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Serum potassium in chronic kidney disease: prevalence, patient characteristics and clinical outcomes

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INTRODUCTION

Serum potassium is typically tightly regulated between 3.5-5.0mmol/L[1, 2]. The kidneys are fundamental to potassium homeostasis[3], so patients with CKD are more likely than the general population to experience hyperkalaemia and hypokalaemia[4]. Hyperkalaemia is commonly the result of a combination of clinical factors superimposed on low renal function, such as diabetes, heart failure and use of renin-angiotensin-aldosterone system inhibitor (RAASi) medications[5]. Hypokalaemia typically occurs as a consequence of potassium-wasting diuretic administration[6].

Potassium plays an important role in cell membrane electrophysiology, particularly in cardiac conduction, smooth muscle tone and neuronal signalling[7-9]. Depending on severity, the clinical manifestations of potassium abnormalities may range from asymptomatic to cardiac arrhythmias and sudden death[10]. For this reason, hyperkalaemia has been linked to a higher risk of mortality in dialysis patients[11, 12]. Similarly, hypokalaemia in dialysis patients has been associated with higher mortality, in part because it can reflect poor nutrition[13]. Recent studies in non-dialysis dependent CKD patients suggest that the relationship between serum potassium and mortality is a U-shaped curve in which both hyperkalaemia and hypokalaemia are associated with increased mortality and hospitalisation risk[5, 9, 14-17]. Little is known, however, about the effect of admission potassium on the risk of in-hospital mortality and other clinical outcomes in hospitalised CKD patients, particularly in the Australian setting.

The present study aimed to examine the prevalence of hyperkalaemia and hypokalaemia in an Australian hospital-based cohort of CKD patients, as well as its associated patient characteristics and clinical outcomes. We hypothesised that potassium disturbances would be associated with poorer inpatient clinical outcomes.

METHOD

Study Design & Source Population

The study used Austin Health Electronic Medical Record (EMR) data extracted from The Data Analytics Research and Evaluation (DARE) Centre. The DARE Centre was cofounded by The University of Melbourne and Austin Health in 2018 to analyse and interpret complex health datasets. All data in The DARE Centre is collected in the process of normal patient care and compiled from several Austin Health digital repositories, including the Patient Administration System (PAS – Trak Health©), Pathology Data Management System, Clinical Coding System, and the inpatient EMR system CERNER Millenium (Cerner© 2011).

Identification of the Study Cohort

The study population included adult patients (aged ≥18 years) with at least two abnormal estimated glomerular filtration rate (eGFR) values (<60mL/min/1.73m^2) measured greater than 90-days apart between 1 January 2014 and 31 December 2018 in an inpatient, outpatient or emergency department setting (Figure 1). Patients were included if they had a serum potassium test performed within 24-hours of any inpatient admission to Austin Health following their first abnormal eGFR result. Only inpatient serum potassium results were used for analysis to ensure that sufficient patient information was available (e.g. comorbidities and medications) because this data was not yet recorded in the EMR in the outpatient setting. Patients with

greater than 20 inpatient admissions during the study period were removed from the dataset entirely as outliers. Patients with end-stage kidney disease (ESKD), defined as maintenance dialysis (haemodialysis or peritoneal dialysis) or renal transplant, were excluded from the time of the procedure. ESKD was identified by International Classification of Diseases, Tenth Revision (ICD-10 Australian Modification) code assignment and from comparison with the Austin Health Department of Nephrology Renal Replacement Therapy Database.

Patient Characteristics

Sociodemographic information including age, sex and Indigenous status was reported for patients who were stratified by their first admission potassium category. Additionally, comorbidities, the principal diagnosis of the admission, and medications administered during the inpatient episode were recorded.

Definition of Chronic Kidney Disease

Although many of the participants were not formally diagnosed with CKD by a clinician, we defined CKD as at least two eGFR values <60mL/min/1.73m^2 measured greater than 90-days apart during the study period in inpatient, outpatient or emergency department settings. This definition was used to reduce the likelihood of including patients suffering from an acute kidney injury (AKI). eGFR was calculated from serum creatinine levels using the Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation[18]. CKD stages were determined from the eGFR measured at the time of the admission potassium result and defined according to current Kidney Disease Improving Global Outcomes (KDIGO) guidelines: Stage 1 eGFR ≥90mL/min/1.73m^2; Stage 2 eGFR ≥60 and <90mL/min/1.73m^2; Stage 3a eGFR ≥45 and <60mL/min/1.73m^2, Stage 3b eGFR ≥30 and <45mL/min/1.73m^2, Stage 4 ≥15 and <30mL/min/1.73m^2, and

Stage 5 <15mL/min/1.73m^2, respectively[19]. Data on albuminuria and structural or pathological renal abnormalities was not available.

Serum Potassium Classification

The admission serum potassium level was defined as the first serum potassium level taken within 24-hours of inpatient admission, inclusive of investigations performed in the emergency department. Admission serum potassium was categorised into six strata (<3.5, 3.5-3.9, 4.0-4.9, 5.0-5.4, 5.5-5.9, ≥6.0mmol/L). The most common serum potassium range (4.0-4.9mmol/L) was selected as the reference group for outcome comparison based on clinical relevance and previous reports[5, 16] (Table 1). Further to this, hyperkalaemia and hypokalaemia were defined as serum potassium ≥5.5mmol/L and <3.5mmol/L, respectively. These thresholds were used for relevance to nephrology clinical practice and to facilitate comparison with previous studies[5, 6, 8, 9, 20].

Identification of Comorbidities, Principal Diagnoses & Medications

Patient comorbidities, including myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes, hemiplegia/paraplegia, malignancy and human immunodeficiency virus were based on the Charlson Comorbidity Index (CCI) at admission and grouped by pre-defined ICD-10 codes according to the method outlined by Quan *et al*[21]. The principal diagnosis was also determined by ICD-10 codes assigned to pre-defined diagnosis groups. Patient medications were recorded if the individual was administered a medication of interest at any time during their admission. Outpatient medication prescription information was not readily available for analysis. Medications of interest included angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), aldosterone antagonists, β-blockers, calcium-

channel blockers, loop diuretics and thiazide diuretics. Patients taking prescription medications containing one or more drug classes were credited with receiving both corresponding medications.

Clinical Outcomes

The clinical outcomes of the study were inpatient mortality and intensive care unit (ICU) requirement. ICU requirement included any patient who was admitted to ICU for any length of time.

Data Handling & Statistical Analysis

All data handling and statistical analyses were performed using Microsoft® Excel (Office 365, 2019) and Stata/IC 15.1 (StataCorp, TX, USA). All figures were produced using Prism 8 (GraphPad Software, 2019). Continuous variables are described as mean ± 1 standard deviation and median with interquartile range, whereas categorical variables are described as frequencies and percentages. Baseline patient characteristics were compared across admission serum potassium categories using the Kruskal-Wallis H test for continuous variables, all of which were not normally distributed, and the Chi-square test for categorical variables. Two separate logistic regression analyses were performed in the total study population to assess the association of various demographic and clinical characteristics with hyperkalaemia and hypokalaemia, respectively. The inclusion of variables in univariate analysis was based on existing knowledge of potassium abnormalities in CKD patients. These include age, gender, eGFR, comorbidities, principal diagnoses, and use of potassium-altering medications. Variables were tested for interaction and included in the multivariate model if $p < 0.05$ in univariate analysis. We report unadjusted and adjusted odds ratios with 95% confidence intervals. Two-tailed probability values of $p < 0.05$ were considered statistically significant in the final multivariate models. We also performed logistic regression analyses to evaluate for independent associations between admission

serum potassium categories and in-hospital mortality or ICU admission. These models were adjusted for age, sex, eGFR and CCI scores.

Ethical Approval

This study was approved by the Austin Human Research Ethics Committee (HREC-43815-Austin-2018).

RESULTS

Study Population

36,246 adults with at least one abnormal eGFR <60 mL/min/1.73m^2 during the study period were identified. In an attempt to prevent inclusion of patients with an AKI, 11,227 of these patients were excluded from the study because they only had the one abnormal eGFR measurement, as were a further 10,280 patients who did not have a minimum of 90-days between their first and last abnormal eGFR value. From the 14,710 participants who met the eGFR inclusion criteria, 749 patients with ESKD were removed. 1,757 patients did not have an inpatient admission during the study period and 978 patients did not have an available serum potassium measurement within 24-hours of an inpatient admission. A further 99 patients were excluded from the study because they had greater than 20 Austin Health inpatient admissions during the study period. This resulted in a final sample of 11,156 participants (Figure 1).

Baseline Descriptive Data

The study population comprised 11,156 participants with a mean age of 77.30 ± 12.03 years; 49.14% were male and 0.32% identified as Aboriginal or Torres Strait Islander. The mean eGFR was 45.77 ± 16.55mL/min/1.73m^2. 14.78% of patients had an eGFR ≥60mL/min/1.73m^2 at the time of their first eligible

hospital admission, despite meeting the study eGFR requirements for CKD. Demographic and clinical characteristics of patients were significantly different across potassium categories (Table 1). In total there were 38,708 admissions during the study period, with a median of 5 admissions (IQR 3-8) per patient over 5 years.

