

ORIGINAL RESEARCH ARTICLE

Incidence and trajectories of subclinical and KDIGO-defined postoperative acute kidney injury in patients undergoing major abdominal surgery

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Abstract

Background: Postoperative acute kidney injury is a common occurrence among patients undergoing major abdominal surgery and is associated with adverse outcomes. The effect of an incremental increase in serum creatinine concentration not meeting the KDIGO criteria for acute kidney injury is poorly studied. We evaluated the incidence and trajectories of postoperative subclinical acute kidney injury (sPO-AKI), acute kidney injury (PO-AKI), acute kidney disease (PO-AKD), and their relationships with chronic kidney disease (CKD), major adverse kidney events (MAKE30), and all-cause mortality at 30 days after surgery.

Methods: In a pre-planned, nested cohort sub study of the Myocardial Injury in Noncardiac Surgery in Sweden (MINSS) study, we included 588 patients from two hospitals. We determined the incidence of PO-AKI, PO-AKD, and CKD according to the ADQI-POQI consensus criteria. sPO-AKI was defined as a 25–49% increase in serum creatinine concentration within 7 days of surgery.

Results: A total of 59 (10.2%) patients fulfilled the criteria for sPO-AKI, 41 (7.1%) patients for PO-AKI, 29 (6.2%) for PO-AKD, and 6 (1.2%) for CKD. Similar proportions of patients with sPO-AKI and PO-AKI developed PO-AKD. An association was identified between the combined group of sPO-AKI and PO-AKI and 30-day mortality (Cramer's V: 0.1, $P=0.037$). PO-AKD (Cramer's V: 0.4, $P<0.001$) was associated with MAKE30 and 30-day mortality. All patients with CKD had pre-existing PO-AKD.

Conclusions: Subclinical postoperative kidney injury not fulfilling the KDIGO criteria occurred in every 10th patient, and one in 14 suffered from PO-AKI after major abdominal surgery. A majority of PO-AKD cases was preceded by sPO-AKI and PO-AKI. Early kidney injuries were associated with longer-term adverse outcomes including MAKE30, 30-day mortality, and CKD.

Keywords: abdominal surgery; postoperative; renal failure; subclinical kidney injury; trajectories

Postoperative acute kidney injury (PO-AKI) occurs commonly among patients undergoing major abdominal surgery and is associated with substantial short- and long-term adverse outcomes.^{1–7} PO-AKI occurs in 6–18% of patients undergoing major abdominal surgery.^{1,3,8,9} The Kidney Disease:

Improving Global Outcome (KDIGO) definition is widely adopted, and a recent consensus recommended a 7-day window for the diagnosis of PO-AKI.¹⁰ If the kidney injury extends beyond 7 days after surgery, the term postoperative acute kidney disease (PO-AKD) should be applied.²

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PO-AKI is associated with increased short- and long-term mortality, increased risk of progressing into chronic kidney disease (CKD) and dialysis dependency,^{2,4,5,7,11–14} and increased hospital costs and resource utilisation.¹⁵ As far as we know, the incidence of PO-AKD has not been described, perhaps a reflection of relatively new consensus definitions that were established in 2021. The trajectories of PO-AKI and PO-AKD and their prognostic implications are poorly studied.

The occurrence and implications of subclinical acute kidney injury (sPO-AKI) that do not meet the criteria for PO-AKI or PO-AKD have been sparsely studied. In a large retrospective study, the incidence of sPO-AKI (defined as minor serum creatinine concentration [sCr] increases of 25–49% above baseline but $<0.3 \text{ mg dl}^{-1}$, i.e. not fulfilling the KDIGO AKI criteria) was 2.9%.³ Despite not fulfilling the criteria for AKI, the patients undergoing noncardiac surgery had a five-fold increased risk of death (odds ratio [OR] 5.4; 95% confidence interval [CI] 1.5–20.3; $P<0.001$) and 3 days longer hospital length of stay ($\beta_{\text{noncardiac}}=2.87$; 95% CI 1.07–4.68, $P<0.001$).

