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Original Article

ORIGINAL ARTICLE

Mild Stage 1 post-operative acute kidney injury: association with chronic kidney disease and long-term survival

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ABSTRACT

Background. Mild cases of acute kidney injury (AKI) are identified by a small rise in serum creatinine (SCr) according to the KDIGO AKI definition. The aim of this study was to examine the long-term outcomes of individuals with mild AKI.

Methods. This was a retrospective cohort study of all adult patients who underwent abdominal, cardiothoracic, vascular or orthopaedic surgery at Landspítali–The National University Hospital of Iceland in 1998–2015. Incident chronic kidney disease (CKD), progression of pre-existing CKD and long-term survival were compared between patients with mild Stage 1 AKI (defined as a rise in SCr of $\geq 26.5 \mu\text{mol/L}$ within 48 h post-operatively without reaching $1.5 \times$ baseline SCr within 7 days), and a propensity score-matched control group without AKI stratified by the presence of CKD.

Results. Pre- and post-operative SCr values were available for 47 333 (42%) surgeries. Of those, 1161 (2.4%) had mild Stage 1 AKI and 2355 (5%) more severe forms of AKI. Mild Stage 1 AKI was associated with both incident CKD and progression of pre-existing CKD ($P < 0.001$). After exclusion of post-operative deaths within 30 days, mild Stage 1 AKI was not associated with worse 1-year survival in patients with preserved kidney function (94% versus 94%, $P = 0.660$), and same was true for patients with pre-operative CKD (83% versus 82%, $P = 0.870$) compared with their matched individuals.

Conclusions. Mild Stage 1 AKI is associated with development and progression of CKD, but not with inferior 1-year survival. These findings support the inclusion of a small absolute increase in SCr in the definition of AKI.

Keywords: acute kidney injury, chronic kidney disease, KDIGO criteria, serum creatinine, survival

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INTRODUCTION

Acute kidney injury (AKI) is a common complication of surgery [1] that has been associated with the development and/or progression of chronic kidney disease (CKD) and increased mortality [2–6].

In addition to a relative increase in serum creatinine (SCr) to at least 1.5× baseline within 7 days [7], an absolute rise in SCr of $\geq 26.5 \mu\text{mol/L}$ within 48 h without reaching 1.5× baseline SCr within 7 days is sufficient to make the diagnosis of AKI according to current definitions [8, 9]. This is justified by several retrospective studies demonstrating an association between such a small increase in SCr and short-term mortality [10, 11]. The use of absolute changes in SCr to define AKI is, however, potentially limited given the variability of baseline SCr, particularly among those with underlying CKD [12]. Therefore, it is possible that the subgroup of patients who fulfil the criteria for the diagnosis of AKI solely by the small increase in SCr of $\geq 26.5 \mu\text{mol/L}$ differs from other patients with AKI.

Few studies have focused on long-term outcomes after small acute increases in SCr [11, 13–15]. Considering the sensitivity of a small change in SCr measurements, there is a substantial risk of both under- and over-diagnosing mild AKI depending on the timing of the baseline value. Nevertheless, studies have shown that adverse outcomes associate with even very small absolute or relative in-hospital increases in SCr, although these studies have primarily focused on mortality and the development of end-stage kidney disease (ESKD) [12–14]. Further studies are needed to examine whether the small absolute increase in SCr, as included in current definitions, associates with long-term survival and development of CKD or progression of pre-existing CKD.

The aim of this study was to examine if post-operative mild Stage 1 AKI, defined as the increase in SCr of $\geq 26.5 \mu\text{mol/L}$ within 48 h, without reaching 1.5× baseline SCr within 7 days, is associated with long-term development of CKD, the progression of pre-existing CKD and survival.

MATERIALS AND METHODS

Ethical approval

Approval for the study was obtained from the National Bioethics Committee (14-139-V1) and the Data Protection Authority in Iceland.

