Short- and long-term outcomes of intensive care patients with acute kidney disease

Mark Andonovic,[a]* Jamie P. Traynor,[b] Martin Shaw,[a] Malcolm A.B. Sim,[a,c] Patrick B. Mark,[b,d] and Kathryn A. Puxty [a,e]

[a]Academic Unit of Anaesthesia, Pain and Critical Care, University of Glasgow, New Lister Building, Glasgow Royal Infirmary, Glasgow G31 2ER, United Kingdom
[b]Department of Nephrology, Queen Elizabeth University Hospital, United Kingdom
[c]Department of Intensive Care, Queen Elizabeth University Hospital, United Kingdom
[d]Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom
[e]Department of Intensive Care Medicine, Glasgow Royal Infirmary, United Kingdom

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Summary

Background Acute kidney disease (AKD) is a proposed definition for acute kidney injury (AKI) lasting 7 days or longer. Little has been reported regarding characteristics of patients with AKD and their short- and long-term outcomes. We describe the epidemiology and risk factors for AKD and outcomes following AKD.

Methods This retrospective observational cohort study identified patients aged 16 or older admitted to the Glasgow Royal Infirmary and Queen Elizabeth University Hospital intensive care units (ICUs) in Scotland between 1st July 2015 and 30th June 2018. Baseline serum creatinine and subsequent values were used to identify patients with de-novo kidney injury (DNKI). Patients with recovery prior to day 7 were classified as AKI; recovery at day 7 or beyond was classified as AKD. Outcomes were in-hospital and long-term mortality, and proportion of major adverse kidney events (MAKEs). Multivariable logistic regression was used to identify risk factors for AKD. A Cox proportional hazards model was used to identify factors associated with long-term outcomes.

Findings Of the 5,334 patients admitted to ICU who were assessed for DNKI, 1,620 (30·4%) suffered DNKI and of these, 403 (24·9%) met AKD criteria; 984 (60·7%) were male and the median age was 60·0 (IQR=48·0–72·0). Male sex, sepsis and lower baseline estimated glomerular filtration rate (eGFR) were associated with development of AKD. In-ICU (16·1%vs6·2%) and in-hospital (26·1%vs11·6%) mortality rates were significantly higher in AKD patients than AKI patients. Long-term survival was not different for AKD patients (HR=1·16; *p*-value=0·261) but AKD was associated with subsequent MAKEs (OR=1·25).

Interpretation One in four ICU patients with DNKI met AKD criteria. These patients had an increased risk of short-term mortality and long-term MAKEs. Whilst the trend for long-term survival was lower, this was not significantly different from shorter-term AKI patients. Patients with AKD during their ICU stay should be identified to initiate interventions to reduce risk of future MAKEs.

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Introduction

Acute kidney injury (AKI) is a significant problem in healthcare worldwide, with associated increased risk in both short- and long-term mortality and development of subsequent chronic kidney disease (CKD).[1–3] Whilst AKI has been recognised as a common occurrence within the context of critical illness, the reported incidence in the intensive care unit (ICU) literature has varied from 30–57%.[3–5] This can be attributed to differences in study populations, increasing recognition of the importance of AKI over time, and variation in the classification system used for diagnosing AKI.

Following publication of the RIFLE classification for AKI,[6] further classifications were produced by the Acute Kidney Injury Network (AKIN)[7] and the Kidney Disease Improving Global Outcomes (KDIGO) group.[8] Current

*Corresponding author.
E-mail address: mark.andonovic@glasgow.ac.uk (M. Andonovic).

Research in context

Evidence before this study

The PubMed, MEDLINE and medRxiv databases were searched on 12th June 2021 using both free text and related MeSH or Emtree terms for studies pertaining to acute kidney disease using the terms "acute kidney disease" AND "acute kidney injury" to identify relevant studies. Chawla and colleagues initially described the updated consensus opinion on the definition of acute kidney disease (AKD) and how this updated the definition from Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines on acute kidney injury (AKI). A Canadian study by James et al. on 1.1 million patients in both the community and hospital setting utilised the broader 2012 definition of AKD and found it was associated with higher risks of both new chronic kidney disease and death, whilst further work by Peerapornratana and colleagues looked at a cohort of hospitalised patients with septic shock and identified AKD as being associated with male sex and pre-existing chronic kidney disease.

Added value of this study

This large retrospective analysis found that AKD is common in the intensive care unit (ICU), with an incidence of 24.9% of all patients with AKI who survived to day 7. Male sex, admission due to sepsis and lower baseline estimated glomerular filtration rate (eGFR) were statistically significant factors associated with progression to AKD and in-ICU and in-hospital mortality rates of AKD patients were significantly higher than demonstrated in patients with a faster resolving AKI. Additionally, progression to AKD was an independent risk factor for future major adverse kidney events (MAKEs).

Implications of all the available evidence

Minimal data exist on this novel definition of AKD, but its incidence within the critically unwell population is common based on the available evidence and this is particularly true of patients admitted due to sepsis. The association between AKD and increased risk of MAKEs over the longer term, warrants further research. Since AKD can be diagnosed shortly after initial insult, this may demonstrate a risk factor which could be used to identify high risk patients who may benefit from further follow up.

KDIGO classification has incorporated and adapted elements of both RIFLE and AKIN criteria to form the most current and internationally accepted criteria for diagnosing and staging AKI. Recent consensus concludes AKI should not be a treated as an isolated event, but as the beginning of a continuum of kidney disease where an initial insult can lead to both persistent kidney injury and CKD.[9] Within this spectrum of disease, it has been postulated that persistent kidney injury should be treated as a separate entity from rapid-reversal AKI. In recognition of these different disease pathways, the Acute Disease Quality Initiative (ADQI) in 2017 proposed the definition of acute kidney disease (AKD) as AKI (KDIGO stage 1 or greater) that persists for 7 days or longer.[9]

This new definition was identified as an important area for research,[9] however, little data exist regarding patients who suffer from AKD and how they differ from patients with AKI that do not develop AKD. A subsequent definition expanded on the concept of AKD being inclusive of patients with estimated glomerular filtration rate (eGFR) < 60 ml/min/1·73m^2 for 7–90 days.[10] This definition offers broader diagnostic criteria but is more difficult to apply in the context of an injury acquired on ICU. Furthermore, it would require the removal of all patients with pre-existing CKD stage 3 or worse, as these patients already have eGFR < 60 ml/min/1·73m^2.