To our knowledge, there is only one prospective study evaluating the impact of early, postoperative, minor increases in [sCr] demonstrating a two-fold increase in 30-day mortality (hazard ratio [HR] 1.92 [1.34–2.77]) among patients undergoing cardiac surgery.¹⁶

Thus, the impact of minor [sCr] increases not fulfilling the KDIGO criteria remains largely unknown but may represent subclinical injury that is associated with detrimental outcomes.^{3,17} Even mild AKI (KDIGO stage 1) is associated with the development and progression of CKD; however, the relationship between sPO-AKI and progression into PO-AKD and CKD is currently not well investigated.^{14,18}

The aim of this study is to evaluate the incidence of sPO-AKI, PO-AKI, and PO-AKD among patients undergoing elective, major abdominal surgery. Secondary aims are to evaluate the relationship between early postoperative kidney injuries (sPO-AKI, PO-AKI, and PO-AKD) and major adverse kidney events (MAKE30), all-cause mortality at 30 days after surgery, and CKD at 1 yr after surgery.

Methods

This is a pre-planned, nested, cohort sub study of the Myocardial Injury in Noncardiac Surgery in Sweden (MINSS) study (NCT03436238)¹⁹ including patients enrolled at Linköping University Hospital and Vrinnevi Hospital, Norrköping, Sweden. MINSS is a prospective observational cohort study designed to investigate cardiac biomarkers and cardiovascular outcomes in patients >50 yr of age undergoing elective, major abdominal surgery.¹⁷ The study was approved by the Regional Ethical Review Committee (Linköping, Sweden; 29 March 2017). Written, informed consent was obtained from all participants. The [sCr] was measured at the following time points: before surgery, after surgery, postoperative day (POD) 1, 2, and 3 after surgery. At POD30 and POD365, patients were contacted and medical records reviewed manually for complications.

The additional information required for this sub study included postoperative [sCr] and estimated glomerular filtration rate after discharge, and ICD codes (N17.9, N18.X, N19.9, N99.9) related to kidney failure. These data were extracted retrospectively from patient charts by independent, trained observers to a predefined template.

The primary endpoint was the incidence of PO-AKI and PO-AKD as defined by the ADQI-POQI consensus criteria (definitions available in [Appendix 1](#)). Only [sCr] was used to assess

the outcomes, because urine output data are unreliable. PO-AKI, PO-AKD, and CKD were defined according to consensus guidelines and were calculated for POD1–7, 8–90, and 91–365, respectively.² sPO-AKI was defined as a 25–49% increase from the preoperative value within 7 days after surgery.

The secondary endpoints were mortality and MAKE at 30 days post-surgery, and CKD at 1 yr post-surgery. Patients undergoing urological and renal surgery were excluded from this sub study, as were patients with pre-existing CKD.

Statistical analysis

Patients' baseline characteristics are reported as mean (standard deviation), median (inter-quartile range), or frequencies (%). sPO-AKI, PO-AKI, PO-AKD, and CKD are reported as number (*n*) and percent (%), and trajectories presented in graphical form.

As the primary aim was to document the incidences of the various types of kidney injuries, a sample size calculation was not required for that part of the study. For the secondary aims, we assumed a frequency of mortality and MAKE30 of 10% based on the incidence described in previous studies.^{1,20,21} To correct for six covariates in a multivariable analysis, 60 outcomes were required using a rule-of-thumb of 10 outcomes per independent variable. Thus, we reasoned that 600 patients would be required for this exploratory analysis. Fisher's exact test was used to determine statistical significance and Cramer's *V* was used to measure strength of association (weak >0.05 , moderate >0.1 , strong >0.15 , and very strong >0.25).²²

All statistical analyses were made using SPSS statistics software version 25.0 (SPSS Inc., Chicago, IL, USA). An alpha value of ≤ 0.05 was considered significant.

Results

The inclusion flow chart is shown in [Fig 1](#). After exclusion of patients undergoing renal or urological procedures ($n=118$), patients with pre-existing CKD ($n=5$), those with missing data ($n=62$), patients whose surgery was cancelled ($n=1$), and those