Prevalence of Hyperkalaemia & Hypokalaemia

The mean admission serum potassium level was 4.5 ± 0.6mmol/L over the study period (Figure 2). The minimum potassium value was 1.6mmol/L, and the maximum potassium value was 9.4mmol/L. The prevalence of hypokalaemia at admission was 2.94%. Another 90.20% of admission potassium levels were normal, whereas hyperkalaemia was present in 6.86% of admissions. Moreover, a total of 1.88% of admissions had severe hyperkalaemia with a potassium level ≥6.0mmol/L.

Patient Characteristics Associated with Hyperkalaemia & Hypokalaemia

The results of the univariate and multivariate logistic regression analyses for patient characteristics associated with hyperkalaemia and hypokalaemia in the study cohort appear in Tables 2 and 3, respectively. Male sex, lower eGFR, cardiac failure, diabetes, liver disease and endocrine or genitourinary pathology showed significantly elevated OR for the development of hyperkalaemia in both univariate and multivariate analyses. ARBs, loop diuretics and thiazide diuretics were associated with lower OR of hyperkalaemia. Conversely, loop diuretics, thiazide diuretics and calcium channel blocker medications were associated with a higher predicted OR of hypokalaemia. Other variables associated with a significantly increased risk of hypokalaemia in univariate and multivariate analyses included malignancy, infectious disease, endocrine pathology, and mental/behavioural diagnoses. Alternatively, male sex, age ≥65 years, lower eGFR, a history

of acute myocardial infarction or diabetes, injury/poisoning, musculoskeletal pathology and ARB administration were associated with lower odds of hypokalaemia.

Clinical Outcomes

Inpatient Mortality

Among the study population, 1,655 (14.84%) patients died during an inpatient admission during the 5-year study period. A U-shaped relationship was observed for admission serum potassium categories and mortality. Both serum potassium <4.0mmol/L and ≥5.0mmol/L was associated with increased mortality risk when adjusted for age, sex, eGFR and CCI (Figure 3a). Mortality rates were highest for patients with potassium ≥6.0mmol/L (OR 2.41, 95% CI 1.89-3.06) and potassium <3.5mmol/L (OR 2.15, 95% CI 1.66-2.79).

Intensive Care Unit Admission

A J-shaped association was found between admission serum potassium category and ICU requirement (Figure 3b). 2,171 (5.61%) patient admissions required ICU admission during the study period. Only admission potassium levels >5.5mmol/L were associated with increased ICU admission risk when adjusted for age, sex, eGFR and CCI (Figure 3b). The risk of ICU admission was highest in patients with a serum potassium ≥6.0mmol/L (OR 2.42, 95% CI 1.94-3.00), and was also elevated in patients with an admission serum potassium of 5.5-5.9mmol/L (OR 1.42, 95% CI 1.17-1.72).

DISCUSSION

This is the first hospital-based Australian study to examine potassium abnormalities in patients with CKD. The results showed that potassium abnormalities are common with 6.86% of CKD inpatient events having hyperkalaemia and 2.94% having hypokalaemia at the time of admission. A recent Australian community-based study of CKD patients prescribed RAASi medications estimated a slightly higher hyperkalaemia prevalence of 9.9%[22]. The prevalence of hyperkalaemia in the current study, however, remains comparable to other recent observational studies in which estimates have ranged from 2-52%, largely as a result of differences in definitions and inclusion criteria[6]. Previous studies have also shown hypokalaemia to be less common than hyperkalaemia in CKD patients, with prevalence estimates of 1-3%[23-25]. This demonstrates that in our Australian hospital-based cohort the prevalence of potassium abnormalities in CKD patients is similar to that witnessed in other cohorts.

In the current study, male sex, lower eGFR, cardiac failure, diabetes, liver disease, endocrine pathology and genitourinary pathology were identified as characteristics associated with increased risk of hyperkalaemia. Males had a 49% higher adjusted OR of hyperkalaemia than females (OR 1.49, 95% CI 1.37-1.61), similar to other observational studies where men had a 50% higher risk of hyperkalaemia in multivariate analyses[26-28]. The pathophysiological basis for this sex discrepancy is unknown[29]. The relationship between hyperkalaemia and worsening kidney function is clearer. In the present study, there was a 32% increased risk of hyperkalaemia for every 5mL/min/1.73m^2 decline in eGFR. This is likely explained by the known effects of renal dysfunction on potassium homoeostasis[30]. The association between hyperkalaemia and diabetes also has a plausible pathophysiological mechanism. Diabetes is proposed to interact with serum potassium levels through insulin deficiency or resistance impairing transport of potassium intracellularly, or hyporeninaemic hypoaldosteronism, which is more frequently observed in diabetic patients[1]. Similarly, cardiac failure predisposes to hyperkalaemia as a result of poor cardiac output compromising renal

perfusion[4]. Renal hypoperfusion increases plasma renin levels, which stimulates aldosterone synthesis, causing increased sodium reabsorption in the proximal nephron with consequent reduced potassium excretion in the distal nephron[1]. In addition to this direct effect on potassium homeostasis, therapeutic interventions for cardiac failure, such as RAASi, may also induce hyperkalaemia[31]. In this study, patients with comorbid cardiac failure had a 15% higher adjusted OR of hyperkalaemia than those without (OR 1.15, 95% CI 1.01-1.31), supporting a previous Australian study of CKD outpatients that demonstrated a 38% increased hyperkalaemia risk in CKD outpatients with comorbid cardiac failure[22] (HR 1.38, 95% CI 1.19-1.60).

Conversely, loop diuretic and thiazide diuretic administration was associated with reduced rates of hyperkalaemia at admission. This is an expected relationship because hypokalaemia is a known adverse effect of the mechanism of action of these medications. ARB administration, however, was also associated with reduced rates of hyperkalaemia, and ACEi administration also had a trend towards lower risk of hyperkalaemia in univariate analysis. This is an unusual finding because ACEi and ARB medications are known risk factors for elevated serum potassium[6, 23, 32]. This discrepancy is likely the result of a combination of factors. Firstly, the current study design did not allow for assessment of outpatient prescriptions or compliance to RAASi medications and only those medications that were administered to patients during their hospital admission were recorded. It is likely that RAASi medications were ceased on admission to hospital in patients experiencing hyperkalaemia at presentation. Alternatively, they may have already been ceased or avoided in the outpatient setting if clinicians had previously identified these patients to be at high risk of developing hyperkalaemia.

In contrast to hyperkalaemia, thiazide diuretics, loop diuretics, calcium-channel blockers, malignancy, endocrine pathology, infectious disease, and mental/behavioural diagnoses were identified as being positively associated with hypokalaemia risk. Factors typically associated with hyperkalaemia, such as male sex, age ≥65 years, declining eGFR, diabetes and injury/poisoning were predictably associated with lower odds of hypokalaemia. These findings are consistent with previous studies in which hypokalaemia has commonly been reported in the setting of diuretic use and poor nutritional status[5, 33]. The mental/behavioural diagnosis category was inclusive of eating disorder diagnoses, which are a common cause of such nutritional deficiencies. To our knowledge, this is the first observational study in CKD patients demonstrating an association between infectious disease and hypokalaemia. Patients presenting with an infectious pathology had an adjusted OR of 2.43 (95% CI 1.91-3.08) for concomitant hypokalaemia at admission compared to those without this diagnosis. Infections may be associated with hypokalaemia as a result of vomiting, diarrhoea or antibiotics use, however, the exact reasons for the relationship in this study are unknown[24].

Previous studies from a variety of countries have shown a U-shaped relationship between serum potassium and mortality[5, 8, 9, 16, 34]. This is the first Australian study to confirm this observation. We also observed a relationship between moderate-to-severe hyperkalaemia (5.5-5.9 and ≥6.0mmol/L) and admission to ICU that has not been previously reported in patients with CKD. In view of the relationship between hyperkalaemia and mortality, this may not be surprising. Interestingly, there was no such association with hypokalaemia despite increased mortality. It is possible that clinicians may not identify hypokalaemic patients as requiring ICU because the complication has historically been treated as a less severe derangement than hyperkalaemia[23]. Further investigation into reasons for ICU admission in the study cohort is required to understand this relationship better.

Nephrologists are rarely concerned by mild abnormalities in serum potassium, however, this study suggests that patients with even only mildly deranged potassium levels ≥5.0mmol/L or <4.0mmol/L are associated with severe inpatient clinical outcomes. This significantly adds to the existing evidence that assertive treatment to maintain serum potassium within a narrow normal range is beneficial to neuromuscular outcomes in CKD[35, 36]. Treatment of hypokalaemia is relatively straightforward and typically managed with oral potassium supplements[24]. Therapy for hyperkalaemia therapy is more complex, however, and is currently in a transformative phase. Acute management of hyperkalaemia is effective in the short-term, but longer-term therapies for persistent hyperkalaemia are commonly ineffectual and not well tolerated[37]. The commonly-used potassium binder sodium polystyrene sulfonate is intolerable over the long-term and carries a risk of colonic necrosis[37]. New potassium-binding medications, Patiromer and ZS-9, have been developed, with promising results in phase 3 trials[37]. Whether any of these interventions for hyperkalaemia improve inpatient clinical outcomes in patients with abnormal serum potassium is unknown.