The aim of this study sought to ascertain the epidemiology and short- and long-term outcomes of patients admitted to ICU suffering from AKD and compare them to patients with a more transient AKI. The specific outcomes were to ascertain potential risk factors associated with progression to AKD, determine short- and long-term mortality in AKI and AKD groups and assess the proportion of MAKEs during the follow up period.

Methods

This retrospective observational cohort study utilised prospectively collected data. The study utilised data routinely gathered during patients' ICU admission and follow-up period therefore individualised participant consent was not sought; ethical approval was granted by National Health Services London-Surrey Research and Ethics Committee (Ref.: 18/LO/2060) prior to commencement. The findings are reported based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[11] De-novo kidney injury (DNKI) was identified and classified based on length of kidney injury.

Inclusion criteria

All adult patients aged 16 or older admitted to two large Scottish general adult ICUs in the Glasgow Royal Infirmary and the Queen Elizabeth University Hospital across six health boards were included. Exclusion criteria were patients with long-term kidney replacement therapy (KRT), prior kidney transplantation and readmission to ICU over the total study period. Sample size was determined by number of patients with DNKI who survived to day 7 who were identified over the pre-determined study period.

Outcomes

The outcomes of this study were to determine any risk factors which were significantly associated with progression to AKD, if development of AKD conveyed any additional risk of mortality either during hospital admission or over the longer-term, and if AKD was associated with MAKEs over the total follow up period.

Data collection

Patients admitted to ICU between 1st July 2015 and 30th June 2018 were identified using the Scottish Intensive Care Society Audit Group (SIGSAG) Wardwatcher^{TM} database. The patient identifiers for the ICU patients were input into the *Vitalpulse* Strathclyde Electronic Renal Patient Record (SERPR) database: this covers over 2·6 million people and is used as the renal electronic patient records in six Scottish health boards. It has active interfaces with their systems to automatically retrieve laboratory, radiology and demographic data including date of death which ensured important outcomes were available for this study.

Baseline demographic variables including age, sex, admitting specialty, APACHE II score,[12] admission diagnosis and type of organ support were retrieved from the SICSAG database. Admitting specialty was dichotomised into medical or surgical; admission diagnoses were organised into 26 broad groups based upon coding in the SICSAG database (Supplementary Table 1). These diagnostic groups remained as broad as possible and diagnoses such as sepsis were grouped as one regardless of causative pathogen or presumed source of infection. Organ support was categorised based on receipt of invasive mechanical ventilation (IMV), cardiovascular support (CVS) (infusion of a vasoactive medication including vasopressors or inotropes) and KRT. Pre-existing comorbidities were identified using data in *Philips Carevue*^{TM} electronic patient records and grouped according to cardiovascular disease (including chronic hypertension and ischaemic heart disease), respiratory disease (including obstructive airway disease and interstitial lung disease), liver disease (including alcoholic and non-alcoholic fatty liver disease, hepatitis or cirrhosis) and diabetes mellitus (of all types regardless of severity of disease).

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 reference, comprising either the median value from 8 to 365 days before admission or the lowest value in the week prior to admission[13]; if both values were available then the median value from 8 to 365 days was preferentially selected. Additionally, this reference value was used to calculate baseline eGFR using the CKD-EPI equation.[14] The reference value was then used to diagnose DNKI using KDIGO classification[8] the initial injury was identified as the point at which AKI criteria was met for the first time. Diagnosis of DNKI did not depend on pre-existing CKD and represented a new deterioration in kidney function: this was either injury in patients with no kidney disease or acute-on-chronic kidney injury. Days during which patients received KRT were identified from the SICSAG database, and this superseded serum creatinine values on the days this support was delivered; serum creatinine values within 24 h of discontinuation of KRT were also discounted to avoid artificially lowered creatinine from suggesting early kidney recovery. Severity of injury was classified using the worst creatinine value from the duration of the injury or delivery of KRT.

Kidney recovery was defined as the first point at which KDIGO AKI criteria was no longer met; this included both return of serum creatinine values to non-AKI levels, and no further implementation of KRT. Length of kidney injury was then calculated using this point: AKI was defined as injury lasting six days or less and AKD defined as injury lasting seven days or longer. To prevent sicker, co-morbid patients who died before they may have progressed to AKD from influencing the analysis between groups, patients with DNKI were required to survive until day 7 to be classified as either AKI or AKD. Patients who died without kidney recovery prior to day seven were analysed as a separate group of AKI non-survivors (AKI-NS). Due to lack of urine output data following discharge from ICU preventing diagnosis of kidney recovery, only serum creatinine values and delivery of KRT were used to diagnose DNKI.

For the purposes of post-ICU survival analysis, only patients alive at 30 days following hospital discharge were used to avoid patients discharged for palliative purposes from influencing the results. Date of death was used to calculate length of survival. Major adverse kidney outcomes (MAKEs) were defined as a drop in at least 30% in eGFR from baseline, doubling in serum creatinine and initiation of long-term KRT.[15,16] The final point of collection for all data was 31st March 2020. To identify rates of new CKD stage 3A or worse, patients with a pre-admission eGFR value of > 60 ml/min/1.73m^2 were identified to exclude patients with pre-existing CKD based on eGFR criteria. Patients with two serum creatinine values of < 60 ml/min/1.73m^2 following hospital discharge were classified as having new CKD Stage 3A or worse.

Statistical analysis

All statistical analysis was conducted using the software package R (The R Foundation; R version 3·6·2). Patients without data available for classification of baseline kidney function were excluded; patients from outside the six health boards which SERPR downloads all data from were considered lost to follow-up and excluded from long-term analyses. A sensitivity analysis was pre-planned for patients with missing median serum

creatinine values from the preceding 8–365 days to assess if lack of prior values affected the validity of the data. Variables were summarised using median values and interquartile range (IQR) or by proportions with 95% confidence interval (95%CI); difference in median values were compared using the Wilcoxon rank-sum test whereas difference in proportions were compared using the Pearson Chi-squared test.

Multivariable logistic regression was used to identify risk factors associated with progression to AKD in patients with DNKI. Initial bivariate analysis was performed on each collected variable with the exception of APACHE II score: this avoided co-linearity as age is used in their calculation. Univariable *p*-values of less than < 0·2 were included in the multivariable model unless it was considered a significant variable such as age or sex. Factors were reported as odds ratio (OR) with 95%CI. Kaplan Meier estimators were used to predict long-term outcomes over time; log-rank test was used to determine differences between the survival or event curves.

