Inpatient and outpatient nephrology management of critically ill patients with acute kidney injury

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Running head: Nephrology care after AKI in the critically ill
ABSTRACT

Introduction: Acute Kidney Injury (AKI) during critical illness increases the risk of subsequent chronic kidney disease. Guidelines recommend inpatient nephrology assessment and review at 3 months.

Objectives: To quantify the prevalence and predictors of inpatient and outpatient nephrology follow-up of AKI patients admitted to critical care areas within a tertiary hospital.

Methods: Retrospective study of all critically ill adults with AKI between 1 January 2012 and 31 December 2016 with a baseline eGFR > 30 mL/min/1.73m² and alive and independent of renal replacement therapy for 30 days after hospital discharge. We used logistic regression models to examine the primary outcome of nephrology review at 3 months. Secondary outcomes included inpatient nephrology review, renal recovery at discharge, and the development of a major adverse kidney event (MAKE) at one year.

Results: Of 702 critically ill patients with AKI (mean age 66 years, 64% male, baseline eGFR 78 mL/min/1.73m²), 43 patients (6%) received nephrology follow up at 3 months and 63 patients (9%) at one year. Nephrology follow up occurred more frequently in patients with a higher baseline creatinine, a higher discharge creatinine, and greater severity of AKI. Seventy patients (10%) underwent inpatient nephrology review. Overall, 414 (59%) had recovery of renal function by the time of discharge and 239 (34%) developed a MAKE at 12 months.

Conclusion: Inpatient and outpatient nephrology follow-up of AKI patients after admission to a critical care area was uncommon although one third developed a MAKE. These findings provide the rationale for controlled studies of nephrology follow-up.
INTRODUCTION

Acute Kidney Injury (AKI) is a frequent complication of critical illness, occurring in between one and two thirds of patient admissions to Intensive Care Units (ICUs).\textsuperscript{1,2} Patients with AKI have a 41\% increased risk of mortality attributable to AKI within 2 years of admission, with an association between AKI severity and risk of death.\textsuperscript{3} AKI is also associated with significant non-renal complications, affecting multiple systems and carrying additional mortality and morbidity risk.\textsuperscript{4} There is emerging recognition of the long-term significance of AKI, with a significant association between AKI and patient-centred outcomes including in-hospital and post-discharge mortality, as well as the development of Chronic Kidney Disease (CKD), End-Stage Kidney Disease (ESKD), and cardiovascular complications.\textsuperscript{1,5-7} AKI during hospital admission provides an important opportunity to identify patients at high risk of CKD, with the potential to provide meaningful interventions to prevent or delay progression to CKD.

Among patients with CKD, review by a nephrologist earlier in the disease progress is associated with improved mortality when dialysis becomes necessary.\textsuperscript{8} Moreover, nephrologist follow-up appears associated with greater compliance with recommended CKD screening and risk-factor management.\textsuperscript{9} In the context of AKI, observational evidence supports a benefit from nephrologist review following admission with AKI, though the optimal model of care following AKI remains uncertain.\textsuperscript{10} There appears to be significant disparity between nephrologist opinions regarding hypothetical case follow-up and real-world data, with significant overestimation of the ideal follow-up rate.\textsuperscript{11} International guidelines suggest that all patients with AKI should undergo evaluation at 3 months to screen for new or progressive CKD.\textsuperscript{12}

Previous work has assessed nephrology follow-up after hospital admission with AKI. Estimates of the rate of nephrology follow-up appear to vary between health care systems and by
severity of AKI, and range from 8.6-24% among all patients with AKI\textsuperscript{11,13-15}, to as high as 40.8% among AKI patients requiring acute dialysis\textsuperscript{10}. Although critically ill patients are at higher risk of developing an AKI compared with general ward patients, the rate of nephrology follow-up in this group remains unknown.\textsuperscript{1} We aimed to establish the rate and predictors of follow-up after admission to a critical care unit with AKI, and to investigate the frequency of inpatient nephrology review, renal recovery, and major adverse kidney events (MAKEs) in the 12 months after discharge.