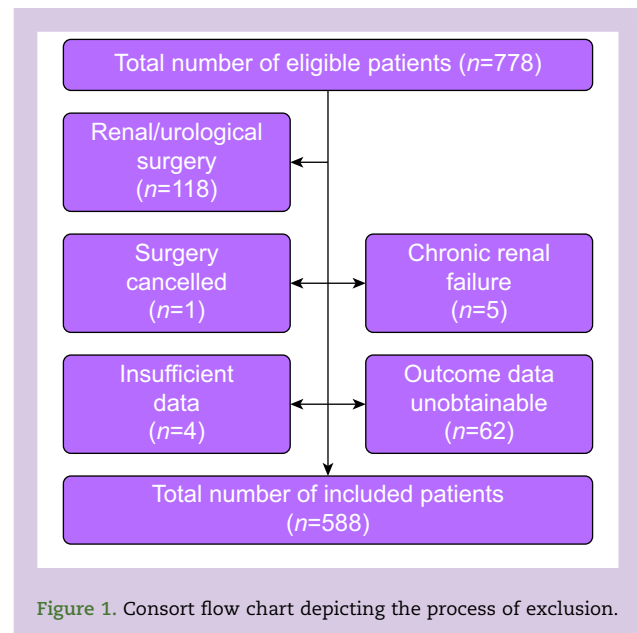


Figure 1. Consort flow chart depicting the process of exclusion.

with insufficient outcome data ($n=4$), 588 patients were included in the study.

Patient characteristics are shown in Table 1. A total of 59 (10.2%) patients fulfilled the criteria for sPO-AKI, 41 (7.1%) patients for PO-AKI, and 29 (6.2%) for PO-AKD. Similar proportions of patients with sPO-AKI (11/59 [18.6%]) and PO-AKI (8/41 [19.5%]) developed PO-AKD. Ten out of 29 (34.4%) patients with PO-AKD did not have pre-existing sPO-AKI or PO-AKI. Every case of CKD had antecedent PO-AKD ($n=6$, 1.2%). The absolute number of events was 10 (1.8%) for MAKE30 and 5 (0.9%) for 30-day mortality; therefore, we refrained from multivariable analysis.

The trajectories of postoperative kidney injury are shown in Fig 2. PO-AKI (Cramer's V: 0.12; $P=0.041$) and PO-AKD (Cramer's V: 0.15, $P=0.021$) were significantly associated with 30-day mortality. There was no significant relationship between sPO-AKI and 30-day mortality. However, a significant association with 30-day mortality was observed when pooling the sPO-AKI and PO-AKI groups (Cramer's V: 0.1, $P=0.037$). sPO-AKI/PO-AKI (Cramer's V: 0.11, $P=0.017$) and PO-AKD (Cramer's V: 0.4, $P<0.001$) were associated with MAKE30. The incidence of CKD was 1.2% ($n=6$); therefore, we did not conduct further statistical analysis of this group. All CKD cases were preceded by PO-AKD.

Discussion

PO-AKI occurred in 7.1% of this population of patients undergoing elective, major abdominal surgery. The incidence of sPO-AKI, defined as a relative [sCr] increase of 25–49%, was higher (10.2%). Assessed together, both sPO-AKI and PO-AKI were associated with MAKE30 underscoring the importance of subclinical kidney injuries that do not fulfil the KDIGO criteria for AKI.

The incidence of PO-AKD was lower (6.2%) than that of sPO-AKI. Approximately one in five patients with sPO-AKI and PO-AKI went on to develop PO-AKD, accounting for the majority (66%) of patients with PO-AKD and *de novo* disease developed in 34%. This suggests that the kidneys were exposed to ongoing and new insults beyond 7 days after surgery. PO-AKD is not well studied within a general surgical setting; however, our findings are in line with recent studies in cardiac and major vascular surgery where the fraction of PO-AKD preceded by AKI ranged from 35.9–38.6%.^{23,24} Moreover, PO-AKD is reportedly a predictor for CKD development, which is in line with our results considering that all six patients who developed CKD had antecedent PO-AKD.^{14,23}

As the majority of patients with PO-AKD had already suffered renal damage in the form of sPO-AKI and PO-AKI, our

Table 1 Patient characteristics and outcomes. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, postoperative chronic kidney disease; COPD, chronic obstructive pulmonary disease; IDDM, insulin-dependent diabetes mellitus; IQR, inter-quartile range; MAKE30, major adverse kidney event within 30 days after surgery; PO-AKD, postoperative acute kidney disease; PO-AKI, postoperative acute kidney injury; SD, standard deviation; sPO-AKI, subclinical postoperative acute kidney injury; TIA, transient ischaemic attack.

