Impact of acute kidney injury on major adverse cardiovascular events in intensive care survivors

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Abstract

Background: Acute kidney injury commonly occurs in patients admitted to ICU. After acute kidney injury, kidney function may not completely recover leading to increased risk of future cardiovascular events. We sought to ascertain the rates of cardiovascular events in ICU survivors and if these rates were affected by the presence of acute kidney injury whilst in ICU.

Methods: This retrospective observational cohort study utilised routinely collected data to identify patients who had survived an admission to one of two ICUs between July 2015 and June 2018. Baseline serum creatinine and subsequent values were used to identify acute kidney injury. Major adverse cardiovascular events described were myocardial injury, coronary artery intervention, or radiological evidence of stroke.

Results: Of the 3994 ICU survivors, major adverse cardiovascular events were identified in 385 patients (9.6%; 95% confidence interval [CI] 8.8–10.6%). Presence of acute kidney injury whilst in ICU was significantly associated with future major adverse cardiovascular events (hazard ratio = 1.38; 95% CI 1.12–1.70; P-value = 0.003) and future biochemical myocardial injury (hazard ratio = 1.48; 95% CI 1.16–1.89; P-value = 0.001). Acute kidney injury did not have a statistically significant association with future coronary artery interventions or future cerebrovascular events.

Conclusions: One in 10 ICU survivors experiences a major adverse cardiovascular event after discharge. Acute kidney injury whilst in ICU was associated with an increased risk of major adverse cardiovascular events and specifically myocardial injury. Further research is warranted on whether ICU survivors with acute kidney injury merit enhanced strategies for cardiovascular protection.

Keywords: acute kidney injury; cardiovascular disease; intensive care; long-term outcomes

Acute kidney injury (AKI) is a significant healthcare burden worldwide. It is associated with increased risk in both short- and long-term mortality and development of subsequent chronic kidney disease (CKD) and cardiovascular disease.1–4 The link between CKD and cardiovascular disease such as coronary artery disease, acute myocardial infarction, and cerebrovascular events has been previously described in detail.5 There are multiple mechanisms implicated in this process: hypertension and kidney function are intrinsically linked; chronic low grade inflammation of blood vessels; and premature arteriosclerosis and vascular calcification.6 A combination of these factors is thought to contribute to increased stimulation of inflammatory pathways and increased risk of developing cardiovascular disease. This is
well documented in patients with CKD, but an increased risk profile has also been expressed after an episode of AKI; a previous study noted that acute myocardial infarction and heart failure are significantly more likely after AKI over long-term follow-up.6

In addition to the increased risk of cardiovascular disease associated with AKI, there are also data indicating that the incidence of major cardiovascular events is elevated after critical illness; a study carried out on survivors of severe sepsis found that they carried a 13-fold higher risk of cardiovascular events compared with a control group.7 A similar cohort of sepsis patients were found to have a higher risk of myocardial infarction, ischaemic stroke, haemorrhagic stroke, heart failure, and sudden cardiac death.8 Sepsis is a common reason for admission to the ICU and ICU survivors may potentially suffer from similar risks.

The aim of this study was to identify rates of adverse cardiovascular outcomes in ICU survivors and to determine if AKI whilst admitted to ICU was independently associated with increased risk of these adverse outcomes.

Methods

This was a retrospective observational study of patients that utilised routine health data. Ethical approval was granted by National Health Services London-Surrey Research and Ethics Committee (Ref: 18/LO/2060); the findings are reported based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.9

Inclusion criteria

All adult patients aged 16 yr or older admitted to two large Scottish general adult ICUs who survived to 30 days after hospital discharge were included. Only the first ICU admission during the study period was included. Patients were excluded if they lived in an area outside the West of Scotland as no follow-up data would be available. Patients receiving long-term kidney replacement therapy, including prior kidney transplantation, were also excluded. The sample size was determined by the number of patients identified over the predetermined study period.

Data collection

Patients admitted to ICU between 1 July 2015 and 30 June 2018 who survived hospitalisation were identified using the Scottish Intensive Care Society Audit Group (SICSAG) Wardwatcher™ database which collects data on all patients admitted to ICU in Scotland. The patient identifiers for those admitted to ICU were input into the Strathclyde Electronic Renal Patient Record (SERPR) database (VitalPulse, Chelmsford, UK): this electronic patient record system was in use in the six Scottish health boards included in the study. SERPR has active interfaces that automatically retrieve data from laboratory, radiology, and death records, which ensured important outcomes were available for this study. Full details are described in previously published work on the same patient cohort.10

Baseline variables including age, sex, admitting specialty and admission diagnosis were retrieved from the ICU SICSAG database. The admitting specialty was dichotomised into medical or surgical; admission diagnoses were organised into 25 broad groups (Supplementary Table S1). Pre-existing comorbidities were identified using data in Philips Carevue™ electronic ICU patient records.

