population projections for 2004.

A)

Year	No. Patients with sARF (%)	Person-years At-risk based on 2000 population counts	Crude Incidence (per 100,000 population) Exact 95% CI
Year 1	65 (27)	708,077	9.2 (7.1-11.7)
Year 2	92 (38)	708,077	12.9 (10.5-15.9)
Year 3	83 (35)	708,077	11.7 (9.3-14.5)
Overall	240 (100)	2,124,231	11.3 (9.9-12.8)

B)

Year	No. Patients with sARF (%)	Person-years At-risk based on 2002 population projection	Crude Incidence (per 100,000 population) Exact 95% CI
Year 1	65 (27)	745,749	8.7 (6.7-11.1)
Year 2	92 (38)	745,749	12.3 (10.0-15.1)
Year 3	83 (35)	745,749	11.1 (8.9-13.8)
Overall	240 (100)	2,237,247	10.7 (9.4-12.2)

C)

Year	No. Patients with sARF (%)	Person-years At-risk based on 2004 population projection	Crude Incidence (per 100,000 population) Exact 95% CI
Year 1	65 (27)	781,724	8.3 (6.4-10.6)
Year 2	92 (38)	781,724	11.8 (9.5-14.4)
Year 3	83 (35)	781,724	10.6 (8.5-13.2)
Overall	240 (100)	2,345,172	10.2 (9.0-11.6)

2. Risk factors for sARF

The median (IQR) age of patients with a diagnosis of sARF was 66.1 (52.6-74.1) years. There was evidence of a significant association between increasing age and the incidence of sARF (Table 5).

Table 5. Age-specific annual incidence of sARF.

Age (Years)	No. Patients with sARF (%)	Person-years At-risk	Age-adjusted Incidence (per 100,000 population) Exact 95% CI
18-49	47 (20)	1,312,088	3.6 (2.6-4.8)
50-64	68 (28)	531,337	12.8 (9.9-16.2)
65-74	73 (30)	195,757	37.2 (29.2-46.9)
≥ 75	52 (22)	142,851	36.4 (27.2-47.7)
Overall	240 (100)	2,182,033	11.0 (9.6-12.5)

There was a significant increase in incidence of sARF when comparing those aged 50-64 to those aged 18-49 [incidence rate difference 9.2, (Exact 95% CI, 6.0-12.4, $p<0.0001$)]. There was a relative plateau in incidence with no significant difference when comparing those aged ≥ 75 to those aged 65-74 [incidence rate difference – 0.8, Exact 95% CI, -1.4 to 1.2, $p=0.9$)]. The incidence of sARF was significant higher in patients aged ≥ 65 years when compared with those aged 50-64 years [36.9 vs. 12.8 per 100,000 population; (IRR 2.9, Exact 95% CI, 2.1-3.9, $p<0.0001$)]. The incidence of sARF was also

significantly higher among those patients aged ≥ 65 years old compared with all those aged <65 years [36.9 vs. 6.0 per 100,000 population; (IRR, 5.9; Exact 95% CI, 4.6-7.7, p<0.0001)].

Of 240 patients with sARF, 58% (n=140) were male. The annual incidence for sARF for males was 13.0 (Exact 95% CI, 10.9-15.3) per 100,000 population. For females, the annual incidence was 9.1 (Exact 95% CI, 7.4-11.0) per 100,000 population (Table 6).

Table 6. Sex-specific annual incidence of sARF.

Sex	No. Patients with sARF (%)	Person-years At-risk	Sex-specific Incidence (per 100,000 population) (Exact 95% CI)
Male	140 (58)	1,078,738	13.0 (10.9-15.3)
Female	100 (42)	1,103,295	9.1 (7.4-11.0)
Overall	240 (100)	2,182,033	11.0 (9.6-12.5)

The annual incidence rate of sARF was significantly higher for males compared to females [incidence rate difference 3.9 (Exact 95% CI, 1.1-6.7) per 100,000 population] suggesting that male sex is associated with higher incidence of sARF [IRR, 1.4; (Exact 95% CI, 1.1-1.9), p=0.006]. The incidence of sARF across age strata appears modified by patient sex. Specifically, the incidence of sARF is significantly higher for males compared with females for those aged 65-74 and ≥ 75 years, respectively (Table 7). There is no significant difference in the

incidence of sARF between males and females for those aged < 65 years [6.4 vs. 5.5 per 100,000 population (IRR 1.2; Exact 95% CI, 0.8-1.7, p=0.44)]. For all those aged ≥ 65 years old, the incidence of sARF is significantly higher in males compared with females [53.0 vs. 24.5 per 100,000 population; (IRR 2.2; Exact 95% CI, 1.5-3.2, p<0.0001)].

Table 7. Age and sex-specific annual incidence of sARF.

Age (Years)	No. Males with sARF (%)	Age-specific incidence for males (per 100,000 population) (Exact 95% CI)	No. Females with sARF (%)	Age-specific incidence for females (per 100,000 population) (Exact 95% CI)	Incidence Rate Ratio (Exact 95% CI)
18-49	26 (55)	3.9 (2.6-5.7)	21 (45)	3.2 (2.0-5.0)	1.2 (0.7-2.3)
50-64	36 (53)	13.4 (9.4-18.6)	32 (47)	12.1 (8.8-17.1)	1.1 (0.7-1.8)
65-74	45 (62)	48.1 (35.1-64.3)	28 (38)	27.2 (18.2-39.6)	1.8 (1.1-2.9)
≥ 75	33 (63)	61.7 (42.5-86.7)	19 (37)	21.3 (12.8-33.2)	2.9 (1.6-5.4)
Overall	140 (58)	13.0 (10.9-15.3)	100 (42)	9.1 (7.4-11.0)	1.4 (1.1-1.9)

Although there was a slight reduction in the incidence of sARF for females aged ≥ 75 years compared with females aged 65-74 years, this was not statistically significant [incidence rate difference 6.2 per 100,000 population (Exact 95% CI, -7.8 to 20.1, p=0.40)], suggesting a plateau in incidence rate for elderly females. Similarly, although the incidence rate of sARF for males aged ≥ 75 years compared with males aged 65-74 years appears to increase considerably, this was not statistically significant [incidence rate difference 13.7 per 100,000

population (Exact 95% CI, -11.6 to 39, p=0.28)]. Overall, these data suggest the both age and sex represent important risk factors for sARF. Furthermore, these data demonstrate that male patients aged ≥ 65 years may be at highest risk.

Several selected co-morbid conditions were identified in the general population with significantly higher risk for development of sARF and are detailed in Table 8. There are several potential limitations to consider with this analysis. First, the accuracy of the incidence rate ratios are dependent of several factors, specifically the precision of the prevalence estimates for each co-morbid condition and counts or projections for the CHR population as previously discussed in the methods and results sections, respectively. The error in the prevalence estimates could result in a biased calculation of a crude incidence rate ratio for each co-morbid condition. In order to assess the effect on the incidence rate ratio of potential error in the prevalence estimates for each co-morbid condition a sensitivity analysis was performed where the prevalence for each condition was increased by 100% resulting in a larger population-at-risk for sARF with each co-morbid condition (Table 9). The results of this sensitivity analysis demonstrated that the crude incidence rate ratio for each co-morbid condition remained statistically significant ($p<0.0001$ for each calculation) suggesting that the calculated incidence rate ratios are relatively robust to error in the prevalence estimates.

Second, these incidence rate ratio calculations are crude estimates and are not adjusted for age, sex or other potential confounders and/or effect modifiers. For example, the risk of sARF may be influenced by the presence of ≥ 1 underlying co-morbid conditions (i.e. cardiac and pulmonary disease). This study was not able to assess the association of age, sex, and several co-morbid conditions simultaneously on the risk for developing sARF in a multivariate model due to the impracticality and feasibility of collecting specific medical information for the entire population of the CHR. One practical solution would be to conduct of a nested case-control study in order to assess the association between several co-morbid factors and the risk for development of sARF. Such a case-control study could either be performed by random sampling of the general population or by random sampling of ICU patients without a diagnosis of sARF admitted during the observation period. The main difficulty in performing such a case-control study would be in identification and selection of source population controls in order to minimize selection bias. This represents another potential avenue for investigation in the future.

Table 8. Risk of sARF associated with selected co-morbid conditions among adult residents of the CHR.

Underlying Condition*	sARF patients with condition (%)	Person-years with condition	Annual Incidence (per 100,000)	sARF patients without condition (%)	Person-years without condition	Crude Incidence Rate Ratio** § (Exact 95% CI)
Heart disease	120 (50)	87,281	137	120 (50)	2,094,752	24.0 (18.5-31.2)
Stroke	44 (18)	21,820	202	196 (72)	2,160,213	22.0 (15.6-31.0)
COPD	83 (35)	65,461	127	157 (65)	2,116,572	17.1 (12.9-22.4)
Alcoholism	57 (24)	56,733	100	183 (76)	2,125,300	11.7 (8.5-15.8)
Cancer	38 (16)	43,641	87	202 (84)	2,138,392	9.2 (6.3-13.1)
DM	72 (30)	98,191	73	168 (70)	2,083,842	9.1 (6.8-12.1)
CTD	12 (5)	21,820	55	228 (95)	2,160,213	5.2 (2.7-9.3)
CKD	45 (19)	98,191	46	195 (81)	2,083,842	4.9 (3.5-6.8)

Abbreviations: sARF = severe acute renal failure; No. = number; CI = confidence interval; CTD = connective tissue disease; COPD = chronic obstructive lung disease; DM = diabetes mellitus; CKD = chronic kidney disease.

* Underlying conditions were defined by using the Charlson co-morbidity Index.[59] The presence of alcohol abuse was defined by documentation in patient medical record.

** Incidence rate ratio calculated by: [(No. of sARF patients with underlying condition/Person-years with condition) / (No. of sARF patients without underlying condition/Person-years without condition)].

§ p-value<0.0001 for each underlying condition incidence rate ratio.

Table 9. Sensitivity analysis for risk of sARF associated with selected co-morbid conditions among adult residents of the CHR where prevalence estimates are increased by 100%.

Underlying Condition*	sARF patients with condition (%)	Person-years with condition	Annual Incidence (per 100,000)	sARF patients without condition (%)	Person-years with condition	Crude Incidence Rate Ratio** § (Exact 95% CI)
Heart disease	120 (50)	174,562	69	120 (50)	2,007,471	11.5 (8.9-14.9)
Stroke	44 (18)	43,640	101	196 (72)	2,138,393	11.0 (7.7-15.3)
COPD	83 (35)	130,922	63	157 (65)	2,051,111	8.3 (6.3-10.9)
Alcoholism	57 (24)	113,466	50	183 (76)	2,068,567	5.7 (4.1-7.7)
Cancer	38 (16)	196,382	37	202 (84)	1,985,651	4.3 (3.2-5.7)
DM	72 (30)	87,282	44	168 (70)	2,094,751	4.5 (3.1-6.4)
CTD	12 (5)	43,640	27	228 (95)	2,138,393	2.6 (1.3-4.6)
CKD	45 (19)	196,382	23	195 (81)	1,985,651	2.3 (1.6-3.2)

Abbreviations: sARF = severe acute renal failure; No. = number; CI = confidence interval; CTD = connective tissue disease; COPD = chronic obstructive lung disease; DM = diabetes mellitus; CKD = chronic kidney disease.
§ p-value<0.0001 for each underlying condition incidence rate ratio.

Therefore, these data would suggest that patients with pre-existing co-morbid heart disease, stroke, chronic lung disease, alcohol abuse, diabetes mellitus, cancer, connective tissue disease and some forms of chronic kidney disease were at increased risk for development of sARF when compared with patients without these co-morbid conditions.

3. Clinical characteristics of patients with sARF

Among the 240 patients with sARF, 203 (85%) had intra-renal, 36 (15%) pre-renal, and one patient had a post-renal cause (0.4%). The clinical features of patients with a diagnosis of sARF stratified by etiology of sARF are presented in detail in Table 10. Several factors would appear associated with the etiology of sARF. A greater proportion of sARF patients with an intra-renal etiology of sARF required mechanical ventilation [76% vs. 53%, p=0.007], respectively. By stratified analysis, there is no evidence that this association was confounded or effect modified by any of age $\geq$ 65 years, patient sex, APACHE II score $\geq$ 25 points, admission type, the presence of pre-existing co-morbid illness, in particular chronic obstructive lung disease, septic shock or modality of renal replacement therapy. Thus, mechanical ventilation may represent a risk factor for the development of an intra-renal etiology of sARF; however, the biologic plausibility of this association is questionable. The presence of oliguria was significantly more common in sARF patients presenting with a pre-renal etiology compared to an intra-renal etiology [92% vs. 74%, p=0.001], respectively. Interestingly, the association of oliguria and sARF etiology does not appear confounded or effect modified by any of age $\geq$ 65 years, patient sex, APACHE II score $\geq$ 25 points, admission type, the presence of pre-existing co-morbid illness in particular heart disease, sepsis, shock or septic shock, modality of RRT or exposure to radiocontrast media. Oliguria as a risk factor for pre-renal sARF remains biologically plausible; however, this association was more likely

demonstrated due to oliguria representing one possible pre-disposing phase in the pathophysiology of pre-renal sARF where reduction in renal blood flow subsequently results in reduction in GFR and thus urine output. In addition, patients with a pre-renal etiology for sARF had significantly lower mean (±SD) pH values prior to initiation of RRT compared to those with an intra-renal etiology for sARF [7.18 (0.15) vs. 7.27 (0.13), p=0.001]. By stratified analysis, there was no evidence to suggest that this association was confounded or effect modified by any of age ≥ 65 years, patient sex, APACHE II score ≥ 25 points, admission type, the presence of pre-existing co-morbid illness in particular liver or heart disease, sepsis, shock or septic shock or modality of renal replacement therapy. Thus, a low serum pH or systemic acidemia may represent a risk factor for development of pre-renal sARF; however, this is only speculative given that the serum pH for those patients with an intra-renal etiology for sARF was also consistent with systemic acidemia.

Toxic exposures included parenteral radiocontrast media in 107 (44%), aminoglycosides in 47 (20%) and amphotericin B in 10 (4%). The indications for institution of RRT were diuretic-resistant fluid overload in 178 (74%), metabolic acidosis in 87 (36%), uremia in 68 (28%), hyperkalemia in 59 (24%) and toxins in 4 (2%) in the setting of renal dysfunction.

The modality of RRT in the ICU was exclusively CRRT in 147, exclusively IHD in 48, and some combination of regimens using both CRRT and IHD in 45

patients. A total of 941 and 343 patient-days of CRRT and IHD were performed, respectively. The median (IQR) duration of RRT in the ICU was 3 (1-9) days.

Table 10. Clinical features of patients with sARF stratified by etiology of sARF.

Clinical Feature	Total (n=240)	Pre-renal (n=36)	Renal (n=203)	p-value
Median Age (IQR)	66 (53-74)	60 (48-71)	67 (54-75)	0.08
Male Sex (%)	139 (58)	17 (47)	122 (60)	0.21
Mean CCI (±SD)	6.2 (3.6)	6.7 (3.9)	6.1 (3.6)	0.35
Mean APACHE II Score (±SD)	33 (8.6)	33 (7.0)	33 (8.9)	0.89
Oliguria (%)	183 (77)	33 (92)	150 (74)	0.01
Hypotension (%)	204 (85)	27 (75)	177 (87)	0.30
Vasopressors (%)	185 (77)	25 (69)	160 (79)	0.28
Shock (%)	178 (74)	23 (64)	155 (76)	0.15
Sepsis Syndrome (%)	167 (70)	23 (64)	144 (71)	0.56
Bloodstream Infection (%)	50 (21)	5 (14)	45 (22)	0.38
Mean Arterial pH (±SD)*	7.26 (0.14)	7.18 (0.15)	7.27 (0.13)	<0.001
Mean Potassium (±SD) (mmol/L)*	4.8 (1.1)	4.9 (1.3)	4.7 (1.1)	0.40
Median Creatinine (IQR) (μmol/L)*	405 (265-515)	357 (247-514)	413 (269-517)	0.56
Median Urea (IQR) (mmol/L)*	24 (16-33)	24 (16-33)	25 (16-33)	0.73
Mechanical Ventilation (%)	174 (73)	19 (53)	155 (76)	0.008
ARDS (%)	91 (41)	14 (39)	85 (42)	0.72
Cardiac Arrest (%)	43 (18)	6 (17)	37 (18)	1.0

Abbreviations: IQR = interquartile range; SD = standard deviation; CCI = Charlson co-morbidity Index; ARDS = acute respiratory distress syndrome.
*measured prior to initiation of RRT.

The overall median (IQR) ICU and hospital length of stay for patients with a diagnosis of sARF was 8.2 (3.5-16) and 22 (9-40) days, respectively. There was no significant difference in ICU length of stay for sARF patients when comparing survivors and non-survivors at 1-year; however, hospital length of stay was significantly longer for those sARF patients alive at 1-year (Table 11). The majority (166/240, 69%) of diagnoses of sARF occurred within two days of ICU admission. The median (IQR) time to diagnosis of sARF was 4 (1-10.5) days after hospital admission and 1 (0-3) day after ICU admission. There was no significant difference in the median (IQR) length of stay in ICU or hospital prior to the diagnosis of sARF for both survivors and non-survivors at 1-year (Table 12).

Table 11. ICU and hospital length of stay for patients with sARF stratified by survival status at 1-year.

Median (IQR) Length of Stay (Days)	Total Cohort (n=240)	Alive (n=87)	Dead (n=153)	p-value
ICU	8.2 (3.5-16)	8.6 (3.7-19.1)	8.2 (3.1-14.4)	0.34
Hospital	22 (9-40)	39 (23-66)	15 (6-27)	<0.0001

Table 12. ICU and hospital length of stay prior to diagnosis of sARF and stratified by survival status at 1-year.

Median (IQR) Length of Stay (Days)	Total Cohort (n=240)	Alive (n=87)	Dead (n=153)	p-value
ICU	1 (0-3)	1 (0-3)	1 (0-3)	0.54
Hospital	4 (1-10.5)	4 (1-9)	4 (1-12)	0.43

4. Mortality Outcome for patients with sARF

Mortality rate for this study was defined as the number of deaths for those fulfilling the case-definition for sARF that occurred in the population-at-risk in the CHR over the period of surveillance and reported as an annual rate per 100,000 population. Of 240 patients that fulfilled the case-definition for sARF, 153 were dead by 1-year for a case-fatality rate of 64%. The accuracy of the mortality rates for sARF are dependent on numerous factors similar to previously discussed for accuracy in the incidence rate for sARF, specifically, precision in the numerator and the denominator. With respect to the accuracy of the numerator for the annual mortality rate calculation, the accuracy was conditional first on correct classification of case-definitions for sARF and also on correct classification of survival status at 1-year. Therefore, the numerator was dependent on accurate ascertainment of outcome at 1-year. The absolute number of sARF patients who are dead at 1-year should be accurate as the outcome status for these patients was obtained from the ICU Tracer database, hospital medical records, Alberta Vital Statistics and the Alberta Health Registry as previously outlined; however, the accuracy of the absolute counts for those sARF patients alive at 1-year was dependent on the assumption that these patients have remained residents of the CHR and/or the province of Alberta, otherwise, they could have potentially been lost to follow-up. If a proportion of those sARF patients presumed alive at 1-year were lost to follow-up and were in fact dead, thus misclassified, this would result in the introduction of information

bias into the annual mortality rate calculations and result in an under-estimation of the case-fatality rate for sARF at 1-year.

The crude annual mortality rate attributable to a diagnosis of sARF was 7.0 (Exact 95% CI, 5.9-8.2) deaths per 100,000 population. There was evidence of a significant association between increasing age and the mortality rate for patients with a diagnosis of sARF (Table 13). The mortality rate for sARF patients aged 50-64 years was significantly higher that for those aged 18-49 years [mortality rate difference 5.7 (Exact 95% CI, 3.2-8.4, $p<0.0001$)]. Thus, the risk of death was significantly higher for those aged 50-64 years compared with those aged 18-49 years (RR 3.7, Exact 95% CI, 2.3-6.3, $p<0.0001$). Similarly, the mortality rate for sARF patients aged 65-74 years was significantly higher than those aged 50-64 years [mortality rate difference 15.3 (Exact 95% CI, 8.2-22.4, $p<0.0001$)]. Interestingly, there was no significant evidence of an increased mortality rate when comparing sARF patients aged ≥ 75 years with those aged 65-74 years [mortality rate difference 5.0 (Exact 95% CI, -6.0 to 16.0, $p=0.37$)]. Therefore, the risk of death was significantly higher in those sARF patients aged ≥ 65 years compared with those < 65 years (RR 8.1, Exact 95% CI, 6.2-10.5, $p<0.0001$).

Table 13. Age-specific annual mortality rate of sARF.

Age (Years)	Case-fatality rate for patients with sARF (%)	Person-years At-risk	Age-specific Mortality Rate (per 100,000 population) (Exact 95% CI)
18-49	27/47 (57)	1,312,088	2.1 (1.4-3.0)
50-64	41/68 (60)	531,337	7.7 (5.5-10.5)
65-74	45/73 (62)	195,757	23.0 (16.8-30.8)
$\geq$ 75	40/52 (77)	142,851	28.0 (20.0-38.1)
Overall	153/240 (64)	2,182,033	7.0 (5.9-8.2)

The sex-specific annual mortality rate of sARF for males was 7.8 (Exact 95% CI, 6.2-9.6) per 100,000 population, whereas for females, the annual mortality rate was 6.3 (Exact 95% CI, 4.9-7.9) per 100,000 population (Table 14). There was no significant difference in the mortality rate when comparing male to female patients with a diagnosis of sARF [mortality rate difference 1.5 per 100,000 population (Exact 95% CI, -0.7 to 3.8, p=0.18)].

Table 14. Sex-specific annual mortality rate of sARF.

Sex	Case-fatality rate for patients with sARF (%)	Person-years At-risk	Sex-specific Mortality Rate (per 100,000 population) (Exact 95% CI)
Male	84/140 (60)	1,078,738	7.8 (6.2-9.6)
Female	69/100 (69)	1,103,295	6.3 (4.9-7.9)
Overall	153/240 (64)	2,182,033	7.0 (5.9-8.2)

The age and sex-specific annual mortality rates are demonstrated in Table 15. There was a trend toward a higher annual mortality rate in males as compared with females (7.8 vs. 6.3 per 100,000 population; RR 1.3; 95% CI, 0.9-1.8, p=0.1); however, when further stratified by age ≥ 65 years, the annual mortality rate was significantly higher for males compared with females (47.5 vs. 23.1 per 100,000 population; RR 2.1; 95% CI, 1.3-3.3, p<0.001). There was no significant difference in mortality rate between sexes for those aged < 65 years (3.6 vs. 3.7 per 100,000 population; RR 0.99; 95% CI, 0.6-1.6, p=0.96).

Table 15. Age and sex-specific annual mortality rate of sARF.

Age (Years)	Case-fatality rate for males with sARF (%)	Age-specific mortality rate for males (per 100,000 population) (Exact 95% CI)	Case-fatality rate for females with sARF (%)	Age-specific mortality rate for females (per 100,000 population) (Exact 95% CI)	Relative Risk (Exact 95%CI)
18-49	13/26 (50)	2.0 (1.0-3.4)	14/21 (67)	2.2 (1.2-3.6)	0.9 (0.4-2.1)
50-64	20/36 (56)	7.5 (4.6-11.5)	21/32 (66)	8.0 (4.9-12.2)	0.9 (0.5-1.8)
65-74	28/45 (62)	29.9 (19.9-43.2)	17/28 (61)	16.7 (9.7-26.7)	1.8 (0.95-3.5)
≥ 75	23/33 (70)	43.0 (27.3-64.6)	17/19 (89)	19.0 (11.1-30.4)	2.3 (1.2-4.5)
Overall	140 (58)	7.8 (6.2-9.6)	100 (42)	6.3 (4.9-7.9)	1.4 (1.1-1.9)

Among the 240 patients with sARF, 50% (n=120) died during their ICU admission and 60% (n=143) died prior to hospital discharge. The 28-day, 90-day,

and 1-year case-fatality rates were 51% (n=123), 60% (n=143), and 64% (n=153), respectively.

First, a stratified analysis exploring several factors that may influence the case-fatality rate 1-year for critically ill patients with a diagnosis of sARF is presented.

Case-fatality rates for sARF patients stratified by admission types demonstrated stability in rates for non-cardiac surgical and cardiac surgical sARF patients with the majority of case-fatalities occurring early, generally within 28 days of admission and completed by 90 days after admission (Table 16). Interestingly, there was no difference in the 1-year case-fatality rates between non-cardiac surgical and cardiac surgical sARF patients, suggesting that these indicator variables could be potentially be collapsed into a single variable termed surgical admissions. All case-fatalities for sARF patients at ≥ 90 days following admission occurred in those designated as medical admissions.

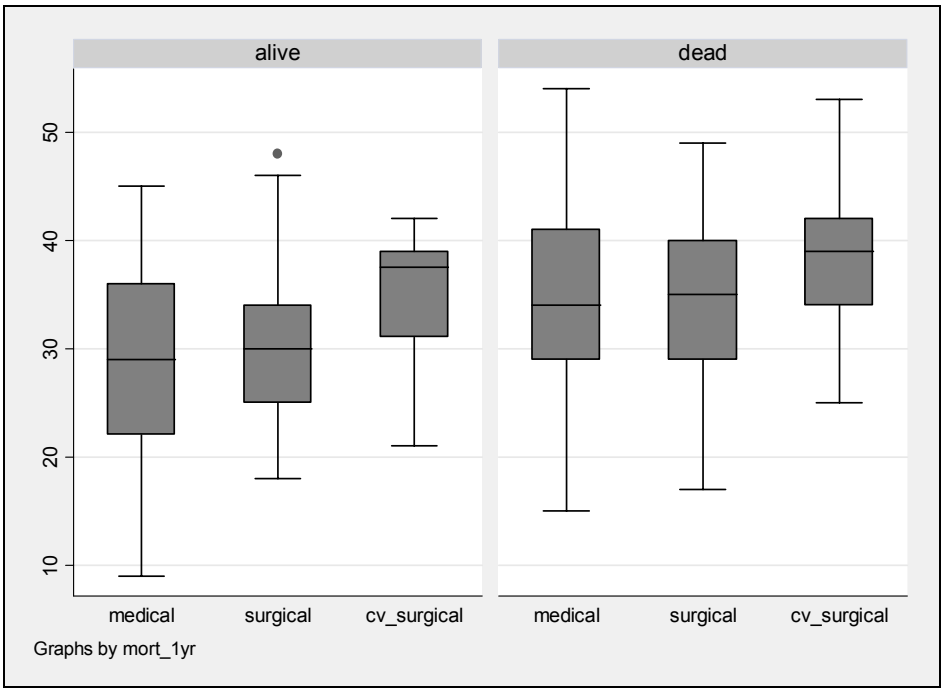
Table 16. Crude case-fatality rates for sARF patients stratified by admission type.

	Crude Total (n=240)	Admission Type		
		Medical (n=151)	Non-cardiac Surgical (n=58)	Cardiac Surgical (n=31)
ICU Death (%)	120 (50)	75 (50)	31 (53)	14 (45)
Hospital Death (%)	143 (60)	94 (62)	32 (55)	17 (55)
28-Day Death (%)	123 (51)	78 (52)	32 (55)	16 (52)
90-Day Death (%)	143 (60)	94 (62)	32 (55)	17 (55)
1-Year Death (%)	153 (64)	104 (69)	32 (55)	17 (55)

When comparing admission type by admission APACHE II score, there was evidence of significantly higher mean (±SD) APACHE II scores for cardiac surgical admission compared with both non-cardiac surgical and medical admissions, respectively (Figure 1). Furthermore, death at 1-year was associated with significantly higher mean (±SD) APACHE II scores for all categories of admission type with cardiac surgical admissions being the highest, suggesting that APACHE II score was an effect modifier of the association of admission type and death at 1-year for patients with sARF. These results are similar to the APACHE II scores stratified by admission type for the entire ICU cohort presented later. The higher APACHE II scores for cardiac surgical admission has a plausible explanation that was not directly related to the overall burden or severity of illness for cardiac surgical patients when compared with medical or non-cardiac surgical patients. The APACHE II scores are usually calculated in the first 24 hours of admission to an ICU and used to provide a measure of severity of illness and to calculate a probability of death. Further, the APACHE II score assesses several parameters including: patient age; chronic health status; and importantly numerous acute physiologic variables to calculate a composite score.[58] Cardiac surgical patients are admitted directly from the operating theatre at which time are recovering from general anaesthetic, cardio-pulmonary bypass, and require advanced life support, such as mechanical ventilation and hemodynamic support often with inotropic or vasopressor drug infusions. Therefore, the APACHE II score calculated in these patients within the

first 24 hours was often exaggerated and not truly reflective of their underlying severity of illness, and therefore did not represent a valid measure in this population for this purpose.

Figure 1. Boxplot of APACHE II score stratified by admission and outcome at 1-year for patients with sARF.



The median (IQR) age of patients with a diagnosis of sARF was 66.1 (52.6-74.1) years. There was evidence to suggest that death at 1-year for sARF patients was associated with a higher median (IQR) age compared with those still alive [67.6 (54.6-75.3) vs. 63.3 (50.9-71.7), p=0.05] (Figure 2). Furthermore, there was evidence that the case-fatality rates for sARF patients increase significantly with increasing age, with the highest rate in those sARF patients aged ≥ 75 years (Table 17). Likewise, the case-fatality rate for sARF patients were higher for those patients aged ≥ 65 years compared with those aged < 65

years [RR 1.15 (95% CI, 0.95-1.4), p=0.18], though this was not statistically significant (Table 18).

Figure 2. Boxplot of age by outcome at 1-year for patients with sARF.

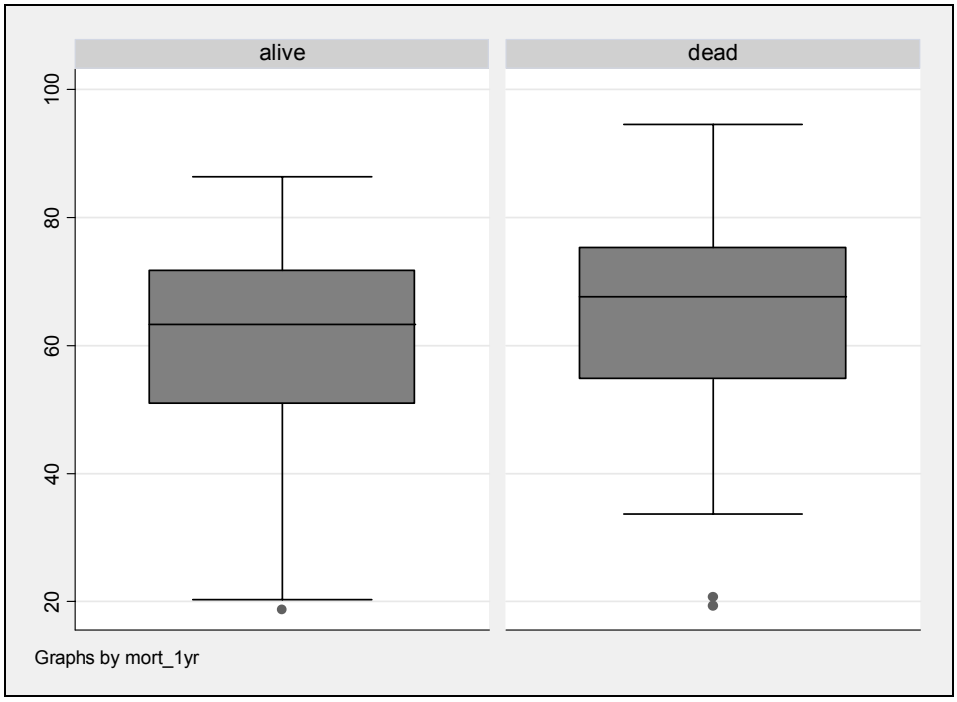


Table17. Age-specific case-fatality rates for sARF.