Study design and patient sample

This was a retrospective cohort study of all patients aged ≥ 18 years who underwent abdominal, cardiothoracic, vascular or orthopaedic surgery at Landspítali–The National University Hospital of Iceland from 1 January 1998 to 31 December 2015. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies [16]. All patients with pre-operative CKD Stage 5 and repeated AKI episodes during surgical admissions were excluded. Patients who died in hospital within 30 days of surgery were excluded from the analysis of long-term outcomes to eliminate the effects of short-term mortality on long-term survival. Analysis that includes early deaths is presented in the [Supplementary Material](#). Patients who died in the first 90 days after surgery and could therefore not be assessed for development or progression of CKD were excluded from the analysis of kidney-specific outcomes.

Data acquisition

Clinical data were extracted from electronic medical records. Surgical codes, based on the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP-IS, version 1.14, www.nowbase.org), were used to classify the procedures. International Classification of Diseases, Tenth revision diagnosis codes were obtained from hospital records to assess pre-operative comorbidity and were used to calculate the van Walraven modification of the Elixhauser Comorbidity Index score [17, 18]. All available pre- and post-operative SCr measurements were collected from a nationwide database containing all SCr measurements performed at the University Hospital in 1998–2007 and all SCr values in Iceland in 2008–16. These values were used to define baseline SCr, determine pre-operative CKD stage, assess post-operative AKI, and evaluate incident and progressive CKD following AKI. Date of death was obtained from Statistics Iceland, censored on 20 May 2016.

Definitions

Baseline SCr was defined as the value closest to the surgery, out of measurements available within 30 days before surgery. All patients with available baseline and post-operative SCr were evaluated for the presence of post-operative AKI according to the SCr component of the KDIGO criteria [9]. Mild Stage 1 AKI was defined as an increase in SCr of $\geq 26.5 \mu\text{mol/L}$ above baseline within 48 h, without reaching a relative increase in SCr of 1.5× baseline within 7 days.

The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate glomerular filtration rate (eGFR) [19]. CKD Stage 3 and above was defined as eGFR $< 60 \text{ mL/min/1.73 m}^2$, sustained for > 90 days and CKD was staged according to the GFR criteria of the KDIGO classification system into Stages 3a, 3b, 4 and 5 [20].

Outcomes

The main outcomes of this study were development of incident CKD, progression of pre-existing CKD and 1-year survival. Incident CKD was defined as any patient who reached Stage 3 CKD and above by a decline in eGFR sustained for > 90 days in patients with a pre-operative eGFR $\geq 60 \text{ mL/min/1.73 m}^2$. Progression of pre-existing CKD was defined as an increase of at least one CKD stage, sustained for > 90 days, in patients with pre-operative CKD Stages 3 and 4.

Statistical analysis and data configuration

All statistical analysis was done in RStudio version 1.0.136 (R Foundation for Statistical Computing, Vienna, Austria). A $P < 0.05$ was considered statistically significant, and 95% confidence intervals (CIs) are reported where appropriate. Data from different datasets were combined and analysed based on individuals' national personal identification number and date of surgery.

The cohort was divided into groups of patients with no AKI, mild Stage 1 AKI and more severe forms of AKI. For outcome analysis, the cohort was further stratified into subgroups with and without preoperative CKD Stage 3 and above. Change in incidence over time was analysed with Poisson regression.

Comparison of baseline characteristics, comorbid conditions and peri-operative factors between groups was carried out using the Chi-square test, the t-test, Wilcoxon rank sum test, Kruskal–Wallis test or analysis of variance as appropriate.

Progression of CKD and survival among patients with mild Stage 1 AKI was compared with a propensity score-matched control group without AKI (1:1) (Supplementary Material). This comparison was performed separately for groups with and without pre-operative CKD Stage 3 and above. The propensity score in the survival analysis was based on: age and sex; baseline eGFR; previous history of hypertension, diabetes mellitus, ischaemic heart disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), liver disease and malignancy; year and type of surgery; and diagnosis of myocardial infarction or sepsis during the hospitalization. The propensity score in analysis of incident or progressive CKD included matching on age, sex, baseline eGFR, previous diagnosis of hypertension, diabetes, ischaemic heart disease or congestive heart failure, and year and type of surgery. The Elixhauser Comorbidity Index did not improve matching and was therefore not included in the final models. Matching was evaluated by comparing standardized differences of the matched variables with a standardized mean difference <0.1 considered adequate (Supplementary data, Tables SI–SIV) [21]. One-year survival and 5-year development of incident CKD or progression of pre-existing CKD were plotted as Kaplan–Meier curves and groups were compared with a stratified log-rank test. To examine the consistency of the results, a subgroup analysis based on the type of surgery was also performed (Supplementary data, Table SV).