Age (yr), median (IQR)	70 (63–75)
Sex, female, n (%)	253 (43.0)
Comorbidities, n (%)	
	Coronary artery disease
	Heart failure
	IDDM
	Stroke or TIA
	Hyperlipidaemia
	Hypertension
	Atrial fibrillation
	Metastatic cancer
	COPD
	Liver cirrhosis
ASA physical status, n (%)	1
	2
	≥3
Preoperative medications, n (%)	Platelet inhibitors
	Statins
	Beta-blockers
	Calcium channel blockers
	ACEi or ARBs
Surgical category, n (%)	Upper gastrointestinal
	Hepatobiliary
	Pancreas
	Colorectal
	Gynaecology
Preoperative anaemia, n (%)	Male (<130 g L ⁻¹)
	Female (<120 g L ⁻¹)
Duration of surgery (h), mean (SD)	3.31 (1.93)
Intraoperative blood loss (ml), median (IQR)	421 (75–500)
Intraoperative hypotension, n (%)	MAP <55 mm Hg at any time
30-Day mortality, n (%)	5 (0.9)
Outcomes, n (%)	sPO-AKI
	PO-AKI
	PO-AKD
	CKD
	MAKE30

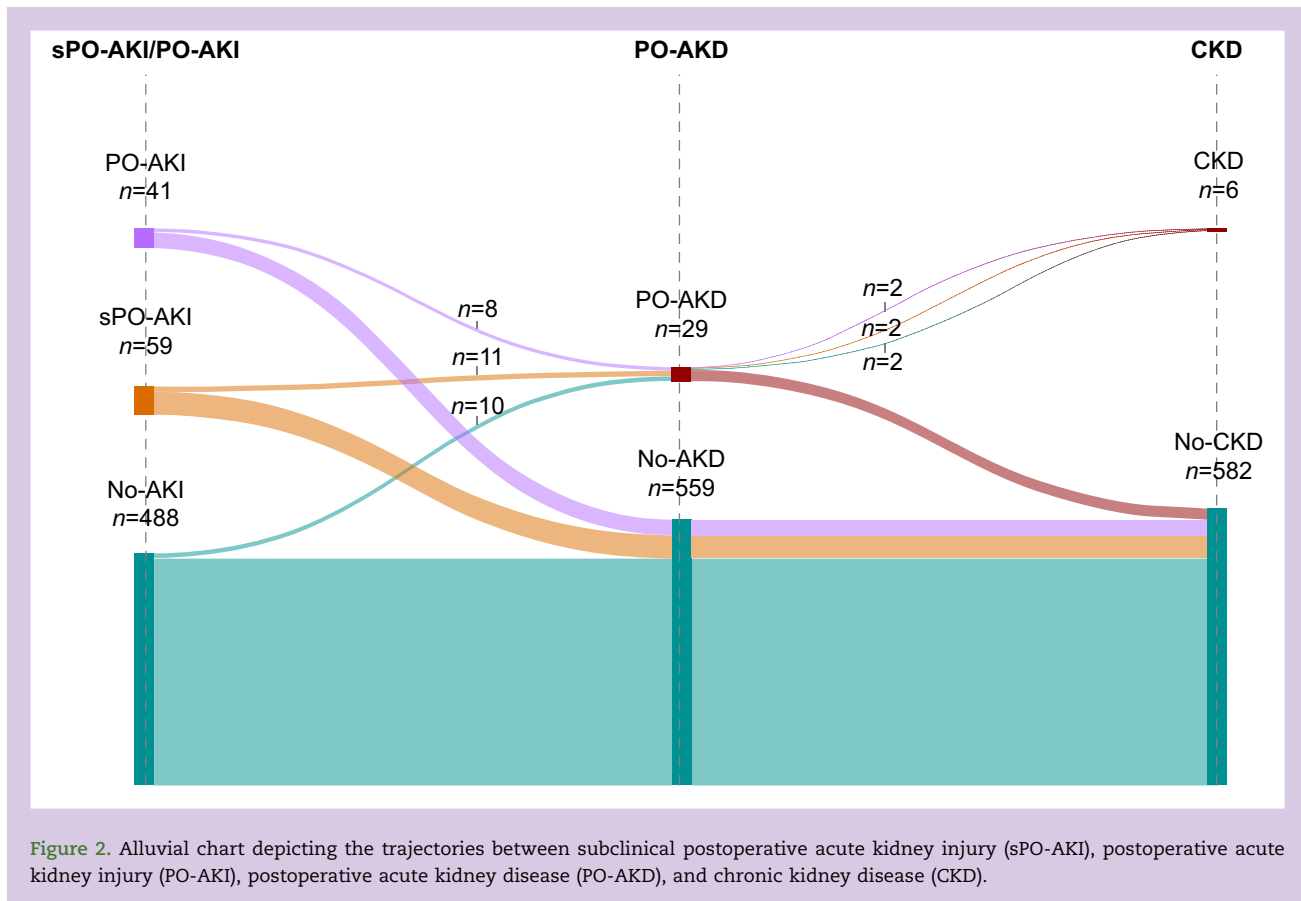


Figure 2. Alluvial chart depicting the trajectories between subclinical postoperative acute kidney injury (sPO-AKI), postoperative acute kidney injury (PO-AKI), postoperative acute kidney disease (PO-AKD), and chronic kidney disease (CKD).