In conclusion, this is the first Australian study to investigate the prevalence, patient characteristics and clinical outcomes of hyperkalaemia and hypokalaemia in a hospital-based CKD population. In this large cohort of CKD patients, abnormalities in potassium were common at hospital admission, with hyperkalaemia being more prevalent than hypokalaemia. The admission potassium level had a potent and statistically significant U-shaped association with inpatient mortality and a J-shaped association with ICU requirement. Further studies are required to determine if aggressive management to return these patients to normokalaemia improves inpatient outcomes.

LIST OF ABBREVIATIONS

ACEi: Angiotensin Converting Enzyme Inhibitor

AKI: Acute Kidney Injury

ARB: Angiotensin II Receptor Antagonist

ATSI: Aboriginal or Torres Strait Islander

CCI: Charlson Comorbidity Index

CKD: Chronic Kidney Disease

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

DARE Centre: The Data Analytics Research and Evaluation Centre

eGFR: Estimated Glomerular Filtration Rate

EMR: Electronic Medical Record

ESKD: End-Stage Kidney Disease

HIV: Human Immunodeficiency Virus

ICD-10: International Classification of Diseases, Tenth Revision

ICU: Intensive Care Unit

IQR: Interquartile Range

KDIGO: Kidney Disease Improving Global Outcomes

OR: Odds Ratio

RAASi: Renin-Angiotensin-Aldosterone System Inhibitor

SD: Standard Deviation

95% CI: 95% Confidence Interval

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FIGURES & TABLES

Figure Legend

Figure 1: Selection of the study cohort
The study cohort included adult patients (aged ≥18 years) with at least two abnormal eGFR values (<60mL/min/1.73m^2) measured greater than 90 days apart between 1st January 2014 and 31st December 2018 in inpatient, outpatient or emergency department settings. Adult patients were included if they had a serum potassium test performed within 24 hours of any inpatient admission to Austin Health following their first abnormal eGFR result. Patients with end-stage kidney disease, defined as maintenance dialysis (both haemodialysis and peritoneal dialysis) or renal transplant, were excluded from the time of the procedure. Patients with greater than 20 inpatient admissions were also excluded.
Abbreviations: eGFR, estimated Glomerular Filtration Rate; measured in mL/min/1.73m^2; sK, serum potassium.

Figure 2: Distribution of admission serum potassium values
The mean admission serum potassium level in the population studied was 4.5 ± 0.6mmol/L. The minimum admission serum potassium value was 1.6mmol/L, and the maximum admission serum potassium value was 9.4mmol/L.

Figure 3: Association between admission serum potassium and clinical outcomes
All graphs show adjusted OR with 95% CI from multivariate analysis for the clinical outcomes of interest by admission serum potassium category, represented by a dot with error bars. The dotted grey line represents an OR of 1.00. Data points with 95% CIs that cross the grey line are not considered statistically significant. Models are adjusted for sociodemographic factors (including sex, age, indigenous status), eGFR, comorbidities, the principal diagnosis of the admission and medications.
Figure 3a: There is a U-shaped relationship between admission serum potassium category and inpatient mortality with a statistically significant increased OR for inpatient mortality in patients with an admission serum potassium category <3.5, 3.5-3.9, 5.0-5.4, 5.5-5.9 and ≥6.0mmol/L compared to patients with the admission serum potassium category 4.0-4.9mmol/L.
Figure 3b There is a J-shaped relationship between admission serum potassium category and ICU requirement with a statistically increased OR for ICU requirement in patients with an admission serum potassium category 5.5-5.9 and ≥6.0mmol/L compared to patients with the admission serum potassium category 4.0-4.9mmol/L.
Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Interval.

Table 1: Baseline patient characteristics of the study cohort by admission serum potassium category

		Serum Potassium Category at Admission (mmol/L)					
Characteristics	**Overall Cohort**	**<3.5**	**3.5-3.9**	**4.0-4.9**	**5.0-5.4**	**5.5-5.9**	**≥6.0**	
n (%)	11156	307 (2.75)	1341 (12.02)	7235 (64.85)	1503 (13.47)	473 (4.24)	297 (2.66)	**Pvalue[e]**
Sex, *n* (%)								<0.001*
Female	5674 (50.86)	214 (69.71)	814 (60.70)	3696 (51.09)	646 (42.91)	185 (39.11)	119 (40.07)	
Male	5482 (49.14)	93 (30.29)	527 (39.30)	3539 (48.91)	857 (57.09)	288 (60.89)	178 (59.93)	
Age, mean ±SD	77.30 ±12.03	72.86 ±14.769	76.64 ±12.46	77.64 ±11.71	77.68 ±11.88	76.75 ±12.92	75.40 ±12.87	<0.001*
Age, median (IQR)	79 (71-86)	76 (65-84)	79 (70-86)	80 (71-86)	80 (71-86)	79 (69-87)	78 (67-84)	<0.001*
Indigenous Status, *n* (%)								0.804
ATSI	36 (0.32)	1 (0.33)	4 (0.30)	22 (0.30)	6 (0.40)	1 (0.21)	2 (0.67)	
Not ATSI	10,982 (98.44)	300 (97.72)	1317 (98.21)	7128 (98.52)	1482 (98.62)	466 (98.52)	289 (97.33)	
Unknown	138 (1.24)	6 (1.95)	20 (1.49)	85 (1.17)	15 (0.99)	6 (1.27)	6 (2.00)	
eGFR, mean ±SD	45.77 ±16.55	48.11 ±19.07	49.10 ±16.46	47.68 ±15.47	40.54 ±16.29	33.51 ±15.57	27.72 ±16.90	<0.001*
eGFR, median (IQR)	46 (35-56)	47 (36-58)	50 (38-58)	48 (38-57)	41 (29-52)	33 (22-43)	26 (14-38)	<0.001*
CKD Stage[a], *n* (%)								
Stage 1/no CKD	80 (0.72)	5 (1.63)	14 (1.04)	53 (0.73)	6 (0.40)	1 (0.21)	1 (0.34)	0.074
Stage 2/no CKD	1569 (14.06)	59 (19.22)	237 (17.67)	1120 (15.48)	125 (8.32)	18 (3.81)	10 (3.37)	<0.001*
Stage 3a	4395 (39.40)	107 (34.85)	576 (42.95)	3122 (43.15)	475 (31.60)	83 (17.55)	32 (10.77)	<0.001*
Stage 3b	3196 (28.65)	82 (26.71)	359 (26.77)	2015 (27.85)	477 (31.74)	181 (38.27)	82 (27.61)	<0.001*
Stage 4	1501 (13.45)	40 (13.03)	131 (9.77)	771 (10.66)	329 (21.89)	135 (28.54)	95 (31.99)	<0.001*
Stage 5	415 (3.72)	14 (4.56)	24 (1.79)	154 (2.13)	91 (6.05)	55 (11.63)	77 (25.93)	<0.001*
Comorbid Conditions[b], *n* (%)								
CCI[c], mean ±SD	5.75 ±2.09	5.25 ±2.18	5.48 ±2.11	5.66 ±2.01	6.15 ±2.19	6.32 ±2.27	6.60 ±2.25	<0.001*
CCI, median (IQR)	5 (4-7)	5 (4-6)	5 (4-6)	5 (4-7)	6 (5-7)	6 (5-8)	7 (5-8)	<0.001*
AMI	313 (2.81)	2 (0.65)	38 (2.83)	208 (2.87)	39 (2.59)	19 (4.02)	7 (2.36)	0.137
Heart Failure	1200 (10.76)	30 (9.77)	130 (9.69)	763 (10.55)	181 (12.04)	60 (12.68)	36 (12.12)	0.205
PVD	201 (1.80)	8 (2.61)	25 (1.86)	130 (1.80)	27 (1.80)	4 (0.85)	7 (2.36)	0.533
Cerebrovascular Disease	416 (3.73)	9 (2.93)	53 (3.95)	299 (4.13)	43 (2.86)	10 (2.11)	2 (0.67)	0.003*
Dementia	279 (2.50)	13 (4.23)	38 (2.83)	176 (2.43)	39 (2.59)	6 (1.27)	7 (2.36)	0.182
Pulmonary Disease	607 (5.44)	20 (6.51)	72 (5.37)	384 (5.31)	93 (6.19)	27 (5.71)	11 (3.70)	0.495
Rheumatic Disease	80 (0.72)	3 (0.98)	6 (0.45)	62 (0.86)	4 (0.26)	3 (0.63)	2 (0.67)	0.156
Peptic Ulcer Disease	87 (0.78)	2 (0.65)	14 (1.04)	43 (0.59)	16 (1.06)	9 (1.90)	3 (1.01)	0.016*
Liver Disease	573 (5.14)	31 (10.10)	91 (6.79)	298 (4.12)	96 (6.39)	34 (7.19)	23 (7.74)	<0.001*
Diabetes Mellitus	3566 (31.96)	74 (24.10)	313 (23.34)	2207 (30.50)	589 (39.19)	215 (45.45)	168 (56.57)	<0.001*
Hemi/Paraplegia	182 (1.63)	5 (1.63)	20 (1.49)	125 (1.73)	25 (1.66)	5 (1.06)	2 (0.67)	0.660
Malignancy	926 (8.30)	34 (11.07)	121 (9.02)	578 (7.99)	138 (9.18)	33 (6.98)	22 (7.41)	0.163
HIV/AIDS	3 (0.03)	0 (0.00)	1 (0.07)	2 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	0.872
Principal Diagnosis[d], *n* (%)								
Infectious Disease	505 (4.53)	28 (9.12)	93 (6.94)	304 (4.20)	58 (3.86)	13 (2.75)	9 (3.03)	<0.001*
Neoplasm	622 (5.58)	14 (4.56)	71 (5.29)	400 (5.53)	99 (6.59)	26 (5.50)	12 (4.04)	0.405
Haematology	289 (2.59)	7 (2.28)	31 (2.31)	182 (2.52)	47 (3.13)	14 (2.96)	8 (2.69)	0.750
Endocrine/Metabolic	466 (4.18)	20 (6.51)	47 (3.50)	215 (2.97)	77 (5.12)	36 (7.61)	71 (23.91)	<0.001*
Mental/Behavioural	323 (2.90)	10 (3.26)	35 (2.61)	217 (3.00)	50 (3.33)	8 (1.69)	3 (1.01)	0.156
Neurological	318 (2.85)	5 (1.63)	39 (2.91)	219 (3.03)	37 (2.46)	13 (2.75)	5 (1.68)	0.443
Cardiovascular	2206 (19.77)	47 (15.31)	229 (17.08)	1499 (20.72)	283 (18.83)	99 (20.93)	49 (16.50)	0.004*
Respiratory	1598 (14.32)	51 (16.61)	208 (15.51)	1069 (14.78)	199 (13.24)	56 (11.84)	15 (5.05)	<0.001*
Gastrointestinal	1360 (12.19)	48 (15.64)	193 (14.39)	873 (12.07)	162 (10.78)	63 (13.32)	21 (7.07)	0.001*
Dermatological	255 (2.29)	6 (1.95)	39 (2.91)	163 (2.25)	34 (2.26)	7 (1.48)	6 (2.02)	0.552
Musculoskeletal	566 (5.07)	13 (4.23)	48 (3.58)	394 (5.45)	87 (5.79)	17 (3.59)	7 (2.36)	0.004*
Genitourinary	858 (7.69)	20 (6.51)	91 (6.79)	518 (7.16)	122 (8.12)	53 (11.21)	54 (18.18)	<0.001*
Injury/Poisoning	1181 (10.59)	19 (6.19)	142 (10.59)	790 (10.92)	157 (10.45)	45 (9.51)	28 (9.43)	0.148
Medication Administrations, *n* (%)								
ACEi	1965 (17.61)	47 (15.31)	216 (16.11)	1305 (18.04)	277 (18.43)	82 (17.34)	38 (12.79)	0.088
ARB	1978 (17.73)	51 (16.61)	238 (17.75)	1304 (18.02)	289 (19.23)	73 (15.43)	23 (7.74)	<0.001*
MRA	891 (7.99)	30 (9.77)	94 (7.01)	547 (7.56)	155 (10.31)	44 (9.30)	21 (7.07)	0.004*
β-Blocker	3709 (33.25)	97 (31.27)	448 (33.41)	2366 (32.70)	529 (35.20)	159 (33.62)	111 (37.37)	0.269
CCB	2381 (21.34)	82 (26.71)	295 (22.00)	1469 (20.30)	329 (21.89)	115 (24.31)	91 (30.64)	<0.001*