RESULTS

A total of 64 535 patients underwent 116 358 abdominal, cardiothoracic, vascular or orthopaedic surgical operations during the study period. Baseline and post-operative SCr measurements for evaluation of AKI were available for 48 873 (42%) surgical procedures. A total of 1540 procedures were excluded due to the presence of pre-operative Stage 5 CKD (Figure 1). Thus, 47 333 surgical procedures were included in the analysis. In the following analysis, the incidence is reported per surgical procedure for the subset of patients with available pre- and post-operative SCr measurements.

Incidence

AKI occurred following 3516 (7.4%) surgical procedures, of which 1161 (2.4%) were classified as mild Stage 1 AKI and 2355 (5.0%) as more severe forms of AKI. The mean annual incidence of AKI was 74.2/1000 surgeries/year. The incidence of mild Stage 1 AKI decreased throughout the study period (–3% per year, 95% confidence interval [CI] –2% to –5%, $P < 0.001$). There were 561 cases of recurrent AKI episodes that were excluded from the remaining analyses (Figure 1).

Patient characteristics

Patients with mild Stage 1 AKI were older (75 versus 68 years, $P < 0.001$), more likely to be male (66% versus 54%, $P < 0.001$), and had longer median (interquartile range [IQR]) length of stay (10 versus 6 days, $P < 0.001$) and a higher comorbidity burden compared with patients without AKI (Table 1). The comorbidities included CKD (56% versus 22%, $P < 0.001$), diabetes (14% versus 6%, $P < 0.001$), ischaemic heart disease (50% versus 29%, $P < 0.001$) and congestive heart failure (24% versus 9%, $P < 0.001$). When compared with patients with more severe forms of AKI, those with mild Stage 1 AKI were more likely to have CKD (56% versus 38%, $P < 0.001$), diabetes (14% versus 11%, $P < 0.001$), ischaemic heart disease (50% versus 42%, $P < 0.001$) and

congestive heart failure (24% versus 17%, $P < 0.001$) (Table 1). Patients with mild Stage 1 AKI had significantly shorter median length of hospital stay than those with more severe AKI, 10 (5–19) versus 12 (6–24) days ($P < 0.001$).

Overall, 11 236 (24%) patients with baseline and post-operative SCr measurements available had pre-existing CKD Stage 3 or 4 prior to surgery. Of these, 1550 (14%) developed post-operative AKI compared with 2009 (5%) patients without CKD ($P < 0.001$). The frequency of mild Stage 1 AKI was 1, 4, 7 and 10% in patients with no CKD and CKD Stages 3a, 3b and 4, respectively ($P < 0.001$).

Development of incident CKD Stages 3–5 or progression of pre-existing CKD

The median (IQR) follow-up time for the assessment of long-term kidney function was 3.7 (1.4–7.3) years. There were 2350 (5%) patients without AKI, 134 (14%) with mild Stage 1 AKI and 516 (26%) patients with more severe AKI who died in the first 90 days after surgery and could therefore not be assessed for development or progression of CKD ($P < 0.001$). After 5 years of follow-up among patients without pre-operative CKD, incident CKD Stages 3–5 occurred in 6888 (26%), 198 (57%) and 497 (60%) patients without AKI, with mild Stage 1 AKI and with more severe AKI, respectively ($P < 0.001$). Progression of pre-existing CKD within 5 years of surgery occurred in 3755 (57%), 260 (74%) and 310 (75%) patients without AKI, with mild Stage 1 AKI and those with more severe AKI, respectively ($P < 0.001$). During 5 years following surgery, 43 (0.1%) patients who did not experience AKI, 4 (1%) with mild Stage 1 AKI and 4 (0.4%) patients with more severe AKI required renal replacement therapy for ESKD ($P < 0.001$).