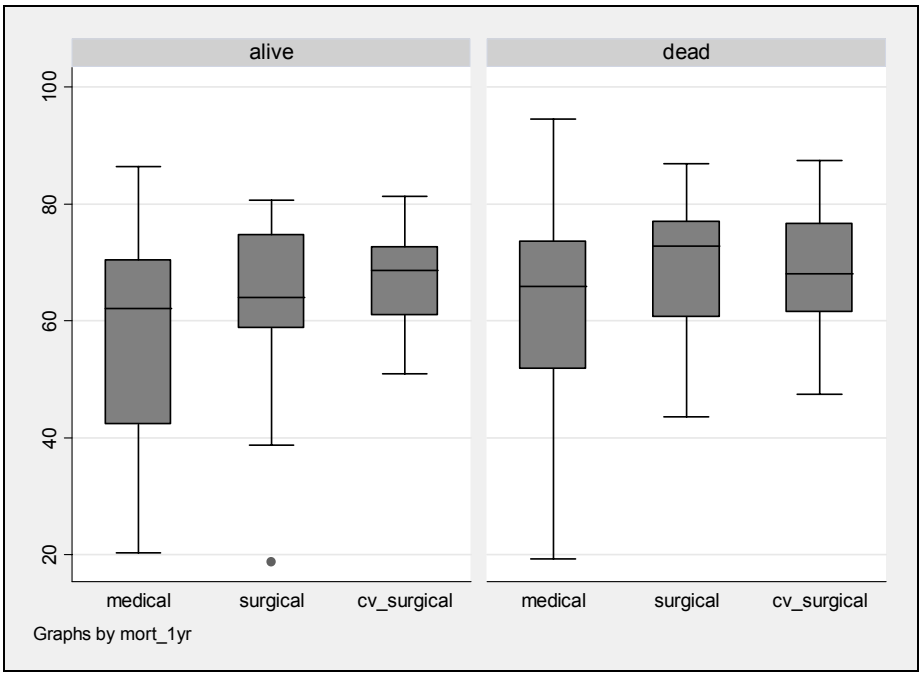
Age (Years)	Case-fatality (%)
18-49	27/47 (57.5)
50-64	41/68 (60.3)
65-74	45/73 (61.6)
≥ 75	40/52 (76.9)
Overall	153/240 (63.8)

Table 18. Case-fatality rates for sARF patients stratified by age ≥ 65 years.

Age (Years)	Case-fatality (%)
≥ 65	85/125 (68.0)
< 65	68/115 (59.1)
Overall	153/240 (63.8)

There was no evidence to suggest that the association of admission type and death at 1-year was either confounded or significantly effect modified by patient age [crude RR 2.68 (95% CI, 2.4-3.0) vs. M-H adjusted RR 2.74 (95% CI, 2.5-3.0)], respectively (Figure 3).

Figure 3. Boxplot of age stratified by admission type and outcome at 1-year for patients with sARF



Of 240 patients with a diagnosis of sARF, 58% were male. The case-fatality rate for sARF was higher in female patients, though not significantly,

when compared to male patients [RR 1.15 (95% CI, 0.95-1.4), p=0.17], respectively (Table 19). By stratified analysis, there was no evidence to suggest that patient age represented a significant confounder [crude RR 1.15 (95% CI, 0.95-1.4) vs. M-H adjusted RR 1.17 (95% CI, 0.97-1.4)] or effect modifier of the association of patient sex and death at 1-year (Tables 20 and 21).

Table 19. Sex-specific case-fatality rates of sARF.

Sex	Case-fatality (%)
Male	84/140 (60)
Female	69/100 (69)
Overall	153/240 (63.8)

Table 20. Age and sex-specific case-fatality rates of sARF.

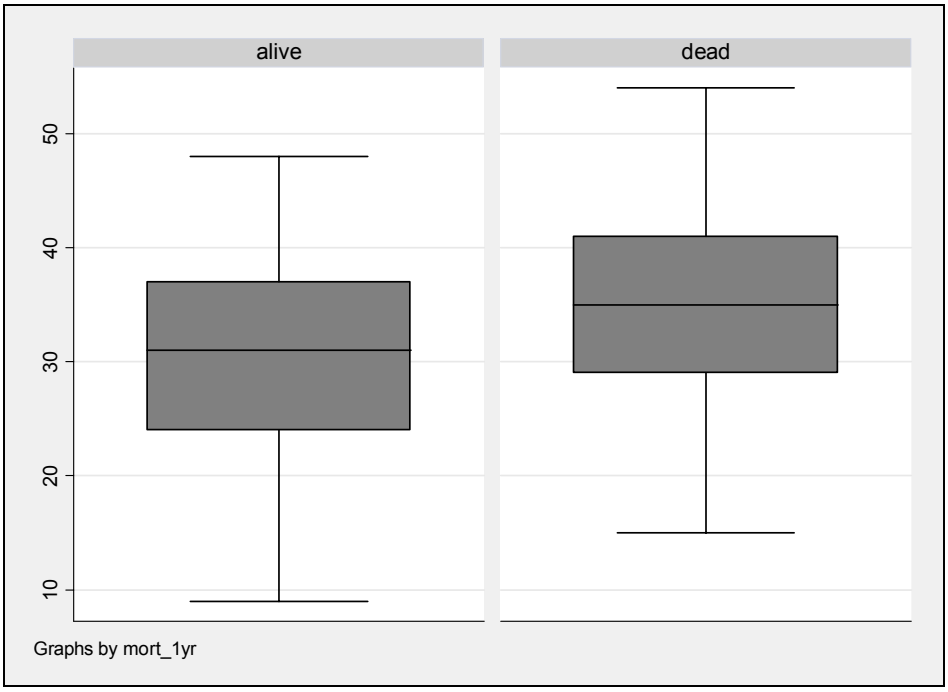
Age (Years)	Male (%)	Female (%)
18-49	13/26 (50)	14/21 (66.7)
50-64	20/36 (55.6)	21/32 (65.6)
65-74	28/45 (62.2)	17/28 (60.7)
$\geq$ 75	23/33 (69.7)	17/19 (89.4)
Overall	84/140 (60)	69/100 (69)

Table 21. Sex-specific case-fatality rates of sARF stratified by age ≥ 65 years.

Age (years)	Male	Female
≥ 65	51/78 (65.4)	34/47 (72.3)
< 65	33/62 (53.2)	35/53 (66.0)
Overall	84/140 (60)	69/100 (69)

Death at 1-year was associated with a significantly higher mean (±SD) APACHE II scores for sARF patients compared to those that were alive at 1-year [34.8 (8.3) vs. 30.3 (8.5), p=0.0001], respectively (Figure 4).

Figure 4. Boxplot of APACHE II score by outcome at 1-year for patients with sARF.



Not surprisingly, the case-fatality rates for patients with a diagnosis of sARF were 1.6 times greater for those with an admission APACHE II score ≥ 25 points compared to those with an APACHE II score < 25 points [68.7% vs. 42.2%, RR 1.63 (95% CI, 1.1-2.3), p=0.002], respectively (Table 22).

Table 22. Case-fatality rates of sARF stratified by APACHE II score ≥ 25 points.

APACHE II score (points)	Case-fatality (%)
≥ 25	134/195 (68.7)
< 25	19/45 (42.2)
Overall	153/240 (63.8)

By stratified analysis, there was no evidence that age stratified at ≥ 65 years was a significant confounder or effect modifier of the association of death at 1-year and APACHE II score [crude RR 1.63 (95% CI, 1.1-2.3) vs. M-H adjusted 1.61 (95% CI, 1.1-12.3)] (Table 23 and Figures 5 and 6).

Table 23. Age-specific case-fatality rates of sARF stratified by APACHE II score ≥ 25 points.

Age (years)	APACHE II Score (points)	
	≥ 25	< 25
≥ 65	76/105 (72.3)	9/20 (45.0)
< 65	58/90 (64.4)	10/25 (40.0)
Overall	134/195 (68.7)	19/45 (42.2)

Figure 5. Boxplot of APACHE II score stratified by age ≥ 65 years and outcome at 1-year for patients with sARF.

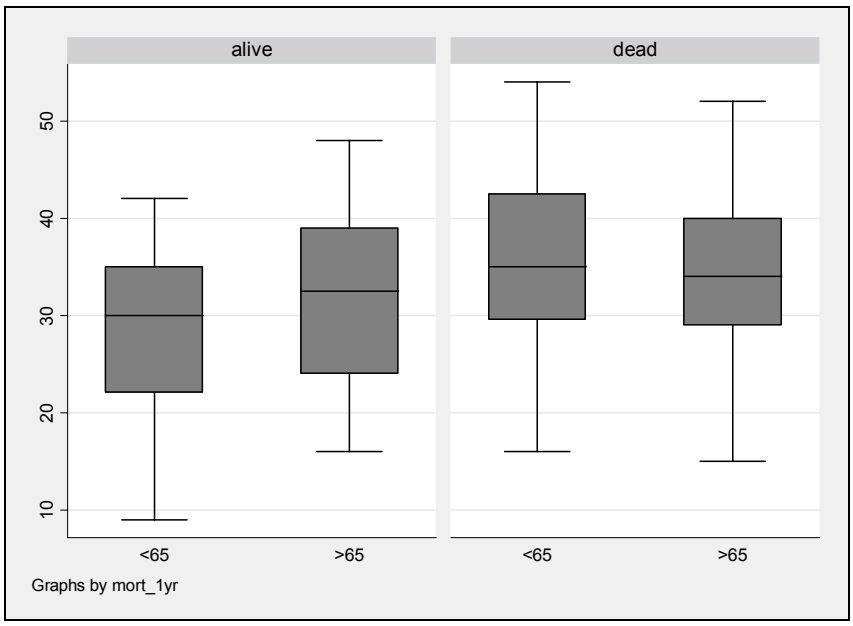
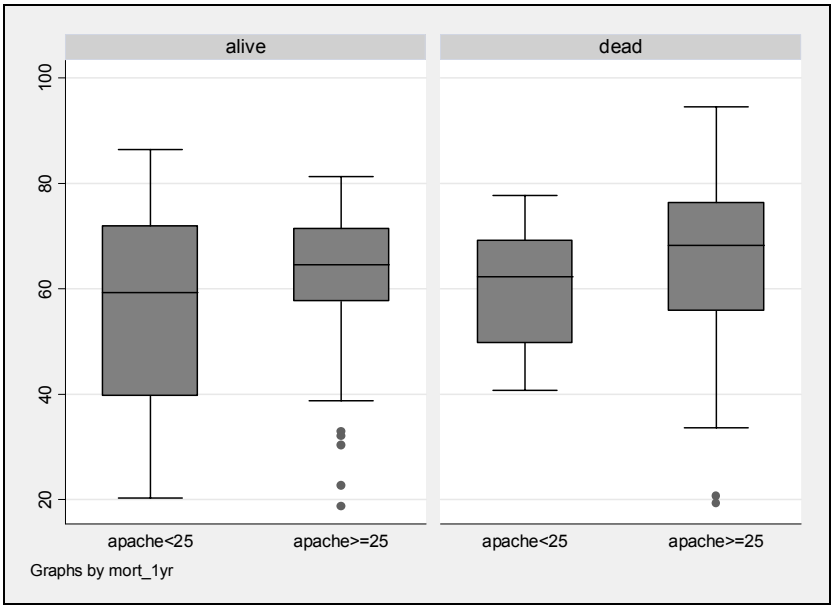


Figure 6. Boxplot of age stratified by APACHE II score ≥ 25 points and outcome at 1-year for patients with sARF.

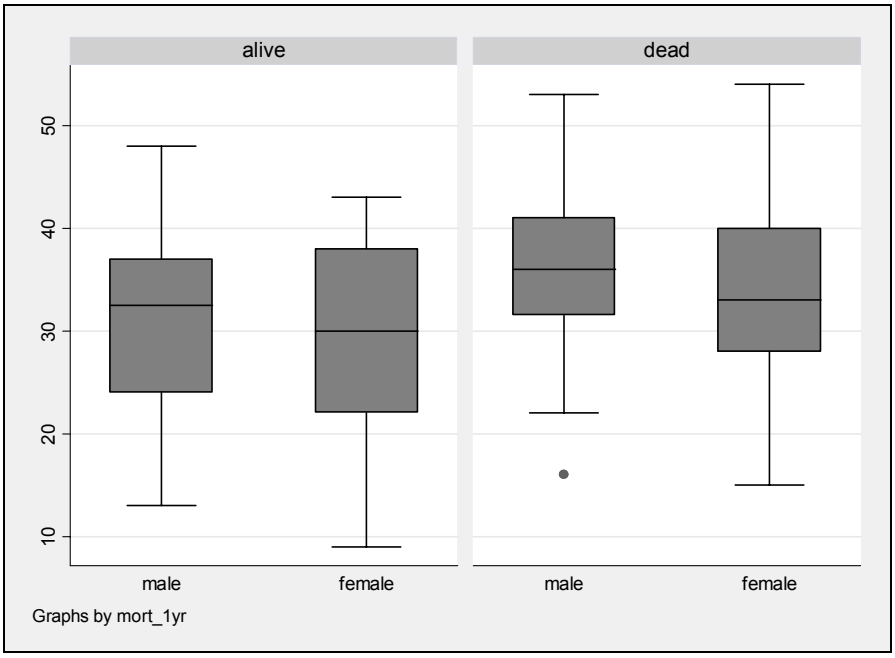


By stratified analysis, patient sex appears to influence the association of APACHE II score and death at 1-year (Table 24 and Figure 7). Although patient sex was not an important confounder [crude RR 1.63 (95% CI, 1.1-2.3) vs. M-H adjusted RR 1.66 (95% CI, 1.2-2.4)], there was suggestion that patient sex was an effect modifier of the association of APACHE II score and death at 1-year, although this was not statistically significant. Specifically, when compared to female patients, male patients with an APACHE II score $\geq$ 25 points have a greater relative risk of death at 1-year than male patients with an APACHE II score < 25 points [male RR 2.2 (95% CI 1.1-4.1) vs., female RR 1.34 (95% CI, 0.9-2.0)]. This difference in relative risk of death at 1-year for APACHE II scores across patient sex was principally related to the low case-fatality rate for male patients with APACHE II scores < 25 points. When restricted to APACHE II scores $\geq$ 25 points, there was no significant difference in death at 1-year between male and female patients with a diagnosis of sARF [RR 1.1 (95% CI, 0.9-1.34)]. There was no significant evidence to suggest that the association of APACHE II score and death at 1-year was confounded or effect modified by both age $\geq$ 65 years and patient sex.

Table 24. Sex-specific case-fatality rates of sARF stratified by APACHE II score ≥ 25 points.

Sex	APACHE II Score (points)	
	≥ 25	< 25
Male	77/117 (65.8)	7/23 (30.4)
Female	57/78 (73.1)	12/22 (54.5)
Overall	134/195 (68.7)	19/45 (42.2)

Figure 7. Boxplot of APACHE II score stratified by sex and outcome at 1-year for patients with sARF.



Death at 1-year was associated with a significantly higher mean (±SD) Charlson co-morbidity index score compared to those sARF patients that were still alive [6.7 (3.5) vs. 5.3 (3.6) points, p=0.02], respectively (Figure 8). Clearly, the case-fatality rates for sARF patients increase with increasing stratified score of Charlson co-morbidity index; however, the case-fatality rate appears to plateau

for Charlson co-morbidity index scores ≥ 4 points (Table 25). By stratified analysis, the mean (±SD) Charlson co-morbidity index scores are significantly higher for those sARF patients aged ≥ 65 years compared to those < 65 years [8.0 (3.0) vs. 4.2 (3.2), p<0.0001]. This relationship was preserved regardless of survival outcome at 1-year (Figure 9). However, there was no evidence that patient age stratified by age ≥ 65 years was a significant confounder or effect modifier of the association of death at 1-year for sARF patients when Charlson co-morbidity index was assessed as a categorical variable. Additionally, there was no evidence that patient sex was a significant confounder or effect modifier on the association of Charlson co-morbidity index and death at 1-year. Interestingly, there was evidence of effect modification when considering both sex and patient age, suggesting the female patients aged ≥ 65 years had a lower relative risk of death at 1-year for Charlson co-morbidity index scores ≥ 4 points compared to those with < 4 points [RR 0.72 (95% CI, 0.6-0.9)]; however, this exploratory analysis should be interpreted cautiously due to the small number of patients across strata.

Figure 8. Boxplot of Charlson co-morbidity index by outcome at 1-year for patients with sARF.

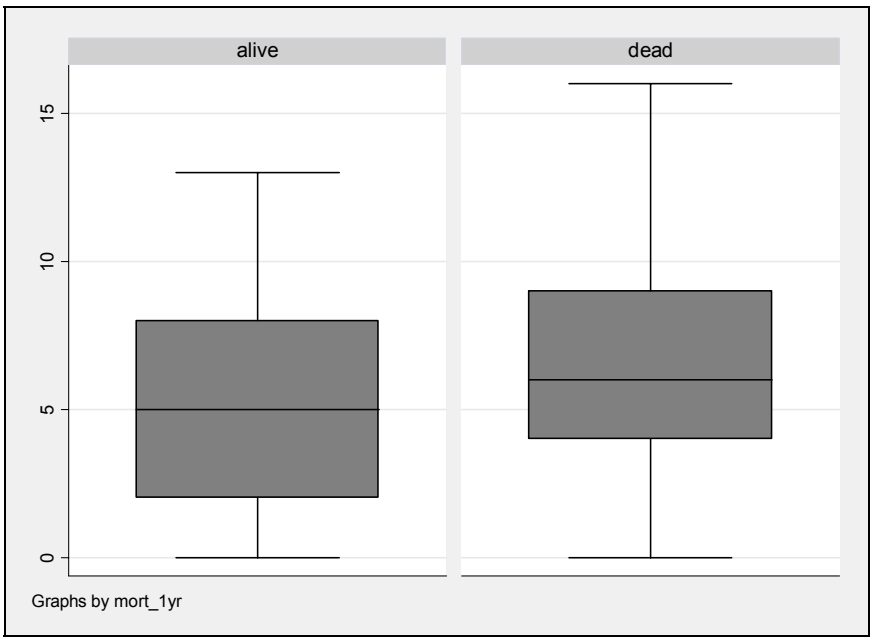
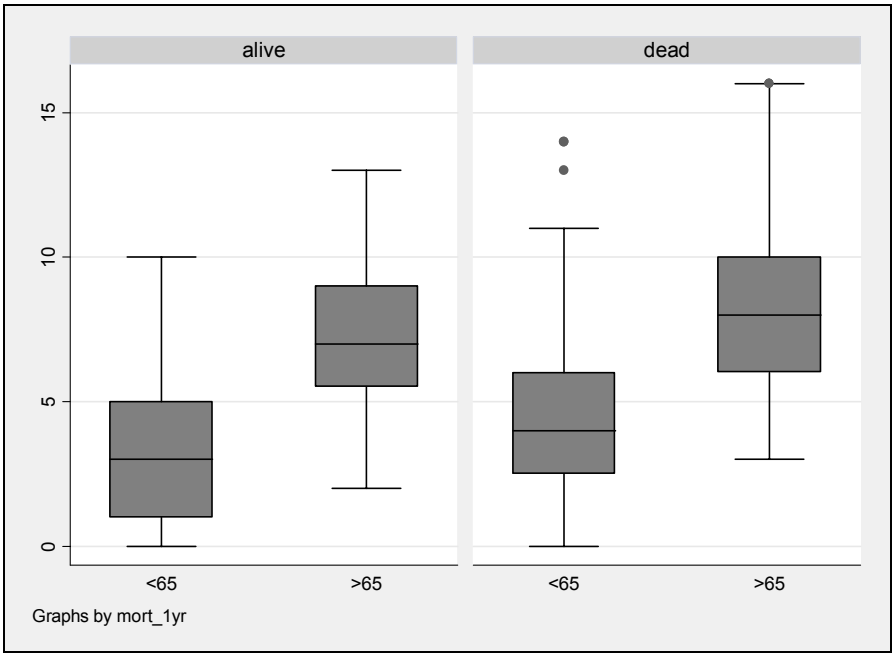


Table 25. Case-fatality rates of sARF stratified by quartiles of Charlson co-morbidity index.

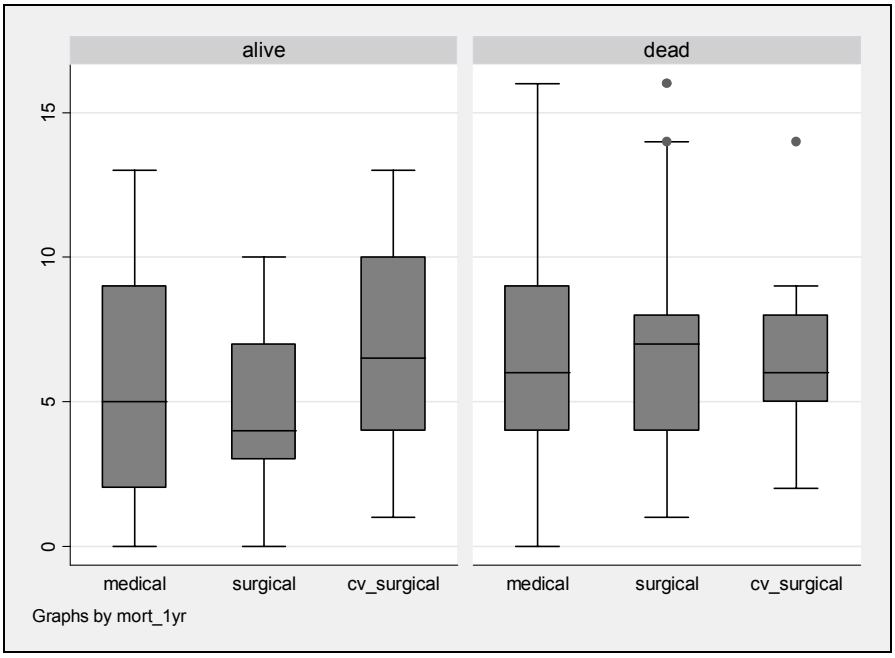
Charlson co-morbidity index (points)	Number of patients (%)	Case-fatality (%)
0-3	64 (26.7)	31/64 (48.4)
4-6	71 (29.8)	49/71 (69.0)
7-9	63 (26.3)	43/63 (68.3)
10-16	42 (17.5)	30/42 (71.4)

Figure 9. Boxplot of Charlson co-morbidity index score stratified by age ≥ 65 years and outcome at 1-year for patients with sARF.



By stratified analysis, there was no evidence to suggest that admission type was a significant confounder or effect modifier of the association of death at 1-year for sARF patients and Charlson co-morbidity index score [crude RR 1.44 (95% CI, 1.1-1.9) vs. M-H adjusted RR 1.43 (95% CI, 1.1-1.9)] (Figure 10).

Figure 10. Boxplot of Charlson co-morbidity index score stratified by admission type and outcome at 1-year for patients with sARF.



By stratified analysis, there was no significant evidence to suggest that APACHE II stratified ≥ 25 points alone or combined with age ≥ 65 years or patient sex was a significant confounder or effect modifier of the association of death at 1-year for sARF patients and Charlson co-morbidity index score (Figures 11 and 12).

Figure 11. Boxplot of Charlson co-morbidity index score stratified by APACHE II score ≥ 25 points and outcome at 1-year for patients with sARF.

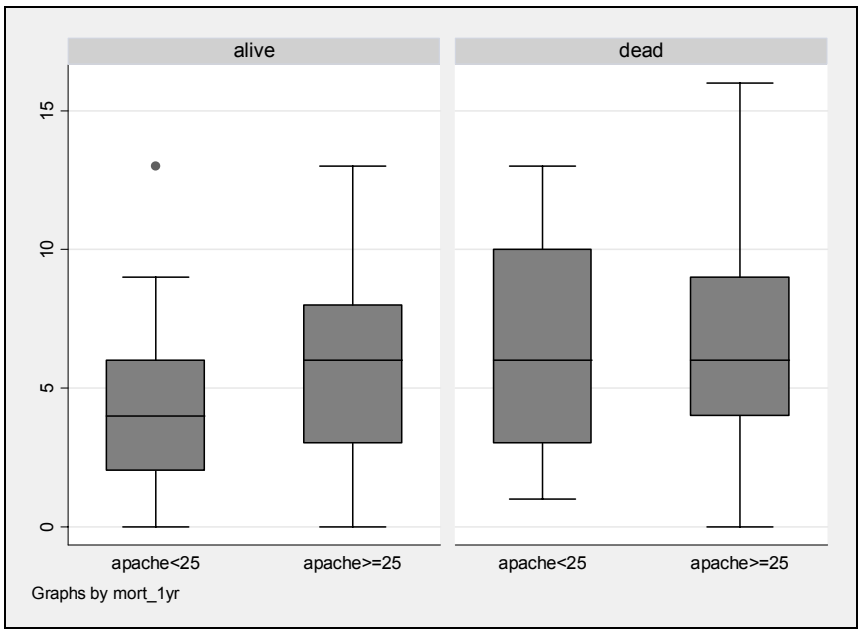
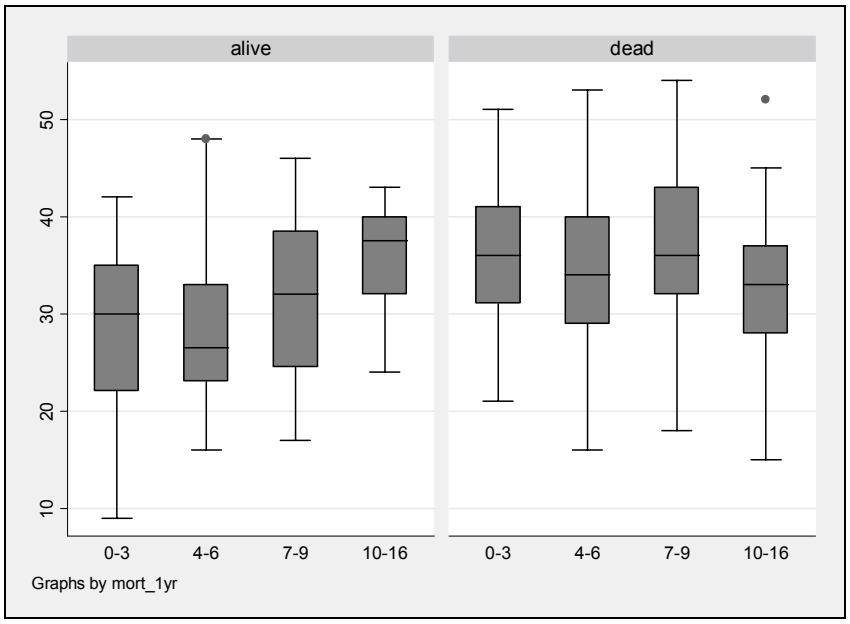


Figure 12. Boxplot of APACHE II score stratified by Charlson co-morbidity index and outcome at 1-year for patients with sARF.



There are several components of the Charlson co-morbidity index that can be individually assessed for association with death at 1-year for patients with a

diagnosis of sARF. In particular, by univariate analysis, pre-existing diabetes mellitus and a diagnosis of cancer were both associated with death at 1-year.

A total of 72 (30%) sARF patients had pre-existing diabetes mellitus. By univariate analysis, diabetes mellitus was actually associated with a reduced risk of death at 1-year for sARF patients compared to those without pre-existing diabetes [crude RR 0.78 (95% CI, 0.6-0.980, p=0.03]. Interestingly, sARF patients with diabetes mellitus had significantly higher median (IQR) pre-dialysis serum creatinine levels compared to those without diabetes mellitus [434 (339-551) vs. 358 (249-498) μmol/L, p=0.001], respectively. There was no evidence of confounding or effect modification the association of diabetes mellitus and death at 1-year by any of age $\geq$ 65 years, patient sex, Charlson co-morbidity index, APACHE II score, admission type, or modality of RRT. There was some evidence to suggest effect modification by septic shock. A diagnosis of septic shock resulted in a higher relative risk of death at 1-year for those sARF patients with diabetes mellitus, though this was not statistically significant [RR 0.98 (95% CI, 0.8-1.2) vs. 0.50 (95% CI, 0.3-0.9)], respectively. When examining only sARF patients with diabetes mellitus, septic shock resulted in a 2.5 times increased risk of death at 1-year compared with no septic shock [RR 2.5 (95% CI, 1.4-4.4), p=0.0003], respectively.

A total of 38 (15.8%) sARF patients had a pre-existing diagnosis of cancer. Of those with cancer, 29 (76.3%) were solid organ tumours and 7

(18.4%) were determined to be metastatic. A diagnosis of any cancer in a patient with sARF was associated with an increased risk of death at 1-year [crude RR 1.4 (95% CI, 1.2-1.7), p=0.005]. Interestingly, the case-fatality rate of sARF for those with metastatic cancer was 100% and the risk of death at 1-year appears higher for those with evidence of cancer that was metastatic compared with non-metastatic cancer [RR 1.24 (95% CI, 1.0-1.5)]; however, this interpretation requires some caution due to the small number of sARF patients with a diagnosis of metastatic cancer. This was likely attributable to complete separation of the data due to 100% case-fatality for metastatic cancer in this cohort of sARF patients. There was no evidence that this association was confounded or effect modified by any of age $\geq$ 65 years, patient sex, admission type or Charlson co-morbidity index score. There was some evidence that APACHE II score modified the association of death at 1-year and a diagnosis of cancer. Specifically, the relative risk of death at 1-year was higher for those sARF patients with cancer and an APACHE II score < 25 points compared to those with APACHE II scores $\geq$ 25 points [RR 2.32 (95% CI, 1.3-4.0) vs. RR 1.3 (1.1-1.5)], respectively. However, this requires cautious interpretation as there were only 6 patients in this category, all were female, and 5 (83.3%) were dead at 1-year.

A total of 44 (18.3%) of sARF patients had documentation of a pre-existing stroke and of these, 18 (41.0%) were reported to have evidence of hemiplegia. Although by univariate analysis, stroke was not a risk factor for death at 1-year

[crude RR 1.18 (95% CI, 0.9-1.5), p=0.22], there was evidence to suggest this association was modified by age ≥ 65 years. Specifically, there was weak evidence to suggest that those sARF patients with a stroke aged ≥ 65 years had a higher relative risk of death at 1-year compared to those aged < 65 years [RR 1.30 (95% CI, 1.0-1.6) vs. RR 0.8 (95% CI, 0.4-1.5)], though this was not statistically significant.

A number of categorical and continuous factors were significantly associated with death at 1-year for patients with a diagnosis of sARF by univariate analysis as shown in Tables 26 and 27. A number of continuous and categorical factors were not significantly associated with death at 1-year for patients with sARF and are presented in Tables 28 and 29.

