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Editorial Comment

EDITORIAL COMMENT

# Anaemia and acute kidney injury: the tip of the iceberg?

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## ABSTRACT

Acute kidney injury (AKI) is a common disorder that complicates the hospital course of many patients. AKI is linked with an independent risk of death, hospital length of stay and chronic kidney disease (CKD). Several preoperative predictors are found to be associated with AKI after surgery independent of its origin (cardiac versus non-cardiac). Among these, anaemia has been widely recognized and studied. Anaemia is more common within the surgical population for various reasons (iron deficiency, blood loss, anaemia of chronic disease such as inflammatory state, malignancy or CKD). Both pre- and postoperative anaemia have a deleterious impact on different clinical outcomes including AKI. In this issue, Nishimoto *et al.* investigated whether AKI could be a risk factor for anaemia (and not the opposite) and whether anaemia could be an independent mediator of mortality after AKI.

**Keywords:** AKI, anaemia, CKD, epidemiology, survival analysis

## INTRODUCTION

Acute kidney injury (AKI) is a critical condition in modern medicine that complicates the hospital course of many patients [1]. Postoperative AKI is a leading cause of morbidity and mortality in patients undergoing surgery [2, 3]. It is also linked with the duration of hospital stay and healthcare costs. The incidence varies between 1 and 36% depending on the type of surgery and the definition of renal failure, but tends to be lower (10%) according to the Risk, Injury, Failure, Loss, End-stage renal disease criteria [3].

Several studies have highlighted the importance of early recognition of AKI by a nephrologist for at least two reasons. First, the delayed nephrology consultation can be associated with increased intensive care unit (ICU) mortality [4]. Second, multiple cohort studies have revealed AKI is an independent risk factor for chronic kidney disease (CKD) progression [5, 6].

## AKI: PREDICTING FACTORS AND LONG-TERM OUTCOME

AKI is consistently associated with increased short- and long-term mortality [1]. The association between AKI and mortality can also be partly explained by confounding factors, as many factors are associated with both AKI and mortality [e.g. CKD, diabetes, heart failure (HF), etc.] [1]. In this context, AKI can be viewed as both a risk factor for mortality and a surrogate marker for global frailty.

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AKI following major surgery is also associated with increased short- and long-term mortality. [2]. Importantly, most studies have focused on cardiac surgery, where AKI occurs frequently—up to 42% [7–9]. Factors associated with AKI occurrence in this context are age, pre-existing CKD, diabetes or HF, combined surgeries, high cardiopulmonary bypass time, low cardiac output and central venous pressure [10]. Factors underlying this increase in mortality associated with AKI are unclear, but in most severe cases of AKI, fluid overload, cardiorenal syndrome and increased length of ICU stay may play a role. Whether early initiation of renal replacement therapy could improve clinical outcomes is still controversial [11, 12]. Early detection of AKI (i.e. before serum creatinine increases) using new biomarkers may be a promising approach, but their use in clinical practice is currently limited, mainly because no therapeutic strategy to prevent AKI occurrence based on biomarkers has been validated [9].

In the context of major non-cardiac surgery, data are lacking, but the same association between AKI and mortality as in cardiac surgery has been described [13]. Interestingly, serum creatinine decreased after surgery, which could reflect significant protein–energy malnutrition, leading to an underestimation of AKI severity and an overestimation of AKI recovery.

## ANAEMIA AND AKI: A STRANGE RELATIONSHIP

Anaemia is more common within the surgical population for various reasons (iron deficiency, blood loss, anaemia of chronic disease such as inflammatory state, malignancy or CKD). Most studies have focused on the impact of preoperative anaemia and clinical outcomes, but with inconsistant results [14–16]. It has been questioned whether anaemia was more an independent marker of the severity of comorbid disease or a risk factor for prognosis?

A recent meta-analysis by Fowler *et al.* [14] showed that perioperative anaemia was associated with increased AKI, stroke, infection and 30-day mortality. Most of the studies included (14 of 24) were non-cardiac surgery. However, these results should be interpreted with caution due to the high levels of heterogeneity between the studies.

Postoperative anaemia and a decrease in haemoglobin levels (pre-haemoglobin level and post-haemoglobin level) have also been reported as predictive factors for AKI and in-hospital mortality in cardiac surgery by other groups [15, 16].

Data regarding the association between anaemia and long-term outcomes such as renal recovery or mortality after AKI are limited and the results are disparate [17, 18].

Collectively these studies emphasize the deleterious impact of anaemia after surgery in different clinical outcomes including AKI. Anaemia has recently been integrated into a simple prediction tool [Simple Postoperative AKI Risk (SPARK)] to estimate the risk of AKI [19].

## HOW DO THE FINDINGS BY NISHIMOTO *ET AL.* CHANGE OUR CURRENT UNDERSTANDING/ PRACTICE?

In this issue of *Clinical Kidney Journal*, Nishimoto *et al.* [20] investigated whether AKI and its interstitial damage could predict anaemia (and not the opposite) and whether anaemia could be an independent mediator of mortality after AKI. They tested their hypothesis using the NARA-AKI study cohort, a single-centre retrospective study that included in the final analysis 6692 patients who underwent non-cardiac surgery.

