Anemia following acute kidney injury after noncardiac surgery and long-term outcomes: the NARA-AKI cohort study

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ABSTRACT

Background. This study was conducted to investigate whether acute kidney injury (AKI) is an independent predictor of anemia and whether anemia following AKI is a mediator of mortality after AKI.

Methods. This is a retrospective cohort study. Adults with noncardiac surgery from 2007 to 2011 were included. Obstetric or urological surgery, missing data or preoperative dialysis were excluded. Subjects were followed until the end of 2015 or lost to follow-up. Exposures of interest were postoperative AKI. Outcome variables were hematocrit values at 3, 6 and 12 months postoperatively and mortality. Associations between AKI and hematocrit or association between AKI and mortality were examined by multivariable linear regression or Cox regression, respectively.

Results. Among 6692 subjects, 445 (6.6%) developed AKI. Among those with postoperative data, AKI was independently associated with lower hematocrit at 3, 6 and 12 months postoperatively, with coefficients of –0.79 [95% confidence interval (CI) –1.47 to –0.11; n = 1750], –1.35 (–2.11 to –0.60; n = 1558) and –0.91 (–1.59 to –0.22; n = 2463), respectively. Higher stages or longer duration of AKI were associated with more severe anemia. AKI was associated with higher mortality after 3 months postoperatively with a hazard ratio of 1.54 (95% CI 1.12–2.12). Further adjustment with hematocrit at 3 months attenuated the association. The mediation effect was significant (P = 0.02) by mediation analysis.

Conclusions. AKI was an independent predictor of anemia following AKI. Higher mortality associated with AKI was at least partially mediated by anemia following AKI. Whether correction of anemia following AKI improves mortality requires further research.

Keywords: acute kidney injury, anemia, postoperative
INTRODUCTION

Multiple previous studies have consistently showed that acute kidney injury (AKI) is independently associated with higher mortality even after adjusting for potential confounders [1–5]. However, the mediators of higher mortality have not been well studied. AKI is also associated with the development of incident CKD [1–3, 6] even if renal function appeared to return to normal [7]. These previous studies suggest that there might be subclinical permanent renal damage after AKI.

A previous study reported that about one-third of AKI developed postoperatively [8]. Most cases of postoperative AKI were considered to be due to tubulointerstitial damage, demonstrated by its strong association with tubular markers [9–11]. Damage to the interstitium might lead to impaired erythropoietin (EPO) production by interstitial fibroblasts [12, 13] and subsequent anemia. Although several studies have demonstrated that anemia is a predictor for AKI [14–17], no large cohort studies exist that examine whether AKI could be a predictor of anemia following AKI.

In chronic kidney disease (CKD), anemia is common. Anemia is a strong predictor for cardiovascular complications and mortality in CKD patients [18, 19].

In this study we hypothesized that AKI leads to permanent interstitial damage even if renal function appears to recover and that AKI is a predictor of anemia by impaired EPO production. We also hypothesized that anemia following AKI might be a mediator of higher mortality after AKI. We tested these hypotheses in the NARA-AKI cohort, which is a retrospective cohort of AKI after noncardiac surgery [20–23].

MATERIALS AND METHODS

Study design and subject

The NARA-AKI cohort study is a single-center, retrospective study. Inclusion criteria were subjects ≥18 years of age who underwent noncardiac surgery under general anesthesia from April 2007, when electronic medical records started at Nara Medical University Hospital, to December 2011. Exclusion criteria were those who underwent obstetric surgery (as an increase in creatinine due to nephrectomy or ureteral manipulation could have different underlying mechanisms from other postoperative AKI), preoperative dialysis or those with missing data for serum creatinine within 1 month before and 1 week after surgery. If subjects underwent multiple surgeries during the study period, then only the first eligible surgery was considered. Subjects were followed through the end of 2015 or loss to follow-up. The hematocrit value was considered to be an indicator of anemia. The study protocol and waiver of consent were approved by the Nara Medical University Ethics Committee (approval no. 1208 and no. 1208-2 for amendment). This study waived the requirement for written informed consent due to its retrospective nature. Rather, research content has been included on the web page of our department (http://nephrology.naramed-u.ac.jp/research/clinical.html). This study was conducted in accordance with the Declaration of Helsinki. The study was registered in the University Medical Information Network (UMIN000037141).