For further analysis of mild Stage 1 AKI, each patient was assigned a propensity score-matched control, stratified by pre-existing CKD. Propensity score matching was complete for all patients with mild Stage 1 AKI (100%) in all the analyses. Matching properties are further demonstrated in Supplementary data, Tables SI–SIV. Patients without pre-operative CKD who developed mild Stage 1 AKI were significantly more likely to develop CKD Stages 3–5 in the ensuing 5 years compared with propensity score-matched control patients without AKI (57% versus 41%, $P < 0.001$; Figure 2A). Patients with pre-existing CKD Stage 3 or 4 who developed mild Stage 1 AKI were more likely to progress to a higher CKD stage than their propensity score-matched controls without AKI (74% versus 63%, $P < 0.001$; Figure 2B). The results were similar when the whole follow-up period was included in the analysis and when surgical procedure subgroups were studied (Supplementary data, Table SV).

Survival

For patients without pre-operative CKD (eGFR >60 mL/min/1.73 m²), the 30-day survival was 98, 92 and 81% in patients without AKI, in those with mild Stage 1 AKI and in patients with more severe AKI, respectively ($P < 0.001$). The 30-day survival of patients with pre-operative CKD was 95% in patients who did not develop AKI, 88% in those with mild Stage 1 AKI and 75% in patients with more severe AKI ($P < 0.001$).

The median (IQR) follow-up time for the assessment of survival was 5.3 (2.3–9.0) years. For the analysis of long-term survival, in-hospital deaths within 30 days were excluded (Figure 1). The 1-year survival among patients without pre-operative CKD was 92, 87 and 71% in patients without AKI, with mild