Table 26. Univariate analysis of significant ($p \leq 0.1$) categorical variables associated with death at 1-year for patients with sARF.

Factor	Fatality Rate With Factor	Fatality Rate Without Factor	Relative Risk (95% CI)	p-value
Cancer Diagnosis (%)	32/38 (84)	121/202 (60)	3.0 (1.3-7.0)	0.005
Diabetes Mellitus (%)	38/72 (53)	115/168 (68)	0.6 (0.4-0.9)	0.03
Liver Disease (%)	44/50 (88)	109/190 (57)	4.2 (1.9-9.4)	<0.0001
CTD (%)	12/12 (100)	141/228 (62)	-	-
Need for Vasopressors (%)	129/186 (69)	24/54 (44)	1.3 (1.1-1.5)	0.001
Dialysis Modality				
CRRT only (%)	117/147 (80)	36/93 (39)	2.2 (1.6-3.0)	<0.0001
IHD only (%)	14/48 (29)	139/192 (72)	0.2 (0.1-0.4)	<0.0001
Both (%)	22/45 (49)	131/195 (67)	0.5 (0.3-0.9)	0.03
Hypotension (%)	140/205 (68)	13/35 (37)	1.2 (1.1-1.4)	0.0006
Shock (%)	125/179 (70)	28/61 (46)	1.3 (1.1-1.6)	0.001
Mechanical Ventilation (%)	119/175 (68)	34/65 (52)	1.2 (1.0-1.4)	0.03
ARDS (%)	75/99 (76)	78/141 (55)	1.8 (1.2-2.6)	0.002
Sepsis Syndrome (%)	118/167 (71)	35/73 (48)	1.4 (1.1-1.7)	0.001
Septic Shock (%)	104/139 (75)	49/101 (49)	1.7 (1.3-2.2)	<0.0001

Abbreviations: CI = confidence interval; CTD = connective tissue disease; CRRT = continuous renal replacement therapy; IHD = intermittent hemodialysis; ARDS = acute respiratory distress syndrome.

Table 27. Univariate analysis of significant ($p \leq 0.1$) continuous variables associated with death at 1-year for patients with sARF.

Factor	Alive (n=87)	Dead (n=153)	p-value
Median Pre-dialysis Creatinine (IQR) (μmol/L)	470 (341-582)	344 (250-475)	0.0001
Median Pre-dialysis Platelets (IQR) ($x10^9$/L)	156 (71-241)	83 (41-170)	0.0001

Abbreviations: IQR = interquartile range

Table 28. Univariate analysis of non-significant ($p > 0.1$) continuous variables for with death at 1-year and sARF.

Factor	Alive (n=87)	Dead (n=153)	p-value
Mean (±SD) Pre-dialysis potassium (mmol/L)	4.9 (1.1)	4.7 (1.1)	0.20
Median (IQR) Pre-dialysis urea (mmol/L)	24 (17-31)	24 (16-36)	0.59
Median (IQR) Duration of ICU RRT (days)	3 (2-12)	4 (1-8)	0.54

Abbreviations: IQR = interquartile range; SD = standard deviation; ICU = intensive care unit; sARF = severe acute renal failure; RRT = renal replacement therapy.

Table 29. Univariate analysis of non-significant (p>0.1) categorical variables for with death at 1-year and sARF.

Factor	Total (n=240)	Fatality Rate with factor	Fatality Rate without factor	Relative Risk (95% CI)	p-value
Alcohol abuse (%)	57 (24)	38 (67)	115 (63)	1.1 (0.9-1.3)	0.64
Prior myocardial infarction (%)	94 (37)	58 (62)	95 (65)	0.9 (0.8-1.2)	0.68
Prior CHF (%)	93 (39)	65 (70)	88 (60)	1.2 (0.9-1.4)	0.13
Peripheral vascular disease (%)	61 (25)	38 (62)	115 (64)	1.0 (0.8-1.2)	0.88
Chronic lung disease (%)	83 (35)	58 (70)	95 (61)	1.2 (1.0-1.4)	0.16
Chronic kidney disease (%)	45 (19)	26 (58)	127 (65)	0.9 (0.7-1.2)	0.40
Peptic ulcer disease (%)	54 (23)	36 (67)	117 (63)	1.1 (0.9-1.3)	0.63
Stroke (%)	44 (18)	32 (73)	121 (62)	1.2 (0.9-1.5)	0.22
Indications for RRT:					
Fluid overload (%)	178 (74)	116 (65)	37 (60)	1.1 (0.9-1.4)	0.45
Metabolic acidosis (%)	87 (36)	56 (64)	97 (63)	1.0 (0.8-1.2)	1.0
Hyperkalemia (%)	59 (25)	35 (59)	119 (65)	0.9 (0.7-1.1)	0.44
Uremia (%)	68 (28)	43 (63)	110 (64)	1.0 (0.8-1.2)	1.0
Bloodstream infection (%)	50 (21)	33 (66)	120 (63)	1.0 (0.8-1.3)	0.74
Nephrotoxin exposure:					
Radiocontrast media (%)	107 (45)	68 (64)	85 (43)	1.0 (0.8-1.2)	1.0
Aminoglycosides (%)	47 (20)	29 (62)	125 (64)	0.9 (0.7-1.2)	0.74
Amphotericin (%)	10 (4)	6 (60)	147 (64)	0.9 (0.6-1.6)	1.0
sARF in 48hr ICU admission (%)	166 (69)	108 (65)	45 (61)	1.1 (0.9-1.3)	0.56

Abbreviations: CI = confidence interval; CHF= congestive heart failure; RRT = renal replacement therapy; sARF = severe acute renal failure; ICU = intensive care unit.

Several of these variables thought to potentially influence the association of death at 1-year for patients with a diagnosis of sARF are presented in a more detailed stratified analysis.

Death at 1-year for patients with sARF appears significantly associated with the modality of RRT employed (Table 30). The crude case-fatality rates are highest for those having received CRRT as the only form of RRT compared to those patients having received either IHD only or a combination of CRRT and IHD (Table 31). Further, the crude case-fatality rate and relative risk of death at 1-year for those having received only IHD would suggest that this modality of RRT may in fact be associated with a reduced risk of death at 1-year.

Table 30. Case-fatality rates for sARF stratified by modality of renal replacement therapy.

Survival Status at 1-year	Renal Replacement Therapy Modality		
	CRRT only	IHD only	Both CRRT and IHD
Dead (%)	117/147 (79.6)	14/48 (29.2)	22/45 (48.9)

Table 31. Crude relative risk for death at 1-year stratified by each category of renal replacement therapy modality.

RRT Modality	Relative Risk	95% CI	p-value
CRRT only	2.05	1.6-2.7	<0.0001
IHD only	0.40	0.3-0.6	<0.0001
Both CRRT and IHD	0.73	0.5-1.0	0.03

Abbreviations: RRT = renal replacement therapy; CI = confidence interval; CRRT = continuous renal replacement therapy; IHD = intermittent hemodialysis.

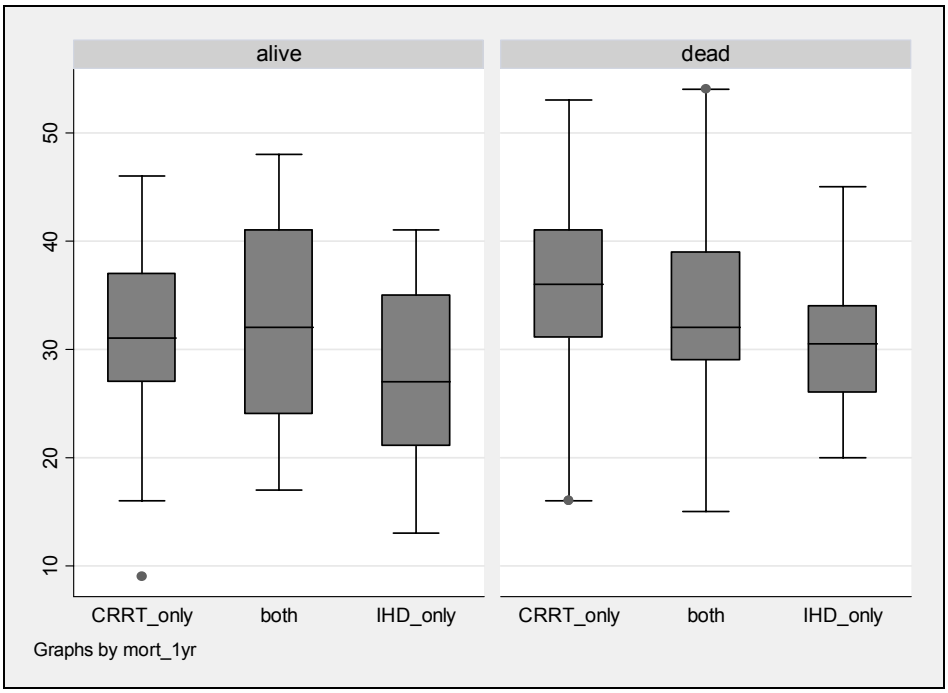
Table 32. Case-fatality rates of sARF stratified by modality of renal replacement therapy and APACHE II score.

APACHE II score (points)	Renal Replacement Therapy Modality		
	CRRT only	IHD only	Both CRRT and IHD
≥ 25	103/128 (80.4)	12/33 (36.4)	19/34 (55.9)
< 25	14/19 (73.7)	2/15 (13.3)	3/11 (27.3)
Overall	117/147 (79.6)	14/48 (29.2)	22/45 (48.9)

By stratified analysis, there was evidence to suggest that APACHE II score when stratified by ≥ 25 points is a potential confounder of the association of death at 1-year for sARF patients and modality of RRT [crude RR 1.79 (95% CI, 1.6-2.0) vs. M-H adjusted RR 1.37 (95% CI, 1.0-1.9)] (Table 32). The mean (±SD) APACHE II scores are highest in those sARF patients having received CRRT only compared to those having received a combination of CRRT and IHD, and were lowest for those having received IHD only [34.7 (8.4) vs. 32.8 (8.9) vs. 28.9 (7.6), p=0.0002], respectively. This relationship was clearly evident for those sARF

patients dead at 1-year; however, less evident for those surviving at 1-year due to the APACHE II scores for those having received CRRT only or a combination of CRRT and IHD being similar (Figure 13). Further, these data require some cautious interpretation, specifically for the case-fatality rates for those sARF patients having received either IHD only or a combination of CRRT and IHD with APACHE II scores < 25 points due to the relatively small number of patients within these strata, whereas the largest proportion of sARF patients received CRRT only and had APACHE II scores ≥ 25 points. This may in general reflect the overall severity of illness for the entire cohort, but in particular for those sARF patients having received CRRT only or in fact having received CRRT at any time.

Figure 13. Boxplot of APACHE II score stratified by renal replacement therapy modality and outcome at 1-year for patients with sARF.



Considering the case-fatality rates appear considerably higher for those sARF patients treated with any CRRT, an exploratory stratified analysis is presented where RRT is dichotomized into either any CRRT or IHD only. Thus, when RRT modality was collapsed, the risk of death at 1-year for sARF patients having received any CRRT relative to having received only IHD becomes more evident [crude RR 2.48 (95% CI, 1.6-3.9), p<0.0001] (Table 33).

Table 33. Case-fatality rates of sARF stratified by having received any CRRT.

Any CRRT	Case-fatality Rate (%)
Yes	139/192 (72.4)
No	14/48 (29.2)
Overall	153/240 (63.8)

Abbreviations: CRRT = continuous renal replacement therapy

Table 34. Case-fatality rates of sARF stratified by having received any CRRT and APACHE II score.

APACHE II score (points)	Any CRRT	
	Yes	No
≥ 25	122/162 (75.3)	12/33 (36.4)
< 25	17/30 (56.7)	2/15 (13.3)
Overall	139/192 (72.4)	14/48 (29.2)

Abbreviations: CRRT = continuous renal replacement therapy

These data suggest that APACHE II score was not an important confounder or effect modifier of the association of death at 1-year and renal replacement

modality as any CRRT or IHD only [crude RR 2.48 (95% CI, 1.6-3.9) vs. M-H adjusted RR 2.3 (95% CI, 1.5-3.6)].

By stratified analysis, there was evidence to suggest that patient age may influence the association of death at 1-year for sARF patients and modality of RRT (Table 35). There is no evidence to suggest confounding by age [crude RR 2.48 (95% CI, 1.6-3.9) vs. M-H adjusted RR 2.48 (95% CI, 1.6-3.9)]; however, there was clear evidence of effect modification when RRT modality was dichotomized as any CRRT or IHD only (Table 36). This would appear mostly attributable to the low case-fatality rates for sARF patients aged < 65 years and treated with IHD only. Notably, there was no significant difference in the case-fatality rates for sARF patients having received any CRRT stratified by age ≥ 65 years [RR 1.03 (95% CI, 0.9-1.2), p=0.84].

Table 35. Age-specific case-fatality rates stratified by modality of renal replacement therapy for patients with sARF.

Age (years)	Renal Replacement Therapy Modality		
	CRRT only	IHD only	Both CRRT and IHD
≥ 65	59/73 (80.8)	12/25 (48.0)	14/27 (51.9)
< 65	58/74 (78.4)	2/23 (8.7)	8/18 (44.4)
Overall	117/147 (79.6)	14/48 (29.2)	22/45 (48.9)

Abbreviations: CRRT = continuous renal replacement; IHD = intermittent hemodialysis

Table 36. Age-specific case-fatality rates for sARF patients stratified by having receiving any CRRT.

Age (years)	Any CRRT	
	Yes	No
≥ 65	73/100 (73.0)	12/25 (48.0)
< 65	66/92 (71.7)	2/23 (8.7)
Overall	139/192 (72.4)	14/48 (29.2)

Abbreviations: CRRT = continuous renal replacement

There was no evidence to suggest that the association of death at 1-year and RRT modality was influenced by patient sex. Specifically, there was no significant evidence to suggest confounding [crude RR 1.22 (95% CI, 1.1-1.3) vs. M-H adjusted RR 1.17 (95% CI, 1.0-1.4)] or effect modification by patient sex. Of note, the case-fatality rates for both male and female sARF patients treated with any CRRT are significantly higher than those for both sexes having received only IHD; however, there was no significant difference in case-fatality rates between

the sexes across strata of RRT modalities (Table 37). Likewise, these results are similar when RRT modality is collapsed further into any CRRT or only IHD.

Table 37. Sex-specific case-fatality rates of sARF stratified by modality of renal replacement therapy.

Sex	Renal Replacement Therapy Modality		
	CRRT only	IHD only	Both CRRT and IHD
Male	66/87 (75.9)	8/29 (27.6)	10/24 (41.7)
Female	51/60 (85.0)	6/19 (31.6)	12/21 (57.1)
Overall	117/147 (79.6)	14/48 (29.2)	22/45 (48.9)

By stratified analysis, was evidence to suggest that the association of death at 1-year and RRT modality may be influenced by a diagnosis of septic shock (Table 38). These data demonstrate that the case-fatality rates for sARF patients were highest in those patients with a diagnosis of septic shock and having received CRRT only. However, when RRT modality is dichotomized into any CRRT or IHD only, there was no significant evidence of confounding or effect modification of the association of death at 1-year and RRT modality by the presence of septic shock.

Table 38. Case-fatality rates of sARF stratified by modality of renal replacement therapy and septic shock.

Septic Shock	Renal Replacement Therapy Modality		
	CRRT only	IHD only	Both CRRT and IHD
Yes	86/102 (84.3)	4/8 (50.0)	14/29 (48.3)
No	31/45 (68.9)	10/40 (25.0)	8/16 (50.0)
Overall	117/147 (79.6)	14/48 (29.2)	22/45 (48.9)

The etiology of sARF was determined as pre-renal in 15% (36/240), intra-renal in 84.6% (203/240) and post-renal in 0.4% (1/240). The patient with a post-renal etiology of sARF was male, aged 57.5 years with an APACHE II score of 31 points admitted to the CVICU following cardiac surgery. This patient survived, recovered renal function and became independent of RRT by 1-year. There was no significant evidence to suggest a difference in risk of death at 1-year for those sARF patients with an intra-renal etiology compared to those with a pre-renal etiology for sARF [crude RR 0.87 (95% CI, 0.7-1.1), p=0.35] (Table 39).

Table 39. Case-fatality rates of sARF stratified by etiology of sARF.

	Case-fatality rate by etiology of sARF (%)		
	Pre-renal	Intra-renal	Post-renal
Dead (%)	26/36 (77.2)	127/203 (62.6)	0/1 (0)

There was no evidence that patient age stratified at ≥ 65 years was a confounder or effect modifier of the association of death at 1-year and etiology of sARF [crude RR 1.15 (95% CI, 0.9-1.5) vs. M-H adjusted RR 1.17 (95% CI, 0.9-1.5)], respectively (Figure 14 and Table 40).

Figure 14. Boxplot of patient age stratified by etiology of sARF by outcome at 1-year.

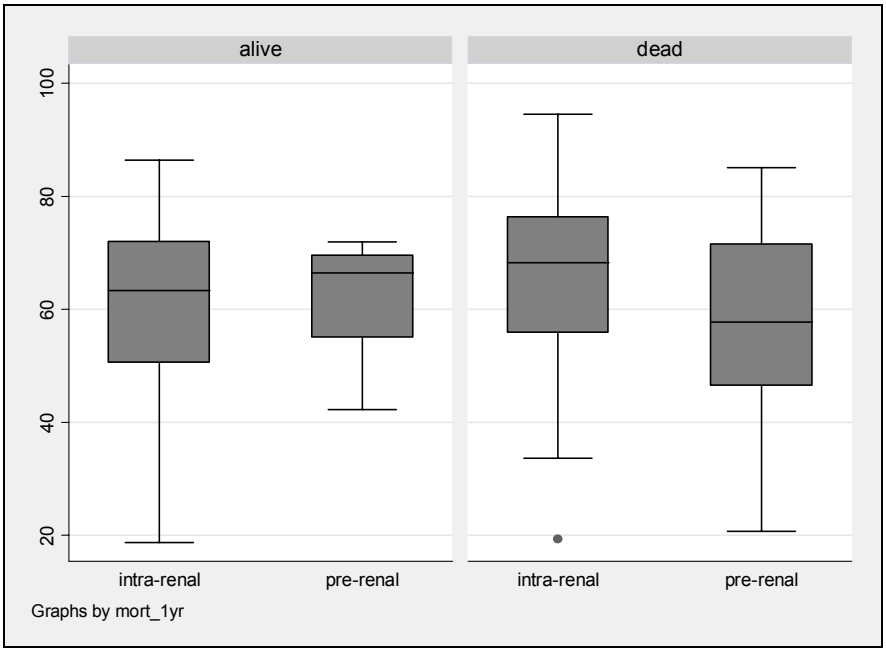


Table 40. Age-specific case-fatality rates stratified by etiology of sARF.

Age (years)	Case-fatality rate by etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
≥ 65	10/16 (62.5)	75/109 (68.8)
< 65	16/20 (80.0)	52/94 (55.3)
Overall	26/36 (77.2)	127/203 (62.6)

By stratified analysis, there was no significant evidence to suggest confounding or effect modification by patient sex on the association of death at 1-year and etiology of sARF (Table 41). There was some evidence to suggest that male patients with a pre-renal etiology of sARF may have a higher case-fatality rate than male patients with an intra-renal etiology of sARF; however, this was not statistically significant [RR 1.31 (95% CI, 0.97-1.8), p=0.20], whereas there was no difference for female patients.

Table 41. Sex-specific case-fatality rates stratified by etiology of sARF.

Sex	Case-fatality by etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
Male	13/17 (76.5)	71/122 (58.2)
Female	13/19 (68.4)	56/81 (69.1)
Overall	6/10 (60)	61/76 (80.2)

A relatively significant proportion of patients with sARF were concomitantly diagnosed with septic shock (139/240 or 57.9%), hypothesizing whether there

was a meaningful difference in death at 1-year stratified by etiology of sARF for these patients. Clearly, the diagnosis of septic shock was associated with a significantly higher case-fatality rate for both pre-renal and intra-renal etiologies of sARF compared to those without a diagnosis of septic shock (Table 42). However, there was no evidence for significant confounding [crude RR 1.15 (95% CI, 0.9-1.5) vs. M-H adjusted RR 1.22 (95% CI, 0.99-1.5)] or effect modification by septic shock on the association of death at 1-year and etiology of sARF.

Table 42. Case-fatality rates stratified by etiology of sARF and septic shock.

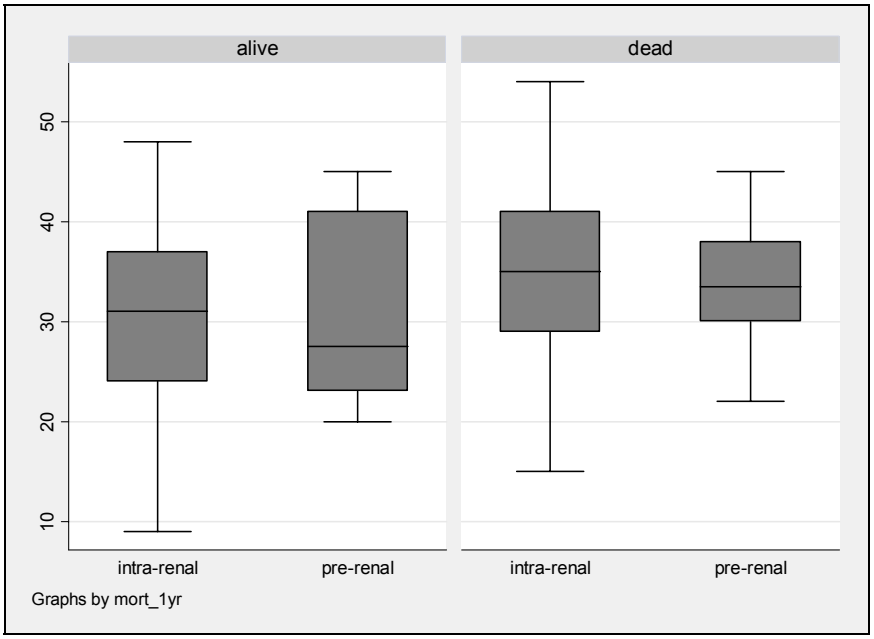
Septic Shock	Case-fatality by etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
Yes	16/17 (94.1)	88/122 (72.1)
No	10/19 (52.6)	39/81 (48.1)
Overall	6/10 (60)	61/76 (80.2)

There was evidence that APACHE II scores of $\geq$ 25 points are associated with increased case-fatality rates for both pre-renal and intra-renal etiologies of sARF compared to those with APACHE II scores < 25 points (Table 43). However, there was no significant evidence that this association was confounded or effect modified by APACHE II score stratified at $\geq$ 25 points (Figure 15).

Table 43. Case-fatality rates stratified by etiology of sARF and APACHE II score.

APACHE II score (points)	Case-fatality by etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
≥ 25	25/32 (78.1)	109/162 (67.3)
< 25	1/4 (25.0)	18/41 (43.9)
Overall	6/10 (60)	61/76 (80.2)

Figure 15. Boxplot of APACHE II score stratified by etiology of sARF by outcome at 1-year.



The presence of liver disease was associated with higher case-fatality rates for both pre-renal and intra-renal etiologies for sARF when compared to those without liver disease (Table 44). However, there was no evidence that liver disease was an important confounder [crude RR 1.15 (95% CI, 0.9-1.5) vs. M-H

adjusted RR 1.05 (95% CI, 0.8-1.3)] or effect modifier of the association of death at 1-year and etiology of sARF. Interestingly, there was complete separation of the data with a case-fatality rate of 100% for those sARF patients with a diagnosis of liver disease and a pre-renal etiology of sARF. One plausible explanation of this finding was that these patients all had advanced end-stage liver disease and were developing pre-renal failure due to hepatorenal syndrome, a diagnosis that is essentially fatal unless liver transplantation can be performed. Furthermore, it would be of interest to know whether life support was ultimately withdrawn on these patients given the historical dismal prognosis in the setting of combined liver and renal failure. Similarly, this was perhaps more evident given the case-fatality rate approaching 100% for those sARF patients with liver disease having received any CRRT (Table 46).

Table 44. Case-fatality rates stratified by etiology of sARF and liver disease.

Liver disease	Case-fatality by etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
Yes	14/14 (100)	30/36 (83.3)
No	12/22 (54.5)	97/167 (58.1)
Overall	6/10 (60)	61/76 (80.2)

The presence of pre-existing liver disease was associated with a significantly higher case-fatality rate in the setting of a diagnosis of sARF when compared to no liver disease [88.0% vs. 57.4%, crude RR 1.5 (95% CI, 1.3-1.8),

p<0.0001], respectively. There was no meaningful evidence to suggest that the association of death at 1-year and pre-existing liver disease for sARF patients was confounded or effect modified by any of age, sex, Charlson co-morbidity index, septic shock, etiology of sARF or modality of RRT (Table 45). Although there was no evidence of confounding by APACHE II score, there was some evidence, though not significant, to suggest that the risk of death at 1-year in sARF patients with liver disease was higher for those with APACHE II scores < 25 points compared to those with APACHE II scores ≥ 25 points [RR 2.70 (95% CI, 1.6-4.6) vs. RR 1.40 (95% CI, 1.2-1.6)], respectively. However, this may be attributable to the small number of patients (n=8) and near complete separation of the data within this strata. Finally, the case-fatality rates of sARF for patients with liver disease are considerable higher in the setting of septic shock; however, there was no evidence to suggest confounding or effect modification of the association of death at 1-year and liver disease (Table 47).

Table 45. Crude and adjusted relative risk for death of sARF with liver disease stratified by several factors.

Factor	Relative Risk	
	Crude RR (95% CI)	M-H Adjusted RR (95% CI)
Age ≥ 65 years	1.53 (1.3-1.8)	1.66 (1.4-2.0)
Sex	1.53 (1.3-1.8)	1.54 (1.3-1.8)
Charlson co-morbidity index ≥ 4 points	1.53 (1.3-1.8)	1.49 (1.3-1.8)
APACHE II score ≥ 25 points	1.53 (1.3-1.8)	1.51 (1.3-1.8)
Septic shock	1.53 (1.3-1.8)	1.46 (1.2-1.7)
Etiology of sARF	1.53 (1.3-1.8)	1.52 (1.3-1.8)
RRT modality	1.53 (1.3-1.8)	1.48 (1.3-1.7)

Abbreviations: RR = relative risk; sARF = severe acute renal failure; RRT = renal replacement therapy.

Table 46. Case-fatality rates stratified by liver disease and modality of renal replacement therapy.

Modality	Case-fatality by liver disease	
	Liver disease (%)	No liver disease (%)
Any CRRT	41/44 (93.2)	98/148 (66.2)
IHD only	3/6 (50.0)	11/42 (26.2)
Overall	44/50 (88.0)	109/190 (57.4)

Table 47. Case-fatality rates of sARF stratified by liver disease and septic shock.

Septic Shock	Case-fatality by liver disease	
	Liver disease (%)	No liver disease (%)
Yes	32/35 (91.4)	72/104 (69.2)
No	12/15 (80.0)	37/86 (43.0)
Overall	44/50 (88.0)	109/190 (57.4)

The presence of oliguria has been suggested in the literature as a risk factor for death for patients with sARF. The majority of patients in this study had oliguria during admission to ICU (183/240 or 76.3%). However, there was no evidence of a significant difference in case-fatality rates for those sARF patients with and without a diagnosis of oliguria [65.0% vs. 59.7%, RR 1.1 (95% CI, 0.9-1.4), p=0.53]. Furthermore, there was no evidence to suggest that the association of death at 1-year and oliguria in patients with sARF was confounded or effect modified by any of age, sex, Charlson co-morbidity index score, APACHE II score, admission type, septic shock, etiology of sARF, or modality of RRT (Table 48).

Table 48. Crude and adjusted relative risk for death of sARF with oliguria stratified by several factors.

Factor	Relative Risk	
	Crude RR (95% CI)	M-H Adjusted RR (95% CI)
Age ≥ 65 years	1.09 (0.9-1.4)	1.66 (1.4-2.0)
Sex	1.09 (0.9-1.4)	1.10 (0.9-1.4)
Charlson co-morbidity index ≥ 4 points	1.09 (0.9-1.4)	1.1 (0.9-1.4)
APACHE II score ≥ 25 points	1.09 (0.9-1.4)	1.07 (0.8-1.3)
Admission type	1.09 (0.9-1.4)	1.04 (0.8-1.3)
Septic shock	1.09 (0.9-1.4)	1.02 (0.8-1.3)
Etiology of sARF	1.09 (0.9-1.4)	1.05 (0.8-1.3)
RRT modality	1.09 (0.9-1.4)	1.03 (0.8-1.3)

Abbreviations: RR = relative risk; sARF = severe acute renal failure; RRT = renal replacement therapy.

Interestingly, there was some evidence to suggest that the etiology of sARF was an effect modifier of the association of death at 1-year and oliguria. It would appear that those patients with a diagnosis of pre-renal sARF and oliguria had the highest case-fatality rate; however, these results are certainly limited by the small number of patients without oliguria and a diagnosis of pre-renal failure (Table 49). Thus, any inferences from these data require cautious interpretation.

Table 49. Case-fatality rates stratified by oliguria and etiology of sARF.

Etiology of sARF	Case-fatality by oliguria	
	Oliguria (%)	No Oliguria (%)
Pre-renal	25/33 (75.8)	1/3 (33.3)
Intra-renal	94/150 (62.7)	33/53 (62.2)
Overall	119/183 (65.0)	34/57 (59.7)

Although serum creatinine has not been reported in the literature as being independently associated with death, arbitrary levels are often used for case-definitions of ARF and for use in the calculation of glomerular filtration rate (GFR). In this study, death at 1-year was associated with a significantly lower median (IQR) pre-dialysis serum creatinine compared to those patients alive at 1-year [344 (250-475) vs. 470 (341-582) μmol/L, p=0.0001]. The case-fatality rates for sARF appear to decrease across strata of increased serum creatinine levels with the lowest rates in those sARF patients with a pre-dialysis serum creatinine $\geq$ 515 μmol/L (Table 50).

Table 50. Crude case-fatality rates of sARF stratified by quartiles of pre-dialysis serum creatinine.

Serum creatinine (μmol/L)	Number of patients (%)	Crude case-fatality (%)
150-264	60 (25.0)	46/60 (76.7)
265-399	59 (24.6)	46/59 (78.0)
400-514	61 (25.4)	32/61 (52.5)
≥ 515	60 (25.0)	29/60 (48.3)
Overall	240 (100)	153/240 (63.8)

There was no evidence to suggest that the association of pre-dialysis serum creatinine with death at 1-year was confounded or effect modified by any of patient sex, Charlson co-morbidity index, septic shock, liver disease, oliguria, etiology of sARF or modality of RRT. However, there was evidence to suggest that patient age represents an effect modifier of the association of death at 1-year and pre-dialysis serum creatinine; however, there was no significant evidence of confounding (Tables 51 and 52 and Figure 16).