METHODS

Study design

This was a single-centre retrospective observational study using patient records from Austin Health, a large teaching hospital in Melbourne, Australia. The collection and analysis of these data was approved by the Austin Health Human Research Ethics Committee (LNR/18/Austin/286) and the need for informed consent was waived because all data were de-identified, and the authors did not have access to identifying information as part of the analysis. All reporting was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.\textsuperscript{16} In the Australian health care setting, continuous renal replacement therapy is prescribed by the intensive care medical team and administered by intensive care nurses. There is variable referral to and consultation from the nephrology service regarding the initiation, prescription, or cessation of continuous renal replacement therapy. Rather, consultations are made at the clinical discretion of the admitting medical officer or treating intensivist, or at the time of intensive care discharge if ongoing renal replacement therapy is required.
Study population

All adult patients (≥18 years) admitted to the intensive care or coronary care units with AKI between 1 January 2012 and 31 December 2016 were included in the study. AKI was identified using the International Classification of Diseases, Tenth Revision (ICD-10) code. The diagnosis of AKI was confirmed using serum creatinine measurements, and its severity was graded according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The KDIGO criteria define AKI as a rise in serum creatinine of at least 26.5 umol/L in 48 hours or as a >50% increase in serum creatinine from baseline within 7 days. Urine output criteria were not assessed. Patients were excluded if they did not meet the KDIGO criteria for AKI, if they had received chronic renal replacement therapy prior to the index hospitalisation, if their estimated glomerular filtration rate (eGFR) was <30 mL/min/1.73m2) at baseline, or if their AKI was attributed to intrinsic renal disease (i.e. glomerulonephritis, vasculitis, lupus nephritis, thrombotic microangiopathy, or pregnancy-related renal disease). Patients who experienced multiple episodes of AKI were only included in the study once.

Data collection

Baseline characteristics (age, sex, comorbidities) were evaluated at hospital admission using hospital administrative and pathology databases. Comorbidities included cigarette smoking, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, chronic heart failure, arrhythmia, valvular heart disease, lung disease, liver disease, haematological malignancy, solid organ malignancy and rheumatoid disease. Data pertaining to admission source (home, nursing home, other), admission type (emergency, elective, other), admitting unit (general medicine, specialty medicine, general surgery, specialty surgery), length of stay (hospital, coronary care, intensive care), requirement for mechanical
ventilation, cause of AKI (sepsis, cardiac surgery, other), discharge destination (home, nursing home, other), and discharging unit (general medicine, specialty medicine, general surgery, specialty surgery) were also collected. The date of death was extracted from the hospital medical record; cause of death was not available. Hospital progress notes were manually reviewed for inpatient nephrology review as this data is not otherwise captured by our administrative databases. All serum creatinine, HbA1c, glucose, lipid, and urine albumin creatinine ratio measurements performed in the 12 months prior to and after index admission were extracted from the pathology database.

Baseline kidney function was derived from serum creatinine measurements within the 12 months prior to index admission and estimated as the median value. For patients who did not have a serum creatinine measurement within that period, the trough inpatient serum creatinine value was used. Baseline eGFR was computed based on age, sex and serum creatinine level using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) equation. Other derived indices included an Accessibility/Remoteness Index of Australia Plus (ARIA+) score, an index of the remoteness of a patients place of residence, as a reflection of the accessibility of services. Regional or remote was defined as an Accessibility/Remoteness Index of Australia (ARIA+) score greater than 3. The start of follow-up was defined as the date of hospital discharge. Patients were followed until death, loss to follow up, or for 365.25 days.

Clinical outcomes

The primary outcome of the study was outpatient nephrology review within the first year of hospital discharge. Secondary outcomes included inpatient nephrology review, renal recovery
at discharge, and the development of a MAKE at one year. The dates of inpatient and outpatient nephrology visits were determined by hand-searching all paper and electronic medical records. Renal recovery was considered to have occurred if the discharge serum creatinine was not >25% higher than the baseline value. A MAKE was defined as the composite of new or progressive chronic kidney disease (25% reduction in eGFR from baseline sustained for a minimum of 3 months), end-stage kidney disease (eGFR ≤15 mL/min/1.73m² sustained for a minimum of 3 months) or initiation of chronic renal replacement therapy in the form of haemodialysis, peritoneal dialysis, or kidney transplantation, or death. Definitions of renal recovery and MAKE are in keeping with previously published work.6,20-21

**Statistical analyses**

Baseline characteristics were expressed as frequencies and percentages, means and standard deviations, or medians and interquartile ranges (IQR), as appropriate. Between group comparisons were performed by the chi squared test, unpaired t-test, or Wilcoxon rank sum test, as dictated by data type. Univariable and multivariable logistic regression models were used to examine the primary and secondary outcomes. The multivariable model included variables associated with the outcome of interest based on univariable analyses with a p value <0.2 or biologic plausibility. Pre-specified first-order interaction terms between covariates were examined (baseline creatinine, discharge creatinine, acute kidney injury stage). Linearity assumptions were verified by dividing continuous variables into quartiles. Only individuals with complete comorbidity and outcome data were included in the final analyses; no imputation for missing data was performed. A sensitivity analysis examining predictors of outpatient nephrology follow up at 12 months was also performed. Data were analysed using Stata/SE14.0 (College Station, TX). Two-sided p values <0.05 were considered statistically significant.
RESULTS