Loop Diuretic	3488	(31.27)	114	(37.13)	442	(32.96)	2159	(29.84)	497	(33.07)	153	(32.35)	123	(41.41)	<0.001*
Thiazide Diuretic	1135	(10.17)	57	(18.57)	208	(15.51)	702	(9.70)	111	(7.39)	32	(6.77)	25	(8.42)	<0.001*

Abbreviations: n, Number; SD, Standard Deviation; IQR, Interquartile Range; ATSI, Aboriginal or Torres Strait Islander; eGFR, Estimated Glomerular Filtration Rate (in mL/min/1.73m^2); CKD, Chronic Kidney Disease; CCI, Charlson Comorbidity Index; PVD, Peripheral Vascular Disease AIDS/HIV, Acquired Immunodeficiency Syndrome/Human Immunodeficiency Virus; ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; MRA, Mineralocorticoid Receptor Antagonist; CCB, Calcium-Channel Blocker.

[a]CKD stage was defined by KDIGO staging guidelines based on the eGFR value at the time of admission serum potassium calculated using the CKD-EPI formula (18, 19). Patients on renal replacement therapy (chronic dialysis or renal transplant) were excluded.

[b]Comorbidities were identified using ICD-10 diagnosis codes.

[c]CCI was calculated based on the method described in Quan *et al* at admission to Austin Health (21).

[d]Principal diagnosis was identified using ICD-10 diagnosis codes.

[e]P values were derived from the Kruskal-Wallis H test for continuous variables and Chi-square tests for categorical variables.

*P value <0.05 indicates a statistically significant difference in the patient characteristic across the serum potassium at admission categories.

Table 2: Patient characteristics associated with hyperkalaemia

	Univariate Analysis		Multivariate Analysis	
Patient Characteristics	**Unadjusted OR (95% CI)**	**P Value**	**Adjusted OR (95% CI)**	**P Value**
Sociodemographic Information				
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	1.49 (1.37-1.61)	<0.001*	1.54 (1.41-1.67)	<0.001*
Age Category				
<65 years	1.00 (reference)		1.00 (reference)	
≥65 years	0.86 (0.78-0.96)	0.008*	0.94 (0.83-1.06)	0.303
Indigenous Status				
Not ATSI or Unknown	1.00 (reference)			
ATSI	1.10 (0.56-2.18)	0.780		
eGFR (per 5mL/min/1.73m^2 decline)	1.32 (1.30-1.34)	<0.001*	1.31 (1.29-1.32)	<0.001*
Comorbidities				
Acute Myocardial Infarction	1.28 (1.00-1.63)	0.048*	1.12 (0.86-1.45)	0.408
Heart Failure	1.28 (1.15-1.42)	<0.001*	1.15 (1.01-1.31)	0.042*
Peripheral Vascular Disease	1.20 (0.90-1.60)	0.209		
Cerebrovascular Disease	0.63 (0.48-0.83)	0.001*	0.94 (0.70-1.25)	0.663
Dementia	0.78 (0.60-1.01)	0.064		
Chronic Pulmonary Disease	0.81 (0.68-0.96)	0.013*	1.00 (0.82-1.21)	0.967
Rheumatic Disease	0.68 (0.38-1.21)	0.190		
Peptic Ulcer Disease	1.53 (0.96-2.43)	0.072		
Liver Disease	1.52 (1.32-1.75)	<0.001*	1.60 (1.35-1.90)	<0.001*
Diabetes Mellitus	1.94 (1.79-2.10)	<0.001*	1.40 (1.28-1.52)	<0.001*
Hemiplegia/Paraplegia	0.85 (0.59-1.20)	0.353		
Malignancy	0.77 (0.66-0.89)	0.001*	0.94 (0.77-1.15)	0.641
AIDS/HIV	2.91 (0.84-10.14)	0.093		
Principal Diagnosis				
Infectious Disease	0.88 (0.72-1.08)	0.216		
Neoplasm	0.68 (0.56-0.83)	<0.001*	1.07 (0.81-1.41)	0.641
Haematology	1.12 (0.89-1.41)	0.344		
Endocrine/Metabolic	3.64 (3.20-4.15)	<0.001*	2.93 (2.50-3.43)	<0.001*
Mental/Behavioural	0.67 (0.52-0.87)	0.003*	0.87 (0.66-1.14)	0.312
Neurological	0.68 (0.52-0.89)	0.005*	1.03 (0.77-1.36)	0.864
Cardiovascular	1.03 (0.93-1.13)	0.622		
Respiratory	0.77 (0.68-0.87)	<0.001*	0.99 (0.85-1.14)	0.858
Gastrointestinal	0.80 (0.71-0.91)	0.001*	0.98 (0.84-1.14)	0.784
Dermatological	0.65 (0.47-0.89)	0.008*	0.74 (0.53-1.04)	0.079
Musculoskeletal	0.63 (0.50-0.78)	<0.001*	0.87 (0.68-1.11)	0.261
Genitourinary	2.15 (1.91-2.43)	<0.001*	1.30 (1.12-1.51)	<0.001*

Injury/Poisoning	0.76 (0.66-0.88)	<0.001*	1.00 (0.85-1.18)	0.987
Medications				
ACEi	0.82 (0.73-0.93)	0.001*	1.01 (0.89-1.15)	0.876
ARB	0.72 (0.63-0.82)	<0.001*	0.90 (0.78-1.03)	0.136*
MRA	0.99 (0.87-1.12)	0.853		
β-Blocker	1.10 (1.01-1.19)	0.022*	0.91 (0.83-1.00)	0.058
Calcium Channel Blocker	1.30 (1.18-1.43)	<0.001*	0.99 (0.89-1.10)	0.850
Loop Diuretic	1.19 (1.10-1.29)	<0.001*	0.89 (0.81-0.99)	0.029*
Thiazide Diuretic	0.82 (0.70-0.96)	0.013*	0.76 (0.64-0.91)	0.003*

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Interval; ATSI, Aboriginal or Torres Strait Islander; eGFR, Estimated Glomerular Filtration Rate; AIDS/HIV, Acquired Immunodeficiency Syndrome/Human Immunodeficiency Virus; ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; MRA, Mineralocorticoid Receptor Antagonist
* Patient characteristics was a P value <0.05 in univariate analysis were selected for inclusion in multivariate analysis.
** P value <0.05 in multivariate was considered statistically significant.

