Tohoku J. Exp. Med., 2015, **237**, 287-295

Anemia Is a Risk Factor for Acute Kidney Injury and Long-Term Mortality in Critically Ill Patients

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Acute kidney injury (AKI) is a major health concern, because AKI is related with an increase in morbidity and mortality. Anemia is related to AKI in several clinical settings. However, the relationship between anemia and AKI and the effect of anemia on long-term mortality are unresolved in critically ill patients. A total of 2,145 patients admitted to the intensive care unit were retrospectively analyzed. We calculated a threshold value of hemoglobin associated with an increased risk of AKI and used this value to define anemia. The odds ratios (ORs) and hazard ratios for AKI and all-cause mortality were calculated after adjusting for multiple covariates. The OR of AKI increased depending on the decrease in hemoglobin level and the ideal threshold point of hemoglobin linked to increasing AKI risk was 10.5 g/dL. We categorized patients into anemia (< 10.5 g/dL) and non-anemia (≥ 10.5 g/dL) groups. The risk of AKI was higher in the anemia group than the non-anemia group and this trend remained significant irrespective of the AKI development time (early vs. late) or duration (< 3 days vs. ≥ 3 days). Both anemia and AKI increased the 10-year mortality risk and this risk prediction was significantly separated by the presence of anemia and AKI. Furthermore, the risk prediction remained consistent irrespective of the AKI severity (i.e., recovery, stage, or duration of AKI). Based on these, we urge clinicians to monitor anemia and AKI in critically ill patients.

Keywords: acute kidney injury; anemia; hemoglobin; intensive care unit; mortality
Tohoku J. Exp. Med., 2015 December, **237** (4), 287-295. © 2015 Tohoku University Medical Press

Introduction

Acute kidney injury (AKI) is a major health concern because AKI is related with an increase in morbidity and mortality (Metnitz et al. 2002; Chertow et al. 2005). Although therapy for AKI has improved in recent years, it is still highly prevalent, especially in critically ill patients admitted to the intensive care unit (ICU) (Clermont et al. 2002). AKI in the ICU results in extremely high mortality rates of up to 80% (Turney 1996), and this rate has remained relatively unchanged despite improved critical care (Ympa et al. 2005). Thus, the detection and management of risk factors related to AKI are important concerns for clinicians managing AKI patients.

Anemia is the most common blood disorder and is associated with substantial morbidity and mortality (Anand et al. 2004; Zakai et al. 2005). Correspondingly, anemia is most frequent complication experienced by the ICU (du Cheyron et al. 2005). Anemia can further aggravate the ICU patients' worse outcomes (Corwin et al. 2004), although the independent impact of anemia, not blood transfusion, has not been explicitly examined. Additionally, the presence of anemia in this subset is associated with frequent use of red blood products. Certain researches emphasized this issue because the quantity of blood transfusion may increase the ICU complications including mortality (Vincent et al. 2002; Corwin et al. 2004). Accordingly, it is needed to determine the anemia-related factors and its proper management for ICU patients, but the researches and guidelines are still lacking.

The relationship between anemia and AKI is important to clinicians for several reasons. First, both diseases impose a large burden on patients, particularly those with comorbidities (Karkouti et al. 2009), because those lead to worse outcomes and economic burden together. Moreover, their high prevalence aggravates this situation. Second, if there is a significant relationship, we could consider the prevention or modification of anemia to reduce the AKI incidence and its worse outcomes. Third, hemoglobin and serum creatinine are easily monitored, and thus clinicians can access these monitoring methods in routine clinical practice. These issues certainly support studying the relationship

Received July 15, 2015; revised and accepted October 16, 2015. Published online November 25, 2015; doi: 10.1620/tjem.237.287.
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between anemia and AKI in the context of applying the results to clinical practice and then improving patient outcomes. However, despite these clinical implications, questions about the relationship between anemia and AKI remain unsolved in ICU patients. Herein, we first addressed the relationship between anemia and AKI in a large cohort of ICU patients. We then followed-up patients for 10 years to examine whether the relationship between anemia and AKI affects long-term mortality.