Exposure of interest and outcome

For the analyses on association between AKI and anemia, the exposure of interest was AKI within 7 days after noncardiac surgery. The outcome variables were hematocrit values measured at 3 months (Hct3m), 6 months (Hct6m) and 12 months (Hct12m) postoperatively. Hematocrit has been used as an indicator for anemia in multiple previous studies on postoperative AKI [24–27]. For the analyses on association between AKI and mortality, the exposure of interest was AKI and the outcome variable was all-cause mortality after 3 months postoperatively.

Data acquisition and definition

The list of subjects who underwent noncardiac surgery under general anesthesia, age, sex, date of surgery and laboratory data were automatically abstracted from electronic medical records. Comorbidities, use of medications and outcomes were hand-searched from electronic medical records by investigators. These data were obtained from detailed chart reviews, including inquiries on prescriptions from other medical facilities.

AKI was defined by Kidney Disease: Improving Global Outcomes criteria (increase in serum creatinine ≥0.3 mg/dL or 150% compared with preoperative baseline value or urine output <0.5 mL/kg/h for ≥6 h) [28]. The duration of AKI was defined as the period from the date when AKI developed to the date when serum creatinine returned to ≤0.2 mg/dL of baseline and ≤149% of baseline in addition to urine output ≥0.5 mL/kg/h for ≥6 h. Baseline laboratory data, including serum creatinine, were defined as values within 1 month before surgery and the closest to the date of surgery. Estimated glomerular filtration rate (eGFR) was calculated using the equation developed for Japanese populations by the Japanese Society of Nephrology, based on the baseline serum creatinine value [29]. Laboratory values at 3, 6 and 12 months postoperatively (shown as data3m, data6m and data12m, respectively) were measured at 3 months ± 15 days, 6 months ± 15 day and 12 months ± 3 months (to maximize the available data), respectively. Values closest to the date at 3, 6 and 12 months postoperatively were selected if subjects had multiple measurements during the periods. Those with missing data were excluded from the analyses at each time point.

Statistical methods

The data were expressed as median and interquartile range (IQR) or number and percentage. Comparisons between groups were made by using the Mann–Whitney U-test or chi-square test as appropriate. A linear regression model was used to examine the associations between AKI and anemia with adjustment for potential confounders including age, sex, body mass index (BMI), diabetes mellitus, hypertension, hemorrhagic stroke, ischemic stroke, ischemic heart disease, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease (COPD), liver cirrhosis, history of cancer, smoking status (never, past and current), baseline hematocrit, baseline eGFR, albumin, natural log-transformed C-reactive protein (lnCRP), regular use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), diuretics, statins, antiplatelet therapy, anti-coagulation therapy, types of surgery (intrathoracic, intra-abdominal, pelvic or major joint and others), emergent surgery, surgery for malignancy (surgery not for malignancy, curative and palliative), chemotherapy within 3 months preoperatively, chemotheraphy within 3 months postoperatively, intraoperative blood loss (<100 and ≥100 mL) and intraoperative use of red cell transfusion in Model A. The data...
were additionally adjusted for postoperative eGFR at each time point in Model B. For the analyses on association between AKI and all-cause mortality, the Kaplan–Meier curve and Cox proportional hazards model were used. For Cox regression analyses, the data were adjusted for variables including age, sex, BMI, diabetes mellitus, hypertension, history of cancer and those undergoing malignancy-related surgery were significantly higher among those with AKI. Hematocrit values were significantly older, had lower eGFR and albumin and higher CRP at baseline. The proportions of subjects with diabetes mellitus, hypertension, hemorrhagic stroke, ischemic heart disease, congestive heart failure, atrial fibrillation, COPD, liver cirrhosis, history of cancer, smoking status, baseline eGFR, proteinuria (≥1+), regular use of ACEIs or ARBs, diuretics, statins, steroids, types of surgery, emergent surgery, surgery for malignancy, chemotherapy within 3-months preoperatively and chemotherapy within 3-months postoperatively in Model 1. The data were further adjusted for Hct3m and the adjusted HRs of AKI were compared. Mediation analyses were performed according to a method described by Discacciati et al. [30]. The mediating effect of Hct3m for association between AKI and all-cause mortality was examined using the same covariates as in Model 1. P-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata version 15 (StataCorp, College Station, TX, USA).