findings support the relevance of sPO-AKI as a marker of potential long-term risk adding to the currently known risk factors for developing CKD, including patient status, the nature of the surgical procedure, and postoperative care.¹⁴

Early detection and treatment of kidney injury is crucial for preventing long-term adverse outcomes.^{1,2,23,24} For early detection, biomarkers such as TIMP-2•IGFBP7 have been successfully used to identify patients with an increased risk of developing postoperative kidney injury and pre-emptively treating them has been shown to be effective in reducing the occurrence of AKI.^{25,26} However, as these biomarkers are expensive and not always available, sPO-AKI could be a useful surrogate as a trigger for clinicians to implement pre-emptive management plans. The pathophysiological relevance of PO-AKD is supported by its relationship with CKD, MAKE30, and 30-day mortality, and it therefore makes sense to prevent its occurrence.

The strength of this study lies in its prospective data collection and blinded assessment of outcomes. We used the ADQI-POQI consensus definitions that specifically apply to postoperative populations.² Compared with previous studies,^{13,14} our focus has been somewhat different in investigating the trajectories of consensus-defined kidney injury and subclinical disease. Our data suggest that even a small change in [sCr] is deleterious and contributes to an increased risk of overt injury, which in turn is associated with adverse outcomes such as 30-day mortality, MAKE30, and CKD. Although our data are limited by the small sample size, we believe that they may contribute to the understanding of how

irreversible injury develops. This could also help clinicians differentiate postoperative kidney disease from *de novo* disease emerging beyond the routine postoperative period and provide shorter times to diagnosis and treatment. Our findings should be confirmed in future studies.

Our study has several limitations, the most obvious being the limited number of outcomes. [sCr] was not routinely collected between POD7 and POD365. Any [sCr] measurements registered during that time interval were not planned and although most patients had their [sCr] measured routinely, we acknowledge a loss of data that may have resulted in an underestimation of PO-AKD and CKD. We did not use the urinary output criteria to define AKI. This is likely to have underestimated the number of outcomes, as recently demonstrated in the EPIS-AKI study.¹ However, these data were not consistently available from all patients' charts, and we therefore included only [sCr] in the analysis. Nephrotoxic drugs are a known risk factor for PO-AKI; in a secondary analysis of the EPIS-AKI study, it was shown that perioperative and postoperative use of nephrotoxic agents not only increased the risk for PO-AKI but probably also increased the risk for PO-AKD.²⁷ Other known risk factors for PO-AKI are hypovolaemia and hyperglycaemia.^{28,29} Detailed information about these risk factors and information about postoperative care beyond POD4 may have modified the outcomes, and the lack of this information also limits our study.

Furthermore, because of the limited number of outcomes, we were unable to perform a multivariable analysis. Consequently, we could not evaluate the risk factors contributing to

the increased incidence of kidney injury. It also limited our assessment of the relative contributions of the different stages of kidney injury to the long-term risk. In order to better understand whether sPO-AKI might be a reflection of preoperative kidney impairment, we tested for the association between preoperative [sCr] and sPO-AKI and sPO-AKI/PO-AKI. There was no statistical association observed implying that sPO-AKI in this population is a *de novo* disease.

Conclusions

sPO-AKI not fulfilling the KDIGO criteria occurred in every 10th patient, and one in 14 suffered from PO-AKI after major abdominal surgery. A majority of patients with PO-AKI had antecedent sPO-AKI and AKI. PO-AKI was associated with longer-term adverse outcomes including MAKE30, 30-day mortality, and CKD.

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Authors' contributions

Study design and conception: MC, JZ, JF

Data acquisition: MC, JZ, LE

Statistical analysis: JZ, LE

Manuscript drafting: MC, JZ, LE

Critical revisions of the manuscript and approval of the final version: all authors.

Declaration of generative AI in scientific writing

Generative AI was not used for this article.

Declarations of interest

MSC is an editorial board member of the *British Journal of Anaesthesia*. The other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bjao.2024.100345>.

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