Definition of AKI

Pre-admission serum creatinine results were used to calculate a baseline value for each patient: a validated automated system was used to select the most appropriate reference11 which comprised either the median value from 8 to 365 days before admission or the lowest value in the week leading up to the time of admission. In addition, this reference value was used to calculate a baseline estimated glomerular filtration rate (eGFR) using the CKD-EPI equation.12 The highest serum creatinine value during admission was then compared against the reference value or records indicating receipt of kidney replacement therapy were then used to diagnose AKI using Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.13

Definition of cardiovascular events

The primary outcomes for this study were rates of major adverse cardiovascular events (MACE) in ICU survivors and analysis of variables which may be associated with change in risk of developing these events. MACE was defined as a composite endpoint of myocardial injury as identified by troponin positive events, coronary artery interventions, and cerebrovascular events. Secondary outcomes were rates of individual outcomes in ICU survivors, and analyses of potentially associated variables.

All high sensitivity cardiac troponin values from 30 days after hospital discharge onwards were collected—a myocardial injury was registered if the plasma concentration of high sensitivity troponin-I was found to be higher than the laboratory’s standard upper limit for normal: 34 ng L⁻¹. All troponin measurements were performed using the Abbott Laboratories assay. Angiography results were collected using linkage to databases which contained the reported results: these were each reviewed to identify subsequent percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) that occurred from 30 days after hospital discharge.

All cerebral radiology reports from 30 days after hospital discharge onwards were collected using linkage to databases with stored reports. These were subsequently interpreted for the presence of either haemorrhagic or ischaemic cerebrovascular events by a radiologist: the first occurrence of either of these for an individual patient was taken as the time point for a positive cerebrovascular event.

Statistical analysis

All statistical analyses were conducted using the software package R (version 3.6.2; R Foundation for Statistical Analysis, Vienna, Austria). Variables were summarised using median values and inter-quartile range (IQR) or by proportions with 95% confidence interval (95% CI). Differences in median values were compared using the Wilcoxon rank-sum test, whereas differences in proportions were compared using the Pearson χ² test. A sensitivity analysis was pre-planned for patients with missing median serum creatinine values from the preceding year. Kaplan–Meier estimators were used to predict time to event; log-rank test was then used to determine differences between the event curves.
Regression analysis was used to identify factors associated with MACE, subsequent myocardial injury, cerebrovascular events, or coronary artery interventions. Initial univariable analyses were performed on each collected variable. Univariable P-values <0.2 were included in any multivariable model; key variables of presence of AKI, age, and sex were included regardless of univariable values.

For myocardial injury, analyses of variables were conducted using a Cox proportional hazards model which were reported as hazard ratio (HR) and 95% CIs. To ascertain if each variable met the proportionality assumption, Schoenfeld residuals were calculated. For cerebrovascular events/coronary artery interventions, where there was a small number of events, logistic regression was used to calculate adjusted odds ratios (OR) and 95% CIs—this was done at 12 months to ensure a complete follow-up period for all patients in the study population.

For all analyses, a statistical significance was set at a two-sided P-value of <0.05.

Results
A total of 5334 patients were admitted to ICU during the study period: 3994 eligible patients survived to 30 days after hospital discharge (Fig. 1). The median age of all patients was 56.0 yr (IQR 43.0–69.0 yr), 54.8% were male (95% CI 53.3–56.4%), 63.0% were admitted from surgical specialties (95% CI 61.5–64.5%), and the median baseline eGFR was 92.3 ml min⁻¹ 1.73 m⁻² (IQR 73.7–106.8 ml min⁻¹ 1.73 m⁻²) (Table 1). The most common comorbidity was cardiovascular disease (36.3%; IQR 34.8–37.8%), and sepsis was the most common reason for admission (19.5%; IQR 18.3–20.7%) (Supplementary Table S1).