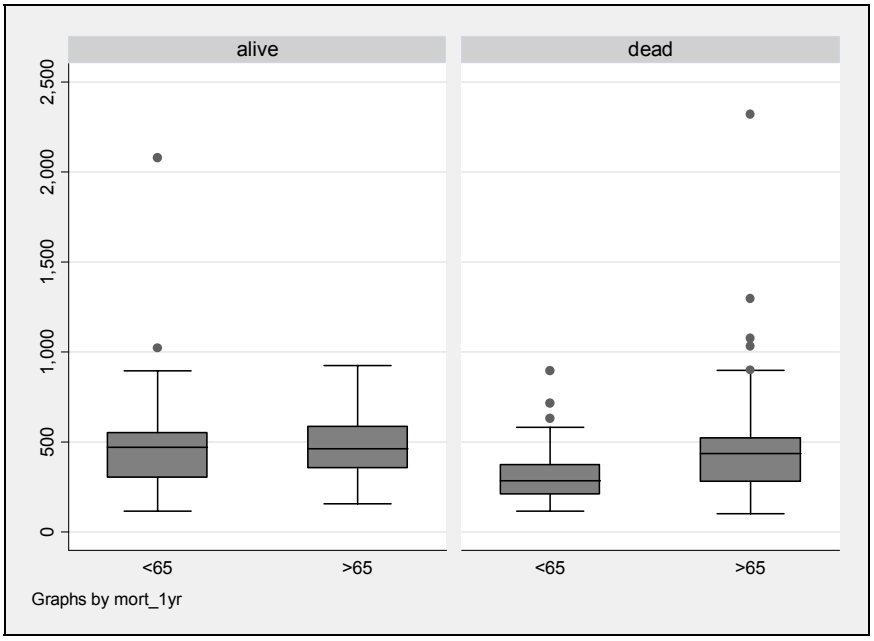
Table 51. Age-specific case-fatality rates of sARF stratified by quartiles of serum creatinine.

Age (years)	Pre-dialysis serum creatinine stratified by quartiles (μmol/L)			
	150-264	265-399	400-514	≥ 515
≥ 65	15/20 (75.0)	24/32 (75.0)	22/33 (66.7)	24/40 (60.0)
< 65	31/40 (77.5)	22/27 (81.5)	10/28 (35.7)	5/20 (25.0)
Overall	46/60 (76.7)	46/59 (78.0)	32/61 (52.5)	29/60 (48.3)

Table 52. Age-specific case-fatality rates of sARF stratified by serum creatinine

Age (years)	Case-fatality rate stratified by serum creatinine (μmol/L) (%)	
	150-399	≥ 400
≥ 65	39/52 (75.0)	46/73 (63.0)
< 65	53/67 (79.1)	15/48 (31.3)
Overall	92/119 (77.3)	61/121 (50.4)

Figure 16. Boxplot of pre-dialysis serum creatinine stratified by age ≥ 65 years and outcome at 1-year.



Clearly, there was evidence that the case-fatality rates are significantly lower for those patients aged < 65 years with pre-dialysis serum creatinine levels in the ranges of 400-514 and ≥ 515 µmol/L. This small group likely accounts for the significant difference in case-fatality rates noted at 1-year by pre-dialysis serum creatinine levels. Thus the risk of death for sARF patients aged < 65 years with a pre-dialysis serum creatinine ≥ 400 µmol/L is 2.5 times greater when compared to those aged < 65 years with a pre-dialysis serum creatinine < 400 µmol/L [RR 2.5 (95% CI, 1.6-3.9)]. For those sARF patients aged ≥ 65 years, there was no significant difference in the risk of death at 1-year across categories of serum creatinine (Table 52). Further, there was some evidence to suggest that this effect modification by age ≥ 65 years was further modified by patient sex with males demonstrating a higher relative risk for death at 1-year compared to

females [RR 3.66 (95% CI, 1.5-8.7) vs. RR 2.0 (95% CI, 1.2-3.4)], respectively. Similarly, there was evidence to suggest that this effect modification by age ≥ 65 years was also modified when considered with APACHE II score ≥ 25 points. Those sARF patients aged < 65 years with APACHE II scores < 25 points had a higher relative risk of death at 1-year compared to those sARF patients aged < 65 years with APACHE II scores ≥ 25 points [RR 7.10 (95% CI, 1.0-47.7) vs. RR 2.2 (95% CI, 1.4-3.4)], respectively. There was also some evidence to suggest that diabetes mellitus was an effect modifier of the association of pre-dialysis serum creatinine and death at 1-year. Again, this was most evident for those sARF patients with diabetes mellitus aged < 65 years, whereas there was no significant difference for those aged ≥ 65 years regardless of diabetes mellitus status. One plausible explanation for these data would be that the institution of RRT was delayed in these younger sARF patients, perhaps because these patients were considered healthier or due to the presence of diabetes mellitus masking the existence of pre-existing kidney disease not evident by measuring only serum creatinine, resulting in a greater pre-dialysis serum creatinine level. However, these data would suggest this that a low pre-dialysis serum creatinine represents a risk factor for death at 1-year, in particular in diabetic patients aged < 65 years with APACHE II scores < 25 points. On further examination, this small cohort of sARF patients aged < 65 years with a pre-dialysis serum creatinine level 150-399 μmol/L (n=67), most had APACHE II scores ≥ 25 points (79.1%), with predominantly intra-renal etiologies

for sARF (79.1%) and principally treated with CRRT (92.5%) suggesting that these patients had a high severity of illness that was not reflected by the absolute change in their serum creatinine. Interestingly, the relative risk of death for this small cohort was higher for those with surgical admissions or pre-existing diabetes mellitus [RR 2.6 (95% CI, 1.6-4.1) and RR 2.2 (95% CI, 1.4-3.3)], respectively.

The variable serum creatinine was not normally distributed as demonstrated in Figure 17, principally due to several outlying values of extremely high, but genuinely elevated serum creatinine levels. Therefore, in order to potentially assess the association of pre-dialysis serum creatinine level on death at 1-year in a multivariate model, a data transformation would be required and following a logarithmic transformation the covariate appears near normally distributed (Figure 18).

Figure 17. Histogram of pre-dialysis serum creatinine.

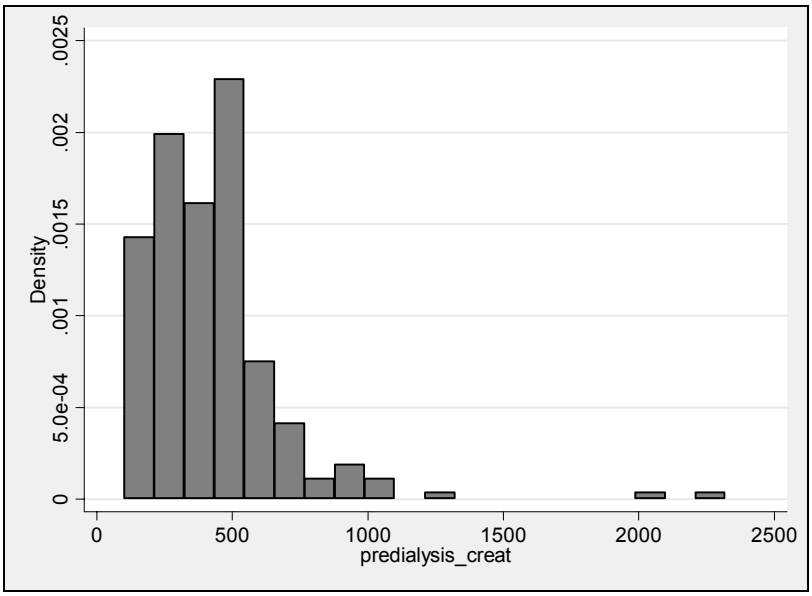
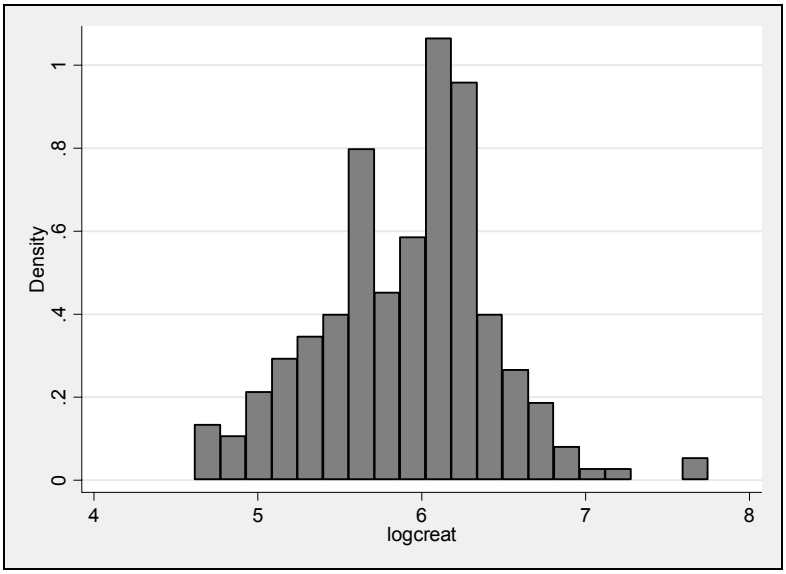


Figure 18. Histogram of logarithmic transformed pre-dialysis serum creatinine.



Several risk factors have been identified by stratified analysis to be associated with death at 1-year for patients diagnosed with sARF. Increasing age appears associated with death at 1-year in patients with a diagnosis of sARF. Likewise, a higher admission APACHE II score was associated with death at 1-year, in particular for male patients when stratified by sex. The Charlson co-morbidity index ≥ 4 points was associated with increased risk of death at 1-year, in particular once adjusted for age and sex. Interestingly, diabetes mellitus was associated with a decreased risk of death at 1-year unless accompanied by septic shock. Additional risk factors include any cancer diagnosis, in particular metastatic cancer, liver disease, septic shock and use of CRRT for RRT compared with IHD only. Further, a lower pre-dialysis serum creatinine (< 400 μmol/L) was associated with an increased risk of death at 1-year, in particular for those aged < 65 years with APACHE II scores < 25 points

or a diagnosis of diabetes mellitus. In contrast, pre-existing diagnosis of stroke, evidence of oliguria and etiology of sARF were not found to be significant risk factors for death at 1-year for patients with a diagnosis of sARF.

5. Characteristics and outcomes for total ICU cohort

During the study period a total of 5,693 adult residents of the CHR had 6,762 admissions to a CHR ICU. In total, 62% (n=3,533) were male, the median (IQR) age was 64.9 (50.6-74.5) years and mean (± SD) APACHE II score was 24.9 ± 8.7 points at ICU admission (Table 53). There was no significant difference in the median (IQR) age between male and female patients, respectively [64.8 (51.1-73.7) vs. 65.4 (49.6-75.7), p=0.06)] (Figure 19). However, with increasing age, the proportion of female patients appears to increase relative to male patients (Table 54).

Table 53. Summary characteristics of adult residents admitted to a CHR ICU based on first admission.

Characteristic	
Number	5,693
Median Age (IQR) (years)	64.9 (50.6-74.5)
Age > 65 years (%)	2,846 (50)
Male Sex (%)	3,533 (62)
Admission Type:	
Medical (%)	2,307 (40.5)
Non-cardiac Surgical (%)	1,511 (26.5)
Cardiac Surgical (%)	1,875 (33)
Admission Diagnostic Category:	
Cardiovascular (%)	2,586 (48)
Respiratory (%)	874 (16.2)
Shock (%)	162 (3)
Neurologic (%)	341 (6.3)
Trauma (%)	83 (1.5)
Gastrointestinal (%)	310 (5.8)
Endocrinologic/Metabolic (%)	158 (2.9)
Poisoning/Psychiatric (%)	771 (14.3)
Monitoring (%)	3 (0.1)
Miscellaneous* (%)	98 (1.8)
Unspecified (%)	307 (5.4)
Mean Admission APACHE II (±SD)	24.9 (8.7)

*Miscellaneous: includes dermatologic, hematologic/oncologic, genitourinary, musculoskeletal primary diagnostic categories on admission to ICU.

Figure 19. Boxplot of patient age stratified by patient sex for total ICU cohort.

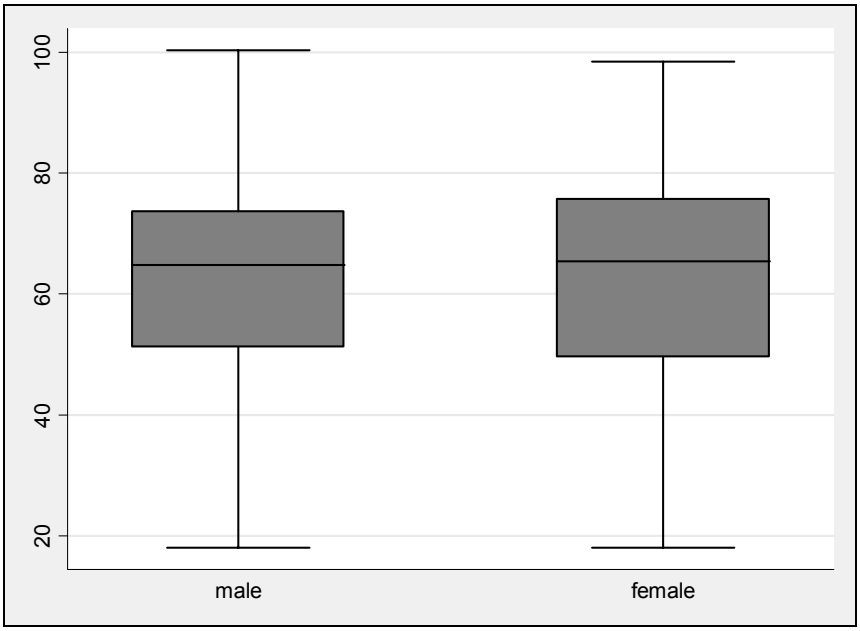


Table 54. Age and sex-specific distributions for total ICU cohort.

Age (Years)	Male (%)	Female (%)
18-49	809 (23)	551 (26)
50-64	997 (28)	510 (23)
65-74	974 (27)	521 (24)
≥ 75	773 (22)	578 (27)
Overall	3,533 (100)	2,160 (100)

There appears no significant difference in the median (IQR) age of those patients admitted for medical, non-cardiac surgical or cardiac surgical indications [64.1 (47.1-75.3) vs. 63.3 (44.5-74.8) vs. 66.4 (57.2-73.4) years], respectively (Figure 20).

Figure 20. Boxplot of patient age stratified by admission type for total ICU cohort.

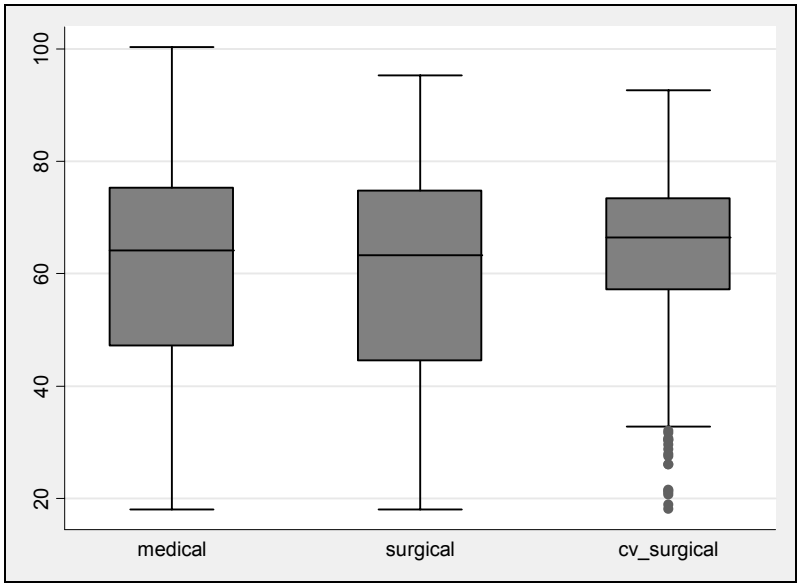
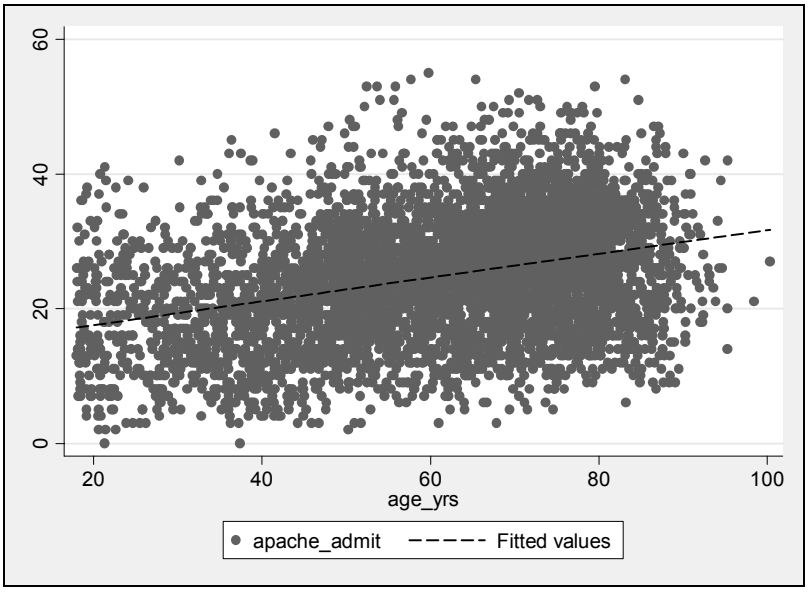


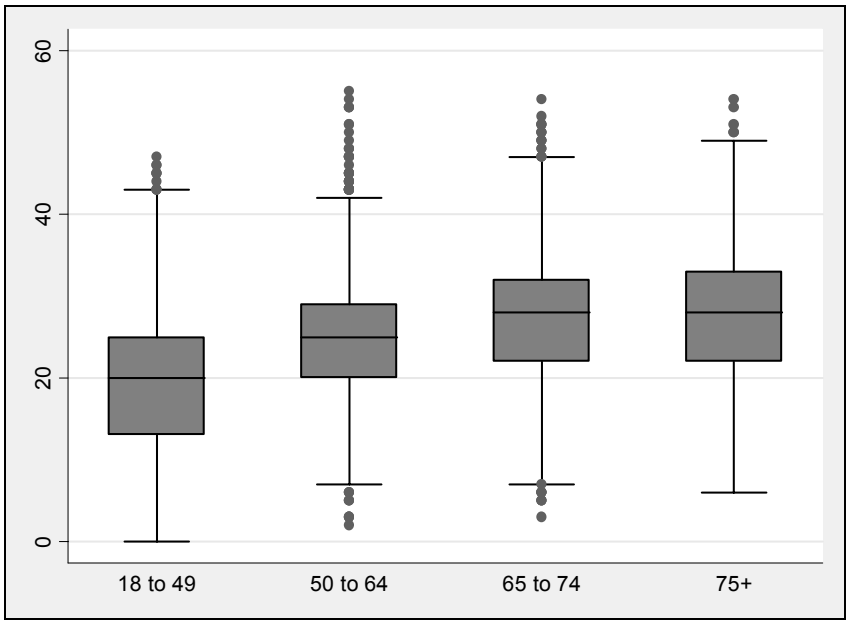
Figure 21. Scatter plot and regression line of fit for patient age and APACHE II score for total ICU cohort.



There was evidence of a positive and linear association between patient age and APACHE II score (Figure 21). The increase in APACHE II score with increasing patient age was evident when age was further stratified (Figure 22

and Table 55). This was plausible given that patient age comprises one component contributing to the calculation of APACHE II score.

Figure 22. Boxplot of APACHE II score stratified by patient age for total ICU cohort.



The APACHE II scores are not significantly different when comparing medical and non-cardiac surgical admissions across age strata; however, the APACHE II scores are significantly higher for cardiac surgical admissions compared to both medical and non-cardiac surgical admissions ($p<0.0001$) (Table 55 and Figure 23). Again, this has a plausible explanation that was not directly related to the overall burden or severity of illness for cardiac surgical patients compared with medical or non-cardiac surgical patients. In general, the APACHE II score is calculated within the first 24 hours of admission to an ICU and assesses several parameters including: patient age, chronic health status; and importantly numerous acute physiologic variables to calculate a composite

score.[58] Cardiac surgical patients are admitted directly from the operating theatre at which time are recovering from general anaesthetic, cardio-pulmonary bypass, and require advanced life support, such as mechanical ventilation and hemodynamic support often with inotropic or vasopressor infusions. Therefore, the APACHE II score calculated in these patients within the first 24 hours was often exaggerated and not truly reflective of their underlying severity of illness, and therefore does not represent a valid measure in this population for this purpose.

Table 55. Stratified analysis of APACHE II scores by age and admission type.

Age (Yrs)	Total No. Patients (%)	Mean APACHE II score (±SD)	Mean APACHE II score (±SD) by Admission Type		
			Medical (n=2,294)	Non-cardiac Surgical (n=1,512)	Cardiac Surgical (n=1,815)
18-49	1,360 (24)	19.9 (8.5)	19.2 (9.4)	19.1 (7.4)	24.5 (6.2)
50-64	1,487 (26)	24.7 (8.1)	24.4 (10.2)	22.1 (8.5)	26.4 (4.9)
65-74	1,495 (26)	27.2 (8.1)	25.3 (9.3)	24.6 (8.9)	30.1 (5.0)
≥75	1,351 (24)	27.6 (8.2)	26.9 (8.9)	24.8 (8.0)	31.7 (5.0)

There was no significant difference in the mean (±SD) APACHE II score stratified by sex [males 25.0 (8.6) vs. females 24.7 (9.0) points, p=0.20] (Figure 24). Furthermore, when APACHE II score was stratified by age ≥ 65 years and patient sex, there remained no significant difference between males and females within each age stratum; however, APACHE II scores were significantly higher for both males and females aged ≥ 65 years compared with those aged < 65 years

[males: 27.5 (8.1) vs. 22.6 (8.4), p<0.0001; females: 27.2 (8.2) vs. 22.1

(9.0), p<0.0001] (Figure 25).

Figure 23. Boxplot of APACHE II score stratified by admission type for total ICU cohort.

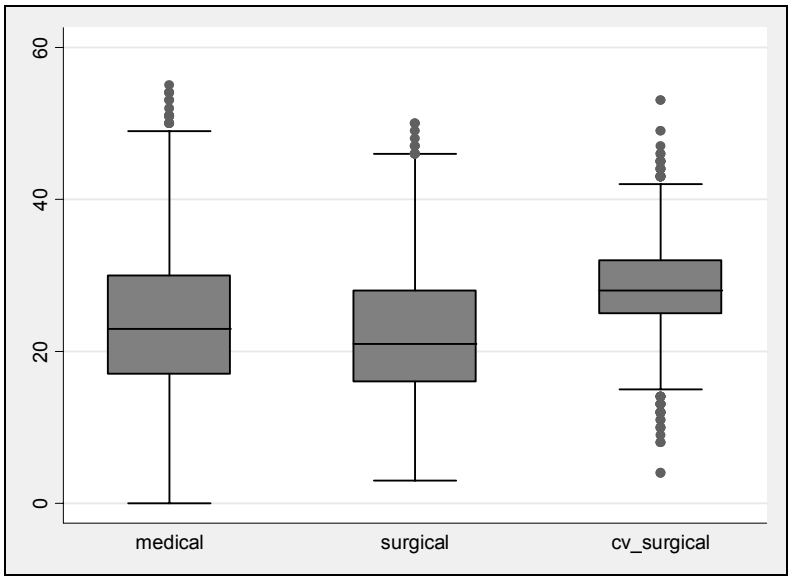


Figure 24. Boxplot of APACHE II score stratified by patient sex for total ICU cohort.

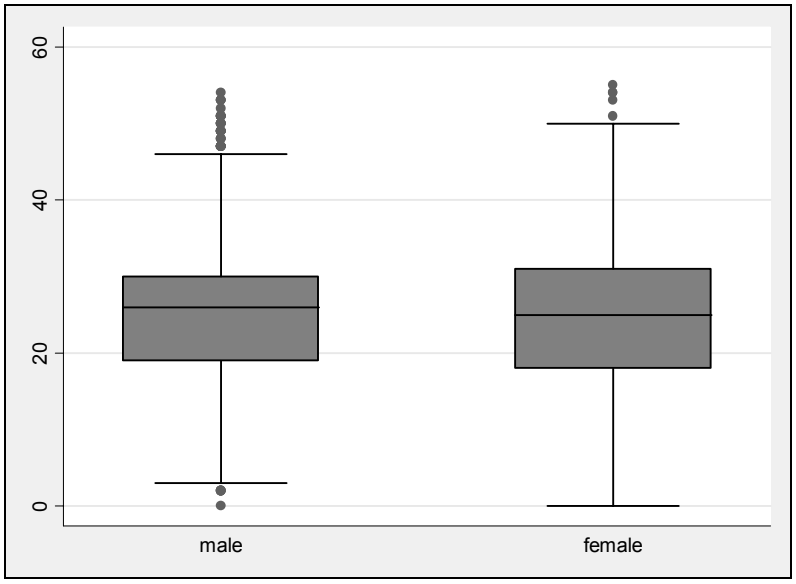
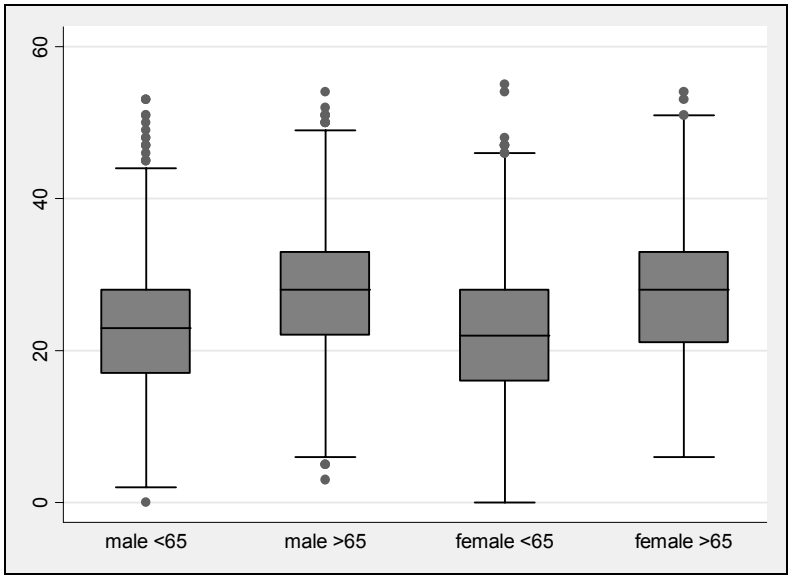


Figure 25. Boxplot of APACHE II score stratified by age ≥ 65 years and patient sex for total ICU cohort.



There are limitations to the assessment of APACHE II scores for the total ICU cohort admitted during the surveillance period. First, as discussed, the APACHE II score was not a valid instrument for determining severity of illness or for predicting death in cardiac surgical patients. Second, approximately 1.1% (n=60) of values for APACHE II score were missing for the total ICU cohort that were not replaced. It was plausible that the missing APACHE II scores could alter the aforementioned associations for age, sex, and admission type; however, this was unlikely a significant source of bias given the large sample size of the study.

The median (IQR) ICU and hospital length of stays comparing survivors and non-survivors at 1-year are presented in Table 56. The median (IQR) ICU length of stay was significantly longer for those patients dead at 1-year, whereas

the median (IQR) hospital length of stay was significantly shorter for those dead at 1year. Although, these differences appear to have questionable clinical significance, they are plausible considering survivors of an episode of critical illness likely require a longer period of total hospitalization for recovery or ultimately require a more brief admission to an ICU. An absolute difference in median hospital length of stay of 1 day between survivors and non-survivors when considered over 6000 patients likely represents considerable resources and therefore may have health economic implications.

The ICU length of stay was slightly longer for patients aged ≥ 65 years compared with those aged < 65 years [1.9 (1.0-4.1) vs. 1.7 (1.0-3.8) days, p<0.0001], respectively; however, this difference was of questionable clinical significance (Table 57). Similarly, hospital length of stay was significantly longer for patients aged ≥ 65 years compared with those aged < 65 years [14 (8-26) vs. 10 (6-20) days, p<0.0001)], respectively,

In general, females have slightly but significantly longer median (IQR) ICU and hospital lengths of stay compared with males (Table 57). The ICU length of stay for females and males was 1.9 (1.0-4.3) vs. 1.8 (1.0-3.7) days (p=0.01), respectively. The hospital length of stay for females and males was 13 (7-26) vs. 11 (7-22) days (p=0.01), respectively.

Table 56. ICU and hospital length of stay for total ICU cohort stratified by survival status at 1-year.

Median (IQR) Length of Stay (Days)	Total Cohort (n=5,693)	Alive (n=4,293)	Dead (n=1,400)	p-value
ICU	1.9 (1.0-3.9)	1.8 (1.0-3.2)	2.5 (0.9-6.6)	<0.0001
Hospital	12 (7-23)	12 (7-23)	11 (3-24)	<0.0001

Table 57. ICU and hospital length of stay for total ICU cohort stratified by age, sex and survival status at 1-year: A) ICU length of stay; B) Hospital length of stay.

A)

Age (years)	Alive (n=4,293)		Dead (n=1,400)	
	Male	Female	Male	Female
≥ 65	1.8 (1.0-3.0)	2.0 (1.1-3.8)	2.5 (1.0-6.8)	2.4 (0.9-6.0)
< 65	1.6 (1.0-3.0)	1.7 (0.9-3.8)	2.8 (1.0-6.7)	2.2 (0.8-6.7)

B)

Age (years)	Alive (n=4,293)		Dead (n=1,400)	
	Male	Female	Male	Female
≥ 65	14 (8-23)	17 (10-32)	12 (5-26)	12 (4-27)
< 65	10 (6-19)	11 (4-22)	7 (2-20)	6 (2-20)

Legend: IQR given as absolute range around median.

Although a few patterns emerge when examining the ICU length of stay stratified by age ≥ 65 years, sex and survival status at 1-year, there was very little difference in absolute terms across strata (Table 57). Perhaps, within the stratum of dead at 1-year, males tended to have longer ICU lengths of stay

compared with females, whereas within the stratum of alive at 1-year females of all ages tended to have longer ICU lengths of stay; however, this was of questionable clinical significance. Patterns that emerge with assessment of hospital length of stay stratified by age ≥ 65, sex and survival status at 1-year include prolonged length of stay for female patients alive at 1-year, specifically aged ≥ 65 years. However, one limitation to the accuracy hospital length of stay estimates was that approximately 7.5% (n=429) of values were missing for the total ICU cohort that were not replaced.

The crude fatality rates for the total ICU cohort at ICU discharge, hospital discharge and at 1-year were 13.4%, 20.2% and 24.6%, respectively. The median (IQR) age in years was significantly higher for those who died in ICU compared with those who survived to ICU discharge [69.3 (54.6-77.8) vs. 64.3 (50.1-73.8) years, p<0.0001)], respectively. Similarly, the median (IQR) age in years was significantly higher for those who died in hospital compared with those who survived to hospital discharge [71.4 (57.9-78.7) vs. 63.3 (49.0-72.9) years, p<0.0001)], respectively. Likewise, at 1-year, the median (IQR) age was significantly higher for those who were dead compared with those who were still alive [71.6 (58.9-78.8) vs. 62.5 (62.3 (48.4-72.4) years, p<0.0001)], respectively. There was evidence of a significant association between increasing age and increased fatality rate at ICU and hospital discharge and at 1-year (Table 58).

Table 58. Age-specific fatality rates at ICU and hospital discharge and at 1-year for total ICU cohort.