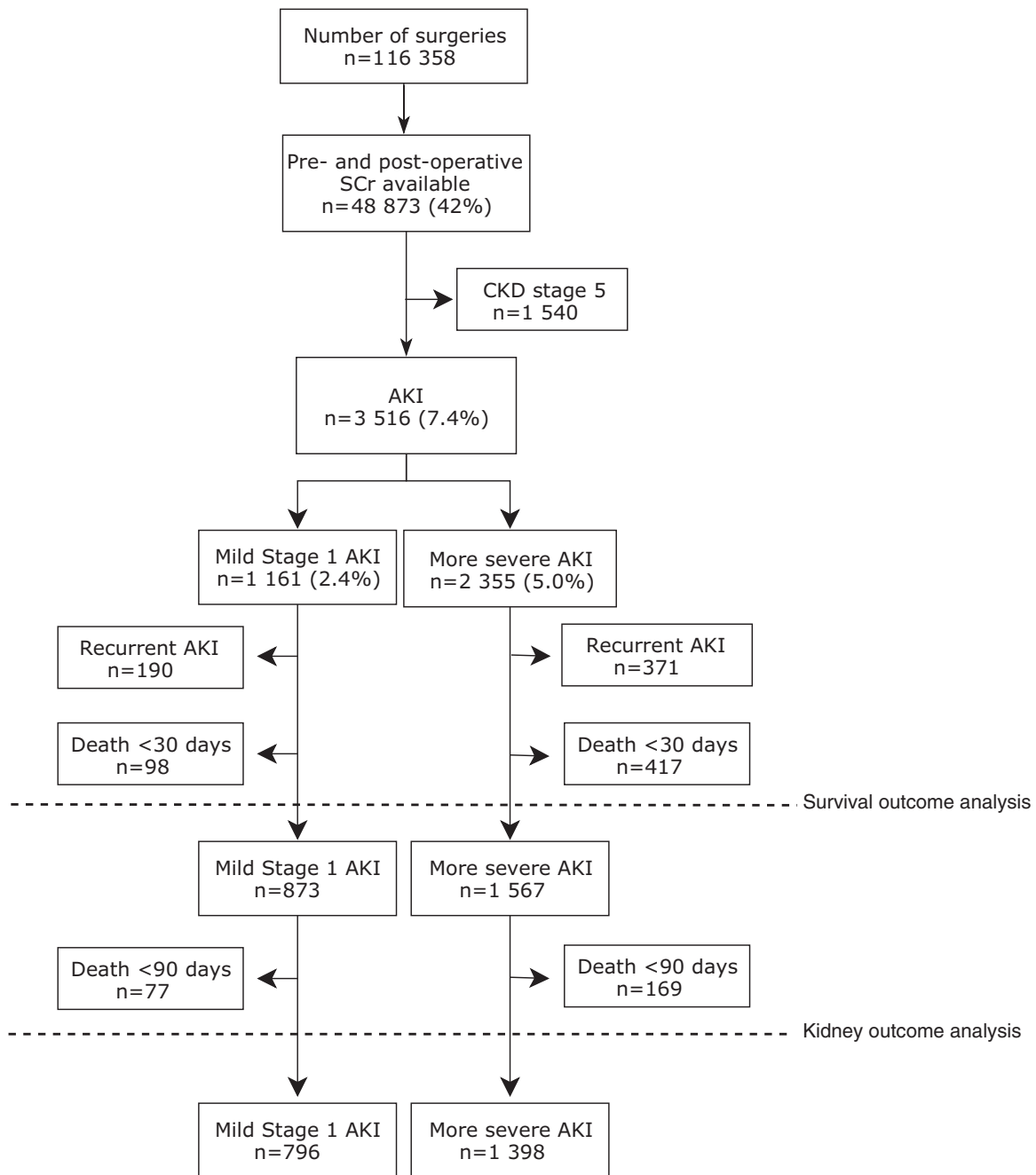


FIGURE 1: Flowchart showing the total study cohort, exclusion of patients and stratification of AKI categories for analysis.

Stage 1 AKI and in patients with more severe AKI, respectively ($P < 0.001$). For patients with pre-operative CKD, the 1-year survival was 80, 73 and 63% in patients without AKI, with mild Stage 1 AKI and with more severe AKI, respectively ($P < 0.001$).

When patients with mild Stage 1 AKI were compared with propensity score-matched controls, stratified by pre-existing CKD, there was no difference in 1-year survival of individuals without pre-operative CKD (94% versus 94%, $P = 0.660$; Figure 3A). Furthermore, 1-year survival of patients with pre-operative CKD Stage 3 and above and mild Stage 1 AKI was similar to the control group without AKI (83% versus 82%, $P = 0.870$; Figure 3B). The results were similar when the whole follow-up period was included in the analysis and for each individual

surgical procedure subgroup (Supplementary data, Table SV). Analyses including patients who died within 30 days of surgery are demonstrated in Supplementary data, Figures S1 and S2.

DISCUSSION

In this study, one-third of all AKI cases were mild Stage 1 AKI. Patients with mild Stage 1 AKI had a higher comorbidity burden than both patients without AKI and those with more severe AKI, most notably a very high rate of pre-existing CKD Stage 3 or 4. Mild Stage 1 AKI was associated with both incident CKD and progression of pre-existing CKD during 5 years of follow-up compared with matched controls. Furthermore, individuals

Table 1. Comparison of baseline characteristics between groups of patients without AKI, with mild Stage 1 AKI and with more severe AKI

	No AKI (n = 43 817)	Mild Stage 1 AKI (n = 1161)	More severe AKI (n = 2355)	P-value
Age, years	68 (57–77)	75 (68–81)*	74 (65–81)	<0.001
Sex, male	23 566 (54)	772 (66)*	1306 (55)	<0.001
Baseline SCr, $\mu\text{mol/L}$	79 (66–96)	110 (88–148)*	87 (68–114)	<0.001
No CKD	34 131 (78)	508 (44)	1458 (62)	–
CKD				
Stage 3a	5739 (13)	264 (23)	447 (19)	–
Stage 3b	3043 (7)	267 (23)	314 (13)	–
Stage 4	904 (2)	122 (10)*	136 (6)	<0.001
Hypertension	7380 (17)	346 (30)*	616 (26)	<0.001
Diabetes mellitus	2848 (6)	167 (14)*	259 (11)	<0.001
Ischaemic heart disease	12 757 (29)	586 (50)*	982 (42)	<0.001
Congestive heart failure	3956 (9)	276 (24)*	409 (17)	<0.001
COPD	2717 (6)	92 (8)*	202 (9)	<0.001
Liver disease	560 (1)	13 (1)	48 (2)	0.005
Neoplasm	11 221 (26)	353 (30)*	698 (30)	<0.001
Preoperative morbidity assessment				
Elixhauser Comorbidity Index >1	10 001 (23)	344 (30)*	680 (29)	<0.001
Type of surgery				
Abdominal				
Major	5928 (14)	133 (11)	375 (16)	–
Minor	4681 (11)	81 (7)	143 (6)	–
Cardiothoracic				
Major	9674 (22)	392 (34)	700 (30)	–
Minor	7649 (17)	224 (19)	424 (18)	–
Vascular				
Major	782 (2)	42 (4)	72 (3)	–
Minor	2337 (5)	44 (4)	85 (4)	–
Orthopaedic				
Major	9706 (22)	204 (18)	454 (19)	–
Minor	3060 (7)	41 (4)*	102 (4)	<0.001
Length of stay (days)	6 (3–10)	10 (5–19)*	12 (6–24)	<0.001