RESULTS

During the study period, 12,771 subjects underwent noncardiac surgeries under general anesthesia at Nara Medical University Hospital. After applying the exclusion criteria, data for 6692 subjects were available for analyses (Figure 1). Among 6692 subjects, 445 (6.6%) developed AKI (the number of patients with AKI Stage 1, 2 and 3 was 258, 149 and 38, respectively. The duration of AKI was ≤1 day and ≥2 days for 211 and 234, respectively). Patient demographics are shown in Table 1. Those with AKI were significantly older, had lower eGFR and albumin and higher CRP at baseline. The proportions of subjects with diabetes mellitus, hypertension, history of cancer and those undergoing malignancy-related surgery were significantly higher among those with AKI. Hematocrit values were significantly and consistently lower before and after surgery among those with AKI (P < 0.001) (Figure 2).

Association between AKI and anemia during long-term follow-up

Multivariable linear regression analyses showed that AKI was independently associated with lower values of Hct3m, Hct6m and Hct12m with coefficients of −0.79 [95% confidence interval (CI) −1.47 to −0.11; n = 1750], −1.35 (−2.11 to −0.60; n = 1558) and −0.91 (−1.59 to −0.22; n = 2463), respectively (Table 2, Model A). In Model B, the median eGFR3m with and without AKI was 71.5 (IQR 49.7–91.1) and 78.1 (65.7–93.6), the eGFR6m with and without AKI was 66.6 (IQR 45.0–87.4) and 76.4 (IQR 63.7–89.3) and the eGFR12m with and without AKI was 65.0 (IQR 42.2–78.5) and 73.6 (IQR 60.5–85.8), respectively (P < 0.001). Even after adjustment for eGFR at each time point (3, 6 and 12 months), the associations between AKI and postoperative hematocrit values were still significant [−0.77% (95% CI −1.47 to −0.07; n = 1639), −1.38 (−2.17 to −0.60; n = 1449) and −0.87 (−1.56 to −0.17; n = 2382, respectively) (Table 2, Model B). Sensitivity analyses restricted to surgery for nonmalignancy yielded similar results. The association between AKI and slopes of hematocrit from baseline to 3, 6 and 12 months postoperatively were also examined and the decline in hematocrit was larger among those with AKI [−0.26%/month (95% CI −0.49 to −0.04; n = 1750), −0.23 (−0.35 to −0.10; n = 1558) and −0.08 (−0.13 to −0.02; n = 2463), respectively]. Higher stages of AKI and longer duration of AKI were associated with more severe anemia at 3 and 6 months postoperatively, but not at 12 months postoperatively (Table 3).

Association between AKI and all-cause mortality

During a median follow-up of 4.2 years, 1016 of 6692 subjects died (3.97 events/100 person-years). After exclusion of subjects who died within 3 months or who had missing data at 3 months postoperatively, 1113 of 6692 were eligible for further analyses and 359 of 1113 died during the study period. The causes of death were cardiovascular [n = 14 (3.9%)], infection [n = 25 (7.0%), malignancy [n = 281 (78.3%)] and others [n = 39 (10.9%)]. All-cause mortality was significantly higher among those with AKI (Figure 3). The multivariable Cox proportional hazards model showed that AKI was a predictor for all-cause mortality with a hazard ratio (HR) of 1.54 (95% CI 1.12–2.12). This association was attenuated by further adjustment for Hct3m [HR 1.45
Table 1. Characteristics of subjects

|                          | No AKI (n = 6247) | AKI (n = 445) | P-value |
|--------------------------|-------------------|---------------|---------|
| Age (years), median (IQR)| 63 (49–72)        | 68 (57–75)    | <0.001  |
| Male sex                 | 2927 (46.9)       | 259 (58.2)    | <0.001  |
| BMI, median (IQR)        | 22.3 (20.2–24.8)  | 23.2 (20.9–25.7) | <0.001  |
| Diabetes mellitus        | 911 (14.6)        | 99 (22.3)     | <0.001  |
| Hypertension             | 2141 (34.3)       | 203 (45.6)    | <0.001  |
| Hemorrhagic stroke       | 316 (5.1)         | 37 (8.3)      | 0.003   |
| Ischemic stroke          | 363 (5.8)         | 24 (5.4)      | 0.72    |
| Ischemic heart disease   | 281 (4.5)         | 30 (6.7)      | 0.03    |
| Congestive heart failure | 79 (1.3)          | 22 (4.9)      | <0.001  |
| Atrial fibrillation      | 160 (2.6)         | 22 (4.9)      | 0.003   |
| COPD                     | 153 (2.5)         | 9 (2.0)       | 0.57    |
| Liver cirrhosis          | 72 (1.2)          | 18 (4.0)      | <0.001  |
| History of cancer        | 2493 (39.9)       | 227 (51.0)    | <0.001  |