Table 3: Patient characteristics associated with hypokalaemia

	Univariate Analysis		Multivariate Analysis	
Patient Characteristics	**Unadjusted OR (95% CI)**	**P Value**	**Adjusted OR (95%CI)**	**P Value**
Sociodemographic Information				
Sex				
Female	1.00 (reference)		1.00 (reference)	
Male	0.52 (0.46-0.59)	<0.001*	0.48 (0.42-0.54)	<0.001*
Age Category				
<65 years	1.00 (reference)		1.00 (reference)	
≥65 years	0.47 (0.41-0.54)	<0.001*	0.53 (0.45-0.62)	<0.001*
Indigenous Status				
Not ATSI or Unknown	1.00 (reference)			
ATSI	0.85 (0.27-2.66)	0.774		
eGFR (per 5mL/min/1.73m^2 decline)	0.95 (0.93-0.97)	<0.001*	0.95 (0.93-0.96)	<0.001*
Comorbidities				
Acute Myocardial Infarction	0.42 (0.23-0.77)	0.005*	0.52 (0.28-0.96)	0.038*
Heart Failure	0.92 (0.77-1.10)	0.365		
Peripheral Vascular Disease	1.12 (0.72-1.73)	0.620		
Cerebrovascular Disease	0.60 (0.39-0.91)	0.018*	0.67 (0.43-1.04)	0.76
Dementia	1.22 (0.88-1.69)	0.228		
Chronic Pulmonary Disease	0.95 (0.74-1.20)	0.646		
Rheumatic Disease	1.95 (1.13-3.36)	0.016*	1.37 (0.77-2.44)	0.279
Peptic Ulcer Disease	0.85 (0.35-2.08)	0.728		
Liver Disease	1.90 (1.57-2.31)	<0.001*	1.26 (1.00-1.59)	0.052
Diabetes Mellitus	0.75 (0.65-0.85)	<0.001*	0.73 (0.64-0.84)	<0.001*
Hemiplegia/Paraplegia	0.90 (0.54-1.51)	0.699		
Malignancy	1.62 (1.37-1.92)	<0.001*	1.64 (1.30-2.06)	<0.001*
AIDS/HIV	7.08 (2.03-24.68)	0.002*	4.41 (0.95-20.41)	0.058
Principal Diagnosis				
Infectious Disease	2.31 (1.88-2.84)	<0.001*	2.43 (1.91-3.08)	<0.001*
Neoplasm	1.32 (1.05-1.66)	0.018*	0.85 (0.61-1.18)	0.321
Haematology	1.07 (0.75-1.52)	0.718		
Endocrine/Metabolic	1.54 (1.21-1.97)	0.001*	1.70 (1.28-2.25)	<0.001*
Mental/Behavioural	1.35 (1.00-1.80)	0.047*	1.60 (1.17-2.20)	0.004*
Neurological	0.73 (0.49-1.07)	0.110		
Cardiovascular	0.75 (0.64-0.89)	0.001*	0.94 (0.77-1.15)	0.566
Respiratory	0.85 (0.72-1.01)	0.067		
Gastrointestinal	1.30 (1.01-1.52)	0.002*	1.21(0.99-1.48)	0.063
Dermatological	0.79 (0.50-1.23)	0.300		
Musculoskeletal	0.70 (0.51-0.97)	0.030*	0.68 (0.48-0.98)	0.039*
Genitourinary	0.76 (0.59-0.99)	0.039*	1.01 (0.76-1.35)	0.922
Injury/Poisoning	0.77 (0.62-0.96)	0.018*	0.84 (0.66-1.08)	0.168*
Medications				
ACEi	0.84 (0.71-1.00)	0.057		
ARB	0.79 (0.66-0.96)	0.016*	0.60 (0.49-0.74)	<0.001*
MRA	1.11 (0.92-1.33)	0.290		
β-Blocker	0.87 (0.76-0.98)	0.024*	0.91 (0.79-1.04)	0.171
Calcium Channel Blocker	1.19 (1.03-1.38)	0.019*	1.29 (1.11-1.51)	0.001*
Loop Diuretic	1.19 (1.05-1.34)	0.005*	1.48 (1.29-1.69)	<0.001*
Thiazide Diuretic	2.11 (1.78-2.50)	<0.001*	2.76 (2.27-3.35)	<0.001*

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence Interval; ATSI, Aboriginal or Torres Strait Islander; eGFR, Estimated Glomerular Filtration Rate; AIDS/HIV, Acquired Immunodeficiency Syndrome/Human Immunodeficiency Virus; ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; MRA, Mineralocorticoid Receptor Antagonist

* Patient characteristics was a P value <0.05 in univariate analysis were selected for inclusion in multivariate analysis.

** P value <0.05 in multivariate was considered statistically significan

ABSTRACT

Background & Aims: Abnormalities in serum potassium are a well-known complication of chronic kidney disease (CKD), but little is known about their impact on inpatient outcomes. To better understand the role of dyskalaemia in hospital in-patients, we assessed the epidemiology of potassium disorders among CKD patients, and the association between admission potassium and inpatient mortality or intensive care unit (ICU) requirement.

Methods: This retrospective hospital-based cohort study (*n=11,156*) included patients with eGFR<60mL/min/1.73m^2 admitted to Austin Health between 2014 and 2018 and who had an admission potassium value. Dialysis patients or those with a renal transplant were excluded. Multivariate logistic analysis was conducted to identify factors associated with hyperkalaemia (≥5.5mmol/L) and hypokalaemia (<3.5mmol/L). Odds ratios for inpatient mortality and ICU admission between potassium categories were obtained by multivariate regression with adjustments for demographics, renal function and comorbidities.

Results: Hyperkalaemia and hypokalaemia were present in 6.86% and 2.94% of hospital admissions, respectively. In multivariate regression male sex, lower eGFR, diabetes and cardiac failure were associated with higher odds of hyperkalaemia. Thiazide diuretics, loop diuretics, infectious disease and endocrine pathology were associated with higher odds of hypokalaemia. A U-shaped association was noted between potassium and inpatient mortality. Potassium <4.0mmol/L and ≥5.0mmol/L was associated with increased mortality. Only patients with potassium ≥5.5mmol/L had increased ICU admission risk.

Conclusion: Derangements in potassium frequently occur in CKD inpatients and are independently associated with higher mortality and ICU requirement. Further studies are required to determine whether interventions to maintain normokalaemia improve outcomes in this population.

Key Words: Chronic Kidney Disease, Hyperkalaemia, Hypokalaemia, epidemiology, mortality