Age (Years)	Fatality rates (%)		
	ICU	Hospital	1-Year
18-49	135/1,360 (9.9)	166/1,360 (12.2)	189/1,360 (13.9)
50-64	166/1,487 (11.2)	228/1,487 (15.3)	275/1,487 (18.5)
65-74	202/1,495 (13.5)	317/1,495 (21.2)	394/1,495 (26.4)
≥ 75	259/1,351 (19.2)	436/1,351 (32.3)	542/1,351 (40.1)
Overall	762/5,693 (13.4)	1,147/5,693 (20.2)	1,400/5,693 (24.6)

Table 59. Sex-specific fatality rates at ICU and hospital discharge and at 1-year for total ICU cohort.

Sex	Fatality rates (%)		
	ICU	Hospital	1-Year
Male	417/3,533 (11.8)	656/3,533 (18.6)	189/1,360 (13.9)
Female	345/2,160 (16)	491/2,160 (22.7)	275/1,487 (18.5)
Overall	762/5,693 (13.4)	1,147/5,693 (20.1)	1,400/5,693 (24.6)

TABLE 60. Age and sex-specific fatality rates at 1-year for total ICU cohort.

Age (years)	1-Year Fatality Rate (%)		
	Males	Females	Overall
≥ 65	544 /1,747 (31.1)	392/1,099 (35.7)	936/2,846 (32.9)
< 65	259/1,786 (14.5)	205/1,061 (19.3)	464/2,847 (16.3)
Overall	189/1,360 (13.9)	275/1,487 (18.5)	1,400/5,693 (24.6)

Within the total ICU cohort, the fatality rate at 1-year was significantly higher for females compared with males [18.5% vs. 13.9% (RR 1.2, 95% CI, 1.1-

1.3, p<0.0001] (Table 59). There was no significant evidence to suggest that age (either dichotomized at age 65 year or stratified as in Table 58) was a confounder of the association of death at 1-year and sex [crude RR 1.22, Mantel-Hanzel (M-H) adjusted 1.18]. Interestingly, there was some evidence to suggest that sex may represent an effect modifier of the association of age and fatality rate at 1-year; however, this was not statistically significant (Table 60). Specifically, the relative risk for death at 1-year was higher for women aged < 65 years compared with men aged < 65 years (RR 1.33, 95% CI, 1.1-1.6) when compared across both women and men aged ≥ 65 years (RR 1.15, 95% CI, 1.0-1.3).

The fatality rates during ICU and hospital admission and at 1-year for patients admitted to a CHR ICU were greater in medical admissions compared with non-cardiac surgical or cardiac surgical admissions [39.3% vs. 26.7% vs. 4.9%], respectively (Table 61).

Table 61. Fatality rates at ICU and hospital discharge and at 1-year stratified by admission type for total ICU cohort.

	Fatality Rate by Admission Type (%)		
	Medical (n=2,294)	Non-cardiac Surgical (n=1,512)	Cardiac Surgical (n=1,875)
ICU	505 (22.1)	210 (13.9)	45 (2.4)
Hospital	735 (32)	337 (22.3)	73 (3.9)
1-Year	901 (39.3)	404 (26.7)	92 (4.9)

Although the data suggest that age was not a significant confounder of the association of admission type and death at 1-year, there was evidence to

suggest significant effect modification by age ≥ 65 years across each type of admission category (Table 62). The relative risk of death for patients aged ≥ 65 years by admission type was highest at 2.6 (95% CI, 2.2-3.1) for non-cardiac surgical, followed by 2.5 (95% CI, 1.6-4.0) for cardiac surgical, and finally 2.0 (95% CI, 1.8-2.2) for medical admissions, respectively.

Table 62. Age-specific fatality rates at 1-year stratified by admission type for total ICU cohort.

Age (years)	1-Year Fatality Rate by Admission Type (%)		
	Medical (n=2,294)	Non-cardiac Surgical (n=1,512)	Cardiac Surgical (n=1,875)
≥ 65	584/1,110 (56.2)	282/711 (39.7)	69/1,020 (6.7)
< 65	317/1,184 (26.8)	122/801 (15.2)	23/855 (2.7)
Overall	901 (39.3)	404 (26.7)	92 (4.9)

Table 63. Sex-specific fatality rates stratified by admission type for total ICU cohort.

Sex	1-Year Fatality Rate by Admission Type (%)		
	Medical (n=2,294)	Non-cardiac Surgical (n=1,512)	Cardiac Surgical (n=1,875)
Males	495/1,229 (40.3)	239/929 (25.7)	67/1,367 (4.9)
Females	406/1,065 (38)	165/583 (28.3)	25/508 (4.9)
Overall	901 (39.3)	404 (26.7)	92 (4.9)

There was some evidence to suggest that the association of admission type and fatality rate at 1-year was confounder by patient sex [crude RR 1.22 (95% CI, 1.1-1.3); M-H adjusted RR 0.99 (95% CI, 0.91-1.1)]. Specifically, the data suggests that women have a higher fatality rate at 1-year for non-cardiac

surgical admissions compared with men, whereas men have slightly higher fatality rates than women for medical admissions (Table 63).

6. Characteristics and outcome of total ICU cohort by severity of renal dysfunction

Several characteristics and outcomes in critically ill patients were assessed across a range in severity of renal dysfunction while admitted to ICU. Thus, in order to further explore the association of death at 1–year and the presence of renal dysfunction in critically ill patients, renal function was stratified by severity ranging from no evidence of renal dysfunction (serum creatinine < 150), mild dysfunction (serum creatinine 150 - 299 μmol/L), moderate dysfunction (serum creatinine ≥ 300 μmol/L), severe acute dysfunction requiring renal replacement (sARF) and the presence of pre-existing end-stage renal disease (ESRD) requiring long-term dialysis prior to ICU admission. The crude fatality rates at ICU and hospital discharge and at 1-year by severity of renal dysfunction are presented in Table 64.

Table 64. Crude fatality rates at ICU and hospital discharge and at 1-year stratified by severity of renal dysfunction.

Severity of Renal Dysfunction	No renal dysfunction (n=4,411)	SCr 150-299 μmol/L (n=790)	SCr > 300 μmol/L (n=160)	sARF (n=240)	ESRD (n=92)
ICU Death (%)	361 (8.2)	224 (28.4)	42 (26.3)	120 (50)	15 (16.3)
Hospital Death (%)	592 (13.4)	316 (40)	65 (41)	143 (60)	31 (34)
1-Year Death (%)	763 (17.3)	370 (47)	77 (48)	153 (64)	37 (40)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease/chronic renal replacement therapy

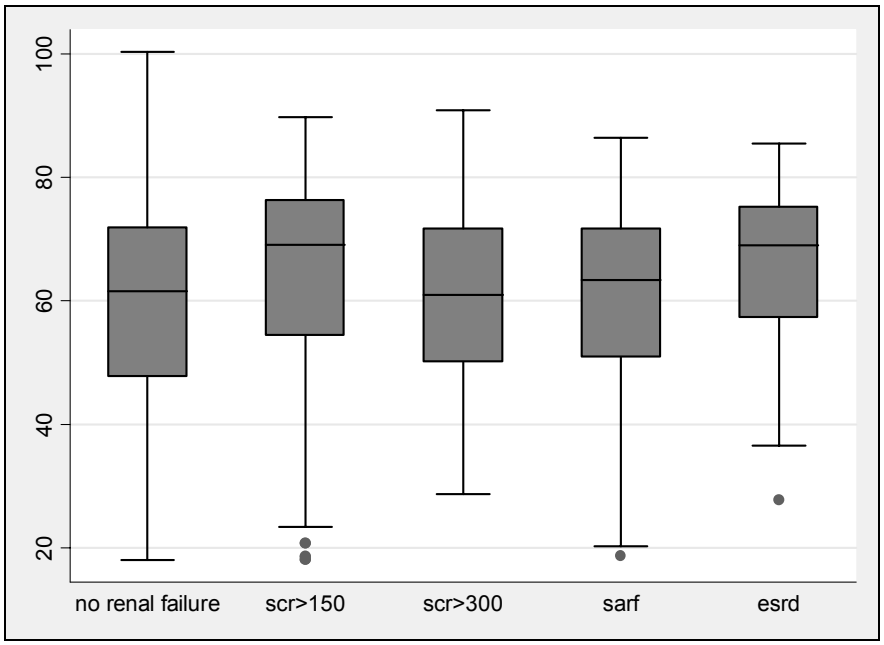
The crude fatality rates appear to increase with increasing severity of renal dysfunction. The crude 1-year fatality rate for critically ill patients was 17.3% (n=763/4,411) with no renal dysfunction; 46.8% (n=370/790) for mild dysfunction; 48.1% (n=77/160) for moderate dysfunction; 64% (n=153/240) for patients with a diagnosis of sARF; and 40.2% (n=37/92) for patients with ESRD. First, a stratified analysis exploring several factors that may influence the association of death at 1-year and severity of renal dysfunction is presented.

The fatality rate by severity of renal dysfunction appears significantly associated with age (Figure 26). Specifically, within each increased age strata, the fatality rate increases across all strata of renal dysfunction (Tables 65 and 66). However, age stratified either at several levels or age ≥ 65 years was not an important confounder; however, age appears to significantly effect modifier the association of severity of renal dysfunction and death at 1-year. Interestingly, the relative risk of death at 1-year for those patients ≥ 65 years was highest for those

patients with no renal failure [RR 2.1 (95% CI, 1.9-2.5)] when compared to those with serum creatinine levels ≥ 300 μmol/L and 150-299 μmol/L [RR 2.1 (95% CI, 1.4-3.2) and RR 1.4 (95% CI, 1.2-1.7)], respectively. Notably, the relative risk for death at 1-year in the sARF and ESRD groups was not statistically significant [RR 1.15 (95% CI, 0.9-1.4) and RR 1.06 (95% CI, 0.6-1.77)] due to the high fatality rates for these groups regardless of age ≥ 65 years. Thus, the effect modification by age ≥ 65 years for the association of death at 1-year and severity of renal dysfunction appear most important for those groups with either no renal dysfunction or mild to moderate renal dysfunction.

Figure 26. Boxplot of age stratified by severity of renal dysfunction and survival status at 1-year: A) alive; B) dead.

A)



B)

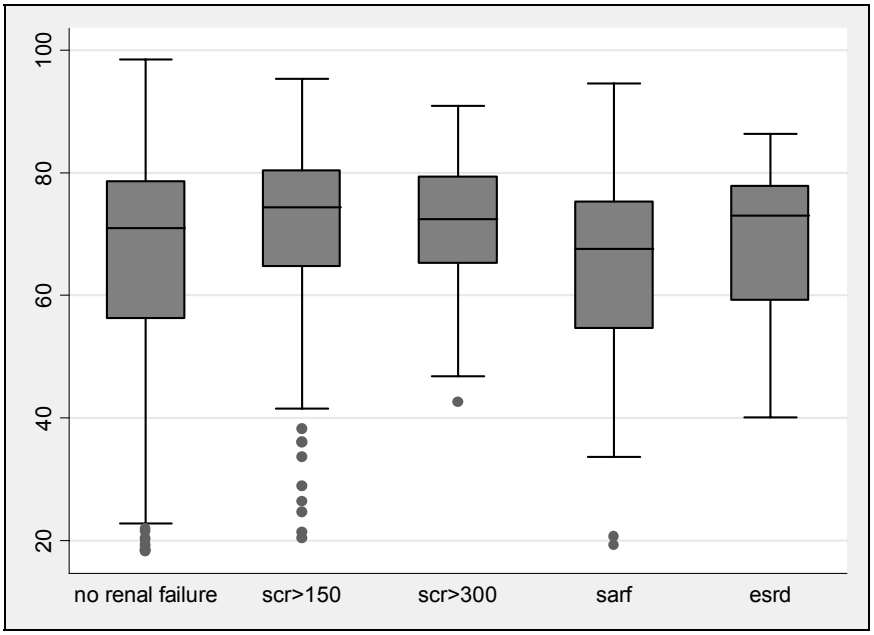


Table 65. Age-specific fatality rates by severity of renal dysfunction.

Age (Years)	No renal dysfunction (%)	SCr 150-299 μmol/L (%)	SCr > 300 μmol/L (%)	sARF (%)	ESRD (%)
18-49	123/1,164 (10.5)	33/112 (29.5)	2/22 (9.1)	20/47 (42.5)	4/15 (26.7)
50-64	146/1,209 (12.1)	61/145 (42.1)	17/44 (38.6)	41/68 (60.3)	10/21 (47.6)
65-74	215/1,118 (19.2)	99/228 (43.4)	28/50 (56)	45/73 (61.6)	7/26 (26.9)
≥ 75	279/920 (30.3)	177/305 (58)	30/44 (68.2)	40/52 (76.9)	16/30 (53.3)
Overall	763/4,411 (17.3)	370/790 (46.8)	77/160 (48.1)	153/240 (64)	37/92 (40.2)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

Table 66. Age-specific fatality rates by severity of renal dysfunction.

Age (Years)	No renal dysfunction (%)	SCr 150-299 μmol/L (%)	SCr > 300 μmol/L (%)	sARF (%)	ESRD (%)
≥ 65	494/2,038 (24.2)	276/533 (51.8)	58/94 (61.7)	85/125 (68)	23/56 (41.1)
< 65	269/2,373 (11.3)	94/257 (36.6)	19/66 (28.8)	68/115 (59.1)	14/36 (38.9)
Overall	763/4,411 (17.3)	370/790 (46.8)	77/160 (48.1)	153/240 (64)	37/92 (40.2)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

The fatality rate at 1-year by severity of renal dysfunction does not appear to be significantly associated with patient sex (Table 67). Specifically, patient sex does not appear to be an important confounder [crude RR 1.22 (95% CI, 1.1-1.3) vs. M-H adjusted RR 1.23 (95% CI, 1.1-1.3)] or effect modifier of the association of death at 1-year and severity of renal dysfunction.

Table 67. Sex-specific fatality rates by severity of renal dysfunction.

Sex	No renal dysfunction (%)	SCr 150-299 μmol/L (%)	SCr > 300 μmol/L (%)	sARF (%)	ESRD (%)
Males	418/2,724 (15.3)	229/504 (45.4)	49/108 (45.3)	84/140 (60)	23/57 (40)
Females	345/1,687 (20.5)	141/286 (49.3)	28/52 (53.8)	69/100 (69)	14/35 (40)
Overall	763/4,411 (17.3)	370/790 (46.8)	77/160 (48.1)	153/240 (64)	37/92 (40.2)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

The fatality rate at 1-year by severity of renal dysfunction would appear to be significantly associated with APACHE II score (Table 68 and Figure 27). The mean (±SD) APACHE II score was significantly higher for those with evidence of renal dysfunction, and highest for those patients with sARF, when compared to no renal dysfunction ($p<0.0001$) (Table 68). Furthermore, when the mean (±SD) APACHE II scores are stratified by admission type, the cardiac surgical has significantly higher scores compared with either medical or non-cardiac surgical admissions. The higher mean (±SD) APACHE II scores for cardiac surgical

patients are understandable and are not necessarily a true reflection of their severity of illness as previously discussed. With APACHE II score dichotomized at ≥ 25 points, there was evidence of a significant increase in fatality at 1-year with a progressive increase in severity of renal dysfunction, with the greatest fatality rates in those with a diagnosis of sARF (Table 69).

Table 68. Stratified analysis of APACHE II scores by severity of renal dysfunction and admission type.

Severity of renal dysfunction	Mean APACHE II score (±SD)	Mean APACHE II score (±SD) by Admission Type		
		Medical (n=2,294)	Non-cardiac Surgical (n=1,512)	Cardiac Surgical (n=1,815)
No renal dysfunction (n=4,351)	23.2 (8.0)	20.5 (8.5)	20.3 (7.4)	27.8 (5.2)
SCr 150-299 μmol/L (n=790)	29.8 (8.7)	29.5 (9.1)	28.2 (8.5)	34.3 (5.9)
SCr ≥ 300 μmol/L (n=160)	30.7 (9.6)	30.4 (10.2)	31.2 (8.1)	34.5 (7.7)
sARF (n=240)	33.2 (8.6)	32.8 (9.0)	32.2 (7.9)	37 (6.9)
ESRD (n=92)	29.7 (7.9)	27.5 (9.0)	28.9 (6.1)	35 (4.2)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease; SD = standard deviation.

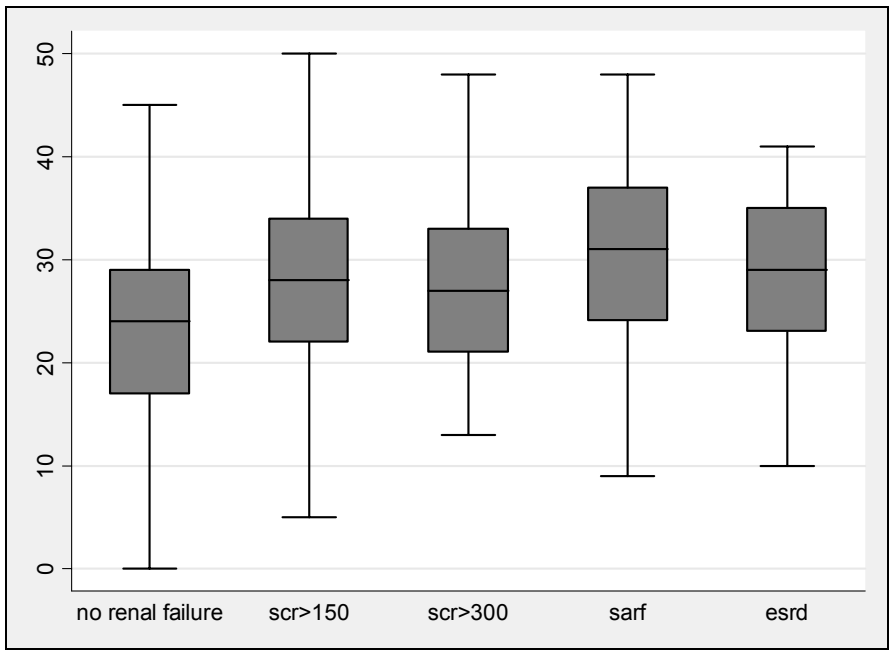
Table 69. Fatality rates by severity of renal dysfunction stratified by APACHE II score ≥ 25 points.

APACHE II Score (points)	No renal dysfunction (%)	SCr 150-299 μmol/L (%)	SCr > 300 μmol/L (%)	sARF (%)	ESRD (%)
≥ 25	420/2,097 (20)	297/565 (52.6)	61/110 (55.5)	134/195 (68.7)	33/70 (47.1)
< 25	340/2,254 (15.1)	73/225 (32.4)	16/50 (32)	19/45 (42.2)	4/22 (18.2)
Overall	763/4,411 (17.3)	370/790 (46.8)	77/160 (48.1)	153/240 (64)	37/92 (40.2)

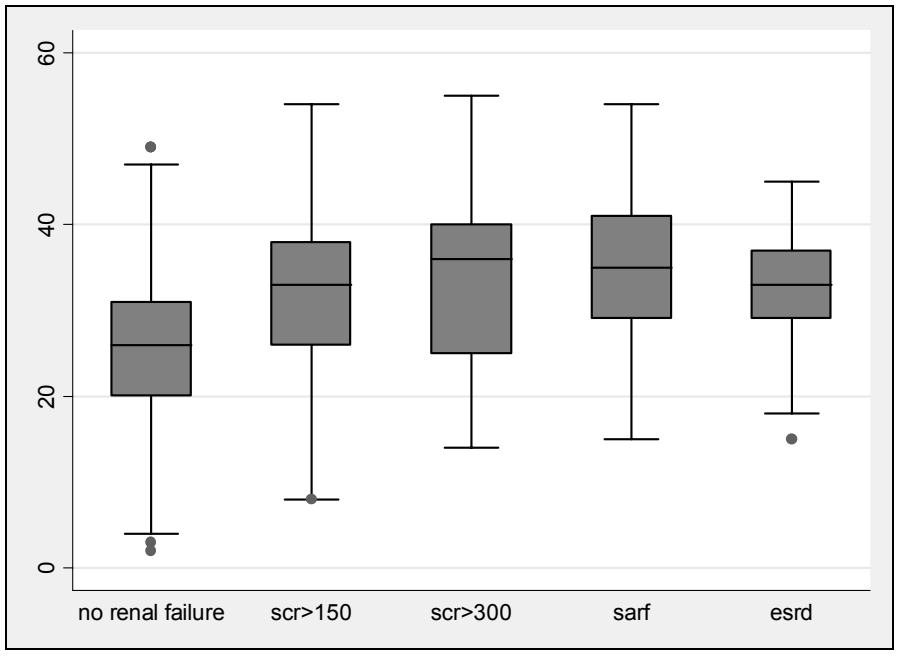
Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

Figure 27. Boxplot of APACHE II score stratified by severity of renal dysfunction and shown by survival status at 1-year: A) alive; B) dead.

A)



B)



The relative risk of death at 1-year for APACHE II scores ≥ 25 points are 1.3 [(95% CI, 1.2-1.5), p<0.0001] for no renal dysfunction, 1.6 [(95% CI, 1.3-2.0), p<0.0001) for mild dysfunction, 1.7 [(95% CI, 1.1-2.7), p=0.007] for moderate dysfunction, 1.6 [(95% CI, 1.1-2.3), p=0.002] for sARF and 2.6 [(95% CI, 1.0=6.5), p=0.02] for ESRD (Table 70). When the categories for mild and moderate renal dysfunction were collapsed, the relative risk of death at 1-year for those with APACHE II scores ≥ 25 points compared to those with APACHE II scores < 25 points was 1.6 [(95% CI, 1.4-2.0), p<0.0001]. Of note, the fatality rates at 1-year for those with ESRD are lower than for patients with mild or moderate renal dysfunction; however, the relative risk of death in patients with ESRD across APACHE II scores was considerably higher than for those with any other form of renal dysfunction (Table 69). APACHE II score dichotomized at ≥ 25 points demonstrated evidence of significant confounding [crude RR 1.79 (95% CI, 1.6-2.0) vs. M-H adjusted RR 1.44 (95% CI,1.3-1.6)]; however, there was no significant evidence of effect modification on the relationship of death at 1-year and severity of renal dysfunction.

Table 70. Relative risk of death at 1-year by severity of renal dysfunction stratified by APACHE II score ≥ 25 points.

Severity of renal dysfunction	Relative Risk	95% CI	p-value
No renal dysfunction	1.33	1.2-1.5	<0.0001
SCr 150-299 μmol/L	1.62	1.3-2.0	<0.0001
SCr > 300 μmol/L	1.73	1.1-2.7	0.007
sARF	1.63	1.1-2.3	0.002
ESRD	2.60	1.0-6.5	0.02

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

Table 71. Fatality rates by severity of renal dysfunction stratified by admission type.

Admission Type	No renal dysfunction (%)	SCr 150-299 μmol/L (%)	SCr > 300 μmol/L (%)	sARF (%)	ESRD (%)
Medical	473/1,538 (30.8)	246/443 (55.5)	60/118 (50.8)	104/151 (68.9)	18/44 (40.9)
Non-cardiac surgical	239/1,168 (20.4)	103/225 (45.8)	16/35 (45.7)	32/58 (55.2)	14/26 (53.8)
Cardiac Surgical	49/1,697 (2.9)	20/119 (16.8)	1/6 (16.7)	17/31 (54.8)	5/22 (22.7)
Overall	763/4,411 (17.3)	370/790 (46.8)	77/160 (48.1)	153/240 (64)	37/92 (40.2)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

The fatality rate at 1-year by severity of renal dysfunction demonstrated a significant association with admission type (Table 71). In particular, fatality rates were much higher in medical compared with non-cardiac surgical and cardiac surgical across all strata of severity of renal dysfunction with the exception of

those patients with ESRD, where the highest fatality rate occurred in those patients with a non-cardiac surgical admission. However, the relative risk of death at 1-year for patients with ESRD compared to those without ESRD was highest for those with cardiac surgical admissions compared with non-cardiac surgical and medical admissions, respectively (Table 72).

Table 72. Crude relative risk for death at 1-year by admission type for patients with ESRD.

Admission Type	Relative Risk	95% CI	p-value
Medical (n=44)	1.04	0.7-1.5	0.88
Non-cardiac surgical (n=26)	2.05	1.4-3.0	0.003
Cardiac surgical (n=22)	4.84	2.2-10.7	0.004

Overall, there was evidence to suggest that admission type was a confounder and an effect modifier of the association of death at 1-year and severity of renal dysfunction. The effect modification appeared most apparent for the cardiac surgical admissions across strata of severity of renal dysfunction.

In general, there was evidence to suggest that the median (IQR) ICU and hospital length of stays were longer for those with renal dysfunction, in particular those with a diagnosis of sARF or pre-existing ESRD (Tables 73 and 74).

Table 73. ICU length of stay stratified by severity of renal dysfunction and survival status at 1-year.

Outcome at 1-year	No renal dysfunction (n=4,411)	SCr 150-299 μmol/L (n=790)	SCr > 300 μmol/L (n=160)	sARF (n=240)	ESRD (n=92)
Dead (n=1,400)	2.0 (0.8-4.9)	2.8 (1.2-6.8)	1.7 (0.7-4.1)	8.2 (3.1-14.4)	4.6 (1.2-7.2)
Alive (n=4,293)	1.6 (1.0-2.8)	3.0 (1.5-6.2)	2.3 (1.2-5.1)	8.6 (3.7-19.1)	2.3 (1.8-4.1)
Overall	1.7 (1.0-3.0)	2.9 (1.3-6.4)	2.1 (1.0-4.8)	8.2 (3.5-16)	2.5 (1.6-5.9)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

Table 74. Hospital length of stay stratified by severity of renal dysfunction and survival status at 1-year.

Outcome at 1-year	No renal dysfunction (n=4,411)	SCr 150-299 μmol/L (n=790)	SCr > 300 μmol/L (n=160)	sARF (n=240)	ESRD (n=92)
Dead (n=1,400)	10 (3-24)	11 (4-23)	6 (2-18)	15 (6-27)	14.5 (7-42)
Alive (n=4,293)	11 (7-21)	18 (11-36)	16.5 (9-33)	39 (23-66)	23.5 (11-55)
Overall	11 (7-21)	16 (8-29)	13 (5-23)	22 (9-40)	20 (9-44)

Abbreviations: SCr = serum creatinine; sARF = severe acute renal failure; ESRD = end stage renal disease

In summary, increase in severity of renal dysfunction would appear significantly associated with death at 1-year. Interestingly, the presence of ESRD was associated with an increased risk of death at 1-year; however, this was less than expected considering what has been suggested in the literature. In addition, several factors appear to influence the association of severity of renal

dysfunction and death at 1-year including: increased patient age, higher admission APACHE II scores in particular for sARF and ESRD patients, and admission type, in particular cardiac surgical admissions despite the highest fatality rates occurring in medical admissions. Patient sex does not appear to significantly influence the association of death at 1-year by severity of renal dysfunction.

7. Long-term survival for critically ill patients with sARF and by severity of renal dysfunction

For the purpose of simply describing the long-term survival function experiences of the total ICU cohort in an exploratory analysis, crude and stratified Kaplan-Meier survival function curves were performed. First, a stratified analysis exploring several factors that may influence the association of a diagnosis of sARF with long-term survival experience is presented. Long-term survival was defined as follow-up duration until patient death or follow-up time during the time of study completion, which was generally > 1-year for those patients that survived their episode of critical illness. The long-term case-fatality rate for sARF was 65% (157/240) and not considerable different from the case-fatality at 1-year. Likewise, the long-term fatality rate for all patients without a diagnosis of sARF was 24.9% (1356/5,453) and not significantly different from the 1-year fatality rate.

The diagnosis of sARF was associated with a higher long-term fatality rate compared with no sARF (crude RR 2.6, 95% CI, 2.4-2.9, $p<0.0001$) (Table 75).

Table 75. Long-term fatality rates for the total ICU cohort stratified by sARF.

	Alive (n=4,180)	Dead (n=1,513)
sARF (%)	83 (34.6)	157 (65.4)
No sARF (%)	4,097 (75.1)	1,356 (24.9)

Table 76. Age-specific long-term fatality rates for the total ICU cohort stratified by sARF.

Age	sARF (%)	No sARF (%)
≥ 65	87/125 (69.6)	926/2,721 (34.1)
< 65	70/115 (60.9)	430/2,732 (15.7)
Overall	157/240 (65.4)	1,356/4,097 (24.9)

The long-term fatality rates for those with sARF compared to those without a diagnosis of sARF across age stratified at ≥ 65 years demonstrated no evidence of confounding [crude RR 2.63 (95% CI, 2.4-2.9) vs. M-H adjusted 2.59 (95% CI, 2.3-2.8)]; however, evidence of effect modification (Table 76). For those aged < 65 years, the risk of long-term death with sARF was approximately 3.9 times greater than for those without a diagnosis of sARF [RR 3.9 (95% CI, 3.3-4.6)], whereas for those aged ≥ 65 years the risk of long-term death for those with sARF was approximately 2.0 times greater than those without a diagnosis if sARF [RR 2.0 (95% CI, 1.8-2.3)]. Although the long-term fatality rate of sARF was higher than without a diagnosis of sARF for each age stratum, the lower relative risk for sARF patients aged ≥ 65 years compared with sARF patients

aged < 65 years is likely attributable to the difference in fatality rates across age strata for those patients without a diagnosis of sARF.

The long-term fatality rate for those with sARF compared to those without a diagnosis of sARF stratified by patient sex demonstrated no significant evidence of confounding [crude RR 2.63 (95% CI, 2.4-2.9) vs. M-H adjusted 2.61 (95% CI, 2.4-2.9)] or effect modification (Table 77).

Table 77. Sex-specific long-term case fatality rates for the total ICU cohort stratified by sARF.

Sex	sARF (%)	No sARF (%)
Male	88/140 (62.9)	785/3,393 (23,1)
Female	69/100 (69)	571/2,060 (27.7)
Overall	157/240 (65.4)	1,356/4,097 (24.9)

Table 78. Age and sex-specific long-term fatality rates for the total ICU cohort stratified by sARF.

Sex	Age (years)	sARF (%)	No. without sARF (%)
Male	≥ 65	51/78 (65)	493/1,176 (42)
	< 65	33/62 (53)	226/1,724 (13)
Female	≥ 65	34/47 (72)	358/1,052 (34)
	<65	35/53 (66)	170/1,008 (17)

The long-term fatality rate for those with sARF compared to those without a diagnosis of sARF stratified by both age ≥ 65 years and sex demonstrated no evidence of confounding [crude RR 2.63 (95% CI, 2.4-2.9) vs. M-H adjusted RR

2.58 (95% CI, 2.3-2.8); however, evidence suggestive of effect modification of the association of long-term fatality and a diagnosis of sARF (Table 78). Specifically, the relative risk of long-term death was highest for males and females aged < 65 years [male: RR 3.94 (95% CI, 3.1-5.0); female: RR 3.64 (95% CI, 2.9-4.6)] when compared to both males and females aged ≥ 65 years [male: RR 2.11 (95% CI, 1.8-2.5); female: RR 1.96 (95% CI, 1.6-2.4)], respectively. Therefore, it would appear that the effect modification evident with age ≥ 65 years was preserved across strata of patient sex.