Patients were assessed for AKI during ICU admission: 1340 (33.6%) were found to have an AKI. Differences between the

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**Fig 1.** Flow diagram of patients assessed for inclusion and separated based on presence of acute kidney injury. RRT, renal replacement therapy.
group with AKI and the group without AKI in the ICU are presented in Table 1. Patients with AKI were more likely to be older, male, admitted from medical specialties, and have sepsis as their admission diagnosis compared with patients without kidney injury. AKI patients were also more likely to have lower baseline eGFR and pre-existing cardiovascular disease or diabetes compared with patients with no injury (Table 1).

The sensitivity analysis removing patients with no median reference value from the preceding year showed similar proportions of patients in each group with baseline characteristics similar to the total study population (Supplementary Table S2). APACHE II scores were collected for each patient to assess severity of illness, but they were excluded from final analyses as they include both age and a measure of kidney function—this was felt to introduce a degree of collinearity with respect to the key variable of interest.

Minimum and maximum follow-up periods for ICU survivors were 355 days and 1465 days, respectively; the median follow-up time was 848 days.

### Major adverse cardiovascular events

MACE were identified in 385 out of the 3994 patients in the total study population (9.6%; 95% CI 8.8–10.6%). In the group of 2654 patients who did not suffer from AKI whilst in the ICU, 209 suffered from a MACE over the total follow-up period (7.9%; 95% CI 6.9–8.9%). In the AKI group, 176 out of the 1340 patients experienced a MACE after discharge from hospital (13.1%; 95% CI 11.4–15.0%). The rate of MACE was higher for ICU survivors in the AKI group compared with ICU survivors without AKI whilst in ICU (Fig. 2) with a log-rank test P-value <0.001.

A multivariable analysis of factors associated with subsequent MACE after ICU survival can be found in Table 2. The presence of AKI was significantly associated with MACE (HR=1.48; 95% CI 1.16–1.89; P-value=0.001). Increasing age (HR=1.84 and HR=2.73), decreased baseline eGFR (HR=1.48 and HR=1.72), cardiovascular (HR=1.41) and respiratory comorbidities (HR=1.73) were all associated with increased risk of an event. Admission from surgical specialties (HR=0.60) was associated with decreased risk.

### Coronary artery interventions

From the total study population, 49 patients (1.2%; 95% CI 0.9–1.6%) had a coronary artery intervention over the total follow-up period. Admission from surgical specialties (HR=0.54) was associated with a decreased risk of MACE.

### Myocardial injury

Troponin data were available from all routinely sampled blood tests: patients required a clinical indication to have sampling performed. A total of 1924 patients (48.2%) from the total study population had troponin values available for analysis. The median troponin value for all these patients was 7 ng L$^{-1}$; patients in the group without AKI whilst in ICU had a median value of 5 ng L$^{-1}$, whilst patients in the AKI group had a median value of 12 ng L$^{-1}$.

Myocardial injury was identified in 295 patients (7.4%; 95% CI 6.6–8.2%): 154 of 2654 patients without AKI in ICU (5.8%; 95% CI 5.0–6.7%) and 141 of 1340 AKI patients (10.5%; 95% CI 9.0–12.2%). The rate of myocardial injury was higher for ICU survivors with AKI compared with ICU survivors without AKI (Supplementary Fig. S1) with a log-rank test P-value <0.001.