Figure 1: Selection of the study cohort

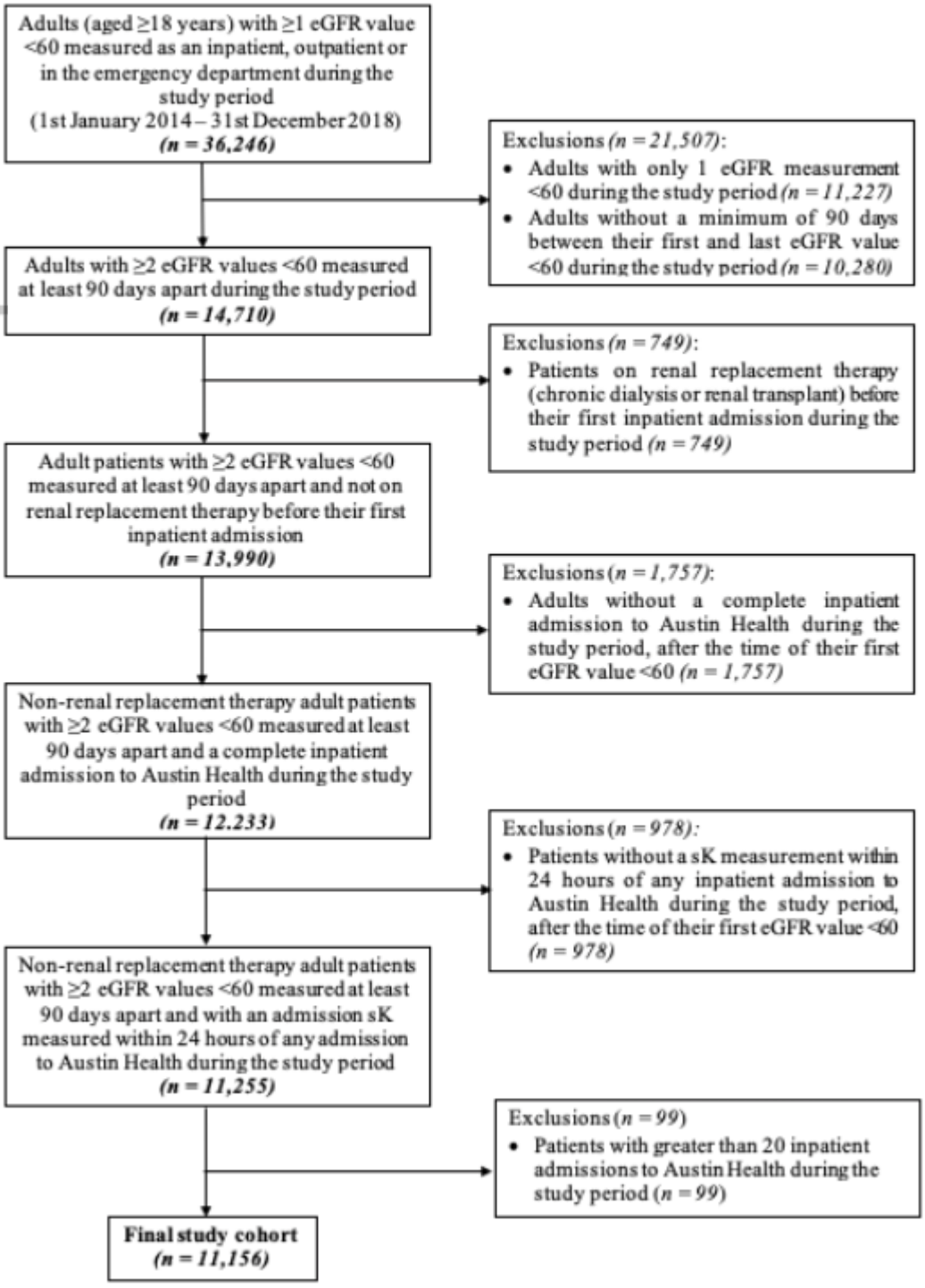


Figure 2: Distribution of admission serum potassium values

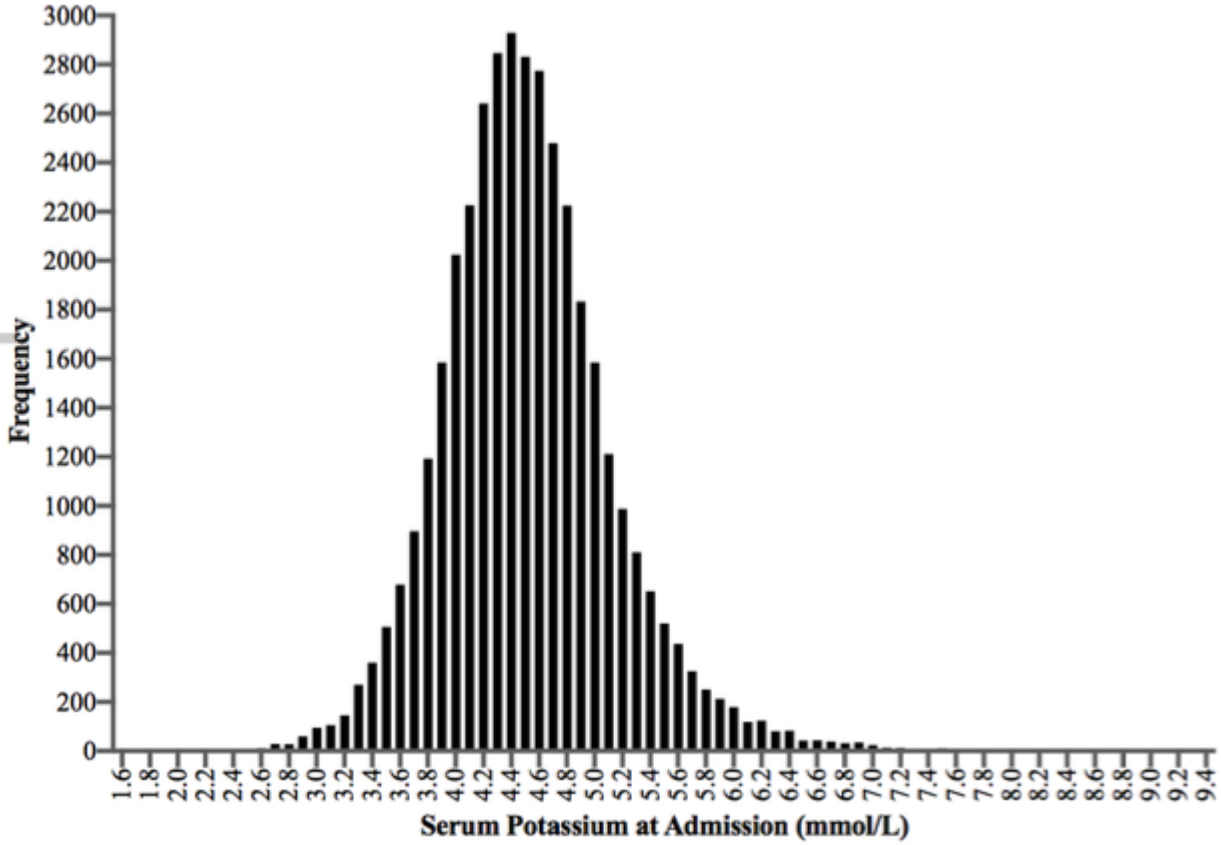


Figure 3a: Association Between Admission Serum Potassium and Inpatient Mortality