Between 1 January 2012 and 31 December 2016, 778 critically ill patients were allocated an ICD-10 code for AKI (Figure 1). Of these, 328 patients met the criteria for stage 1 AKI (47%), 185 met the criteria for stage 2 AKI (26%), 119 met the criteria for non-dialysis stage 3 AKI (17%), and 70 patients (10%) met the criteria for acute dialysis-requiring stage 3 AKI. Seventy-six patients did not meet the KDIGO criteria for AKI and were excluded from the study. A total of 483 patients (69%) were admitted to ICU, 81 were admitted to the coronary care unit (CCU) (12%), and 138 patients (20%) were admitted to both ICU and CCU. The most common diagnoses were sepsis (27%) and cardiac surgery (17%).

The mean patient age was 66 ± 14 years, 64% were males (n=447), and 17% lived in a regional or remote area (n=122). The mean baseline creatinine was 85 ± 29 umol/L and the mean baseline eGFR was 78 ± 25 mL/min/1.73m². By the time of discharge, the mean creatinine had increased to 106 ± 50 umol/L, while the mean eGFR had decreased to 66 ± 27 mL/min/1.73m². The median number of blood tests performed in the 12 months prior to admission, during admission, and between discharge and the end of follow up were 5 (IQR 2-12), 25 (IQR 12-48) and 11 (IQR 4-27), respectively. Only 7 people had missing data on covariates for the primary analysis (<1%). Baseline characteristics of the study population are described in Table 1.

Outpatient Nephrology review

At 3 months, a total of 43 (6%) patients had been reviewed by a nephrologist (Supplementary table S1). Patients who underwent nephrology review were more likely to have a higher baseline serum creatinine value (OR 1.34 per 10 umol/L increase, 95% CI 1.20 to 1.49, p<0.001),
a greater severity of AKI (stage 2 OR 2.12, 95% CI 0.75 to 6.01; stage 3 OR 9.04, 95% CI 3.76 to 21.73, overall p value <0.001), or a history of peripheral vascular disease (OR 2.24, 95% CI 1.07 to 4.68, p=0.03) (Figure 2). Age (OR 0.83 per decade, 95% CI 0.64 to 1.06, p=0.14) was not significantly associated with outpatient nephrology follow up. There was no interaction between AKI stage and baseline serum creatinine (p = 0.98). Linearity assumptions were not violated for baseline serum creatinine (quartile 1 OR 1.00; quartile 2 OR 1.44; quartile 3 OR 2.93; quartile 10.64) or age (quartile 1 OR 1.00; quartile 2 OR 0.86; quartile 3 0.68; quartile 4 OR 0.53). All variables included in the final multivariable model were included on the basis of both statistical significance and biological plausibility.

**Inpatient nephrology review**

Only 70 critically ill patients with AKI (10%) underwent review by the nephrology team during their inpatient stay. This included 2% of patients with stage 1 AKI (n=5), 6% of patients with stage 2 AKI (n=12) and 28% of patients with stage 3 AKI (n=53) (Figure 3). Fewer than half (n=34, 48%) of patients who received acute renal replacement therapy were seen by the nephrology team. Of all patients seen as an inpatient, only 41% (n=29) were followed up within 3 months as an outpatient, while only 2% of patients (n=14) who were not seen as an inpatient were subsequently reviewed as outpatients. Inpatient review was more likely in patients with more severe AKI and in those with a higher baseline serum creatinine or a history of hypertension.

**Renal recovery at discharge**

More than half of patients experienced recovery of renal function to within 25% of baseline by hospital discharge (n=414, 59%; Supplementary table S2). Only 13 (3%) patients who recovered renal function received outpatient follow up compared to 30 (10%) of those who did
not fully recover. Recovery was more likely in patients with a higher baseline serum creatinine and less likely in patients with more severe AKI or cardiovascular disease (Figure 4). Diabetic status and liver disease were not significant predictors of the likelihood of recovery.