There was evidence to suggest that admission type both confounds [crude RR 2.63 (95% CI, 2.4-2.9) vs. M-H adjusted RR 2.03 (95% CI, 1.8-2.2)] and significantly effect modifies the association of long-term fatality with a diagnosis of sARF (Table 79). The stratified risk for long-term death for those with sARF compared to those without a diagnosis of sARF was highest for cardiac surgical admissions [RR 12.4 (95% CI, 8.8-17.5)] compared with non-cardiac surgical [RR 1.93 (95% CI, 1.5-2.5)] and medical [RR 1.78 (95% CI, 1.6-2.0)] admissions, respectively.

Table 79. Long-term fatality rates for total ICU cohort stratified by sARF and admission type.

	Long-term Case-Fatality Rate by Admission Type (%)		
	Medical	Non-cardiac Surgical	Cardiac Surgical
sARF	106/151 (70.2)	32/58 (55)	19/31 (61.3)
No sARF	846/2,143 (39.5)	416/1,454 (28.6)	91/1,844 (4.9)
Overall	901/2,294 (39.3)	404/1,512 (26.7)	92/1,875 (4.9)

The long-term fatality rate for those with sARF compared to those without a diagnosis of sARF stratified by APACHE II score ≥ 25 points demonstrated no significant evidence of confounding [crude RR 2.63 (95% CI, 2.4-2.9) vs. M-H adjusted 2.31 (95% CI, 2.1-2.6)] or effect modification (Table 80). The difference in the crude and M-H adjusted relative risk are of questionable clinical importance given that the 95% confidence limits for the RR overlap across strata of APACHE II score. Although the stratified risk for death for those with sARF compared to those without a diagnosis of sARF was higher for those with APACHE II scores ≥ 25 points [RR 2.3 (95% CI, 2.1-2.6)] compared to those with APACHE II scores < 25 points [RR 2.2 (95% CI, 1.5-3.1)], this difference in relative risk was of questionable statistical and clinical significance, suggesting that regardless of whether the APACHE II score was greater than or less than 25 points, a diagnosis of sARF resulted in a significant increased risk of long-term death compared to those without a diagnosis of sARF.

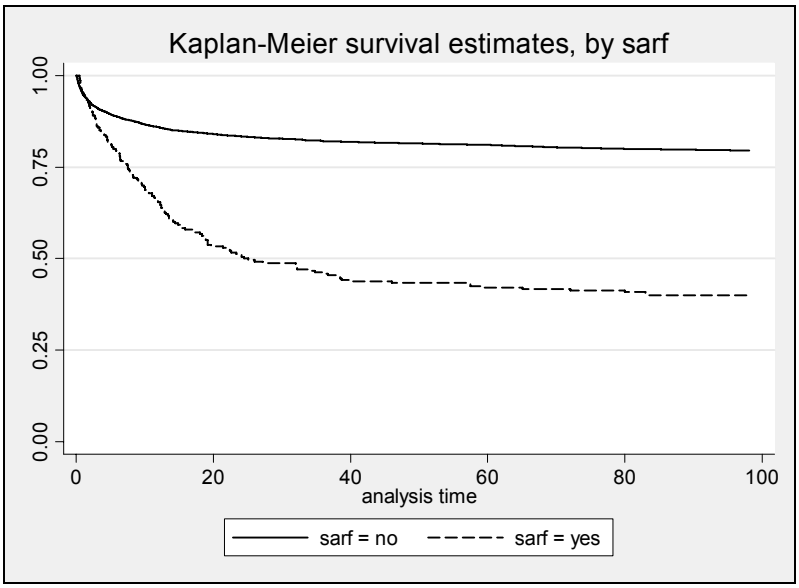
Table 80. Long-term fatality rates for total ICU cohort stratified by sARF and APACHE II score.

APACHE II Score (points)	sARF (%)	No sARF (%)
≥ 25	138/195 (70.8)	862/2,842 (30.3)
< 25	19/45 (42.2)	491/2,551 (19.2)
Overall	157/240 (65.4)	1,356/4,097 (24.9)

Therefore, to describe the long-term survival experience of critically ill patients with and without a diagnosis of sARF, crude Kaplan-Meier survival curves were generated. Furthermore, the Kaplan-Meier survival function curves for those with a diagnosis of sARF were further stratified by age ≥ 65 years, patient sex, age ≥ 65 years and patient sex, admission type, and APACHE II score ≥ 25 points. All Kaplan-Meier survival curves were truncated at 100 days due to the majority of deaths occurring within that period [145/157 (92%)]. There was a total of 7.6% (12/157) of deaths in patients with a diagnosis of sARF that occurred after 100 days. The majority (n=10) occurred in those patients with medical admissions while 2 occurred in patients with a cardiac surgical admissions; most were male (n=9) compared to female (n=3); most were aged ≥ 65 years (n=10) rather than < 65 years; and all had APACHE II scores ≥ 25 points (n=12).

Those patients with a diagnosis of sARF had a reduced survival function compared to patients with no sARF (Wilcoxon-rank, $p<0.0001$); however, this survival curve requires cautious interpretation due to concern of failure of the assumption of proportional hazards (Figure 28). The estimated median survival time for those with a diagnosis with sARF was 24.5 (95% CI, 18-40) days.

Figure 28. Crude Kaplan-Meier survival curve estimates stratified by sARF.



The estimated median time to death for patients with sARF stratified by age was not significantly different for those sARF patients aged < 65 years [22.6 (95% CI, 13.5-98.1) days] compared with those aged ≥ 65 years [27.2 (95% CI, 18.3-65.0) days] (Wilcoxon-rank, p=0.76) (Figure 29). Similarly, there was no significant difference in survival function estimates between males and females. For male patients with a diagnosis of sARF, the estimated median time to death was 25.1 (95% CI, 18.0-190) days, whereas for females the median time to death was 22.6 (95% CI, 12.7-36.7) days, respectively (Wilcoxon-rank, p=0.27) (Figure 30). Figure 31 demonstrates the estimated survival curves for sARF patients stratified by age ≥ 65 years and patient sex (Wilcoxon-rank, p=0.53).

Figure 29. Kaplan-Meier survival curve estimates for sARF patients stratified by age ≥ 65 years.

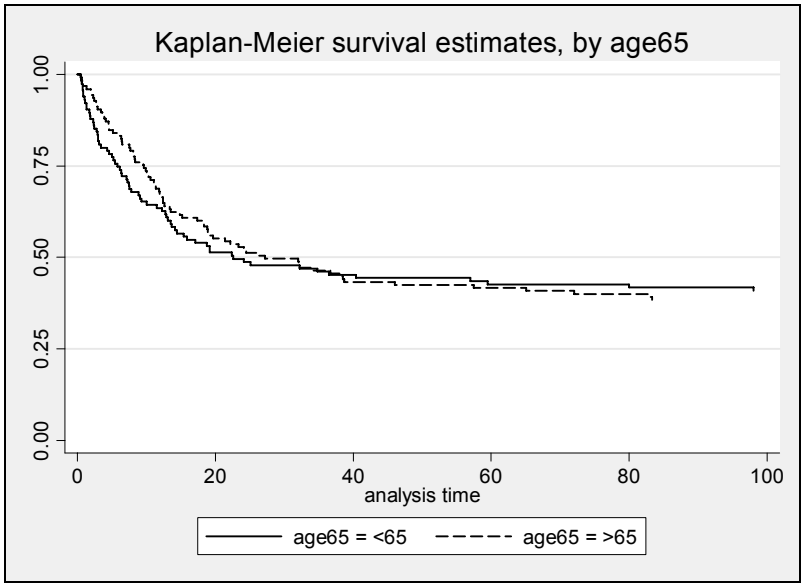


Figure 30. Kaplan-Meier survival curve estimates for sARF patients stratified by sex.

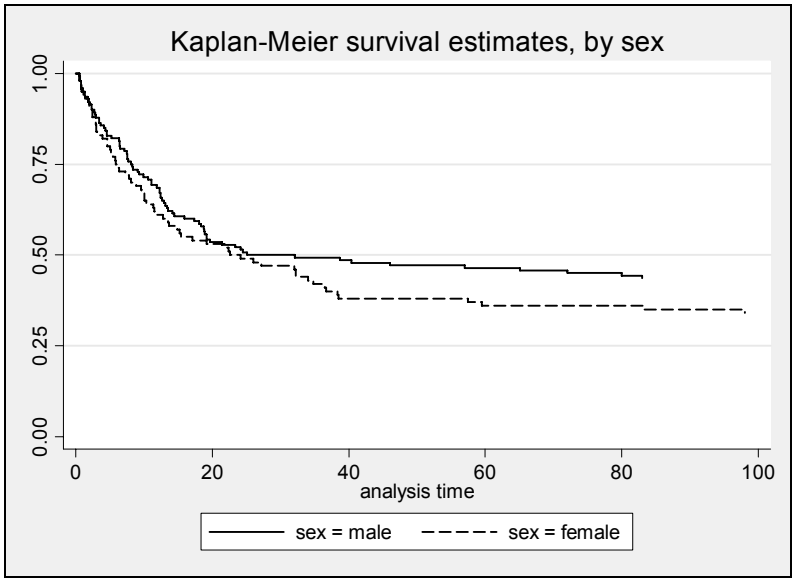
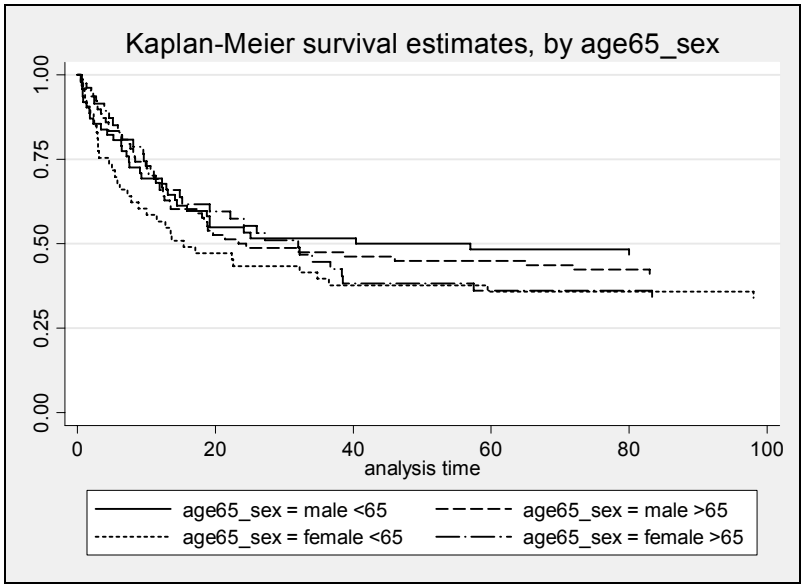


Figure 31. Kaplan-Meier survival curve estimates for sARF patients stratified by both sex and age ≥ 65 years.



There was no significant difference in survival function estimates for sARF patients stratified by admission type (Wilcoxon-rank, p=0.40) (Figure 32). The median time to death for patients with sARF stratified by admission type was 24.1 days for medical, 27.2 days for non-cardiac surgical, and 18.8 days for cardiac surgical admissions, respectively.

For the covariates age ≥ 65 years, patient sex, and admission type, the survival curves require cautious interpretation due to concern for violation of the assumption of proportional hazards.

Those sARF patients with APACHE II scores ≥ 25 points had a reduced survival compared with those with APACHE II scores < 25 points (Figure 33) (Wilcoxon-rank, p=0.002). There was no evidence to suggest violation of the assumption of proportional hazards. Thus, those patients with a diagnosis of

sARF and an APACHE II score ≥ 25 points had a median time to death of 19.1 (95% CI, 13.3-32.1) days (Figure 33). An estimate for the median time to death for sARF patients with an APACHE II score < 25 points was not possible because more than 50% were still alive at 100 days follow-up.

Figure 32. Kaplan-Meier survival curve estimates for sARF patients stratified by admission type.

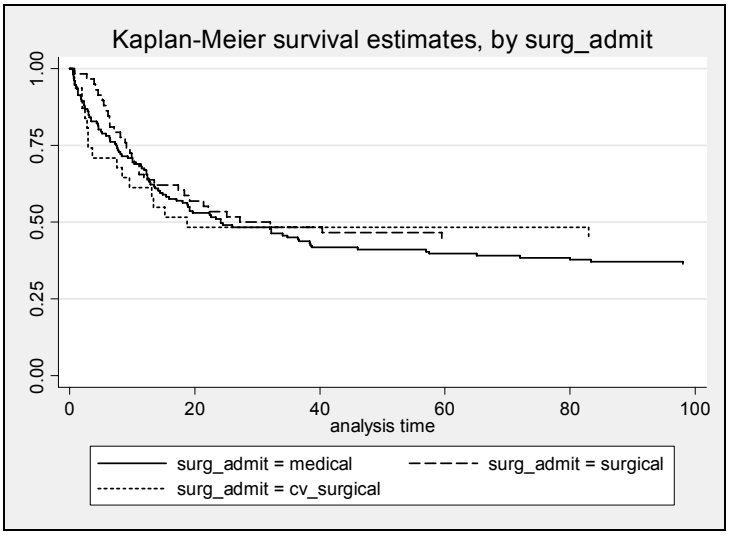
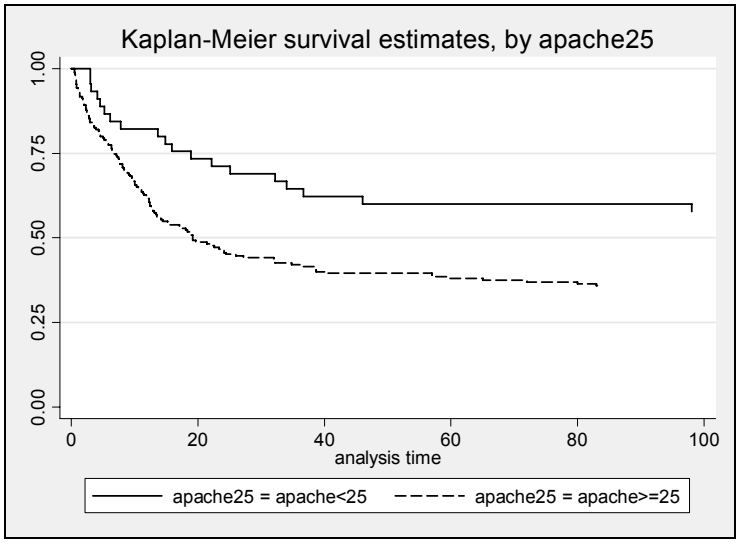
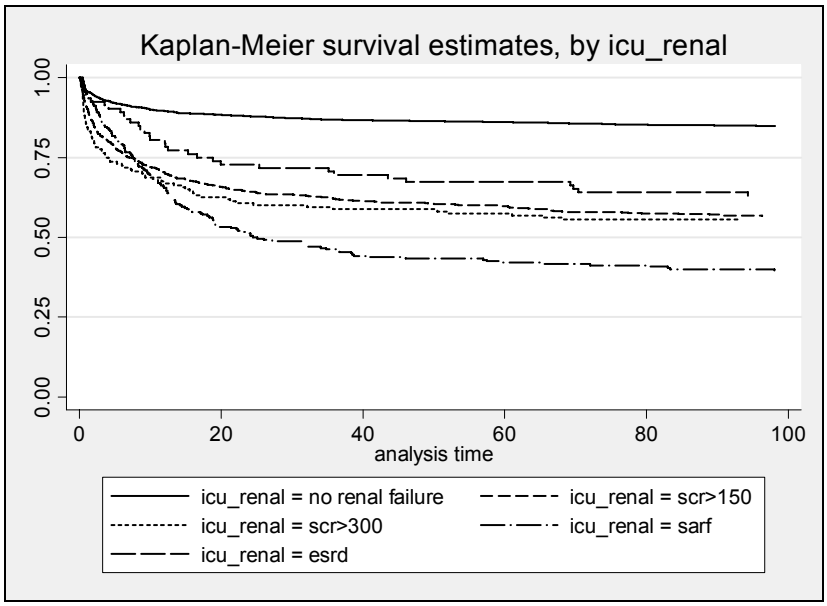


Figure 33. Kaplan-Meier survival curve estimates for sARF patients stratified by APACHE II score ≥ 25 points.



In addition to describing the long-term survival experience for adult critically ill patients stratified by a diagnosis of sARF, crude Kaplan-Meier survival curves were generated and stratified by severity of renal dysfunction (Figure 34). This Kaplan-Meier survival curve was stratified by severity of renal dysfunction and was truncated at 100 days. This time was chosen due to the majority of deaths having already occurred [1263/1513 (83%)] with no significant difference in the survival curves evident after this point.

Figure 34: Crude Kaplan-Meier survival function estimates for total ICU cohort stratified by severity of renal dysfunction.



Based on the crude survival function curves stratified by severity in renal dysfunction, there was evidence to suggest that those patients with more severe renal dysfunction had a reduced survival function when compared to those critically ill patients with no renal dysfunction (Wilcoxon-rank, $p<0.0001$). However, these survival curve estimates require cautious interpretation and are

exploratory only due to concern for violation of the assumption of proportional hazards. In particular, these estimated survival curves would suggest that the lowest survival function occurred in those patients with a diagnosis of sARF. Interestingly, there does not appear to be a significant difference noted for those patients with mild dysfunction (serum creatinine 150-299 μmol/L) when compared to those with moderate renal dysfunction (serum creatinine 300 μmol/L). In addition, those patients with a diagnosis of ESRD would appear to have had a crude survival function greater than those with mild or moderate renal dysfunction. Furthermore, when examining the crude survival function curves for patients with mild and moderate dysfunction compared with those for sARF there was evidence to suggest the survival function estimates change with time and are not proportional, specifically within the first 10-15 days following admission to an ICU (Figure 34). Thus, one plausible hypothesis generated from this data that may explain this finding was that those patients with mild and moderate renal dysfunction initially have lower survival function because they were not offered RRT and died or they had advanced life support measures withdrawn, whereas the survival function for those with a diagnosis of sARF were higher due to having had RRT initiated and perhaps a more intense or prolonged period of advance life support.

In summary, this exploratory analysis assessing the crude survival function of critically ill patients suggested a reduced survival for patients with a diagnosis of sARF compared with no sARF. Furthermore, when restricted to only

those patients with a diagnosis of sARF, there was no apparent difference in survival when stratified by age, sex, or admission type; however, there was evidence that a higher APACHE II score was associated with reduced survival.

In the exploratory analysis assessing the differences in crude survival stratified by severity of renal dysfunction, some interesting patterns emerged that may be hypothesis generating. Specifically, the lowest survival occurred in those patients with a diagnosis of sARF. In addition, there was no apparent difference in the survival function of those patients with mild or moderate dysfunction, though their survival was lower than those with no evidence of renal dysfunction. Interestingly, those patients with ESRD had a greater survival than those with all other forms of renal dysfunction. Finally, there was evidence that the first 10-15 days following admission to ICU represent an important determinant in survival and warrants further exploration in order to understand why the early survival for those with mild to moderate dysfunction was lower than those with sARF.

8. Renal recovery outcome for patients with sARF

Of patients with sARF who survived to ICU and hospital discharge, 38% (46/120) and 68% (66/97) had recovered renal function and were RRT independent, respectively. The rates of renal recovery in survivors at 28 and 90 days were 55% (64/117) and 71% (69/97), respectively. Of the 87 patients with a diagnosis of sARF who survived to at least 1-year following admission to ICU, 78% (68/87) became independent of RRT after a median (IQR) duration of 11 (3-

20) days of RRT, while the remainder continued to receive chronic RRT. Thus at 1-year following the diagnosis of sARF, only 28% (68/240) were alive and free from RRT. In order to explore potential factors associated with renal recovery at 1-year, a detailed stratified analysis is presented.

The median (IQR) age for those recovering renal function compared with those requiring long-term RRT among those diagnosed with sARF was not significantly different [66.4 (60.2) vs. 62.7 (48.5-71.8) years, p=0.76), respectively (Figure 35 and Table 81). There was some evidence to suggest, though not significant, that renal recovery is more likely to occur in patients aged < 65 years compared with those aged ≥ 65 years [83% vs. 73%, p=0.30], respectively.

Figure 35. Boxplot of age stratified by recovery of renal function at 1-year.

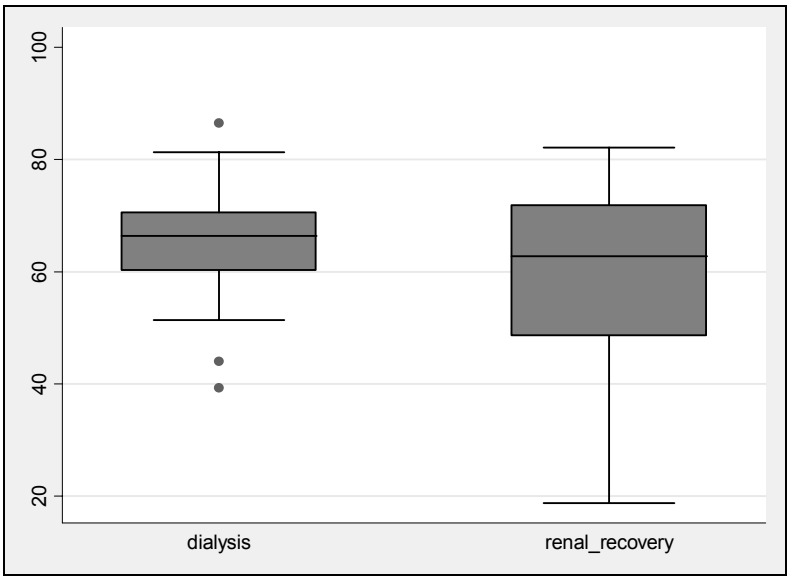


TABLE 81. Long-term renal recovery status stratified by age ≥ 65 years.

Age (years)	Renal Recovery (%)	Dialysis Dependent (%)
≥ 65	29/40 (72.5)	11/40 (27.5)
< 65	39/47 (83)	8/47 (17)
Overall	68/87 (78.2)	19/87 (21.8)

There was evidence to suggest male patients are approximately 1.5 times more likely to recover renal function and become independent of RRT compared with female patients [RR 1.53 (95% CI, 1.1-2.1, p=0.002)] (Table 82) Furthermore, there was some evidence to suggest that age ≥ 65 years may represent an effect modifier of the association of long-term renal recovery and patient sex; however, there was no significant evidence of confounding [crude RR 1.53 (95% CI, 1.1-2.1) vs. M-H adjusted RR 1.56 (95% CI, 1.1-2.1) (Table ZZ). Thus, male patients aged ≥ 65 years are more likely to recover renal function compared with female patients aged ≥ 65 years [RR 2.3 (95% CI, 1.1-4.7)] and this association would appear similar though not as strong when comparing renal recovery by patient sex for those aged < 65 years [RR 1.2 (95% CI, 0.9-1.7)];. Further, this effect modification was most likely attributable to the low rate of renal recovery for female patients aged ≥ 65 years, compared to all other groups and a surprisingly high rate of renal recovery for male patients in the same age group (Table 83).

Table 82. Long-term renal recovery status stratified by patient sex.

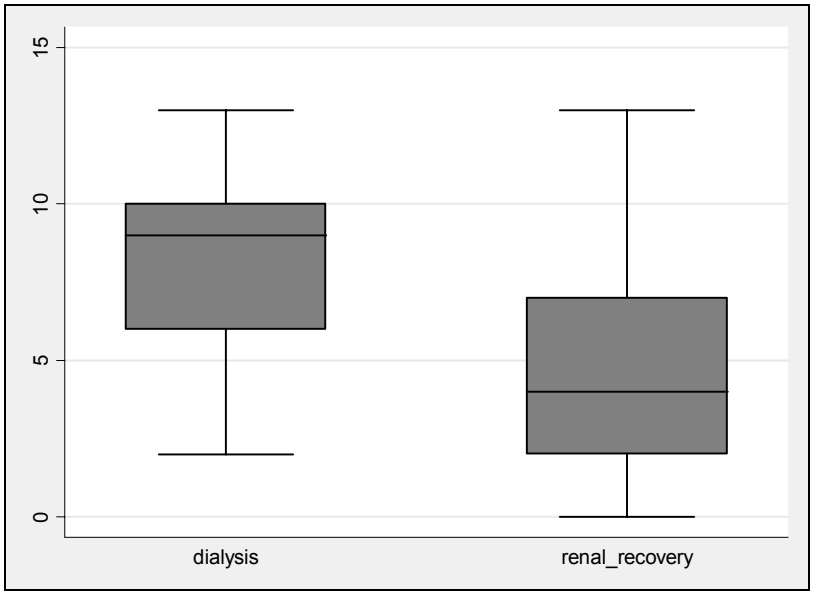
Sex	Renal Recovery (%)	Dialysis Dependent (%)
Male	50/56 (89.3)	6/56 (10.7)
Female	18/31 (58.1)	13/31 (41.9)
Overall	68/87 (78.2)	19/87 (21.8)

Table 83. Age and sex-specific long-term renal recovery rates.

Age (years)	Renal Recovery Rates stratified by patient sex (%)	
	Male	Female
≥ 65	24/27 (88.9)	5/13 (38.4)
< 65	26/29 (89.6)	13/18 (72.2)
Overall	50/56 (89.3)	18/31 (58.1)

There was evidence that Charlson co-morbidity index was an important factor contributing to the long-term renal recovery of patients diagnosed with sARF. The mean (±SD) Charlson co-morbidity index for those recovering renal function was significantly lower than for those who require long-term RRT therapy [4.6 (3.4) vs. 7.7 (3.1) points, p=0.0006], respectively (Figure 35).

Figure 36. Boxplot of Charlson co-morbidity index stratified by recovery of renal function at 1-year.



Thus, a higher baseline Charlson co-morbidity index was associated with a lower rate of long-term renal recovery that become more evident when the Charlson co-morbidity index scored are stratified by quartiles (Table 84). There was no evidence to suggest that the association of renal recovery and Charlson co-morbidity index score was confounded or effect modified by any of age, sex, APACHE II score, admission type, etiology of sARF or modality of RRT.

TABLE 84. Long-term renal recovery rates stratified by quartiles of Charlson co-morbidity index.

Charlson co-morbidity index (points)	Renal Recovery Rate (%) (n=68)
0-3	30 (44.1)
4-6	19 (27.9)
7-9	13 (19.1)
10-16	6 (8.8)

As may be expected, patients with pre-existing diabetes mellitus appeared to have a lower rate of long-term renal recovery compared to those with no pre-existing diabetes mellitus [65% vs. 87% (crude RR 0.75 (95% CI, 0.57-0.98), p=0.02], respectively. However, the association between renal recovery and diabetes mellitus was confounded by the presence of pre-existing co-morbid illness in general as measured by the Charlson co-morbidity index. The M-H adjusted relative risk for renal recovery for the presence of diabetes mellitus was not significant [M-H adjusted RR 0.96 (95% CI, 0.67-1.4), p=0.6] after adjusting for patient baseline Charlson co-morbidity score. There was no evidence that the association of diabetes mellitus and long-term renal recovery was confounded or effect modified by any of age, sex, APACHE II score, admission type, etiology of sARF or modality of RRT.

There was no significant association of admission APACHE II scores and the rates of long-term renal recovery with APACHE II score as a continuous

variable [mean (±SD) APACHE II score 30.3 (8.7) vs. 29.8 (7.9), p=0.8] or stratified at ≥ 25 points [crude RR 1.1 (95% CI, 0.8-1.4), p=0.6], respectively (Figure 37 and Table 85).

Figure 37. Boxplot of APACHE II scores stratified by long-term renal recovery.

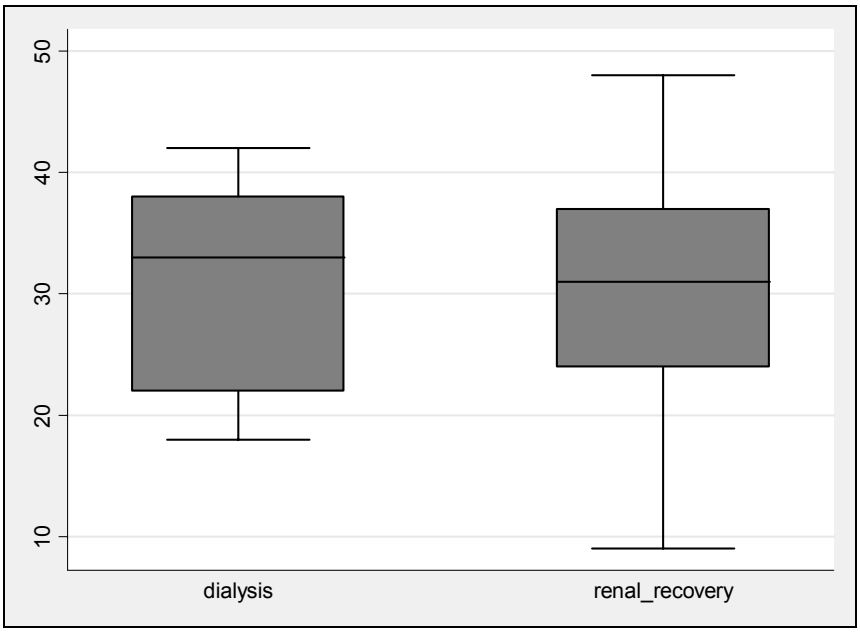


Table 85. Long-term renal recovery status stratified by APACHE II score ≥ 25 points.

APACHE II score (points)	Renal Recovery (%)	Dialysis Dependent (%)
≥ 25	49/61 (80.3)	12/61 (19.6)
< 25	19/26 (73.1)	7/26 (26.9)
Overall	68/87 (78.2)	19/87 (21.8)

There was no evidence to suggest significant confounding or effect modification of the association of renal recovery and APACHE II score by any of

age ≥ 65 years, patient sex, etiology of sARF or modality of RRT. There was significant evidence of effect modification by admission type. Specifically, the relative risk of requiring long-term RRT for those sARF patients with APACHE II scores ≥ 25 points was greatest in cardiac surgical compared with medical or non-cardiac surgical admissions, respectively.

The rates of long-term renal recovery appeared higher for those with an intra-renal etiology of sARF compared to those patients diagnosed with a pre-renal etiology of sARF; however, this was not statistically significant and should be interpreted with caution due to the small number of patients surviving at 1-year with pre-renal sARF (Table 86). As discussed previously, the only patient with a post-renal etiology of sARF was male, aged 57.5 years with an APACHE II score of 31 points admitted to the CVICU following cardiac surgery. As expected with a post-renal etiology for sARF, this patient recovered renal function and became independent from RRT by 1-year.

Table 86. Long-term renal recovery status stratified by etiology of sARF.

Renal Recovery Status	Etiology of sARF		
	Pre-renal	Intra-renal	Post-renal
Renal Recovery (%)	6/10 (60)	61/76 (80.2)	1/1 (100)
Dialysis Dependent (%)	4/10 (40)	15/76 (19.7)	-
Survival at 1-year (%)	10/36 (27.8)	76/203 (37.4)	1/1 (100)

There was no evidence that patient age ≥ 65 years represented a significant confounder [crude RR 1.33 (95% CI, 0.8-2.2) vs. M-H adjusted 1.31 (95% CI, 0.8-2.2)] or effect modifier of the association of etiology of sARF and recovery renal function.

Table 87. Long-term rates of renal recovery stratified by etiology of sARF and age ≥ 65 years.

Age (years)	Etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
≥ 65	3/6 (50)	26/61 (42.6)
< 65	3/6 (50)	35/61 (57.3)
Overall	6/10 (60)	61/76 (80.2)

Table 88. Long-term rates of renal recovery stratified by etiology of sARF and patient sex.