Methods

Participants and data collection

The study protocol complies with the Declaration of Helsinki and received full approval from the institutional review boards at the Seoul National University Bundang Hospital (no. B-1407/258-114). The ICU patient data were obtained from a cohort that consisted of patients from a tertiary referral center (Seoul National University Bundang Hospital, Gyeonggi-do, Korea). A total of 2,823 patients were admitted from June 2004 through June 2010 to the ICU and were followed-up until February 2015. We excluded patients younger than 18 years old (n = 49) and patients previously diagnosed with end-stage renal disease on dialysis (n = 94). Among the study subjects, nine patients were excluded due to missing serum creatinine or urine output data. If the patients were admitted more than once to the ICU, then the first admission was counted as the single case. Consequently, 2,145 patients were reviewed retrospectively using electronic medical records. A standardized data form approved by the institutional review board was used to collect the data.

The following clinical parameters were recorded at the time of ICU admission: age, sex, weight, systolic/diastolic blood pressure, primary diagnosis, underlying chronic kidney disease, history of non-hematologic and hematologic malignancies, previously diagnosed anemia, evidence of bleeding, the need for mechanical ventilation, and the use of vasoactive drugs. The primary diagnoses included cardiovascular disease, sepsis, surgical emergency, and others. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was used to assess illness severity (Knaus et al. 1985). The changes in serum creatinine and urine output after ICU admission were measured, and the urine output data were recorded hourly. The serum hemoglobin levels were collected until 3 days after admission. Three hundred and thirty eight patients did not have the 2nd or 3rd day serum hemoglobin levels. Other blood parameters recorded included albumin, electrolyte (sodium and potassium), and C-reactive protein, but these parameters were available only in 1,187 patients.

The risk of AKI was determined during the first 15 days of the ICU admission. The definition and staging of AKI was based on both the serum creatinine and urine output criteria in the guideline proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012). Recovery from AKI was considered at discharge: recovered and non-recovered AKI cases were defined by the subsequent serum creatinine levels (at discharge) "less than or equal to the baseline level" and "more than the baseline level", respectively. The risks of AKI and all-cause mortality were considered as the primary outcome. Except the death-censored cases, all subjects were followed until February 2015. The mortality data were obtained from the national database of Statistics Korea; this was feasible because all Koreans have a resident registration number and death events are recorded and stored at the national level.

Statistical analysis

All of the analyses and calculations were performed using STATA software (version 12.0, StataCorp LP, College Station, Texas, USA). The data are presented as the means ± standard deviations for continuous variables and as the proportions for categorical variables. The variables with non-normal distributions are expressed as the median [interquartile range (IQR)] based on variable distributions using histograms. The chi-squared test was used to compare categorical variables. The comparisons between normally and non-normally distributed continuous variables were performed using Student's t-test and Mann-Whitney *U* test, respectively. A restricted cubic spline analysis was initially applied to account for a possible nonlinear relationship between serum hemoglobin, AKI, and mortality risk. We determined a threshold value of serum hemoglobin to predict AKI risk by calculating the Youden index of the receiver operating characteristic (ROC) curve (Youden 1950). Subsequently, we divided the patients into either the anemia group (< threshold point) or the non-anemia group (≥ threshold point). The odds ratios (ORs) and confidence intervals (CIs) were calculated using the logistic regression analysis with and without the adjustment of all covariates, such as age, sex, body weight, systolic/diastolic blood pressure, primary diagnosis, chronic kidney disease, diabetes mellitus, non-hematologic/hematologic malignancy, previously diagnosed anemia, bleeding, need for mechanical ventilation, use of vasoactive and nonsteroidal anti-inflammatory drugs (NSAID), contrast media, and APACHE II score. Other blood parameters, which were not available in all the patients, were additionally adjusted as a sensitivity analysis. The survival curves were drawn using the Kaplan-Meier method. To compare survival curves between groups, the log-rank test was initially applied. A Cox proportional hazard model was used to calculate the hazard ratios (HRs) of mortality risk. Predicted probability was calculated with the logistic or Cox proportional hazard model. A *P* value less than 0.05 was considered significant.