Data are presented as median (IQR) for continuous variables or number (percentage) for categorical variables. Data were compared between no AKI, mild Stage 1 AKI and more severe AKI. *Significantly different from no AKI patients, $P < 0.001$.

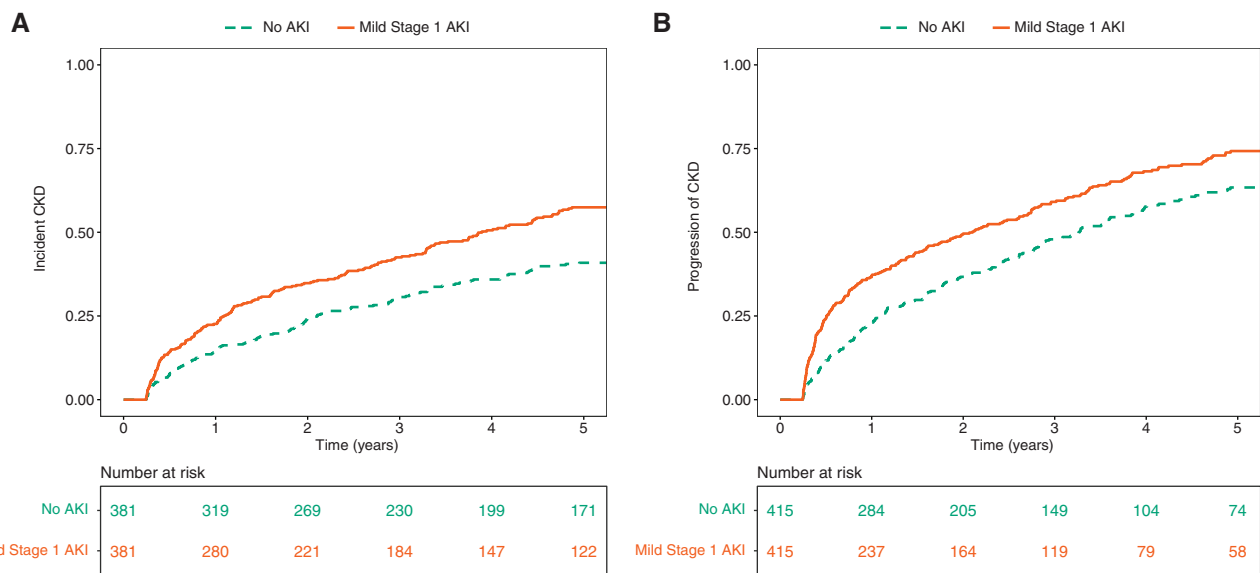


FIGURE 2: (A) Incident CKD within 5 years following surgery in patients without preoperative CKD who experienced mild Stage 1 AKI compared with a propensity score-matched control group without AKI ($P < 0.001$). (B) Progression of CKD within 5 years after surgery in patients with pre-operative CKD who developed mild Stage 1 AKI and compared with a propensity score-matched control group without AKI ($P < 0.001$). Propensity score matched for: age, sex, year of surgery, type of surgery, baseline eGFR, and previous diagnosis of hypertension, diabetes mellitus, ischaemic heart disease and congestive heart failure.