Sex	Etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
Male	4/6 (60)	45/61 (73.8)
Female	2/6 (40)	16/61 (26.2)
Overall	6/10 (60)	61/76 (80.2)

Patient sex appeared to have a significant association with etiology of sARF and long-term renal recovery. The rates of renal recovery were significantly higher for male patients compared with female patients for both pre-renal and intra-renal etiology of sARF (Table 88). These data suggest that patient sex was not a significant confounder [crude RR 0.75 (95% CI, 0.5-1.3) vs. M-H adjusted 0.84 (95% CI, 0.5-1.3)]; however, perhaps more importantly, was

an effect modifier of the association of renal recovery and etiology of sARF demonstrating that male sARF patients with a pre-renal etiology were significantly more likely to recover renal function compared to female patients with a pre-renal etiology for sARF [males: RR 1.13 (95% CI, 1.0-1.3) vs. females: RR 0.52 (95% CI, 0.2-1.7)], respectively.

There was no evidence that any of APACHE II score, modality of RRT or the presence of liver disease were significant confounders or effect modifiers of the association of etiology of sARF and renal recovery.

There was evidence that Charlson co-morbidity index influenced the association of etiology of sARF and renal recovery. Although there was no evidence of confounding [crude RR 0.75 (95% CI, 0.5-1.3) vs. M-H adjusted RR 0.79 (95% CI, 0.5-1.3)], there was evidence of effect modification. Those sARF patients with both pre-renal and intra-renal etiologies of sARF with Charlson co-morbidity scores < 4 points were more likely to recovery renal function [Charlson index < 4 points: RR 1.11 (95% CI, 1.0-1.2) vs. Charlson index $\geq$ 4 points: RR 0.68 (95% CI, 0.3-1.4)], respectively (Table 89).

Table 89. Long-term rates of renal recovery stratified by etiology of sARF and Charlson co-morbidity index.

Charlson co-morbidity index score (points)	Etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
≥ 4	4/8 (50)	33/45 (73.3)
< 4	2/2 (100)	28/31 (90.3)
Overall	6/10 (60)	61/76 (80.2)

In addition, there was evidence of influence of a diagnosis of septic shock on the association of renal recovery and etiology of sARF. Again, no evidence to suggest confounding [crude RR 0.75 (95% CI, 0.5-1.3) vs. M-H adjusted RR 0.84 (95 % CI, 0.5-1.4)]; however, clear evidence to suggest effect modification. Those sARF patients with septic shock were more likely to recovery renal function compared to those without septic shock for both pre-renal and intra-renal etiologies for sARF (Table 90)

Table 90. Long-term rates of renal recovery stratified by etiology of sARF and septic shock.

Septic shock (n=35)	Etiology of sARF	
	Pre-renal (%)	Intra-renal (%)
Yes	1/1 (100)	32/34 (94.1)
No	5/9 (55.6)	29/42 (69.0)
Overall	6/10 (60)	61/76 (80.2)

However, the results for the influence of septic shock on the association of Charlson co-morbidity index and renal recovery require cautious inference given

that the confidence interval for both stratified estimates cross over one another and due to the small sample of patients in the stratified groups with a pre-renal etiology of sARF, in particular only 1 patient with a diagnosis of septic shock with a pre-renal etiology of sARF who recovered renal function.

The long-term rates of renal recovery appeared influenced by the modality of RRT employed during ICU admission (Table 91). The modalities are stratified by sARF patients having received only CRRT, only IHD, or having received both CRRT and IHD, and therefore are categorized as mutually exclusive. Specifically, the rates of renal recovery and RRT independence are significantly higher for those patients that received CRRT as the only form of renal replacement compared to those patients diagnosed with sARF having received either IHD or both CRRT and IHD (Table 92).

Table 91. Long-term renal recovery rates stratified by modality of renal replacement therapy.

Renal Recovery Status	Renal Replacement Therapy Modality		
	CRRT only	IHD only	Both CRRT and IHD
Renal Recovery (%)	28/30 (93.3)	23/34 (67.7)	17/23 (73.9)
Dialysis Dependent (%)	2/30 (6.7)	11/34 (32.3)	6/23 (26.1)
Survival at 1-year (%)	30/147 (20.4)	34/48 (70.8)	23/45 (51.1)

Table 92. Crude relative risk for renal recovery at 1-year stratified by each category of renal replacement therapy modality.

RRT Modality	Relative Risk	95% CI	p-value
CRRT only	1.33	1.1-1.6	0.01
IHD only	0.80	0.6-1.0	0.07
Both CRRT and IHD	0.93	0.7-1.2	0.57

Abbreviations: RRT = renal replacement therapy; CI = confidence interval; CRRT = continuous renal replacement therapy; IHD = intermitted hemodialysis.

Furthermore, when modality of renal replacement was stratified by either any CRRT or IHD only, those sARF patients having received CRRT were 1.3 times more likely to recovery renal function compared to those having received IHD only [crude RR 1.26 (95% CI, 1.0-1.6), p=0.07); however, this was of borderline clinical significance. There was no significant evidence by stratified analysis to suggest that the association of long-term renal recovery and renal replacement modality was confounded or effect modified by any of age ≥ 65 years, patient sex, APACHE II score ≥ 25 points, admission type, Charlson co-morbidity index ≥ 4 points, diabetes mellitus, liver disease, oliguria or etiology of sARF.

There was evidence that renal recovery was significantly associated with the presence or absence of a diagnosis of septic shock in sARF patients (Table 93). In fact, the rates of long-term renal recovery were 1.4 times more likely for those with septic shock compared to those without septic shock [RR 1.4 (95% CI, 1.1-1.7), p=0.003].

Table 93. Long-term renal recovery status stratified by the presence of septic shock.

Septic Shock (n=35)	Renal Recovery (%)	Dialysis Dependent (%)
Yes	33/35 (94.2)	2/35 (5.7)
No	35/52 (67.3)	17/52 (32.7)
Overall	68/87 (78.2)	19/87 (21.8)

There was no evidence of significant confounding or effect modification of the association of renal recovery and the presence of septic shock by any of APACHE II score, admission type, diabetes mellitus, liver disease, etiology of sARF, modality of renal replacement, pre-dialysis serum creatinine or oliguria. Interestingly, age $\geq$ 65 and patient sex appeared to effect modify the association of renal recovery and a diagnosis of septic shock in sARF patients; however, many of the strata have small numbers of patients with complete separation of the data, thus making strong inferences difficult (Table 94).

Table 94. Long-term renal recovery rates stratified by the age $\geq$ 65 years, patients sex and septic shock.

Sex	Age (years)	Septic Shock (%)	
		Yes	No
Male	≥ 65	16/16 (100)	8/11 (72.7)
	< 65	8/8 (100)	18/21 (85.7)
Female	≥ 65	2/2 (100)	3/11 (27.3)
	<65	7/9 (77.8)	6/9 (66.7)

There was some evidence to suggest that those sARF patients that had received aminoglycosides were more likely to recover renal function compared to those sARF patients not having received aminoglycosides [RR 1.28 (95% CI, 1.1-1.5), p=0.11]; however, the association was of questionable statistical and clinical significance due to the small number of sARF patients exposed to aminoglycosides during the surveillance period from which only 1 patient ultimately required long-term RRT (Table 95). There was no evidence of significant confounding or effect modification of the association of aminoglycoside use and renal recovery by any of age $\geq$ 65 years, APACHE II score $\geq$ 25 points, admission type, Charlson co-morbidity index $\geq$ 4 points, diabetes mellitus, liver disease, septic shock, pre-dialysis serum creatinine or oliguria. There was evidence of effect modification by patients sex with female sARF patients having received aminoglycosides more likely to recovery renal function than males who had received aminoglycosides [females: RR 2.0 (95% CI, 1.4-2.9) vs. males: RR 1.04 (0.9-1.3)], respectively. This was mainly attributable to the fact that of the 5 female sARF patients who had been exposed to aminoglycosides, all recovered renal function. Thus, this finding was of questionable clinical significance.

Table 95. Long-term renal recovery status stratified by the use of aminoglycosides.

Aminoglycosides (n=17)	Renal Recovery (%)	Dialysis Dependent (%)
Yes	17/18 (94)	1/17 (5.6)
No	51/69 (73.9)	18/69 (26.1)
Overall	68/87 (78.2)	19/87 (21.8)

The median (IQR) pre-dialysis serum creatinine was significantly higher for those sARF patients requiring long-term RRT compared with those sARF patients recovering renal function [531 (439-645) μmol/L vs. 436 (322-556) μmol/L, p=0.03], respectively (Table 96). The rate of renal recovery was 1.2 times more likely for those sARF patients with a pre-dialysis serum creatinine level in the ranges of 150-399 μmol/L compared to those with a pre-dialysis serum creatinine level ≥400 μmol/L [RR 1.21 (95% CI, 1.0-1.5), p=0.2); however, this was of questionable statistical significance. There was no evidence to suggest either confounding or effect modification of the association of pre-dialysis serum creatinine and renal recovery by any of age ≥ 65 years, patient sex, APACHE II score ≥ 25 points, Charlson co-morbidity index ≥ 4 points, diabetes mellitus, liver disease, septic shock, etiology of sARF, or modality of renal replacement.

Table 96. Renal recovery rates stratified by quartiles of pre-dialysis serum creatinine.

Serum creatinine (μmol/L)	Number of patients (%)	Renal Recovery (%)
150-264	14 (16.1)	13/14 (92.9)
265-399	13 (14.9)	11/13 (84.6)
400-514	29 (33.3)	23/29 (79.3)
≥ 515	31 (35.6)	21/31 (67.7)
Overall	87 (00)	68/87 (78.2)

There was evidence that admission type influenced the association of pre-dialysis serum creatinine and renal recovery. Although there was no evidence of confounding [crude RR 1.21 (95% CI, 1.0-1.5) vs. M-H adjusted RR 1.16 (1.0-1.4)], there was evidence of effect modification. Specifically, renal recovery was more likely for those sARF patients with low pre-dialysis serum creatinine levels with cardiac surgical [RR 1.71 (95% CI, 1.1-2.8)] compared with non-cardiac surgical [RR 1.54 (95% CI, 1.1-2.1)] and medical admissions [RR 1.0 (95% CI, 0.8-1.3)], respectively. Although these data suggest that those sARF patients with medical admissions are less likely to recovery renal function regardless of pre-dialysis serum creatinine when compared with cardiac surgical and non-cardiac surgical admissions, this requires some cautious interpretation due to small numbers of patients in both the cardiac surgical (n=2) and non-cardiac surgical (n=6) with serum creatinine levels in the range 150-399 μmol/L, who all recovered renal function.

There was no evidence to suggest a difference in the median (IQR) number of days from either admission to hospital or to ICU prior to a diagnosis of sARF and long-term renal recovery (Table 97). In contrast, there was evidence that sARF patients recovering renal function had significantly longer median (IQR) hospital and ICU lengths of stay compared with those sARF patients remaining on chronic RRT (Table 98).

Table 97. ICU and hospital length of stay in days prior to diagnosis of sARF and stratified by long-term renal recovery.

Median (IQR) Length of Stay (Days)	Total Cohort (n=87)	Renal Recovery (n=68)	Dialysis Dependent (n=19)	p-value
ICU	1 (0-3)	1 (0-3)	1 (0-3)	0.4
Hospital	4 (1-10.5)	4 (1-9)	3 (1-7)	0.5

Table 98. Total ICU and hospital length of stay for sARF patients stratified by long-term renal recovery.

Median (IQR) Length of Stay (Days)	Total Cohort (n=87)	Renal Recovery (n=68)	Dialysis Dependent (n=19)	p-value
ICU	8.6 (3.2-17.4)	11.8 (4..0-19.5)	4.9 (2.2-12.4)	0.08
Hospital	39.5 (23.5-71)	40 (24.7-71)	15 (6-27)	0.09

In summary, though the case-fatality rate for sARF is high, in those patients that survive, the majority proceed to renal recovery and independence from RRT by 1-year.

In general, by stratified analysis, the rates of renal recovery appear to be higher in those males patients aged < 65 years, patients with lower pre-existing co-morbid illness, patients with an intra-renal etiology for sARF in particular with a low Charlson co-morbidity index or a diagnosis of septic shock, patients having received either CRRT only or in combination with IHD, and in those sARF patients with a diagnosis of septic shock.

H. DISCUSSION

This is the first study to provide an annual incidence rate of sARF in a Canadian and North American population. This study used a population-based cohort design where all patients with sARF were identified in a well-defined population in order to minimize the presence of selection bias, a potential limitation identified in other similar studies assessing the incidence of ARF or sARF. The annual incidence of sARF in the CHR of 11.0 per 100,000 population per year is similar to that reported from Australia, 8.0-13.4 per 100,000 and higher than that reported from Europe, 4.2-8.0 per 100,000, respectively.[3, 11, 20, 32] The higher incidence of sARF reported in this study compared with those studies from Europe may be attributed to several differences in the studies. First, the European studies failed to clarify whether the study ICUs are closed units managed by attending intensive care clinicians only, whereas in the CHR, all ICU patients are managed under the direct supervision of intensive care clinicians. This may be important when considering there may be significant differences in

patient populations under study, in particular with respect to severity of illness or admission type. Furthermore, this may impact on the decision process for initiation of RRT. Second, in many ICUs in Europe, RRT is prescribed by attending consultant nephrologists and not the intensive care clinicians; therefore, there may be significant differences in the understanding of the indication for RRT in critically ill patients and prescription of RRT when compared to prescription of chronic RRT for ESRD. In the CHR, the decision to initiate RRT and the prescription of RRT is under the direct supervision of the intensive care clinician. Furthermore, in the CHR, a regional protocol has been implemented to aid the intensive care clinicians in the initial prescription and modality of anticoagulation of RRT, specifically CRRT only, of which the majority of patients will receive, that may have allowed for earlier and more aggressive implementation when compared with other centers, specifically in Europe, without similar protocols. [87] Finally, these other studies are potentially biased due to failure in clearly defining the geographic boundaries and classification of residency status of the study referral population for which the incidence of sARF was determined.[7, 11, 26] This was unlikely to be a major source of bias in the present study because in the CHR, as all critical care services are provided by ICUs included within this surveillance and the CHR is geographically relatively isolated as a single provider of healthcare, thus the calculated incidence from this study should be accurate and unbiased as outlined in the results section.

Therefore, this study is the first to clearly establish the major burden of disease attributable to sARF in a Canadian and North American population.

Recent consensus recommendations for defining and categorizing ARF have been presented; however have not been prospectively validated with long-term outcomes such as mortality or renal recovery at 1-year.[86] Thus, the primary outcome for this study was ARF severe enough, in the opinion of the treating intensivist, to warrant the initiation of RRT. Severe acute renal failure was selected as the primary case-definition for this study for two important reasons. First, the initiation of RRT in critically ill patients has clinical relevance both in terms of severity of illness but also in terms of utilization of resources. Thus, a diagnosis of sARF and institution of RRT represents a considerable escalation in patient management. Second, sARF was selected principally due to the greater simplicity for potential generalizing the results of this study across similar multi-disciplinary critically ill patient populations or at the very least representing a valid account of the incidence of sARF in critically ill patients for which other ICUs or perhaps population-based studies can use to compare with. The indications and threshold for initiation of RRT in critically ill patients with multi-organ dysfunction admitted to an ICU may differ when compared with indications in patients with single-organ sARF, in particular as mentioned previously in closed versus open ICUs. Although this has yet to be prospectively studied, one important aspect of this difference may relate specifically to the decision of the attending intensivist to initiate RRT, a factor not addressed in this study. Further, there is heterogeneity

across ICUs regarding who prescribed RRT: the attending intensivist or consulting nephrologist. However, in this regional critical care system, as mentioned, the decision to initiate RRT is made by the attending intensivist only, and a regional protocol has been implemented to guide in the initial prescription of RRT.[87]

1. Risk Factors for sARF

This study has demonstrated that the incidence rates for sARF in the CHR are significantly higher in males compared with females. Furthermore, this difference in incidence between males and females was most evident for older compared with younger patients. One plausible explanation, though only speculation, for this finding may be that fewer females, in particular in older age categories are offered RRT compared to their male counterparts. This may represent an identifiable determinant of health in terms of equality and access to medical services for females compared with males that, if in fact true, would warrant further study.

A novel aspect of this study was that several selected underlying co-morbid conditions were determined to be associated with an increased risk for development of sARF. While previous investigators have suggested that several factors, most notably increasing age, pre-existing renal insufficiency, co-morbid liver or cardiac disease, cancer, sepsis, and greater severity of illness upon admission to ICU as assessed by APACHE II scores are potential risk factors for

sARF, no previous studies have been designed to actually determine and quantify risk in a general population.[6, 11, 16, 21, 43] This study has shown that critically ill patients with underlying co-morbid illnesses, specifically those with pre-existing heart disease, stroke, pulmonary disease and alcohol abuse were at higher risk for developing sARF. Thus, critically ill patients with these co-morbidities may represent a target population for surveillance or earlier interventions that may prevent sARF. However, as previously discussed, there are limitations when considering these calculated risk factors for sARF. First, the estimates for the prevalence of selected underlying co-morbid conditions were taken from Canadian and United States survey data and may be prone to sampling error. However, this is not likely a major source of error as each of these conditions remained significant risks for sARF in a sensitivity analysis where the underlying population prevalence was doubled to account for potential error in estimated prevalence. Second, the calculated incidence rates in this study are also dependent on the assumption of accuracy in the counts of the dynamic population of the CHR over the 3-years duration of the study. Third, the incidence rate ratio calculations for individual risks for sARF are unadjusted for potential confounders, in particular age, sex and other co-morbidities. Specifically, some patient's risk of sARF may be confounded or modified by the presence of ≥ 1 underlying co-morbid conditions (i.e. cardiac and pulmonary disease). Although several prior hospital-based studies have attempted to define risk factors for sARF at the time of admission to ICU by multivariate analysis,

none of these studies were population-based, none focused primarily on sARF and none assessed general population risks for sARF, therefore, significantly limiting there inference. [6, 11, 12, 16, 18, 27, 29] This study was not able to assess the association of general population risk factors and the diagnosis of sARF while adjusting for several confounders and/or assessing for the presence of effect modifiers in a multivariate model due to the impracticality of needing to obtain specific medical information for the entire population of the CHR. Conduct of a nested case-control study would represent one method to assess the association between several co-morbid factors and the risk for development of sARF. As previously discussed, such a study would be difficult to perform and potentially prone to bias. Specifically, one difficulty of performing a case-control study would be identifying and selecting representative controls from the source population (i.e. CHR). Further, a case-control design would not allow direct calculation of the incidence and mortality rates of sARF in the CHR; as was performed in the cohort design used for this study.

Exposure to various nephrotoxins, specifically radiocontrast media, aminoglycosides and amphotericin, could potentially contribute to and/or perpetuate renal injury and need for RRT in critically ill patients.[88, 89] Although this study was unable to demonstrate an association with long-term mortality or renal recovery outcome, there was notably a high rate of exposure to potential nephrotoxins, specifically the administration of radiocontrast media prior to or during RRT in the ICU. The administration of radiocontrast media to critically ill

patients is common and represents a potential preventable factor that may contribute to the development of sARF; however, the incidence of radiocontrast-induced nephropathy or the contribution of radiocontrast media to sARF in this population remains unknown. This represents an important area warranting further investigation, results of which that may have clinically and economically important implications.

2. Mortality outcome for critically ill patients with sARF

This is the first study to clearly describe the annual population-based mortality rates associated with sARF using the CHR as the source population. Further, this study has demonstrated that the annual mortality rates for sARF are higher in males compared with females, specifically in older compared with younger patients.

Most studies of sARF in the critically ill have focused on death and rates of renal recovery at ICU and hospital discharge, therefore often only viewing sARF as an illness with only immediate and short-term implications.[3, 4, 11, 16, 17, 20, 32, 40, 47] However, assessment of these outcomes at the time of discharge from hospital may provide a biased underestimation of the overall burden of disease attributable to sARF, particularly in jurisdictions where patients are transferred to lower acuity hospitals once critical illness has resolved. Data from this study indicates that, while the majority of deaths occur early, specifically in the non-cardiac surgical and cardiac surgical population, critically ill patients with sARF

may remain ill with an increased risk for death for a duration greater than the total ICU or hospital length of stay and that use of such lengths of follow-up may underestimate the burden of disease. This has been similarly shown with sepsis and septic shock, where patients exhibit an increased risk of death for periods clearly longer than duration of hospitalization.[90-92] Thus, the use of hospital discharge as the primary time to determine mortality and long-term renal recovery is limited and potentially introduces bias in these previous studies. Clearly, there is evidence of considerable variation in follow-up duration in this study cohort and ascertainment of survival status and renal recovery at 1-year allows for greater determination of burden of illness attributable to sARF, despite the majority of patients deaths having occurred by 90 days. Therefore, clearly defined long-term outcomes, such as the overall death at 1-year of 64% and the overall rate of renal recovery at 1-year in survivors of 78% demonstrated in this study, provides a more accurate and informative description of the morbidity and mortality associated with sARF and admission to an ICU. This study is the first to describe both the long-term mortality outcome and long-term prognosis for renal recovery in critically ill patients with sARF. This study would be further strengthened if discharge location (i.e. independent living vs. long-term care) and long-term quality of life outcomes had been determined. The study by Korkeila *et al* is the only to describe the quality of life (QoL) outcome at 6-months for critically ill patients surviving an episode of sARF.[3] Although the total cohort was small and the response rate was 50% to mailed questionnaires, thus limiting any

significant inferences, the overall QoL was reportedly good, with loss of energy and limited physical mobility the most common complaints. These results identify an area requiring further investigation when considering that the decision by the attending intensivist to initiation of RRT therapy may in fact be modified by knowledge that this cohort of survivors were predominantly discharged to long-term care facilities, were not able to function independently or perhaps experience a poor QoL.

This study has identified several important factors associated with an increased risk of death at 1-year for patients with a diagnosis of sARF by stratified analysis. Note surprisingly, the case-fatality at 1-year of sARF were significantly higher in older patients, those with higher admission APACHE II scores and in those designated as medical compared with non-cardiac surgical or cardiac surgical admissions. However, one novel finding of this study not previously reported in the literature was the contribution of a Charlson co-morbidity index ≥ 4 points to an increased risk of death at 1-year, in particular once adjusted for age and sex.[59] A level of 4 points was selected due to stratified analysis demonstrating no significant further increase in case-fatality rates for Charlson co-morbidity index scores at levels above 4 points. Previous hospital-based studies have included prior health status as an independent predictor of death; however, this was generally only assessed by use of the chronic health points component of the APACHE II score or the McCabe scale.[12, 13, 21] Although Metcalfe *et al* reported the median Charlson co-morbidity index score for patients

with ARF in their small population-based study; results were not assessed in the context of mortality outcome.[34] This study has demonstrated that the presence of pre-existing co-morbid illness was significantly associated with death at 1-year. The only exception in this study were females aged ≥ 65 years with Charlson co-morbidity index scores ≥ 4 points demonstrating a lower relative risk of death; however, these results are of limited inference due to only 1 female with a Charlson co-morbidity score < 4 points.

Interestingly, another novel finding of this study was the presence of pre-existing diabetes mellitus being associated with a reduced risk of death at 1-year even after adjustment for evidence of chronic kidney disease and other co-morbid illness, specifically for those diabetic patients with pre-dialysis serum creatinine levels ≥ 400 μmol/L. One plausible explanation to account for this finding was that these diabetic patients had occult pre-existing chronic kidney disease that resulted in a lower threshold for renal injury during critical illness and a diagnosis of sARF. However, in the setting of a diagnosis of septic shock, pre-existing diabetes mellitus was associated with an increased risk of death at 1-year.

Further this study has demonstrated that additional risk factors for death at 1-year in patients with a diagnosis of sARF include a pre-existing diagnosis of cancer, in particular with evidence of metastases, liver disease, septic shock and use of any CRRT as the primary modality of renal replacement when compared with IHD only. Although the presence of co-morbid liver disease, septic shock,

and need for CRRT have been previously suggested, these studies are potentially biased due to the aforementioned limitations in assessment of mortality at ICU or hospital discharge. [1, 6, 11, 13, 15, 16, 20-24]

In contrast to previous hospital-based studies and pre-analysis prediction in this study, presence of pre-existing renal disease, etiology of sARF or oliguria were not significantly associated with death at 1-year. [1, 6, 11, 13, 15, 16, 20, 21, 23, 86] This may have been the result of small sample sizes, failure to account for potential confounding variables, and selection bias in previous studies. The apparent lack of association of chronic kidney disease with death at 1-year in this study would appear counterintuitive considering the independent risk of co-morbid illness. However, the presence of pre-existing renal disease in these patients likely afforded greater susceptibility to overt renal injury prompting RRT. Although not associated with death, sARF in patients with co-morbid renal disease may represent a cohort less likely to recover renal function and subsequently develop long-term RRT dependence.

Another interesting finding in this study was of a lower pre-dialysis serum creatinine (< 400 μmol/L) being associated with an increased risk of death at 1-year, in particular for those aged < 65 years with APACHE II scores < 25 points or a diagnosis of diabetes mellitus. Although speculation, it is conceivable that survivors of sARF had higher pre-dialysis serum creatinine levels due to increased serum creatinine representing a surrogate for healthier patients with greater muscle mass or a bias for delayed initiation for patients who are healthier

with less co-morbid illness, despite no evidence of confounding or effect modification by Charlson co-morbidity index score.[17]

Previous studies have reported that the prognosis for elderly patients with sARF is very poor compared with younger patients.[93, 94] Although the case-fatality rate was high in critically ill elderly patients with sARF, findings in this study would suggest that elderly patients who survive an episode of sARF have an overall survival and rate of recovery of renal function comparable to younger patients. This may partially be accounted for by pre-existing co-morbidity acting as a confounding factor when considering the association of increased patient age for death. Findings in this study demonstrated that 23% and 16% of patients aged >65 and >80 years, respectively, were alive and independent of RRT at 1-year.

The need for CRRT was significantly associated with death at 1-year in this study after assessing for important confounders such as age, sex, co-morbid illness, APACHE II score, etiology of sARF and a diagnosis of septic shock. This is plausible considering that in clinical practice CRRT is utilized in more unstable patients with great severity of illness, and a poorer expected outcome. Although similarly reported by Chertow *et al*[17], this would appear to contradict several randomized studies suggesting no difference in mortality outcome between CRRT and IHD; however, these studies have significant methodological concerns including failure of randomization, inadequate power to assess clinically meaningful differences in primary mortality outcome and importantly, none

assessed the impact of modality of renal replacement therapy on long-term outcomes such as death at 1-year.[95-99]

3. Mortality outcome for critically ill patients by severity of renal dysfunction

Another interesting and novel finding of this study was the influence of severity of renal dysfunction on survival at 1-year. Although there was a decrease in survival when comparing patients with any renal dysfunction to those without evidence of renal dysfunction, the difference appeared most pronounced for patients with sARF, suggesting that the diagnosis of sARF in critically ill patients represents a significant escalation in management associated with an increased crude relative risk of death at 1-year and reduced long-term survival. In addition, there was no apparent difference in the relative risk of death at 1-year or long-term survival for those patients with mild or moderate dysfunction, although it was increased when compared to those critically ill patients with no evidence of renal dysfunction. Thus, results from this study would further support defining renal dysfunction in critically ill patients as sARF, specifically the need for RRT during admission to ICU, rather than variable and arbitrary definitions of ARF based solely on changes in serum creatinine or urine output. Furthermore, the finding of no difference in the risk of death at 1-year for those with mild or moderate renal dysfunction is potentially very relevant due to several studies defining ARF or renal dysfunction in critically ill patients simply by arbitrary

elevations in serum creatinine.[6, 11-18, 37] Again, although these patients with biochemical evidence of renal dysfunction represented by elevations in serum creatinine experience an increase risk of death at 1-year and reduced long-term survival compared to patients with no evidence of renal dysfunction, it remains unclear whether any particular threshold in serum creatinine can be used to clearly define long-term mortality prognosis in critically ill patients. The results of this study further highlight the limitations and difficulties in arbitrarily defining ARF in critically ill patients.[86]

This study further describes the clinical characteristics and outcomes of a cohort of critically ill patients admitted to the ICU with pre-existing ESRD receiving outpatient chronic RRT. All these patients required RRT during their ICU admission. Although this study suggests that ESRD is associated with a relatively high fatality rate; the risk of death at 1-year for ESRD patients was not significantly different than for patients with no renal dysfunction during admission to ICU and in fact, was higher than for those patients with mild to moderate renal dysfunction. This is similar to smaller cohort studies reporting increased mortality in ESRD patients receiving RRT during ICU admission; however, risk of death being less than for patients with sARF.[43, 100]

Finally, another potentially relevant finding in this study was evidence that the first 10-15 days following admission to ICU may represent an important determinant in survival and likely warrants further investigation in order to define and understand why the early survival for those with mild to moderate

dysfunction was lower than those with sARF whereas after this period of time those patients with sARF experienced lower survival.

4. Renal recovery in critically ill patients with sARF

This is the first study to describe the long-term renal recovery outcome for a cohort of critically ill patients with sARF. The assessment of long-term renal recovery outcome is important given the high cost associated with RRT in the ICU and economic burden of continuing long-term chronic RRT.[2-4] Despite the high overall mortality rates for patients with sARF, this study has demonstrated that in those who survive their episode of critical illness, the majority (78%) proceed to recovery of renal function with independence from RRT by 1-year. Independence from RRT is associated with improved overall quality of life and functional status.[2] Spurney *et al* reported that 88% of patients with sARF requiring RRT for >4 weeks duration recovered renal function to become independent of RRT; however, these results are difficult to generalize due to a highly selected population from a single, predominantly surgical ICU that employed only intermittent hemodialysis and reported no long-term follow-up.[40] Renal replacement therapy dependence at hospital discharge and at 90 days has been estimated to occur in 5-33% and 16% of patients, respectively in hospital-based studies.[3, 4, 16, 17, 40, 47, 49] Renal replacement therapy dependence reported in population-based studies at hospital discharge has been reported to occur between 8-18%.[3, 11, 20] However, this does not necessarily translate into long-

term RRT dependence. While the overall rate of RRT dependence at hospital discharge in this study was comparably higher than other population-based studies, only 8% overall or 21% of survivors at 1-year remained RRT dependent, an assessment duration more likely associated with permanent need for chronic RRT therapy.

Likewise, this is the first study to examine factors contributing to the long-term renal recovery of patients with a diagnosis of sARF. This study has demonstrated that several factors appear associated with an increased likelihood of renal recovery with independence from RRT including: male sex, in particular those aged < 65 years, lower pre-existing co-morbid illness as determined by the Charlson co-morbidity index, those with an intra-renal etiology for sARF, in particular with a low Charlson co-morbidity index or a diagnosis of septic shock, patients having received either CRRT only or in combination with IHD, and finally in those sARF patients with a diagnosis of septic shock. Thus, the factors represent potential identifiable determinants of renal recovery in patients with sARF during admission to ICU that may ultimately aid physicians, patients, and families in difficult management decisions regarding continued renal replacement support and life sustaining therapies.