A Cox proportional hazards model was used to determine the impact of multiple variables on survival. This reported a hazard ratio (HR) with 95%CI. To ascertain if each variable met the proportionality assumption, Schoenfeld residuals were calculated for each individual variable as well as for the multivariable model.[17] If the *p*-value of the residuals calculated on any variable was found to be < 0·2, it was removed from the multivariable model as it was presumed to not obey the proportionality assumption. For all adjusted analyses, a statistical significance was set at a two-sided *p*-value of < 0·05.

Results

A total of 5334 patients were identified: 22 patients were removed as no data were available for calculation of baseline kidney function; a further 103 were removed due to long-term requirement for KRT or kidney transplantation prior to admission. Of these 5209 patients, 2147 suffered a new kidney injury during their ICU admission: 527 of these patients died prior to kidney recovery in the initial seven days and were excluded from all analyses. The final study population consisted of 1620 patients who were found to have DNKI (Figure 1).

Median age of the population with DNKI was 60·0 years (IQR 48·0–72·0), 60·7% were male (95%CI 58·4–63·1) 56·7% were admitted from surgical specialties (95%CI 54·2–59·1) and 75·4% had baseline eGFR of > 60 ml/min/1·73m^2 (95%CI 73·3–77·5) (Table 1). Patients had a median APACHE II score of 20·0 (IQR 15·0–26·0); the most prevalent comorbidity was pre-existing cardiovascular disease (43·3%; 95%CI 40·9–45·7). The most frequent admission diagnosis was sepsis (29·3%, 95%CI 27·1–31·6) (Supplementary Table 1); 57·8% (95%CI 55·4–60·2) of patients required multi-organ support with 21·2% (95%CI 19·2–23·2) requiring KRT (Table 1). The two KRT modalities used during this study were intermittent haemodialysis and continuous veno-venous haemofiltration (50·5% vs 49·5% respectively); the two included centres used one modality exclusively. Higher proportions of patients in the AKD group required invasive mechanical ventilation and cardiovascular support (Table 1).

The 1620 patients with DNKI were grouped based on length of kidney injury: 1217 were categorised as AKI (75·1%; 95%CI 73·0–77·2) whilst 403 progressed to AKD (24·9%; 95%CI 22·8–27·0). The sensitivity analysis removing patients with no median reference value from the preceding year showed similar proportions of patients in each group: 4188 of the 5334 patients initially identified (78·5%); 1708 of the 2147 with DNKI (79·6%); and 1288 of 1620 survivors at day 7 (79·5%); 313 of these patients progressed to AKD (24·3%) (Supplementary Table 2).

Comparison of demographic features between patients in the DNKI group and patients in the AKI-NS group can be found in Table 2. Patients in the AKI-NS group were shown have a significantly older median age and less likely to be admitted from surgical specialties than patients who survived to day 7. In addition, non-survivors had significantly higher median APACHE II scores and need for multi-organ support.

Comparison of AKI and AKD demographic features

Patients with AKI and AKD had a similar median age; AKD patients were more likely to be admitted from medical specialties or with sepsis, had a lower baseline eGFR, a higher median APACHE II score, and higher rates of pre-existing diabetes (Table 1). Patients with AKD were also more likely to require multi-organ support or kidney replacement therapy (Table 1). AKD patients also had a statistically significant higher median length of stay for both ICU and hospital.

Factors assessed initially using univariable analyses included age (reference value < 45 years); male sex (reference value female sex); admission from surgical specialties (reference value admission from medical specialties); baseline eGFR (reference value > 60 ml/min/1.73m^2); admission due to sepsis (reference value admission due to other reason); presence of comorbidities (reference value comorbidity not present); and progression to stage 3 injury (reference value limited to stage 1 or 2 injury).

Multivariable analysis found male sex (OR=1·25; 95%CI 1·02–1·54; *p*-value=0·037) and ICU admission with sepsis (OR=1·35; 95%CI 1·10–1·66; *p*-value=0·004) to be associated with increased risk of AKD in ICU patients with DNKI (Table 3). Reduced baseline eGFR was also associated with an increased risk of developing AKD (OR=1·44 and OR=1·95). Initial multivariable