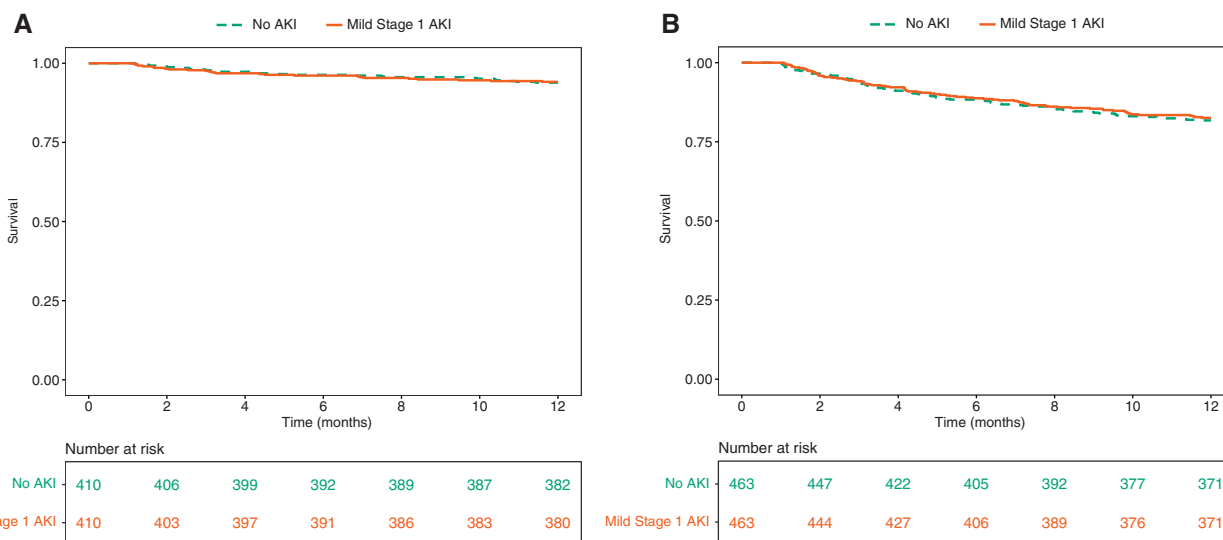


FIGURE 3: (A) One-year survival of patients without pre-operative CKD who developed mild Stage 1 AKI compared with a propensity score-matched control group without AKI. Individuals who died within 30 days after surgery were excluded. One-year survival was 94% in both the mild Stage 1 AKI group and in the propensity score-matched control group ($P = 0.660$). (B) One-year survival of patients with preoperative CKD who developed mild Stage 1 AKI compared with a propensity score-matched control group without AKI. Individuals who died within 30 days of surgery were excluded. One-year survival was 83% in the mild Stage 1 AKI group and 82% in the propensity score-matched control group ($P = 0.870$). Propensity score matched for: age, sex, year of surgery, type of surgery, baseline eGFR, diagnosis of myocardial infarction or sepsis during hospitalization and previous history of hypertension, diabetes mellitus, ischaemic heart disease, congestive heart failure, COPD, liver disease and malignancy.

with mild Stage 1 AKI had increased 30-day mortality compared with those without AKI, but when these early deaths were excluded, the 1-year survival was similar to controls, regardless of pre-operative kidney function.

Numerous studies have demonstrated an association between severe AKI and the development or progression of pre-existing CKD [22, 23]. However, there are limited data available on the association of small rises in SCr with long-term development or progression of CKD. A study of Medicaid beneficiaries with myocardial infarction showed an association of small absolute in-hospital SCr increase with both development of kidney failure requiring renal replacement therapy and death [14]. Increase in SCr of $>9 \mu\text{mol/L}$ was associated with both outcomes, but the study did not assess more subtle kidney-specific outcomes such as incident or progressive CKD. In another study of $>29\,000$ veterans undergoing cardiac surgery, Ishani et al. [13] showed an increase in SCr of $1.01\text{--}1.24\times$ baseline over the first seven post-operative days to associate with both incident CKD and progression of pre-existing CKD. The results of these two studies are in line with our findings despite differences in the cohorts and the definitions of mild AKI used. Indeed, neither of the aforementioned studies conforms with the current AKI definitions, although several of the patients are likely to have had an absolute increase of $\geq 26.5 \mu\text{mol/L}$ above baseline SCr.