**Smoking**
- Never smoker          | 2956 (54.6) | 177 (48.1) | 0.03   |
- Past smoker           | 1180 (21.8) | 101 (27.4) |
- Current smoker        | 1278 (23.6) | 90 (24.5)  |

**Proteinuria**
- Negative              | 4170 (84.0) | 210 (66.0) |
- Positive              | 370 (7.5)   | 32 (10.1)  |
- 1+                    | 264 (5.3)   | 30 (9.4)   |
- 2+                    | 135 (2.7)   | 34 (10.7)  |
- 3+                    | 24 (0.5)    | 12 (3.8)   |

**eGFR (mL/min/1.73 m²), median (IQR)**
- No AKI (n = 4963) | 78.9 (66.1–93.3) |
- AKI (n = 318)    | 70.6 (49.3–88.9) | <0.001 |

**Hematocrit (%), median (IQR)**
- No AKI (n = 6225) | 37.9 (34.3–41.3) |
- AKI (n = 443)     | 35.5 (31.0–39.6) | <0.001 |

**Serum albumin (g/dL), median (IQR)**
- No AKI (n = 5996) | 4.2 (3.9–4.5) |
- AKI (n = 423)     | 3.9 (3.4–4.3)  | <0.001 |

**CRP (mg/dL), median (IQR)**
- No AKI (n = 6201) | 0.1 (0.1–0.4) |
- AKI (n = 441)     | 0.3 (0.1–1.6)  | <0.001 |

**ACEIs or ARBs**
- No AKI (n = 1093) | 175 (28.2) |
- AKI (n = 119)    | 119 (26.7)  | <0.001 |

**Diuretics**
- No AKI (n = 470) | 74 (16.6) |
- AKI (n = 74)    | 57 (12.8)  | 0.06   |

**Steroids**
- No AKI (n = 326) | 37 (8.3) |
- AKI (n = 37)    | 37 (8.3)  | 0.005  |

**Antiplatelet therapy**
- No AKI (n = 769) | 73 (16.4) |
- AKI (n = 73)    | 73 (16.4)  | 0.01   |

**Anticoagulation therapy**
- No AKI (n = 261) | 62 (2.3) |
- AKI (n = 23)    | 62 (2.3)  | 0.03   |

**Types of surgery**
- Intrathoracic surgery | 539 (8.6) |
- Intra-abdominal surgery | 450 (23.2) |
- Pelvic or major joint surgery | 895 (14.3) |
- Other types of surgery | 3363 (53.8) |
- Emergent surgery | 787 (12.6) |

**Surgery for malignancy**
- Surgery for nonmalignancy | 4122 (66.0) |
- Curative resection | 1764 (28.2) |
- Palliative resection | 361 (5.8) |
- Chemotherapy within 3 months preoperatively | 383 (6.1) |
- Chemotherapy within 3-months postoperatively | 838 (13.4) |
- Intraoperative blood loss (mL), median (IQR) | 75 (0–310) |
- Intraoperative use of red cell transfusion | 955 (15.3) |

Data are presented as or n (%) unless stated otherwise. P-values were determined using Mann–Whitney U-test or chi-square test as appropriate. When there were missing values, numbers for available data are shown.
The association between AKI and anemia fulfill three of Hill’s criteria [31] for a causal relationship between exposure and outcome in observational studies. First, AKI preceded anemia (temporality). Second, higher stages of AKI or longer duration of AKI were associated with more severe anemia at 3 and 6 months (biological gradient). Higher stages of AKI and longer duration of AKI were not associated with more severe anemia at 12 months. This might be due to selection bias. Those with severe AKI had higher mortality. Despite severe AKI, those who survived for 1 year might be a less sick population. In addition, the number of subjects who developed Stage 3 AKI was small. Third, there are possible mechanisms to explain the association between AKI and anemia (plausibility). Most cases of postoperative AKI were likely due to acute tubular necrosis, suggested by its close association with tubular injury markers [9–11], although renal biopsies were rarely performed in postoperative AKI. For example, liver-type fatty acid-binding protein (L-FABP), one of the biomarkers, is a small cytoplasmic protein localized predominantly in the proximal tubule. Basic research demonstrated that the urinary L-FABP level significantly correlated with the degree of tubulointerstitial damage throughout the extension and recovery phases after AKI [9]. Clinical studies have suggested that urinary L-FABP levels significantly increase among those with postoperative AKI [10, 11], indicating postoperative AKI is mainly due to proximal tubular injury. Renal fibroblasts in the renal interstitium are responsible for the production of EPO and in basic research they transform into myofibroblasts, hindering EPO production in CKD [12]. Severe proximal tubular injury plays an important role in the AKI-to-CKD transition and reduction of EPO [13].