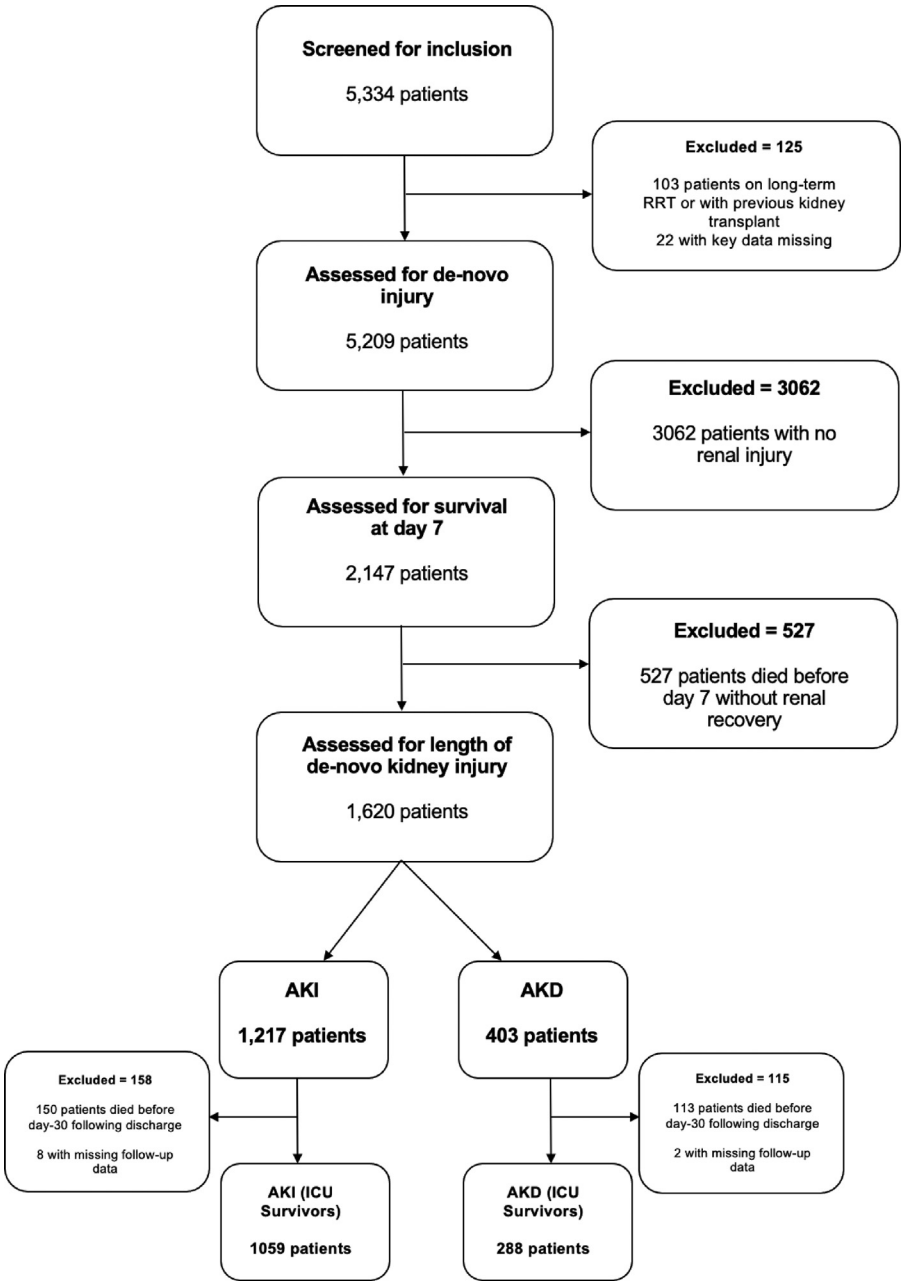

Figure 1. Flow diagram of patients
AKI = acute kidney injury; AKD = acute kidney disease.

analysis included progression to stage 3 injury: the effect of this variable was so significant that it masked the effect of other variables (OR=8·57), so it was removed from the final analysis (Table 3) (Supplementary Figure 1). The results of the sensitivity analysis are shown in Supplementary Table 3: the risk factors associated with progression to AKD in these patients were the same as the results from the total study population.

Short- and long-term mortality

ICU mortality was 8·7% (95%CI 7·4–10·2) across the population with DNKI (Table 1): AKD patients had a 16·1% (95%CI 12·8–19·9) ICU mortality rate compared with 6·2% (95%CI 5·0–7·7) in AKI patients (*p*-value< 0·001). In-hospital mortality was 15·2% (95%CI 13·6–17·1) for all patients: AKD patients had a mortality rate of 26·1% (95%CI 22·1–30·7) compared to 11·6% (95%CI 9·9–13·5) in AKI patients (*p*-value< 0·001).

	De-novo kidney injury (*n* = 1620)	Acute kidney injury (*n* = 1217)	Acute kidney disease (*n* = 403)	*p*-value
Age — median (IQR)	60·0 (48·0 — 72·0)	60·0 (48·0 — 72·0)	61·0 (48·5 — 71·0)	0·984
Male — No. [% (95% CI)]	984 [60·7% (58·4% - 63·1%)]	723 [59·4% (56·6% - 62·2%)]	261 [64·8% (60·0% - 69·3%)]	0·064
Surgical admission — No. [% (95% CI)]	918 [56·7% (54·2% - 59·1%)]	713 [58·6% (55·8% - 61·3%)]	205 [50·9% (46·0% - 55·7%)]	0·008
General surgery	530 [32·7% (30·5% - 35·0%)]	428 [35·2% (32·5% - 37·9%)]	102 [25·4% (21·3% - 29·8%)]	<0·001
Orthopaedics	133 [8·2% (6·9% - 9·6%)]	104 [8·5% (7·1% - 10·2%)]	29 [7·2% (5·0% - 10·0%)]	0·460
Vascular surgery	86 [5·3% (4·3% - 6·5%)]	53 [4·4% (3·3% - 5·6%)]	33 [8·2% (5·8% - 11·2%)]	0·004
Urology	72 [4·4% (3·5% - 5·5%)]	50 [4·1% (3·1% - 5·3%)]	22 [5·5% (3·5% - 8·0%)]	0·312
Other	97 [5·9% (4·8% - 7·1%)]	78 [6·4% (5·1% - 7·9%)]	19 [4·5% (2·7% - 6·8%)]	0·194
Baseline eGFR — No. [% (95% CI)]				
>60 ml/min/1·73m^2	1222 [75·4% (73·3% - 77·5%)]	958 [78·7% (76·4% - 81·0%)]	264 [65·5% (60·8% - 70·0%)]	<0·001
30 — 60 ml/min/1·73m^2	293 [18·1% (16·3% - 20·0%)]	201 [16·5% (14·5% - 18·7%)]	92 [22·8% (18·9% - 27·1%)]	<0·001
< 30 ml/min/1·73m^2	105 [6·5% (5·4% - 7·7%)]	58 [4·8% (3·7% - 6·1%)]	47 [11·7% (8·8% - 15·0%)]	<0·001
APACHE II score — median (IQR)	20·0 (15·0 — 26·0)	19·0 (14·0 — 24·0)	24·0 (20·0 — 29·0)	<0·001
Admitted with sepsis — No. [% (95% CI)]	475 [29·3% (27·1% - 31·6%)]	327 [26·9% (24·4% - 29·4%)]	148 [36·7% (32·1% - 41·5%)]	<0·001
Comorbidities — No. [% (95% CI)]				
Cardiovascular disease	701 [43·3% (40·9% - 45·7%)]	514 [42·2% (39·5% - 45·0%)]	187 [46·4% (41·6% - 51·3%)]	0·160
Respiratory disease	323 [19·9% (18·0% - 21·9%)]	251 [20·6% (18·4% - 23·0%)]	72 [17·9% (14·3% - 21·8%)]	0·249
Liver disease	166 [10·3% (8·8% - 11·8%)]	129 [10·6% (9·0% - 12·4%)]	37 [9·2% (6·6% - 12·3%)]	0·416
Diabetes mellitus	306 [18·9% (17·0% - 20·8%)]	208 [17·1% (15·1% - 19·3%)]	98 [24·3% (20·3% - 28·7%)]	0·002
Malignancy	113 [7·0% (5·8% - 8·3%)]	88 [7·2% (5·9% - 8·8%)]	25 [6·2% (4·1% - 8·8%)]	0·556
Organ support type — No. [% (95% CI)]				
Invasive mechanical ventilation	1118 [69·0% (66·7% - 71·2%)]	812 [66·7% (64·0% - 69·3%)]	306 [75·9% (71·6% - 79·9%)]	<0·001
Cardiovascular support	1112 [68·6% (66·4% - 70·9%)]	807 [66·3% (63·6% - 68·9%)]	305 [75·7% (71·3% - 79·7%)]	<0·001
Kidney replacement therapy	343 [21·2% (19·2% - 23·2%)]	107 [8·8% (7·3% - 10·5%)]	236 [58·6% (53·7% - 63·3%)]	<0·001
Degree of organ support — No. [% (95% CI)]				
None	216 [13·3% (11·7% - 15·1%)]	194 [15·9% (14·0% - 18·1%)]	22 [5·5% (3·5% - 8·0%)]	<0·001
Single	468 [28·9% (26·7% - 31·1%)]	389 [32·0% (29·4% - 34·6%)]	79 [19·6% (15·9% - 23·7%)]	<0·001
Multi	936 [57·8% (55·4% - 60·2%)]	634 [52·1% (49·3% - 54·9%)]	302 [74·9% (70·6% - 79·0%)]	<0·001
ICU mortality — No. [% (95% CI)]	141 [8·7% (7·4% - 10·2%)]	76 [6·2% (5·0% - 7·7%)]	65 [16·1% (12·8% - 19·9%)]	<0·001
ICU length of stay in days — median (IQR)	5·0 (2·0 - 10·0)	4·0 (2·0 - 8·0)	7·0 (3·0 - 14·0)	<0·001
Hospital mortality — No. [% (95% CI)]	246 [15·2% (13·6% - 17·1%)]	141 [11·6% (9·9% - 13·5%)]	105 [26·1% (22·1% - 30·7%)]	<0·001
Hospital length of stay in days — median (IQR)	17·0 (10·0 - 30·0)	16·0 (9·0 - 29·0)	20·0 (11·0 - 36·0)	<0·001