They showed that AKI was an independent predictor of anaemia during the first year (at 3, 6 and 12 months) following surgery. The slopes of haematocrit levels from baseline to 3, 6 and 12 months postoperatively were also greater among patients with AKI [−0.26 %/month (−0.49 to −0.04), −0.23 (−0.35 to −0.10) and −0.08 (−0.13 to −0.02), respectively].

The rate of death events was 3.97/100 years during the follow-up after a median follow-up of 4.2 years. They confirmed that AKI was a strong predictor of all-cause mortality [hazard ratio 1.54 (95% confidence interval 1.12–2.1)], but more importantly they showed that the haematocrit level at 3 months after surgery was also an independent predictor of mortality. This association between haematocrit at 3 months and mortality was similar even after further adjustment for potential confounders such as C-reactive protein, albumin or surgery for malignancy, which represented the main cause of death in the cohort.

Unfortunately the specific cause of anaemia could not be investigated because information regarding iron levels, medications (chemotherapy, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers) and anaemia management (blood transfusion) were not available. The authors suggested that AKI-induced damage to the renal interstitium might lead to impaired erythropoietin production and subsequent anaemia, but this hypothesis (not tested here) is probably the tip of the iceberg.

Finally, because cancer was frequent in this population, we might also wonder if anaemia reflected current guidelines in order to avoid adverse events of specific treatments (e.g. erythropoietin-stimulating agents) [21]. Whether the correction of anaemia after AKI improves clinical outcomes remains elusive.

## CONCLUSIONS

Nishimoto *et al.* highlight for the first time in a large cohort the negative impact of anaemia during long-term follow-up and address new perspectives on the management of anaemia following AKI. Their results emphasize the importance of detecting and correcting anaemia in this cohort. It is mandatory to first focus on the causes of anaemia and second to define specific groups at risk. Future studies should determine whether correction of anaemia following AKI improves mortality.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

1. Hoste EAJ, Kellum JA, Selby NM *et al.* Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018; 14: 607–625
2. Bihorac A, Yavas S, Subbiah S *et al.* Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg* 2009; 249: 851–858
3. Hoste EAJ, Bagshaw SM, Bellomo R *et al.* Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015; 41: 1411–1423
4. Ponce D, Zorzenon CDPF, Santos NYD *et al.* Early nephrology consultation can have an impact on outcome of acute kidney injury patients. *Nephrol Dial Transplant* 2011; 26: 3202–3206

5. Ozrazgat-Baslanti T, Thottakkara P, Huber M. Acute and chronic kidney disease and cardiovascular mortality after major surgery. *Ann Surg* 2016; 264: 987–996
6. Kellum JA, Sileanu FE, Bihorac A *et al*. Recovery after acute kidney injury. *Am J Respir Crit Care Med* 2017; 195: 784–791
7. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol* 2006; 1: 19–32
8. Hobson CE, Yavas S, Segal MS *et al*. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* 2009; 119: 2444–2453
9. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. *Nat Rev Nephrol* 2017; 13: 697–711
10. Palomba H, De Castro I, Neto ALC *et al*. Acute kidney injury prediction following elective cardiac surgery: AKICS score. *Kidney Int* 2007; 72: 624–631
11. Zarbock A, Kellum JA, Schmidt C *et al*. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. *JAMA* 2016; 315: 2190–2199
12. Gaudry S, Hajage D, Schortgen F *et al*. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016; 375: 122–133
13. O'Connor ME, Hewson RW, Kirwan CJ *et al*. Acute kidney injury and mortality 1 year after major non-cardiac surgery. *Br J Surg* 2017; 104: 868–876
14. Fowler AJ, Ahmad T, Phull MK *et al*. Meta-analysis of the association between preoperative anaemia and mortality after surgery. *Br J Surg* 2015; 102: 1314–1324
15. Arai T, Morice M-C, O'Connor SA *et al*. Impact of pre- and post-procedural anemia on the incidence of acute kidney injury and 1-year mortality in patients undergoing transcatheter aortic valve implantation (from the French Aortic National CoreValve and Edwards 2 [FRANCE 2] Registry). *Cathet Cardiovasc Intervent* 2015; 85: 1231–1239.
16. Gorla R, Tsagakis K, Horacek M *et al*. Impact of preoperative anemia and postoperative hemoglobin drop on the incidence of acute kidney injury and in-hospital mortality in patients with type B acute aortic syndromes undergoing thoracic endovascular aortic repair. *Vasc Endovasc Surg* 2017; 51: 131–138
17. Hu SL, Said FR, Epstein D *et al*. The impact of anemia on renal recovery and survival in acute kidney injury. *Clin Nephrol* 2013; 79: 221–228
18. Sasaki S, Kawarazaki H, Hasegawa T *et al*. Anemia and long-term renal prognosis in patients with post-renal acute kidney injury of nonmalignant cause. *Nephron* 2017; 135: 129–136
19. Park S, Cho H, Park S *et al*. Simple postoperative AKI risk (SPARK) classification before noncardiac surgery: a prediction index development study with external validation. *J Am Soc Nephrol* 2019; 30: 170–181
20. Nishimoto M, Murashima M, Kokubu M *et al*. Anemia following acute kidney injury after noncardiac surgery and long-term outcomes: the NARA-AKI cohort study. *Clin Kid J* 2021; 14: 673–680
21. Bohlius J, Bohlke K, Castelli R *et al*. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *Blood Adv* 2019; 3: 1197–1210