Few studies have focused on long-term survival following a small increase in SCr in the hospital or post-operative setting. A large retrospective study of patients with acute myocardial infarction who survived to hospital discharge showed that increase in SCr of only $\geq 9 \mu\text{mol/L}$ during hospitalization, when compared with stable or reduced SCr, was associated with worse long-term mortality (median follow-up 4.1 years). However, the baseline SCr was determined on the day of admission, which may have resulted in an overestimation of the baseline SCr [14]. In contrast, another study that included >4300 patients undergoing cardiac or thoracic aortic surgery found that small post-operative increase in SCr of $0\text{--}44 \mu\text{mol/L}$ within

48 h following surgery, compared with a decrease in SCr of -9 to $-26.5 \mu\text{mol/L}$, was associated with a nearly 3-fold increase in 30-day mortality, but was not associated with long-term mortality [11]. These results are similar to our findings. A recent study of $>76\,000$ patients with myocardial infarction carried out in the USA showed that mild AKI, defined as a rise in SCr of $26.5\text{--}44 \mu\text{mol/L}$ during admission, regardless of the baseline SCr, was associated with increased 1-year mortality after excluding in-hospital mortality [15]. This finding differs from our results, possibly because of discrepancies in the definition of mild AKI, as baseline SCr, which was not considered in the American study, would be expected to substantially affect the classification of AKI [24]. In parallel with our study, the majority of patients who developed mild AKI had pre-operative CKD, but in general, the prevalence of CKD in the US study was higher than in our cohort.

The mechanism behind the observed association between mild Stage 1 AKI and the development and progression of CKD is unclear. Results of animal studies suggest several pathobiological pathways leading to kidney disease progression, such as maladaptive repair and dysfunctional regeneration [25, 26]. It has been proposed that the failure of regenerating tubules to differentiate following an AKI episode drives tubulointerstitial inflammation and fibrosis [26]. Furthermore, endothelial injury may induce a vicious cycle of tissue hypoxia that perpetuates cellular injury, dampens repair and causes progressive tissue damage [26]. While a full recovery would generally be expected following an episode of mild AKI, it cannot be ruled out that even mild episodes could lead to tissue hypoxia and damage resulting in the development and progression of CKD. On the other hand, the high comorbidity burden observed in patients with mild Stage 1 AKI might suggest that mild AKI does not reflect a true kidney injury, but rather reduced renal physiological reserve uncovered by the stress of the surgery and the associated haemodynamic instability and inflammatory response [23]. This notion could also explain why these patients are

prone to subsequent development of incident CKD or progression of pre-existing CKD.

The main strength of our study is the extensive nationwide SCr database that allows accurate detection and thorough long-term evaluation of incident CKD and progression of pre-existing CKD. Furthermore, the data on mortality are complete for all patients residing in Iceland. Nevertheless, the study has certain limitations including the retrospective observational design that we have attempted to mitigate by comparing the outcomes with propensity score-matched control groups. Unfortunately, information on the aetiology of AKI in our cohort is lacking, but the occurrence in the peri-operative period makes haemodynamic alterations leading to ischaemia and tubular injury a likely pathophysiological mechanism. Daily measurements of SCr were not available for all patients and, therefore, it is possible that some AKI episodes were missed or misclassified. Finally, baseline or post-operative SCr was missing in 58% of our surgical cohort. However, patients without pre- and/or post-operative SCr measurements were generally healthier and underwent less extensive surgical procedures and, thus, would be considered less likely to develop post-operative AKI.

In conclusion, our study showed that mild Stage 1 AKI accounts for one-third of all post-operative AKI episodes and is associated with incident CKD, progression of pre-existing CKD and early mortality, but not with 1-year survival. We believe that these findings support the inclusion of a small absolute increase in SCr in the definition of AKI. Finally, our results emphasize the importance of meticulous follow-up of patients who experience mild Stage 1 AKI.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj online](http://ckjonline.com).

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AUTHORS' CONTRIBUTIONS

T.E.L. was involved in designing and conducting the study, analysing the data and writing the manuscript. D.H., S.H., G.H.S. and R.P. were involved in designing the study and revising the manuscript. M.I.S. and O.S.I. were involved in designing and conducting the study, analysing the data and revising the manuscript. All authors have read and approved the final version of the manuscript. The results presented in this article have not been published previously in whole or part, except in abstract form.

CONFLICT OF INTEREST STATEMENT

None declared.

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