***Table 1*: Characteristics and Outcomes of ICU patients with De-Novo Kidney Injury and difference between AKI and AKD.**
eGFR = estimated glomerular filtration rate; ICU = intensive care unit; CI = confidence interval.
For APACHE II calculations, data was unavailable for 37 patients — only 1583 patients used in these calculations (Acute kidney injury = 1190; acute kidney disease = 393).

Of the 1620 patients identified with DNKI, 1350 survived to 30 days after hospital discharge and were classified as ICU survivors; three patients originated from outside the six health boards, had no follow-up data and were excluded from the analyses. From the remaining 1347 patients, 1059 patients met AKI criteria and 288 were classified as AKD patients. Demographic features for these patients are described in Supplementary Table 4.

Minimum and maximum follow-up periods for ICU survivors were 355 days and 1612 days respectively; the median follow-up time was 872 days. The estimated survival over 4 years was found to be 67·6% (95%CI 60·9 —75·0) in the AKD group and 71·3% (95%CI 67·9 —74·8) for the AKI group: these differ from the absolute numbers displayed in Table 3 due to the Kaplan Meier estimating lower survival to account for patients with right censoring. Log-rank test showed the difference in survival curves (Figure 2) between AKI and AKD patients was not statistically significant (*p*-value=0·200). In DNKI ICU survivors, AKD was not found to be significantly associated with survival on multivariable analysis (HR=1·16; 95%CI 0·89—1·52; *p*-value=0·261) (Supplementary Table 5). Increasing age (HR=1·50 and HR=2·54), pre-existing liver disease (HR=1·46; 95%CI 1·03—2·07) and pre-existing malignancy (HR=1·90;