As for long-term prognosis, the results of our study suggest that association of AKI with all-cause mortality is at least partially mediated by anemia. The HR of AKI decreased from 1.54 to 1.45 (5.8%) by adjustment for Hct3m. Although the attenuation of effect size was relatively small, the mediation effect was significant by mediation analysis. The proportion explained by the mediating effect of Hct3m was 24.8%. This suggests that anemia among those with postoperative AKI is mainly due to proximal tubular injury. Renal fibroblasts in the renal interstitium are responsible for the production of EPO and in basic research they transform into myofibroblasts, hindering EPO production in CKD [12]. Severe proximal tubular injury plays an important role in the AKI-to-CKD transition and reduction of EPO [13].

By mediation analysis, the regression coefficient of pure indirect effect (mediation effect) was 0.08 (95% CI 0.01–0.14, P = 0.02) for Hct3m. The proportion explained by the mediating effect of Hct3m was 24.8%. Of note, Hct3m was independently associated with all-cause mortality (95% CI 0.93–0.98). Even after further adjustment for lnCRP3m and albumin3m, Hct3m was still independently associated with all-cause mortality (0.97 [95% CI 0.95–0.99]). The association between Hct3m and mortality was similar regardless of whether or not subjects underwent surgery for malignancy (P for interaction = 0.80).

DISCUSSION

This cohort study demonstrated that AKI was independently associated with anemia during long-term follow-up, even after adjustment for potential confounders. The association between AKI and anemia was independent of eGFR change. With regard to long-term prognosis, AKI was a predictor for all-cause mortality and the association was attenuated by additional adjustment for Hct3m. The mediating effect of Hct3m was 24.8% by mediation analysis. Anemia after AKI is also an independent predictor for all-cause mortality, even after adjustment for indicators of chronic inflammation.

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mortality. Thus advanced malignancy could be a confounder for association between AKI and anemia or association between anemia and mortality. However, the associations between AKI and post-operative hematocrit values were still significant in the analysis restricted to nonmalignancy surgery. Furthermore, the association between Hct3m and all-cause mortality was similar among those with or without surgery for malignancy (P for interaction = 0.80). These results suggest that more advanced malignancy is not an explanation for an association between AKI and anemia or an association between anemia and mortality.

There are several strengths to our study. First, a large number of subjects was included and the data were vigorously adjusted for potential confounders in each analysis. Second, to the best of our knowledge, this is the first study that demonstrated a direct association of AKI and anemia following AKI irrespective of renal function and a mediating effect of anemia between AKI and all-cause mortality.

There are a few limitations to our study. First, histological assessment was not performed and it is uncertain whether the degree of proximal tubular injury after AKI correlates with anemia during long-term follow-up. In addition, the EPO concentration was not measured due to the retrospective nature of a cohort study. Second, information on management for anemia, including transfusion, induction or dose adjustment of ACEIs or ARBs, iron status (ferritin or transferrin saturation) and iron supplementation during long-term follow-up, was unclear from the medical record (many patients were also receiving medical care from other medical facilities) and was not included in the analyses. Third, there must have been indication biases for autologous blood transfusion. For example, those who underwent less invasive surgery or had no surgical complications...
would not be followed frequently. This would result in a large number of missing data at each time point.

In conclusion, AKI was independently associated with anemia during long-term follow-up. This might be due to permanent interstitial damage and impaired EPO production. Higher mortality associated with AKI was at least partially mediated by anemia following AKI. Whether correction of anemia following AKI improves mortality requires further research.

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**AUTHORS’ CONTRIBUTIONS**

M.N. and M.M. were responsible for the research idea and study design. M.M., M.N. and M.K. were responsible for data acquisition. M.M., M.E., K.S., Y.A. and K.T. were responsible for supervision or mentorship. All authors provided intellectual content of critical importance to the work and approved the final version of the manuscript. The data are available upon reasonable request.

**CONFLICT OF INTEREST STATEMENT**

None declared. The results presented in this article have not been published previously in whole or part, except in abstract form.

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