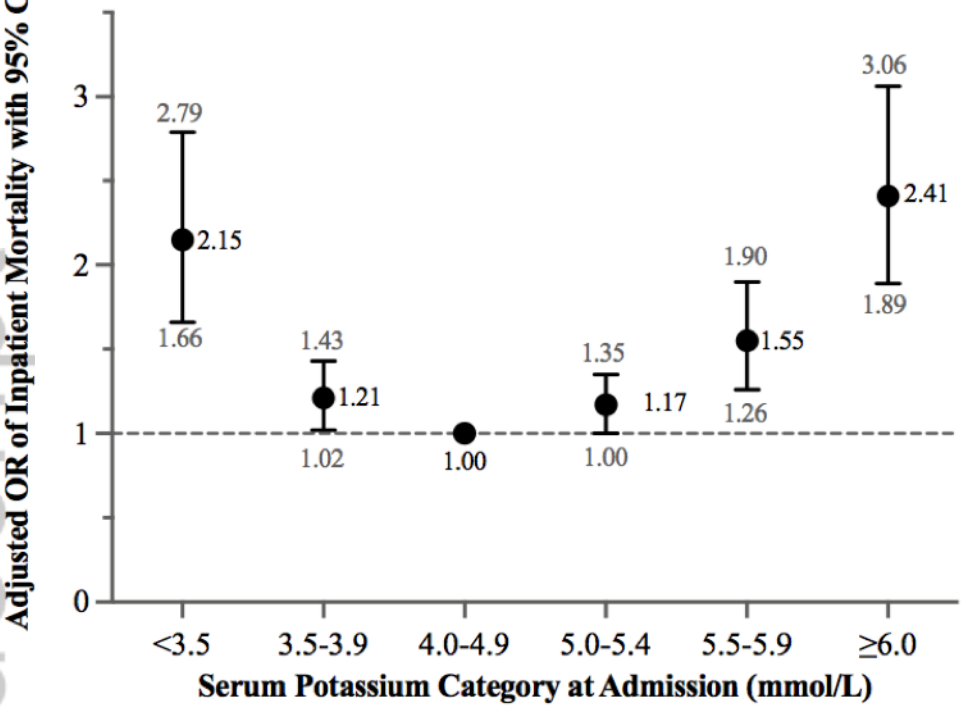


Figure 3b: Association Between Admission Serum Potassium and ICU Admission

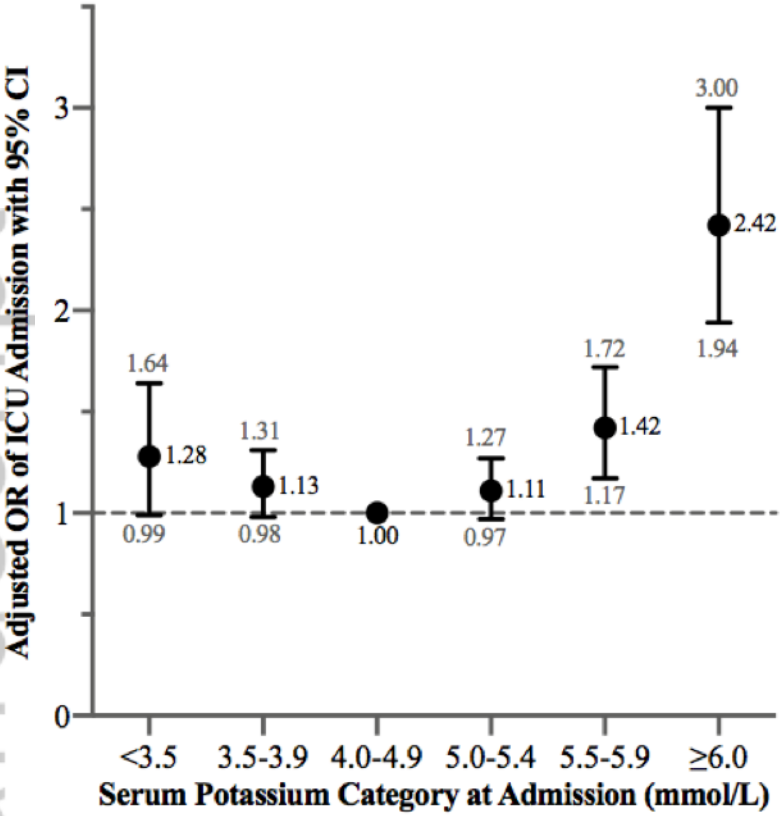
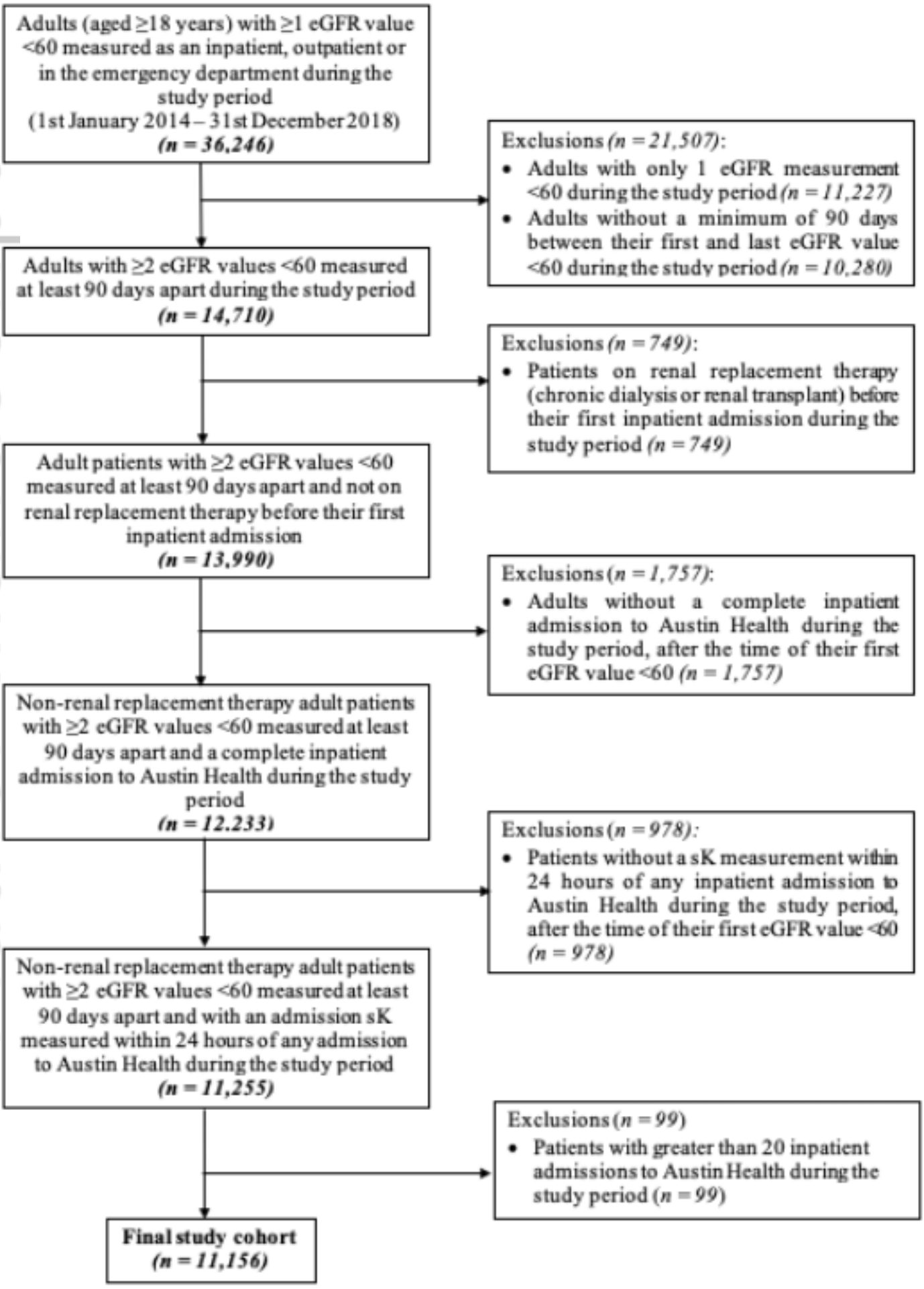
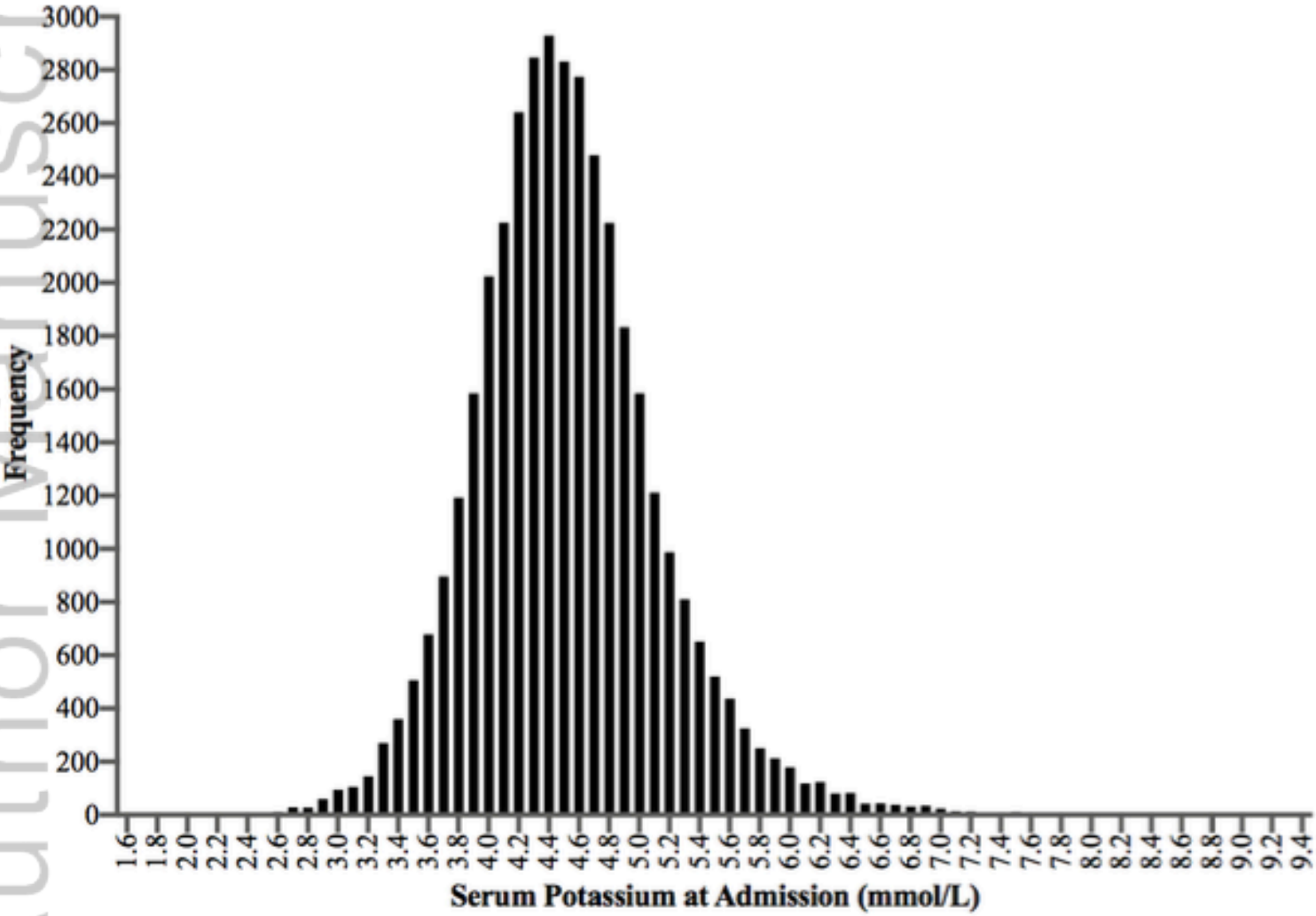