Table 3 reports multivariable analysis of factors associated with myocardial injury after ICU survival. The presence of AKI was significantly associated with a myocardial injury (HR=1.48; 95% CI 1.16–1.89; P-value=0.001). Increasing age (HR=1.84 and HR=2.73), decreased baseline eGFR (HR=1.48 and HR=1.72), cardiovascular (HR=1.41) and respiratory comorbidities (HR=1.73) were all associated with increased risk of an event. Admission from surgical specialties (HR=0.60) was associated with decreased risk.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients (N=3994)</th>
<th>No kidney injury (N=2654)</th>
<th>Acute kidney injury (N=1340)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>56.0 (43.9–69.0)</td>
<td>54.0 (41.0–68.0)</td>
<td>59.0 (47.0–71.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (% [95% CI])</td>
<td>2190 (54.8 [53.3–56.4])</td>
<td>1381 (52.0 [50.1–53.9])</td>
<td>809 (60.4 [57.7–63.0])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical admission, n (% [95% CI])</td>
<td>2516 (63.0 [61.5–64.5])</td>
<td>1729 (65.1 [63.3–66.9])</td>
<td>787 (58.7 [56.1–61.3])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline eGFR (ml min$^{-1}$ 1.73 m$^{-2}$), median (IQR)</td>
<td>92.3 (73.7–106.8)</td>
<td>95.5 (80.7–109.4)</td>
<td>83.7 (61.8–99.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admitted with sepsis, n (% [95% CI])</td>
<td>778 (19.5 [18.3–20.7])</td>
<td>382 (14.4 [13.1–15.8])</td>
<td>396 (29.6 [27.1–32.0])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comorbidities, n (% [95% CI])</td>
<td>1449 (36.3 [34.8–37.8])</td>
<td>875 (33.0 [31.2–34.8])</td>
<td>574 (42.8 [40.2–45.5])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>782 (19.6 [18.4–20.8])</td>
<td>517 (19.5 [18.0–21.0])</td>
<td>265 (19.8 [17.7–22.0])</td>
<td>0.857</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>330 (8.3 [7.4–9.1])</td>
<td>204 (7.7 [6.7–8.7])</td>
<td>126 (9.4 [7.9–11.0])</td>
<td>0.072</td>
</tr>
<tr>
<td>Liver disease</td>
<td>533 (13.3 [12.3–14.4])</td>
<td>280 (10.6 [9.4–11.8])</td>
<td>253 (18.9 [16.8–21.0])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>293 (7.3 [6.6–8.2])</td>
<td>202 (7.6 [6.6–8.7])</td>
<td>91 (6.8 [5.5–8.2])</td>
<td>0.382</td>
</tr>
</tbody>
</table>
Table 2 Multivariable analysis of factors associated with development of major adverse cardiovascular outcomes. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariable HR (95% CI)</th>
<th>P-value</th>
<th>Multivariable HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of acute kidney injury</td>
<td>1.73 (1.42–2.11)</td>
<td>&lt;0.001</td>
<td>1.38 (1.12–1.70)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>1.88 (1.36–2.59)</td>
<td>&lt;0.001</td>
<td>1.63 (1.17–2.27)</td>
<td>0.004</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.18 (0.96–1.44)</td>
<td>0.116</td>
<td>1.23 (1.00–1.52)</td>
<td>0.046</td>
</tr>
<tr>
<td>Surgical admission</td>
<td>0.59 (0.48–0.72)</td>
<td>&lt;0.001</td>
<td>0.54 (0.44–0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline eGFR, ml min⁻¹ 1.73 m⁻²</td>
<td>&gt;60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular comorbidities</td>
<td>1.74 (1.42–2.12)</td>
<td>&lt;0.001</td>
<td>1.36 (1.09–1.70)</td>
<td>0.006</td>
</tr>
<tr>
<td>Respiratory comorbidities</td>
<td>1.56 (1.24–1.95)</td>
<td>&lt;0.001</td>
<td>1.49 (1.18–1.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-existing diabetes</td>
<td>1.63 (1.26–2.09)</td>
<td>&lt;0.001</td>
<td>1.22 (0.93–1.58)</td>
<td>0.145</td>
</tr>
<tr>
<td>Pre-existing liver disease</td>
<td>1.16 (0.82–1.65)</td>
<td>0.392</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Admitted with sepsis</td>
<td>1.09 (0.85–1.40)</td>
<td>0.484</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pre-existing malignancy</td>
<td>1.07 (0.74–1.55)</td>
<td>0.730</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Fig 2. Time to major adverse cardiovascular events based on presence of kidney injury. Time 0 is taken from day 30 after hospital discharge. P-value <0.001. AKI, acute kidney injury.
Plasma troponin assays are a well-established method of assessing patients for myocardial injury, and trends in individual patients are often used as a sensitive measure of diagnosing acute myocardial infarction.\(^6\)\(^,\)\(^23\) Whilst it is not possible to diagnose myocardial infarction using a single elevated plasma troponin concentration, it is useful as a surrogate marker of potential cardiac injury; although raised troponin values may be secondary to alternative pathologies, negative tests are highly sensitive for ruling out myocardial damage.\(^20\)

Risk factors for myocardial injury included increased age, pre-existing cardiovascular disease, and pre-existing respiratory disease; median baseline eGFR was also lower in troponin-positive patients. Whilst a single raised troponin value is not pathognomonic of myocardial injury, these trends are in keeping with well-established evidence linking increased age and pre-existing comorbidities with increased likelihood of suffering from an acute myocardial infarction.\(^21\)\(^,\)\(^22\)

AKI was also associated with post-ICU myocardial injury; this is in keeping with prior studies describing the increased risk of acute myocardial infarction after an episode of AKI.\(^6\)\(^,\)\(^23\) with a 48% increased risk demonstrated in this study compared with 40% increase in previous work. This study has demonstrated that ICU admission from medical specialties conferred an increased risk profile. This is consistent with the findings from a large retrospective study by Porter and colleagues\(^24\) which used an electronic alert system for identifying AKI in >15 000 patients and documented a higher incidence of AKI within medical specialties compared with surgical specialties.