I. CONCLUSIONS

In summary, this study represents the first population-based study of sARF that documents the major burden of disease in a Canadian and North American setting and identifies this as an important area requiring increased attention. Further, this study identifies and quantifies several risk factors for acquisition of sARF and may serve as a rationale means for targeted surveillance in these patients. Although this study reports that the case-fatality during the acute phase of sARF is very high, this data supports that survivors of sARF have an excellent prognosis for renal recovery and independence from RRT. This information is valuable for physicians, patients, and their families. Knowledge of the long-term outcomes after acquisition of sARF has the potential to greatly impact the care of critically ill patients by aiding in and providing well-informed overall management decisions.

REFERENCES

1 Metnitz, P, C Krenn, H Steltzer, et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Critical Care Medicine 2002;30:2051-8.

2 Hamel, M, R Phillips, R Davis, et al. Outcomes and cost-effectiveness of initiating dialysis and continuing aggressive care in seriously ill hospitalized patients. Annals of Internal Medicine 1997;127:195-202.

3 Korkeila, M, E Ruokonen and J Takala. Costs of care, long-term prognosis and quality of life in patients requiring renal replacement therapy during intensive care. Intensive Care Medicine 2000;26:1824-31.

4 Manns, B, C Doig, H Lee, et al. Cost of acute renal failure requiring dialysis in the intensive care unit: Clinical and resource implications of renal recovery. Critical Care Medicine 2003;31:449-55.

5 Druml, W. Prognosis of acute renal failure 1975-1995. Nephron 1996;73:8-15.

6 Schwilk, B, H Wiedeck, B Stein, et al. Epidemiology of acute renal failure and outcome of haemodiafiltration in intensive care. Intensive Care Medicine 1997;23:1204-11.

7 Liano, F, E Junco, J Pascual, R Madero and E Verde. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. Kidney International 1998;66:S16-S24.

8 Sural, S, R Sharma, M Singhal, et al. Acute renal failure in an intensive care unit in India--prognostic factors and outcome. J Nephrol 1999;12:390-4.

9 Bagshaw, S, P Boiteau, A Izakson, R Shahpori and T Godinez-Luna. Outcome of critically ill patients requiring continuous renal replacement therapy in a large Canadian region (Abstract). Intensive Care Medicine 2004;30:S29.

10 Bernieh, B, M Al Hakim, Y Boobes, E Siemkovics and H El Jack. Outcome and predictive factors of acute renal failure in the intensive care unit. Transplant Proc 2004;36:1784-7.

11 Cole, L, R Bellomo, W Silvestor and J Reeves. A prospective, multi-center study of the epidemiology, management, and outcome of severe acute renal failure in a "closed" ICU system. American Journal of Respiratory and Critical Care Medicine 2000;162:191-6.

12 Guerin, C, R Girard, J Selli, J Perdrix and L Ayzac. Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. American Journal of Respiratory and Critical Care Medicine 2000;161:872-9.

13 Brivet, F, D Kleinknecht, P Loirat and P Landais. Acute renal failure in intensive care units--causes, outcome, and prognostic factors of hospital mortality: a prospective, multicenter study. Critical Care Medicine 1996;24:192-8.

14 Schaefer, J, F Jochimsen, F Keller, K Wegscheider and A Distler. Outcome prediction of acute renal failure in medical intensive care. Intensive Care Medicine 1991;17:19-24.

15 Spiegel, D, M Ullian, G Zerbe and T Bert. Determinants of survival and recovery in acute renal failure patients dialyzed in intensive-care units. American Journal of Nephrology 1991;11:44-7.

16 Cosentino, F, C Chaff and M Piedmonte. Risk factors influencing survival in ICU acute renal failure. Nephrol Dial Transplant 1994;9:179-82.

17 Chertow, G, C Christiansen, P Cleary, C Munro and J Lazarus. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. Archives of Internal Medicine 1995;155:1505-11.

18 Jensen, M, E Ejlersen, K Eliasen and H Lokkegaard. Prognosis for patients admitted to intensive care units with acute renal failure requiring dialysis. Ugeskr Laeger 1995;157:2564-9.

19 Douma, C, W Redekop, J van der Meulen, et al. Predicting mortality in intensive care patients with acute renal failure treated with dialysis. Journal of the American Society of Nephrology 1997;8:111-7.

20 Silvestor, W, R Bellomo and L Cole. Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. Critical Care Medicine 2001;29:1910-5.

21 Groeneveld, A, D Tran, J van der Meulen, J Nauta and L Thijs. Acute renal failure in the medical intensive care unit: predisposing, complicating factors and outcome. Nephron 1991;59:602-10.

22 Mukau, L and R Latimer. Acute hemodialysis in the surgical intensive care unit. Am Surg 1988;54:548-52.

23 Jochimsen, F, J Schaefer, A Maurer and A Distler. Impairment of renal function in medical intensive care: predictability of acute renal failure. Critical Care Medicine 1990;18:480-5.

24 McCarthy, J. Prognosis of patients with acute renal failure in the intensive care unit: a tale of two eras. Mayo Clin Proc 1996;71:117-26.

25 Jacka, M, X Ivancinova and N Gibney. Continuous renal replacement therapy improves renal recovery from acute renal failure. Can J Anesth 2005;52:327-32.

26 Laupland, K. Population-based epidemiology of intensive care: critical importance of ascertainment of residency status. Critical Care 2004;8:R431-R6.

27 Eliahou H, Modan B, Leslau V, Bar-Noach N, Tchiya P, Modan, M. Acute renal failure in the community: An epidemiological study (Abstract). 1973; Acute Renal Failure Conference, New York.

28 Abraham, G, R Gupta, Senthilselvan, A and J van der Meulen. Cause and prognosis of acute renal failure in Kuwait: A 2-year prospective study. J Trop Med Hyg 1989;92:325-9.

29 Sanchez-Rodriguez, I, E Martin-Escobar, L Lozano, F Garcia-Martin and G de Arriba. Aspectos epidemiologicos de fracaso renal agudo en el area sanitaria de Cuenca. Nefrologia 1992;12:87-91.

30 McGregor E, Brown I, Campbell H, Isles C, Rodger RSC, Junor BJR, Briggs JD. Acute renal failure: A prospective study on incidence and outcome (Abstract). 1992; XXIX Congress of EDTA-ERA, Paris, France, pg 54.

31 Feest, T, A Round and S Hamad. Incidence of severe acute renal failure in adults: results of a community based study. BMJ 1993;306:481-3.

32 Liano, F and J Pascual. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Kidney International 1996;50:811-8.

33 Witczak, B, A Asberg and A Hartmann. Acute dialysis-dependent renal failure at the Rikshospital in 1998. Tidsskr Nor Laegeforen 2001;121:1216-9.

34 Metcalfe, W, M Simpson, I Khan, et al. Acute renal failure requiring renal replacement therapy: incidence and outcome. Q J Med 2002;95:

35 Robertson, S, K Newbigging, C Isles, et al. High incidence of renal failure requiring short-term dialysis: a prospective observational study. Q J Med 2002;95:585-90.

36 Tran, D, M Cuesta and P Oe. Acute renal failure in patients with severe civilian trauma. Nephrol Dial Transplant 1994;9:121-5.

37 Neveu, H, D Kleinknecht, F Brivet, P Loirat and P Landais. Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. Nephrol Dial Transplant 1996;11:293-9.

38 Hoste, E, N Lameire, R Vanholder, et al. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol 2003;14:1022-30.

39 Routh, G, J Briggs, J Mone and I Ledingham. Survival from acute renal failure with and without multiple organ dysfunction. Postgrad Med J 1980;56:244-7.

40 Spurney, R, W Fulkerson and S Schwab. Acute renal failure in critically ill patients: prognosis for recovery of kidney function after prolonged dialysis support. Critical Care Medicine 1991;19:8-11.

41 Chertow, G, E Levy, K Hammermeister, F Grover and J Daley. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998;104:343-8.

42 Morgera, S, A Kraft, G Siebert, F Luft and H Neumayer. Long-term outcomes in acute renal failure patients treated with continuous renal replacement therapies. Am J Kid Dis 2002;40:275-9.

43 Clermont, G, C Acker, D Angus, et al. Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. Kidney International 2002;62:986-96.

44 Mehta, R, M Pascual, S Soroko, et al. Spectrum of acute renal failure in the intensive care unit: The PICARD Experience. Kidney International 2004;66:1613-21.

45 Liano, F, A Gallego, J Pascual, et al. Prognosis of acute tubular necrosis: An extended prospectively contrasted study. Nephron 1993;63:21-31.

46 Halstenberg, W, M Goormastic and E Paganini. Validity of four models for predicting outcome in critically ill acute renal failure patients. Clin Nephrol 1997;47:81-6.

47 Silvestor, W. Outcome studies of continuous renal replacement therapy in the intensive care unit. Kidney International 1998;1998:S109-S11.

48 Parker, R, J Himmelfarb, N Tolkoff-Rubin, et al. Prognosis of patients with acute renal failure requiring dialysis: results of a multicenter study. Am J Kid Dis 1998;32:432-43.

49 Bhandari, S and J Turney. Survivors of acute renal failure who do not recover renal function. Q J Med 1996;89:415-21.

50 Gokal, R. Quality of life in patients undergoing renal replacement therapy. Kidney International 1993;40:S23-S7.

51 Churchill, D, G Torrance, D Taylor, et al. Measurement of quality of life in end-stage renal disease: the time trade-off approach. Clin Invest Med 1987;10:14-20.

52 Churchill, D. Results of the Canadian morbidity study in end-stage renal disease patients treated by hemodialysis. Semin Nephrol 1990;1990:66-72.

53 Manns, B, K Taub and C Donaldson. Economic evaluation and end-stage renal disease: From basic to bedside. Am J Kid Dis 2000;36:12-28.

54 Calgary Health Region Website. Available at: <http://www.crha-health.ab.ca/hocr/influ/demo/popage.htm> Access date February 4, 2005

55 de Mendonça, A, J Vincent, P Suter, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Medicine 2000;26:915-21.

56 Levey, A, J Bosch, J Lewis, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Internal Med 1999;130:461-79.

57 Kang, Y, K Han, S Han, H Kim and D Cha. Characteristics of population with normal serum creatinine impaired renal function and: the validation of the MDRD formula in a health general population. Clin Nephrol 2005;63:258-66.

58 Knaus, W, E Draper, D Wagner and J Zimmerman. APACHE II: A severity of disease classification system. Critical Care Medicine 1985;13:818-29.

59 Charlson, M, P Pompei, K Ales and C MacKenzie. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.

60 ACCP/SCCM. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Critical Care Medicine 1992;20:864-74.

61 Bernard, G, A Artigas, K Brigham, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Resp Crit Care Med 1994;149:818-24.

62 Calgary Health Region Website. Available at: <http://www.crha-health.ab.ca> Access date February 4, 2005

63 Statistics Canada. 1994/95 National Population Health Survey. Available at <http://www.acs.ucalgary.ca/cgi-bin/landru> Access date February 4, 2005.

64 Statistics Canada. 1996/97 National Population Health Survey. Available at <http://www.acs.ucalgary.ca/cgi-bin/landru> Access date February 4, 2005.

65 Statistics Canada. 1998 National Population Health Survey. Available at <http://www.acs.ucalgary.ca/cgi-bin/landru> Access date February 4, 2005.

66 Statistics Canada. 2000/01 Canadian Community Health Survey. Available at <http://www.acs.ucalgary.ca/cgi-bin/landru> Access date February 4, 2005.

67 National Health and Nutritional Examination Survey (NHANES III) 1988/1994. Available at: <http://www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm#description1> Access date: July 20, 2005.

68 Coresh, J, B Astor, T Greene, G Eknoyan and A Levey. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey (NHANES III). Am J Kid Dis 2003;41:1-12.

69 Jamerson, K. Preventing chronic kidney disease in special populations. Am J Hypertens 2005;18:106S-11S.

70 McClellan, W. Epidemiology and risk factors for chronic kidney disease. Med Clin North Am 2005;89:419-45.

71 Benabe, J and E Rios. Kidney disease in the Hispanic population: facing the growing challenge. J Natl Med Assoc 2004;96:789-98.

72 The Heart and Stroke Foundation of Canada. The Changing Face of Heart Disease and Stroke in Canada 2000. Available at: <http://www.statcan.ca> Access date: Feb 4, 2005.

73 Millar, W and T Young. Tracking diabetes: prevalence, incidence and risk factors. Health Rep 2003;14:35-47.

74 Tjepkema, M. Alcohol and illicit drug dependence. Health Rep 2004;15:9-19.

75 Gariel, S, C Crowson and W O'Fallon. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. Arthritis Rheum 1999;42:415-20.

76 Chen, Y, K Breithaupt and N Muhajarine. Occurrence of chronic obstructive pulmonary disease among Canadians and sex-related factors. J Clin Epidemiol 2000;53:755-61.

77 Mao, Y, H Morrison, R Semenciw, S Robson and D Wigle. The prevalence of cancer in Canada. Can J Public Health 1991;82:61-2.

78 Field, T, T Green, K Roy, J Pedersen and M Hill. Trends in hospital admission for stroke in Calgary. Can J Neurol Sci 2004;31:387-93.

79 Manns, B, G Mortis, K Taub, et al. The Southern Alberta Renal Program database: a prototype for patient management and research initiatives. Clin Invest Med 2001;24:164-70.

80 Newcombe HB. Handbook of Record Linkage. New York: Oxford University Press, 1988.

81 Cullen, D, J Civetta, B Briggs and L Ferrara. Therapeutic interventions scoring system: a method of quantitative comparison of patients care. Critical Care Medicine 1974;2:57-60.

82 Charlson, M, T Szatrowski, J Peterson and J Gold. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245-51.

83 Pompei, P, M Charlson and R Douglas. Clinical assessments as predictors of one year survival after hospitalization: implications for prognostic stratification. J Clin Epidemiol 1988;41:275-84.

84 Balk, R. Severe sepsis and septic shock. Definitions, epidemiology, and clinical manifestations. Critical Care Clinics 2000;16:179-92.

85 Davies, D, A McGeer, B Schwartz, et al. Invasive group A streptococcal infections in Ontario, Canada. New Engl J Med 1996;335:547-54.

86 Bellomo, R, C Ronco, J Kellum, R Mehta and P Palevsky. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care 2004;8:R204-R12.

87 Bagshaw, S, K Laupland, P Boiteau and T Godinez-Luna. Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement

therapy? A prospective observational study in an adult regional critical care system. Journal of Critical Care 2005;20:In Press.

88 Barrett, B. Contrast nephropathy. Journal of the American Society of Nephrology 1994;5:125-37.

89 Huber, W, B Jeschke, M Page, et al. Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: a prospective comparison to series of patients at similar risk. Intensive Care Medicine 2001;27:1200-9.

90 Perl, T, L Dvorak, T Hwang and R Wenzel. Long-term survival and function after suspected gram-negative sepsis. JAMA 1995;274:338-45.

91 Quartin, A, R Schein, D Kett and P Peduzzi. Magnitude and duration of the effect of sepsis on survival. JAMA 1997;277:1058-63.

92 Laupland, K, D Zygun, C Doig, et al. One-year mortality of bloodstream infection-associated sepsis and septic shock among patients presenting to a regional critical care system. Intensive Care Medicine 2005;31:213-9.

93 Bellomo, R, M Farmer and N Boyce. The outcome of critically ill elderly patients with severe acute renal failure treated by continuous hemodiafiltration. Int J Artif Organs 1994;17:466-72.

94 Akposso, K, A Hertig, R Couprie, et al. Acute renal failure in patients over 80 years old: 25-years' experience. Intensive Care Medicine 2000;26:400-6.

95 Kellum, J, D Angus, J Johnson, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Medicine 2002;28:29-37.

96 Gasparovic, V, I Filipovic-Grcic, M Merkler and Z Pisl. Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD)--what is the procedure of choice in critically ill patients. Ren Fail 2003;25:855-62.

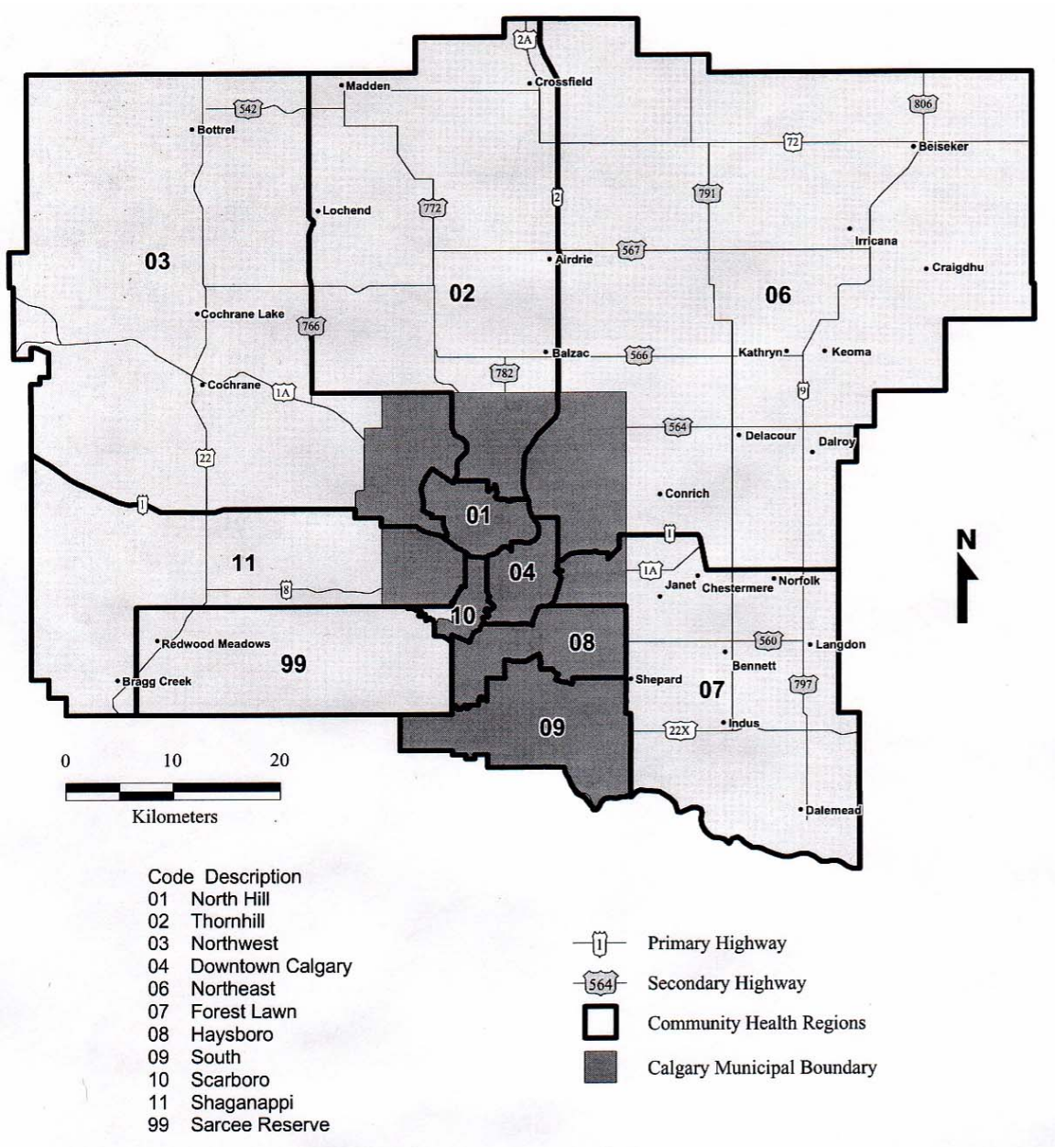
97 Mehta, R, B McDonald, F Gabbai, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney International 2001;60:1154-63.

98 Guerin, C, R Girard, J Selli and L Ayzac. Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: results from a multicentre prospective epidemiological survey. Intensive Care Medicine 2002;28:1411-8.

99 Augustine, J, D Sandy, T Seifert and E Paganini. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kid Dis 2004;44:1000-7.

100 Uchino, S, H Morimatsu, R Bellomo, W Silvestor and L Cole. End-stage renal failure patients requiring renal replacement therapy in the intensive care unit: incidence, clinical features, and outcome. Blood Purif 2003;21:170-5.

APPENDIX 1. Map of the Calgary Health Region (CHR)



APPENDIX 2. Overall age and sex-specific population counts for adult residents of the CHR during the study period.[62]

TOTAL					
Year	CHR Population	<18 years	18-65	>65	Study Population
2000	936,205	228,128	624,579	83,498	708,077
2001	958,610	230,403	641,975	86,232	728,207
2002	977,849	232,100	656,784	88,965	745,749
MALE					
Year	CHR Population	<18 years	18-65	>65	Study Population
2000	466,585	116,733	313,983	35,869	349,852
2001	477,950	117,884	322,934	37,132	360,066
2002	487,675	118,855	330,358	38,462	368,820
FEMALE					
Year	CHR Population	<18 years	18-65	>65	Study Population
2000	469,620	111,395	310,596	47,629	358,225
2001	480,660	112,519	319,041	49,100	368,141
2002	490,174	113,245	326,426	50,503	376,929

APPENDIX 3. Ethical Approval

UNIVERSITY OF CALGARY

FACULTY OF MEDICINE

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

2003-04-09

Dr. K.B. Laupland
Department of Medicine
FMC
Calgary, Alberta

Dear Dr. Laupland:

RE: Population-based Epidemiology of Severe Acute Renal Failure and Prognostic Factors for Renal Recovery

Grant-ID: 17005

The above-named research project has been granted ethical approval by the Conjoint Health Research Ethics Board of the Faculties of Medicine, Nursing and Kinesiology, University of Calgary, and the Affiliated Teaching Institutions. The Board conforms to the Tri-Council Guidelines, ICH Guidelines and amendments to regulations of the Food and Drug Act re clinical trials, including membership and requirements for a quorum.

The study continues to meet the requirements of the Health Information Act.

You and your co-investigators are not members of the CHREB and did not participate in review or voting on this study.

Please note that this approval is subject to the following conditions:

(1) you must obtain approval from your appropriate institution where the research project will be conducted (if applicable);
(2) a copy of the informed consent form must have been given to each research subject, if required for this study;
(3) a Progress Report must be submitted in one year, 2004-04-09, containing the following information:
    (i) the number of subjects recruited;
    (ii) a description of any protocol modification;
    (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
    (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
    (v) a copy of the current informed consent form;
    (vi) the expected date of termination of this project;
(4) a Final Report must be submitted at the termination of the project.

Please accept the Board's best wishes for success in your research.

Yours sincerely,

Ian Mitchell, MB, FRCPC
Acting Chair, Conjoint Health Research Ethics Board

IM/mc

c.c. Adult Research Committee Dr. J. Conly (information) Research Services Ms. Linda Knox

APPENDIX 4. Data Collection Form

A. Enrollment Information

Patient identifier #: _____

Date of birth: _____/_____/_____
YY/MM/DD

[ ] M [ ] F Gender

[ ] Y [ ] N CHR resident?

Date of hospital admission: _____/_____/_____
YY/MM/DD

Date of ICU admission: _____/_____/_____
YY/MM/DD

Date of first dialysis treatment:_____/_____/_____
YY/MM/DD

Admission diagnosis:_____

[ ] Y [ ] N Admission from OR or < 24 hr from surgery?

[ ] Y [ ] N Trauma patient?

Inclusion criteria (*include if all present*)

a) [ ] At least one dialysis treatment given
b) [ ] Admitted to ICU within 48 hours of first dialysis treatment

Exclusion criteria (*exclude if any present*)

a) [ ] Chronic renal-replacement therapy
b) [ ] First dialysis treatment ≥48 hours prior to ICU admission
c) [ ] Dialysis only for toxin removal/acidosis in absence ARF
d) [ ] No dialysis provided
e) [ ] Admitted to ICU for dialysis only and not critically ill

[ ] Y [ ] N Entry criteria met?

[ ] Y [ ] N Does this patient have a traumatic brain injury?
(*If yes, complete the last page*)

B. Classification of severe ARF

[ ] Y [ ] N Oliguric ARF (<500 mL urine /24 hours preceding diagnosis of severe ARF)

(*Select only one of prerenal, renal or postrenal*)

[ ] Y [ ] N Postrenal
[ ] Y [ ] N Renal
- [ ] ATN (*check all that may apply*)
  - [ ] Drug
  - [ ] Contrast
  - [ ] Hemodynamic
  - [ ] Septic
  - [ ] Rhabdomyolysis
  - [ ] Other: _____
- [ ] Vascular
- [ ] Glomerular
- [ ] Interstitial

[ ] Y [ ] N Prerenal

C. Most important indication for dialysis for severe ARF (*check all that apply*)

[ ] Acidosis
[ ] Uremia
[ ] Hyperkalemia
[ ] Fluid overload
[ ] Other: _____

Prior to first dialysis, most recent laboratory value for:

pH: _____
Sodium: _____
Potassium: _____
Bicarbonate: _____
Chloride: _____
Urea: _____
Creatinine: _____

D. Risk factors for severe ARF (present within 10 days of diagnosis of severe ARF)

[ ] Y [ ] N Systolic hypotension (<90 mm Hg for >30 minutes)
[ ] Y [ ] N Lowest systolic BP <90 mmHg
[ ] Y [ ] N Reduction systolic BP ≥40 mmHg from baseline
[ ] Y [ ] N Lowest mean arterial pressure (MAP) < 70 mmHg
[ ] Y [ ] N Positive cultures: (organism) *if yes, specify:*
[ ] Blood: (_____): (*do not include typical contaminants such as CONS, Corynebacterium, Propionibacterium, or Bacillus species*)
[ ] CSF: (_____)
[ ] BAL ≥10^4 cfu/mL (_____)
[ ] Deep tissue (_____)
[ ] Urine (_____)
[ ] Peritoneal (_____)

[ ] Y [ ] N Vasopressor use (*check all that apply*)
[ ] Dopamine (>2 ug/kg/min)
[ ] Norepinephrine
[ ] Vasopressin
[ ] Dobutamine/milrinone
[ ] Epinephrine
[ ] Phenylephrine

[ ] Y [ ] N Aminoglycosides (gentamicin, tobramycin, amikacin)

[ ] Y [ ] N Amphotericin B
[ ] Deoxycholate or [ ] Lipid preparation

[ ] Y [ ] N Parenteral radiocontrast
[ ] Y [ ] N > 3 parenteral radiocontrast injections?

1. Investigation:_____ (*Specify: CT head /chest abdo/pelvis/other or angiogram etc.)*
Date/time: _____ (YY/MM/DD; 24hr:min)
Creatinine prior to injection: _____
Dialysis at time of injection: [ ] Y [ ] N

2. Investigation:_____ (*Specify: CT head /chest abdo/pelvis/other or angiogram etc.)*
Date/time: _____ (YY/MM/DD; 24hr:min)
Creatinine prior to injection: _____
Dialysis at time of injection: [ ] Y [ ] N

E. Clinical and laboratory features at diagnosis of severe ARF (<24 hours prior)

[ ] Y [ ] N Ventilated at onset of severe ARF?
[ ] Y [ ] N Cardiac Arrest/Cardiopulmonary Arrest?
[ ] Y [ ] N Documented alcohol abuse or alcoholism

Charlson Index Variables:

[ ] Y [ ] N Myocardial Infarction
[ ] Y [ ] N Congestive heart failure
[ ] Y [ ] N Peripheral vascular disease
[ ] Y [ ] N Cerebrovascular disease
[ ] Y [ ] N Hemiplegia
[ ] Y [ ] N Dementia
[ ] Y [ ] N Chronic pulmonary disease
[ ] Y [ ] N Connective tissue disease
[ ] Y [ ] N Peptic ulcer disease
[ ] Y [ ] N Mild liver disease
[ ] Y [ ] N Moderate or severe liver disease
[ ] Y [ ] N Diabetes mellitus (present < 6 months)
    [ ] Y [ ] N Insulin infusion in ICU?
    [ ] Y [ ] N End-organ damage?
[ ] Y [ ] N Moderate or severe renal disease
    If yes, pre-admission baseline creatinine:_____
[ ] Y [ ] N Any tumor (except skin basal cell carcinoma)
[ ] Y [ ] N Leukemia or lymphoma
[ ] Y [ ] N Metastatic solid tumor
[ ] Y [ ] N AIDS

Laboratory data:

Hemoglobin lowest: _____
Platelets lowest: _____
WBC lowest: _____
WBC highest: _____
Bands highest: _____
Albumin lowest: _____
Bilirubin highest: _____
INR highest: _____
Arterial pH lowest: _____
Blood lactate highest: _____
CK highest: _____
Creatinine highest: _____
Urea highest: _____

Syndromes:

[ ] Y [ ] N Sepsis (suspected or proven infection with SIRS)
[ ] Y [ ] N Signs of infection that are assumed to be a source of sepsis
- [ ] Y [ ] N Perforated viscus
- [ ] Y [ ] N Frank pus
- [ ] Y [ ] N Increased white cells from a normally sterile body site
- [ ] Y [ ] N Evidence organisms in normally sterile body sites/fluids demonstrated either by microscopy or culture growth.
- [ ] Y [ ] N Syndrome associated with a high probability of infection (list syndrome: _____)

[ ] Y [ ] N Adult respiratory distress syndrome (ARDS)
- [ ] Y [ ] N Diffuse infiltrates on CXR
- [ ] Y [ ] N No evidence of left atrial hypertension
- [ ] Y [ ] N Appropriate context/no alternate diagnosis
- [ ] Y [ ] N P/F<200

F. Treatment of ARF in ICU

Dialysis access location(s) (*check as many as apply*)
[ ] femoral
[ ] jugular
[ ] subclavian
[ ] other: _____

[ ] Y [ ] N > 1 dialysis catheter insertion

[ ] Y [ ] N Documented line complication? (arterial puncture/bleeding/infection etc.)

Dialysis type in ICU (*check only one of the following*):
[ ] exclusively CRRT
[ ] exclusively IHD
[ ] combination CRRT/IHD

Date of first CRRT in ICU: _____(YY/MM/DD)

Date of last CRRT in ICU: _____(YY/MM/DD)

Total # days CRRT in ICU: _____

Date of first IHD in ICU: _____(YY/MM/DD)

Data of last IHD in ICU: _____(YY/MM/DD)

Total # IHD treatments in ICU: _____

Total # days any dialysis in ICU: _____(YY/MM/DD)

Approximate time after CRRT that IHD started: _____ (hours)

G. Outcomes

[ ] Y [ ] N Nephrology service consult while in ICU?

[ ] Y [ ] N Dialysis in hospital after discharge from ICU?

[ ] Y [ ] N Dialysis as an outpatient following hospital discharge?

[ ] Y [ ] N Dialysis at 1 year post-severe ARF onset?

If no,
Date of last dialysis: _____/_____/_____
YY/MM/DD

[ ] Y [ ] N Patient alive at 1 year follow-up

If no,
Date of death _____/_____/_____
YY/MM/DD

Cause(s) of death:
_____

[ ] Y [ ] N TRAUMATIC BRAIN INJURY?

[ ] Y [ ] N Pre-hospital hypotension (systolic BP < 90 mmHg)?

[ ] Y [ ] N Pupillary abnormalities on initial assessment?

[ ] Y [ ] N Abnormal initial Head CT scan?

[ ] Y [ ] N Episodes of hypoxemia (PaO2 < 90)?

[ ] Y [ ] N Intracranial hypertension > 25 mmHg for > 10 minutes at any time?

[ ] Y [ ] N Neurosurgical intervention (OR) at any time?