Figure 1: Selection of the study cohort



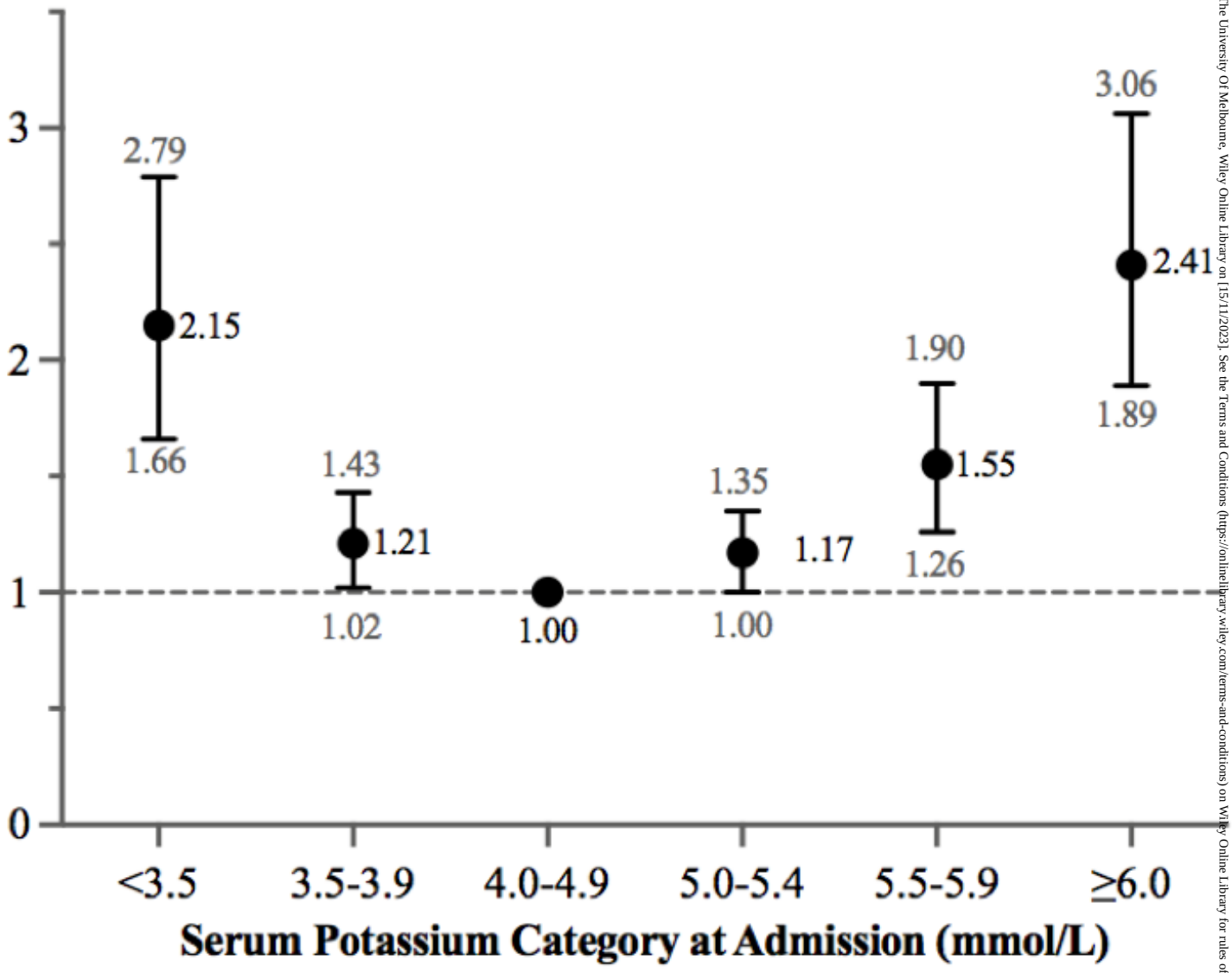
IMJ_14970_Figure 1 for Potassium Paper Submission.png

Figure 2: Distribution of admission serum potassium values



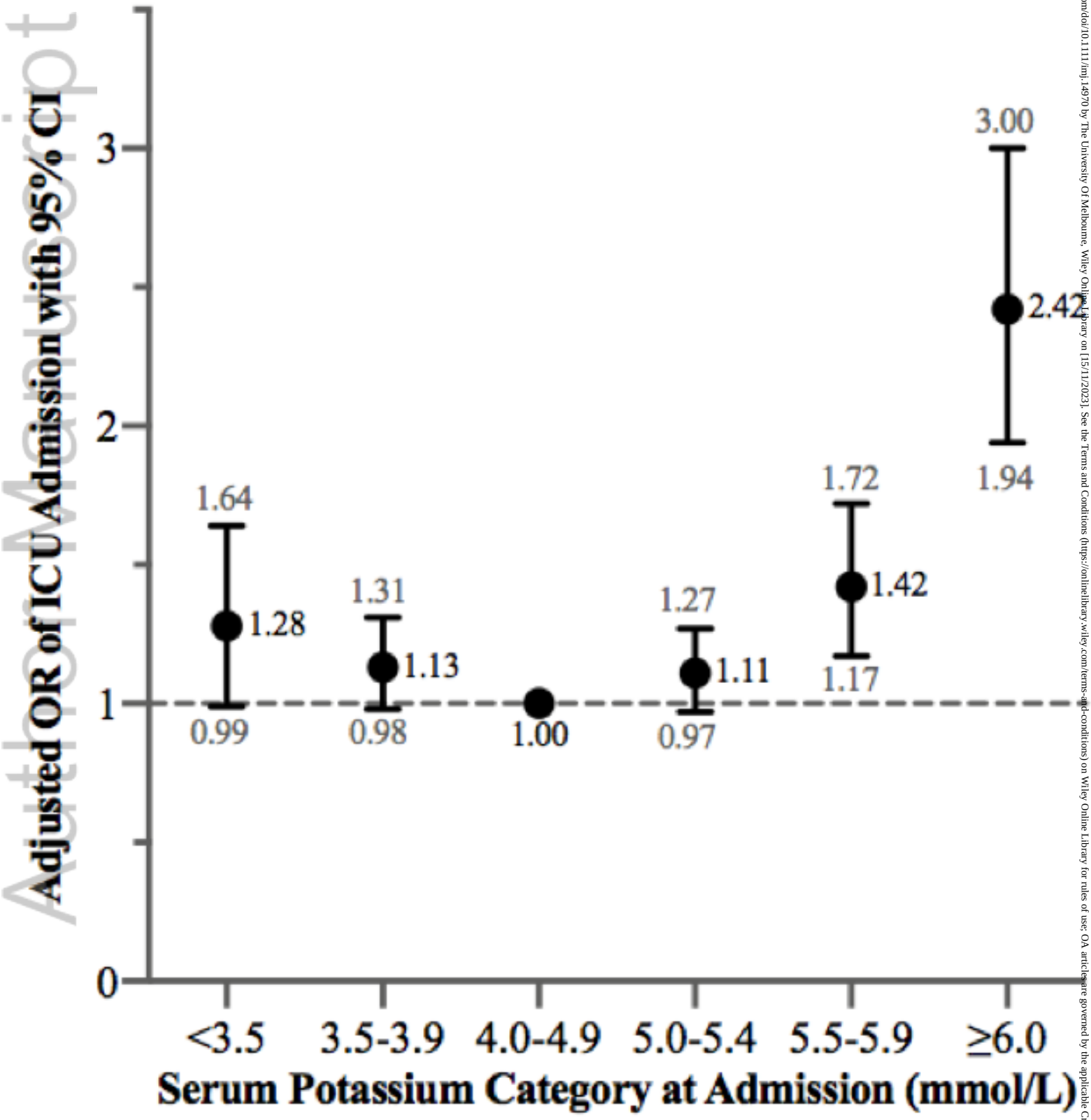
IMJ_14970_Figure 2 for Potassium Paper Submission.png

Figure 3a: Association Between Admission Serum Potassium and Inpatient Mortality



IMJ_14970_Figure 3a for Potassium Paper Submission.png

Figure 3b: Association Between Admission Serum Potassium and ICU Admission



IMJ_14970_Figure 3b for Potassium Paper Submission.png

Serum potassium in chronic kidney disease: prevalence, patient characteristics and clinical outcomes

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ABSTRACT

Background & Aims: Abnormalities in serum potassium are a well-known complication of chronic kidney disease (CKD), but little is known about their impact on inpatient outcomes. To better understand the role of dyskalaemia in hospital in-patients, we assessed the epidemiology of potassium disorders among CKD patients, and the association between admission potassium and inpatient mortality or intensive care unit (ICU) requirement.

Methods: This retrospective hospital-based cohort study (*n=11,156*) included patients with eGFR<60mL/min/1.73m^2 admitted to Austin Health between 2014 and 2018 and who had an admission potassium value. Dialysis patients or those with a renal transplant were excluded. Multivariate logistic analysis was conducted to identify factors associated with hyperkalaemia (≥5.5mmol/L) and hypokalaemia (<3.5mmol/L). Odds ratios for inpatient mortality and ICU admission between potassium categories were obtained by multivariate regression with adjustments for demographics, renal function and comorbidities.

Results: Hyperkalaemia and hypokalaemia were present in 6.86% and 2.94% of hospital admissions, respectively. In multivariate regression male sex, lower eGFR, diabetes and cardiac failure were associated with higher odds of hyperkalaemia. Thiazide diuretics, loop diuretics, infectious disease and endocrine pathology were associated with higher odds of hypokalaemia. A U-shaped association was noted between potassium and inpatient mortality. Potassium <4.0mmol/L and ≥5.0mmol/L was associated with increased mortality. Only patients with potassium ≥5.5mmol/L had increased ICU admission risk.

Conclusion: Derangements in potassium frequently occur in CKD inpatients and are independently associated with higher mortality and ICU requirement. Further studies are required to determine whether interventions to maintain normokalaemia improve outcomes in this population.

Key Words: Chronic Kidney Disease, Hyperkalaemia, Hypokalaemia, epidemiology, mortality