Patients with significant coronary artery disease may require coronary artery intervention, either as PCI or CABG. An association between AKI and subsequent coronary events has been noted by Wu and colleagues,\(^25\) with AKI that required kidney replacement therapy conferring a 67% increase in risk of developing a subsequent coronary event. Our study noted a higher incidence of coronary artery intervention in patients who had suffered an AKI in ICU. Whilst a trend between AKI and requirement for coronary artery intervention was identified, this was not found to be a statistically significant association once it was factored into a multivariable analysis.
model. This is likely to be attributable to the low event rate in both groups with a coronary artery intervention occurring in only 1.2% of the study population. Interpretation of this relationship may also be complicated as patients with AKI and subsequent CKD are less likely to undergo angiography and interventions because of higher complication rates.76

Cerebrovascular events occurred in fewer than one in 50 ICU survivors during the follow-up period. Risk factors which were associated with increased risk of cerebrovascular events were admission from medical specialties, reduced baseline eGFR, pre-existing liver disease, and pre-existing diabetes. Whilst no previous data exist on rates of acute cerebrovascular events based on admitting specialty, there is prior work describing the link between CKD and increased risk of a subsequent stroke.77 There is also a significant body of evidence highlighting the link between pre-existing diabetes mellitus and the risk of future cerebrovascular events.8,29

The association between the presence of AKI and a cerebrovascular event was not found to be statistically significant on adjusted analysis. These data are not in keeping with the current published literature regarding increased risk of stroke after an episode of AKI,76 but this may be because of the small number of events seen in our study population. A limitation of this methodology is that patients who have fatal events without imaging will not be captured in these data.

A major strength of this study is that it uses health records from parent health boards to ensure high-quality follow-up data with minimal missing data. The large and unselected sample size, long observation period, and validation of radiological findings by a specialist in this field are additional strengths. The study has some limitations: only serum creatinine values were used as urine output values were not reliable enough. The methodology used for endpoint capture was also limited as it relied on unadjudicated events which were captured by either laboratory or imaging systems. Whilst troponin-positive events may be used as a surrogate marker of myocardial injury, certain confounders such as development of kidney disease may also result in a troponin increase. Although serum creatinine concentrations returned to baseline before 30 days after hospital discharge in almost all patients, it is possible that kidney function remained impaired at a subclinical level, leading to a residual effect of troponin elevation which may confound results. This could be reflected by the similar rates of coronary artery intervention in the two groups: many of the instances of myocardial injury did not receive subsequent coronary artery intervention, but this may also be because PCI or CABG were not deemed an appropriate treatment for reasons of patient frailty or underlying pathophysiology. APACHE II scores were intentionally excluded from the multivariable models because of risks of collinearity with development of AKI, but not accounting for severity of illness is a potential limitation of this methodology. The small absolute numbers of events for certain secondary endpoints may also make it difficult to draw definitive conclusions. Whilst this patient cohort is likely representative of the ICU population within the UK, it may not be generalisable internationally.

This study has demonstrated an association between AKI in ICU and subsequent MACE and specifically myocardial injury as measured by elevated serum troponin. The risks of coronary intervention or cerebrovascular events were not associated with AKI in this study; however, the small numbers of events may have limited our ability to detect a difference. Given the absolute small numbers of events which occurred in this study, more research using a larger patient cohort is required. Further research is also warranted on whether ICU survivors with AKI merit enhanced strategies for cardiovascular protection.

**Author’s contributions**

Conceptualisation of project and methodology, data interpretation, and review and editing of all drafts: all authors

Data collection: MA, JC, JPT, MS

Data analysis: MA, JC, MS

Initial literature search and writing of original draft: MA

Acted in a supervisory capacity: PBM, KAP

**Ethics**

Ethical approval for this study was sought and granted by National Health Services London-Surrey Research and Ethics Committee (Ref: 18/LO/2060).

**Data availability**

Anonymised patient data collected during this study will be made available in the publicly available Enlighten repository (https://researchdata.gla.ac.uk). The data will be made available for a period of 10 yr after completion of associated work towards attaining a thesis due to be completed no later than March 2024.

**Declarations of interest**

The authors declare that they have no conflicts of interest.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2023.100243.

**References**


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