Major adverse kidney event
In the first year after hospital discharge, one or more MAKEs occurred in approximately one-third of patients (n=239, 34%; Supplementary table S3). Of these, 79 patients (11%) died, 168 patients (24%) developed new or progressive chronic kidney disease, and 7 patients (1%) reached end-stage kidney disease. MAKEs occurred more often in patients who were older and in those with more severe AKI or a history of liver disease, diabetes, or malignancy (Figure 5).
DISCUSSION

Key findings
We studied the practice patterns of inpatient and outpatient nephrology care for critically-ill patients with AKI. Only one in ten patients received inpatient nephrology review, including only one in five patients with stage 3 AKI. Many patients had not experienced renal recovery by the time of hospital discharge and one-third of patients who survived to 30 days after hospital discharge developed a MAKE by the end of the first year. Moreover, despite this poor prognosis, nephrology outpatient follow-up only occurred in 6% of patients at 3 months post-discharge. Even among patients that failed to fully recover their renal function to baseline, outpatient nephrology follow-up only occurred 10% of the time. Finally, nephrology review was predicted by severity of AKI and baseline serum creatinine in both inpatient and outpatient settings, while additional predictors were history of hypertension for inpatient review, and history of peripheral vascular disease for outpatient review.

Relationship to previous studies
This is the first study to report inpatient and outpatient nephrology care practices in an Australian healthcare setting, and the only study to have focused on patients admitted to critical care units, a group particularly vulnerable toMAKEs after AKI. Previous studies reported higher follow up rates after AKI. However many of these studies were biased since they defined AKI by hospital administrative coding and the requirement for renal replacement therapy. After excluding patients over 80 years of age and/or with advanced cancer, Khan et al’s Scottish cohort of 1989-1990 demonstrated a follow-up rate of 34%. The two Canadian studies from Harel et al for 1996-2008 and Karsanji et al for 2005-12 demonstrate similar follow-up rates of 40.8% and 24%. Follow-up practices have also been reported to be low in
the United States: the USRDS data for 2012 reported a 12.7% nephrology review rate at 3 months, increasing to 18.8% by 12 months.\textsuperscript{12}

Although these findings are concerning, few studies have investigated the effect of nephrology follow-up on the risk of major adverse kidney events. A recent systematic review and meta-analysis found that patients who were followed-up had a 22% lower relative risk of mortality compared with patients who were not.\textsuperscript{22} Nephrology follow-up did not appear to improve the composite of permanent dialysis and recurrent AKI. However, all studies were underpowered and at high risk of bias. Active randomised controlled trials (NCT02483039 and ACTRN12618002044202) are expected to provide better quality evidence in relation to this issue.

\textit{Implications of study findings}

This study implies that, in the Australian setting, nephrology follow-up of critical care patients with AKI is likely low and not aligned with international consensus guidelines.\textsuperscript{12} Moreover, it implies that many as one in four patients may develop progressive CKD within the 12 month follow-up period. Finally, it implies that only one in ten AKI patients underwent review by the nephrology team even during their inpatient stay.

\textit{Strengths and limitations}

The primary strength of our study is its nature as the first study to have specifically examined nephrology follow-up of critically-ill patients with AKI in an Australian tertiary hospital setting. Our study benefitted from a large dataset of patient admission data, with capture of both inpatient and outpatient episodes within our hospital network. The analysis was made more robust by the continuous use of the same electronic patient record during the study period,
with laboratory test results from before and during admission in essentially (>99%) all cases. We chose to use standard consensus definitions of AKI, and captured patient data according to ICD-10 coding, which we suggest supports broad representativeness of critically-ill patients with AKI in other Australian tertiary hospitals.

Our findings are limited by the uncertainty around the patients that did not receive nephrology follow-up at our centre. We were unable to capture nephrology follow-up that might have occurred in the private setting or at other health services. We estimate that the effect of this limitation on our findings is small based on the geographically grouped nature of care in our state, the high likelihood of follow-up preferentially taking place in the public hospital of recent admission and the stability of the population served by our institution. Additionally, as a single-centre study, the generalisability of our data to other settings may be limited. However, our hospital has all the typical characteristics of other tertiary referral centres in Australia and, probably, in similar high-income countries. Finally, we have no data to examine the reasons for patients not being reviewed in the nephrology outpatient clinic. Thus, we cannot provide an explanation for the aetiology of failure to follow up.

Conclusions

Inpatient and outpatient nephrology review of patients admitted to a critical care unit of a tertiary teaching hospital with AKI was low and less than recommended by relevant guidelines. The high rate of MAKEs in the 12 months after critical care admission with AKI provides the rationale for future controlled studies of nephrology follow-up.
REFERENCES


FIGURE LEGENDS

Figure 1. CONSORT diagram

Figure 2. Multivariable logistic regression analysis of outpatient nephrology review at 3 months in critically ill adults with acute kidney injury

Figure 3. Multivariable logistic regression analysis of inpatient nephrology review in critically ill adults with acute kidney injury

Figure 4. Multivariable logistic regression analysis of renal recovery at discharge in critically ill adults with acute kidney injury

Figure 5. Multivariable logistic regression analysis of major adverse kidney events at 12 months in critically ill adults with acute kidney injury
Table 1. Baseline characteristics of 702 critically ill patients hospitalised with acute kidney injury between 2012 and 2016 according to 3 month follow up status.