	All kidney injury (*n* = 2147)	De-novo kidney injury with survival to day 7 (*n* = 1620)	Acute kidney injury non-survivors (*n* = 527)	*p*-value
Age — median (IQR)	61·0 (49·0 — 72·0)	60·0 (48·0 — 72·0)	65·0 (52·0 — 73·0)	<0·001
Male — No. [% (95% CI)]	1293 [60·2% (58·1% - 62·3%)]	984 [60·7% (58·4% - 63·1%)]	309 [58·6% (54·4% - 62·8%)]	0·420
Surgical admission — No. [% (95% CI)]	1107 [51·6% (49·4% - 53·7%)]	918 [56·7% (54·2% - 59·1%)]	189 [35·9% (31·8% - 40·0%)]	<0·001
General surgery	642 [29·9% (28·0% - 31·9%)]	530 [32·7% (30·5% - 35·0%)]	112 [21·3% (17·9% - 24·9%)]	<0·001
Orthopaedics	148 [6·9% (5·9% - 8·0%)]	133 [8·2% (6·9% - 9·6%)]	15 [2·8% (1·6% - 4·5%)]	<0·001
Vascular surgery	117 [5·5% (4·5% - 6·5%)]	86 [5·3% (4·3% - 6·5%)]	31 [5·9% (4·1% - 8·1%)]	0·696
Urology	78 [3·6% (2·9% - 4·5%)]	72 [4·4% (3·5% - 5·5%)]	6 [1·1% (0·5% - 2·3%)]	<0·001
Other	122 [5·6% (4·7% - 6·7%)]	97 [5·9% (4·8% - 7·1%)]	25 [4·7% (3·1% - 6·8%)]	0·360
Baseline eGFR — No. [% (95% CI)]				
> 60 ml/min/1·73m^2	1596 [74·3% (72·5% - 76·2%)]	1222 [75·4% (73·3% - 77·5%)]	374 [71·0% (67·0% - 74·7%)]	0·048
30 — 60 ml/min/1·73m^2	404 [18·8% (17·2% - 20·5%)]	293 [18·1% (16·3% - 20·0%)]	111 [21·0% (17·7% - 24·7%)]	0·146
< 30 ml/min/1·73m^2	147 [6·9% (5·8% - 8·0%)]	105 [6·5% (5·4% - 7·7%)]	42 [8·0% (5·9% - 10·5%)]	0·282
APACHE II score — median (IQR)	22·0 (17·0 — 29·0)	20·0 (15·0 — 26·0)	30·0 (25·0 — 36·0)	<0·001
Admitted with sepsis — No. [% (95% CI)]	636 [29·6% (27·8% - 31·6%)]	475 [29·3% (27·1% - 31·6%)]	161 [30·6% (26·7% - 34·6%)]	0·630
Comorbidities — No. [% (95% CI)]				
Cardiovascular disease	960 [44·7% (42·6% - 46·8%)]	701 [43·3% (40·9% - 45·7%)]	259 [49·1% (44·9% - 53·4%)]	0·021
Respiratory disease	437 [20·4% (18·7% - 22·1%)]	323 [19·9% (18·0% - 21·9%)]	114 [21·6% (18·3% - 25·3%)]	0·437
Liver disease	235 [10·9% (9·7% - 12·3%)]	166 [10·3% (8·8% - 11·8%)]	69 [13·1% (10·4% - 16·1%)]	0·082
Diabetes mellitus	402 [18·7% (17·1% - 20·4%)]	306 [18·9% (17·0% - 20·8%)]	96 [18·2% (15·1% - 21·7%)]	0·779
Malignancy	145 [6·8% (5·7% - 7·9%)]	113 [7·0% (5·8% - 8·3%)]	32 [6·1% (4·2% - 8·3%)]	0·600
Organ support type — No. [% (95% CI)]				
Invasive mechanical ventilation	1587 [73·9% (72·0% - 75·7%)]	1118 [69·0% (66·7% - 71·2%)]	469 [89·0% (84·8% - 93·0%)]	<0·001
Cardiovascular support	1451 [67·6% (65·6% - 69·5%)]	1112 [68·6% (66·4% - 70·9%)]	339 [64·3% (60·2% - 68·3%)]	0·074
Kidney replacement therapy	498 [23·2% (21·4% - 25·0%)]	343 [21·2% (19·2% - 23·2%)]	155 [29·4% (25·6% - 33·4%)]	<0·001
Degree of organ support - No [% (95% CI)]				
None	238 [11·1% (9·8% - 12·5%)]	216 [13·3% (11·7% - 15·1%)]	22 [4·2% (2·7% - 6·1%)]	<0·001
Single	603 [28·1% (26·2% - 30·0%)]	468 [28·9% (26·7% - 31·1%)]	135 [25·6% (22·0% - 29·5%)]	0·163
Multi	1306 [60·8% (58·8% - 62·9%)]	936 [57·8% (55·4% - 60·2%)]	370 [70·2% (66·2% - 74·0%)]	<0·001

***Table 2*: Characteristics of ICU patients with De-Novo Kidney Injury and differences between survivors to day 7 and patients who died without renal recovery prior to day 7. eGFR = estimated glomerular filtration rate; ICU = intensive care unit; CI = confidence interval.**
For APACHE II calculations, data was unavailable for 112 patients — only 2035 patients used in these calculations (Survival to day 7 = 1583; non-survivors = 452).

95%CI 1·34—2·70) were all associated with an increase in mortality risk; admission from a surgical specialty (HR=0·73; 95%CI 0·58—0·92) and admission due to sepsis (HR=0·71; 95%CI 0·56—0·94) were both associated with a reduction in mortality risk.

Long-term adverse kidney events

A total of 600 out of 1347 (44·5%) patients suffered from MAKEs over the total follow-up period (Table 4): 156 in the AKD group (54·2%) and 444 in the AKI group (41·9%) ($p < 0·001$). The cumulative incidence of MAKEs over time for both groups are demonstrated in Supplementary Figure 2. AKD patients had a consistently higher rate of MAKEs over the entire follow-up period (log-rank test *p*-value<0·001).

Analysis of risk factors associated with long-term MAKEs can be found in Supplementary Table 6; as shown in Supplementary Figure 2, most events occurred early in the follow-up period therefore ORs were used for this analysis. This showed that progression to AKD remained a statistically significant risk factor once other variables had been accounted for (OR=1·25; 95%CI 1·03—1·51; *p*-value=0·022). Other factors which were shown to have an association with increased risk of a MAKE were: increasing age (OR=1·47 and OR=1·67); pre-existing liver disease (OR=1·36; 95%CI 1·04—1·75); and pre-existing diabetes (OR=1·25; 95%CI 1·03—1·52). Male sex was shown to reduce the risk of a MAKE following ICU discharge (OR=0·84; 95%CI 0·72—0·99).

A total of 771 patients had a pre-admission baseline eGFR of >60 ml/min/1·73m^2 and at least two post-discharge serum creatinine values available for analysis: 185 (24·0%) of these patients were found to have new CKD stage 3A or greater following hospital discharge.

	Univariable OR (95% C.I.)	*p*-value	Multivariable OR (95% C.I.)	*p*-value
Age				
<45 years	Ref	–	Ref	–
45–65 years	1·13 (0·84 – 1·55)	0·420	1·04 (0·79 – 1·38)	0·783
>65 years	1·12 (0·83 – 1·54)	0·451	1·00 (0·74 – 1·35)	0·998
Sex				
Female	Ref	–	Ref	–
Male	1·25 (0·99 – 1·59)	0·064	1·25 (1·02 – 1·54)	0·037
Admitting specialty				
Medical	Ref	–	Ref	–
Surgical	0·73 (0·46 – 0·92)	0·008	0·84 (0·69 – 1·03)	0·099
Baseline eGFR				
> 60 ml/min/1·73m^2	Ref	–	Ref	–
30 – 60 ml/min/1·73m^2	1·66 (1·25 – 2·20)	<0·001	1·44 (1·12 – 1·83)	0·004
< 30 ml/min/1·73m^2	2·94 (1·95 – 4·42)	<0·001	1·95 (1·41 – 2·65)	<0·001
Admission diagnosis				
Non-sepsis diagnosis	Ref	–	Ref	–
Sepsis	1·58 (1·24 – 2·00)	<0·001	1·35 (1·10 – 1·66)	0·004
Cardiovascular comorbidities				
Nil	Ref	–	Ref	–
Pre-existing diagnosis	1·18 (0·94 – 1·48)	0·160	1·04 (0·84 – 1·30)	0·698
Pre-existing diabetes				
Nil	Ref	–	Ref	–
Pre-existing diagnosis	1·56 (1·18 – 2·04)	0·002	1·24 (0·98 – 1·57)	0·072
Respiratory comorbidities			–	–
Nil	Ref	–		
Pre-existing diagnosis	0·83 (0·62 – 1·11)	0·249		
Pre-existing liver disease			–	–
Nil	Ref	–		
Pre-existing diagnosis	0·85 (0·57 – 1·24)	0·416		
Pre-existing malignancy			–	–
Nil	Ref	–		
Pre-existing diagnosis	0·85 (0·53 – 1·32)	0·556		
Stage of kidney injury				
Limited to stages 1 or 2	Ref	–	–	–
Progression to stage 3	12·23 (9·23 – 16·42)	<0·001		

***Table 3*: Univariable and multivariable analyses of risk factors for progression to AKD. Progression to stage 3 injury was not included as its effect was so significant that the effect of other variables was masked.**
eGFR = estimated glomerular filtration rate; OR = odds ratio; CI = confidence interval.

Proportions of new CKD were shown to be statistically higher in the AKD group compared with the AKI group (32·6% vs 22·0%; *p*-value=0·009) (Supplementary Table 7).

Discussion

In the first study of its kind, we have shown that one in four ICU patients with DNKI developed AKD. The risk of AKD was associated with male sex, sepsis, and a lower baseline eGFR. These patients suffered higher ICU and hospital mortality rates and were more likely to develop major adverse kidney events in the years following ICU survival. The development of AKD may therefore play an important role in identifying patients at a higher risk of short-term mortality, and for whom long-term kidney function surveillance would be of benefit.

The incidence of DNKI within this patient cohort was similar to previously reported rates but slightly less than a recent international study looking at rates of AKI in ICU.[3] Male sex was considered a significant factor in progression to AKD; a previous meta-analysis found development of hospital acquired AKI is 2·2x more likely to occur in males.[18] Data from this study suggest this risk profile is also present for progression to AKD. The link between male sex and increased risk of developing AKI can be extrapolated from animal models following ischaemia-reperfusion injury, and it has been suggested that this may be due to the effect of sex

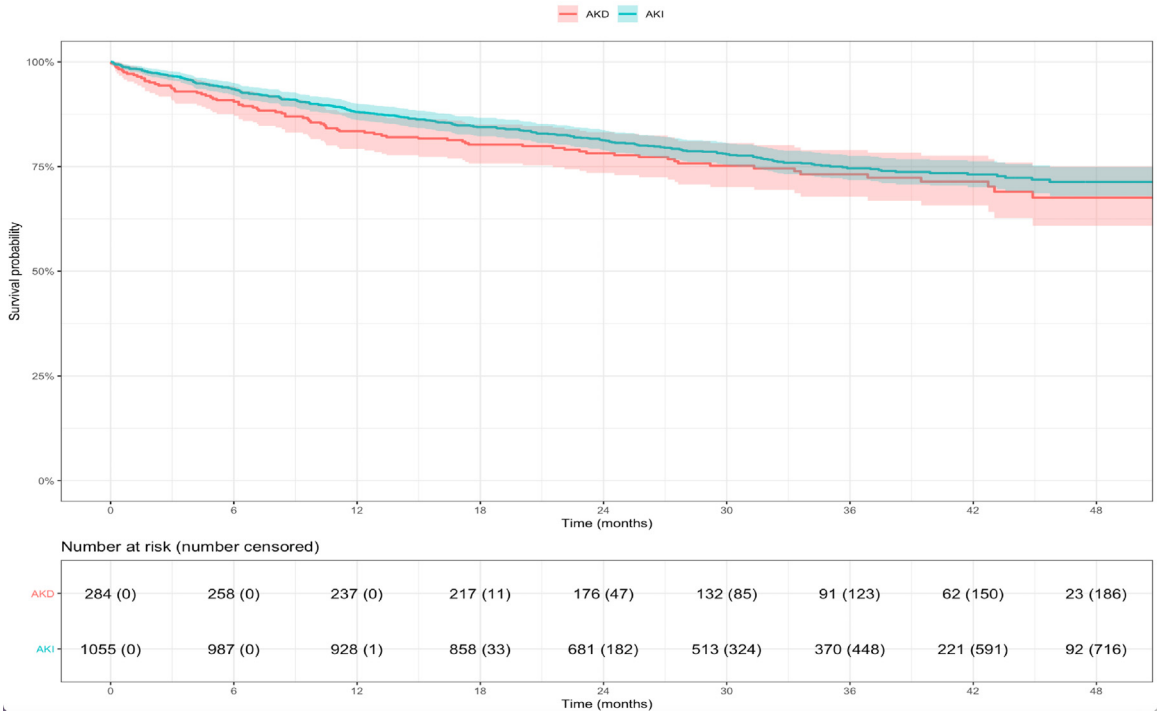

Figure 2. Long-term survival in ICU survivors based on length of kidney injury. The shaded area indicates 95% confidence intervals. Time 0 is taken from day 30 post hospital discharge

AKI = acute kidney injury; AKD = acute kidney disease.

hormones on various cellular processes involved in the development of AKI.[18]

Admission due to sepsis was also a significant factor. This can be explained by the high rates of sepsis linked to multi-organ dysfunction syndrome (MODS), which is linked with high morbidity and mortality[19]; sepsis has been linked to AKI in one third of patients.[20] These data suggest that DNKI due to sepsis is associated with a longer time to recovery than other aetiologies. Similarly, it has previously been stated that AKI can increase the risk of developing sepsis.[21] The other observed association between decreased baseline eGFR and increased risk of AKD is likely a representation of the well-established link between underlying CKD and risk of subsequent AKI.[22] The tubulointerstitial pathology and altered cell signaling in renal tubular cells that predominate in CKD are likely to significantly contribute to prolonging the length of DNKI.[23]

The data produced from this study demonstrate that AKD has a significantly higher in-ICU and in-hospital mortality than AKI. This will obviously be influenced by the removal of patients without kidney recovery who died prior to day 7, however their inclusion in AKI group would likely skew mortality towards this group in