<table>
<thead>
<tr>
<th></th>
<th>All (n = 702)</th>
<th>No follow up (n=659)</th>
<th>Follow up (n=43)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Male</td>
<td>447 (64)</td>
<td>415 (63)</td>
<td>32 (74)</td>
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<td>Age, years</td>
<td>65.6 (14.4)</td>
<td>65.8 (14.3)</td>
<td>61.9 (14.7)</td>
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<td>Smoking</td>
<td>329 (47)</td>
<td>307 (47)</td>
<td>22 (51)</td>
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<td>Diabetes</td>
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<td>256 (39)</td>
<td>19 (44)</td>
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<td>242 (37)</td>
<td>22 (51)</td>
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<td>Vascular disease</td>
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<td>274 (42)</td>
<td>23 (53)</td>
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<td>Cerebrovascular disease</td>
<td>64 (9)</td>
<td>58 (9)</td>
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<td>Cardiovascular disease</td>
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<td>191 (29)</td>
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<td>Peripheral vascular disease</td>
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<td>111 (17)</td>
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<td>Chronic heart failure</td>
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<td>Arrhythmia</td>
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<td>319 (48)</td>
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<td>149 (23)</td>
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<td>Haematological disease</td>
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<td>645 (98)</td>
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<td>Malignancy</td>
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<td><strong>Nil</strong></td>
<td>562 (80)</td>
<td>525 (80)</td>
<td>37 (86)</td>
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<td>88 (13)</td>
<td>85 (13)</td>
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<td>Baseline creatinine umol/L</td>
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<td>83.6 (27.7)</td>
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<td>Baseline eGFR mL/min/1.73m²</td>
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<td>185 (26)</td>
<td>178 (27)</td>
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<td>Stage 3</td>
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<td>189 (27)</td>
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<td>Discharge creatinine umol/L</td>
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<td>&lt;0.001</td>
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<td>15 (9, 28)</td>
<td>21 (13, 29)</td>
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<td>------------------------------</td>
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<td>CCU length of stay, days</td>
<td>2.5 (1.3, 4.1)</td>
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<td>2.2 (1.0, 4.1)</td>
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<td>381 (54)</td>
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<td>Home</td>
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<td>588 (89)</td>
<td>35 (81)</td>
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<td>Nursing home</td>
<td>25 (4)</td>
<td>25 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>54 (8)</td>
<td>46 (7)</td>
<td>8 (19)</td>
<td></td>
</tr>
</tbody>
</table>
778 critically ill adults were allocated an ICD-10 code for acute kidney injury between Jan 2012 and Dec 2016

76 patients did not meet KDIGO criteria for acute kidney injury

702 patients were included
   Stage 1: 328
   Stage 2: 185
   Stage 3: 189
   (Dialysis: 70)

7 patients were missing data on covariates in the primary analysis

43 patients received outpatient Nephrology review at 3 months

78 patients received inpatient Nephrology review

414 patients experienced renal recovery by hospital discharge

239 patients experienced a major adverse kidney event at 1 year
OR 2.12 (95% CI 0.75 to 6.01, p <0.001)

OR 9.04 (95% CI 3.76 to 21.73, p <0.001)

OR 0.83 (95% CI 0.64 to 1.06, p = 0.14)

OR 1.34 (95% CI 1.20 to 1.49, p <0.001)

OR 2.24 (95% CI 1.07 to 4.68, p = 0.03)
NEP_13838_Figure 3.png
AKI stage

Stage 2

Stage 3

Age (per 10 years)

Liver disease

Diabetes

Cancer

Cardiovascular disease

OR 1.76 (95% CI 1.18 to 2.62, p = 0.006)

OR 2.21 (95% CI 1.45 to 3.35, p <0.001)

OR 1.22 (95% CI 1.06 to 1.40, p = 0.005)

OR 2.12 (95% CI 1.38 to 3.25, p = 0.001)

OR 1.43 (95% CI 1.03 to 2.00, p = 0.03)

OR 1.76 (95% CI 1.17 to 2.65, p = 0.006)

OR 1.36 (95% CI 0.92 to 2.00, p = 0.12)
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