	Total ICU survivors (*n* = 1347)	Acute kidney injury (*n* = 1059)	Acute kidney disease (*n* = 288)	*p*-value
Death during follow-up period - No. [% (95% CI)]	322 [23·9% (21·7% - 26·2%)]	247 [23·3% (20·8% - 25·9%)]	75 [26·0% (21·2% - 31·3%)]	0·378
Major adverse kidney event – No. [% (95% CI)]				
>30% eGFR drop from baseline	589 [43·7% (41·1% - 46·3%)]	444 [41·9% (39·0% - 44·9%)]	145 [50·4% (44·6% - 56·1%)]	0·009
Serum creatinine doubled	275 [20·4% (18·2% - 22·6%)]	199 [18·8% (16·5% - 21·2%)]	76 [26·4% (21·4% - 31·7%)]	0·005
Initiation long-term KRT	14 [1·0% (0·6% - 1·7%)]	6 [0·6% (0·2% - 1·1%)]	8 [2·8% (1·3% - 5·1%)]	0·003
Any major adverse kidney event – No. [% (95% CI)]	600 [44·5% (41·9% - 47·2%)]	444 [41·9% (39·0% - 44·9%)]	156 [54·2% (48·8% - 59·8%)]	<0·001

***Table 4*: Long-term outcomes dependent on length of kidney injury.**

ICU = intensive care unit; eGFR = estimated glomerular filtration rate; KRT = kidney replacement therapy; CI = confidence interval.

patients who may have gone on to develop AKD. Similarly, the removal of AKI-NS patients is the likely reason for a relatively low in-ICU mortality rate of 8·7% in the DNKI population. It has been previously established that increasing length of injury is an increased risk factor for increased morbidity and mortality,[24] and these new data likely reflect the interplay between prolonged injury, stage 3 injury and KRT requirement, which has also been previously linked with increased mortality.[25] Requirement for KRT in the context of AKI has long been documented as independent risk factor for increased mortality.[26]

Over the total follow-up period, there was prevailing, but non-statistically significant, trend that AKD patients suffered from reduced long-term survival compared with AKI patients. These data differ from prior studies, which have found increased length of kidney injury to be associated with a reduction in long-term survival in certain subsets of patients.[27] Similarly, one prior study focusing on rates of kidney recovery found significant differences between late reversal kidney injury when compared to rapid reversal injury.[28] This may be a representation of the relatively small sample size of ICU survivors in the AKD group ($n = 288$) and is indicative of further research in this area using a larger study population. It may also represent the effect of the higher in-ICU and in-hospital mortality in AKD patients, which may have led to a survivorship bias.

AKD patients were found to be at significantly higher risk of a MAKE than AKI patients over the follow-up period with an additional burden of 25% higher rates of MAKE demonstrated on multivariable analysis. Using development of CKD as a surrogate marker for MAKEs, this relationship correlates well with previous evidence published regarding increased risk of developing CKD following an episode of AKI.[29] Furthermore, a prior meta-analysis found that increased length of injury is an independent risk factor for progression to CKD[30]; the data produced from this study supports this association.

Previous work on acute kidney disease includes a study by James et al. during which they reported the incidence of AKD in adult patients within a Canadian province. Their work found that the presence of AKD conferred an additional risk of progression to chronic kidney disease.[31] However, this study utilised a prior, broader definition of AKD as suggested in the KDIGO clinical AKI guideline published in 2012; furthermore, the study population included all adult patients in both the community and hospital setting. Further work by Peerapornratana et al. utilised the newly suggested criterion for defining AKD as AKI persisting for 7 days or longer but looked specifically at this is the context of sepsis.[32] The results of this study were consistent with the findings of this one, as they identified male sex and pre-existing CKD as independent risk factors for developing AKD.

This study is the first to look at both short- and long-term outcomes of AKD in a general ICU population following its identification as a key area for future research.[9] It utilises individualised data from a large cohort of patients to quantify baseline kidney function, and results of the sensitivity analyses confirmed that both reference serum creatinine methods from a validated, automated system produced similar results.[13] However, the study has several limitations. Firstly, the lack of urine output data following ICU discharge prevents diagnosis of kidney recovery, consequently urine output criteria were not used to diagnose AKI. This likely reduced the detected incidence of DNKI in this cohort. Similarly, lack of urinalysis data prevented identification of MAKEs based on persistent albuminuria criteria. Secondly, there is no unified definition for kidney recovery following AKI; no longer meeting AKI criteria is one suggested method. These limitations can lead to issues with diagnosing kidney recovery in the critically unwell, as rates of recovery may be influenced by reduction in lean body mass frequently seen in patients. Although creatinine values within 24 h of KRT were discounted to prevent early diagnosis of recovery, residual effects of KRT may have persisted beyond this point. Finally, only length of first injury for each patient was registered: this may mean an initial recovery followed by a prolonged relapse was missed, thus underrepresenting the number of patients with AKD by categorizing them as AKI based on the initial recovery.

Whilst this patient cohort is likely very representative of the ICU population within the United Kingdom, it may not be generalisable internationally. Similarly, it is important to note that this patient population were only identified to have kidney injury in the context of critical illness. This means this cannot be extrapolated to community acquired kidney injury. Prior data from Wonnacott et al. has demonstrated that mortality in hospital acquired kidney injury is significantly higher than community acquired disease.[33]

This study is the first to document short- and long-term outcomes of AKD patients in ICU. Male sex, admission due to sepsis and lower baseline eGFR are significantly associated with progression to AKD. In-ICU and in-hospital mortality rates of AKD patients are significantly higher than patients with a shorter-term AKI. Additionally, progression to AKD is an independent risk factor for a future major adverse kidney event. The trend for long-term survival was lower in AKD patients, but not statistically significantly different to AKI patients. Further research is needed into this novel area to explore this potential association in long-term survival and whether AKD patients should be targeted for long-term nephrology follow up, given the strong association with future MAKEs.

Declaration of interests

PM declares grants from Boehringer Ingelheim, and payment received from Vifor, Novartis, Napp, Astrazeneca, Pharmacosmos and Astellas during the study period: none of the above were for work related to the

above manuscript. All other authors declare no conflicts of interest.

Contributors

MA and MSh were responsible for accessing and analysing the raw data associated with this study. All authors were responsible for interpretation of the data, decision to submit the work for publication and have approved the final version of this manuscript.

Data sharing statement

Anonymised patient data collected during this study will be made available in the publicly available Enlighten repository (https://researchdata.gla.ac.uk). This data will be made available for a period of ten years following completion of associated work towards attaining a thesis due to be completed no later than July 2023.

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Supplementary materials

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