Results

Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. The mean age was 68 years old. Most of the patients were admitted to the ICU because of medical problems (n = 2,099) rather than surgical problems (n = 46). The proportions of subjects with previously known hematologic malignancy, anemia, or bleeding were 3.0%, 0.7%, and 1.9%, respectively. The mean hemoglobin level was 11.6 g/dL. The median length of stay in the hospital was 20 days (IQR, 10 to 43 days). The study subjects were followed for a median duration of 490 days (IQR, 36 to 2,160 days).

Anemia and the risk of acute kidney injury

There were 1,655 subjects (77.2%) with AKI during the first 15 days after admission to the ICU. Each AKI case was diagnosed by serum creatinine criterion alone (66.4%), urine output criterion alone (2.9%), or both (30.7%). The proportions in each AKI stage were as follows: stage 1, 67.0%; stage 2, 24.1%; and stage 3, 8.9%. We examined the relationship between serum hemoglobin and AKI risk. The risk of AKI varied depending on the serum hemoglobin

Table 1. Baseline characteristics of critically ill patients.

Parameters	Non-anemia (n = 1,351)	Anemia (n = 794)	Total (n = 2,145)
Age (years)*	66.9 ± 16.05	68.7 ± 15.53	67.5 ± 15.88
Male sex (%)	60.2	58.9	59.7
Body weight (kg)*	58.8 ± 12.61	57.6 ± 12.31	58.4 ± 12.51
Systolic blood pressure (mmHg)‡	133.0 ± 31.03	124.0 ± 30.30	129.7 ± 31.06
Diastolic blood pressure (mmHg)‡	75.5 ± 20.76	68.2 ± 19.30	72.8 ± 20.52
Primary diagnosis (%)‡			
Cardiovascular disease	36.9	18.9	30.3
Sepsis	4.2	5.0	4.5
Surgical emergency	1.5	3.3	2.1
Others	57.4	72.8	63.1
Underlying chronic kidney disease (%)‡	7.0	12.2	9.0
Diabetes mellitus (%)	14.1	15.2	14.5
Non-hematologic malignancy (%)‡	11.3	19.6	14.4
Hematologic malignancy (%)‡	1.2	6.0	3.0
Previously diagnosed anemia (%)‡	0	1.9	0.7
Bleeding (%)	1.6	2.4	1.9
Need for mechanical ventilation (%)	67.4	69.8	68.3
Use of vasoactive drugs (%)‡	46.4	56.7	50.2
Use of NSAID (%)*	23.5	19.1	21.9
Use of contrast media (%)	33.1	35.2	36.3
Serum hemoglobin (g/dL)‡	13.2 ± 1.87	9.0 ± 1.24	11.6 ± 2.62
Serum creatinine (mg/dL) [a]‡	1.0 (0.80 to 1.30)	1.2 (0.84 to 2.10)	1.0 (0.80 to 1.50)
APACHE II score‡	17.0 ± 7.93	20.1 ± 8.19	18.2 ± 8.17
Length of hospital stay (days) [a]	20 (10 to 42)	21 (11 to 44)	20 (10 to 43)

[a]Data are expressed as the median (interquartile range) when the distribution of data was skewed.
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.
Comparisons were evaluated using the chi-squared test for categorical variables and Student's t-test for normally distributed continuous variables (Mann-Whitney *U* test for non-normally distributed continuous variables).
NSAID, non-steroidal anti-inflammatory drugs; APACHE, Acute Physiology and Chronic Health Evaluation.

levels based on the predicted probability (Fig. 1A) and the ORs (Fig. 1B). The duration of AKI was increased in patients with low serum hemoglobin levels compared to patients with high hemoglobin levels (Fig. 1C). Additionally, there was a prominent non-linear relationship between hemoglobin and AKI risk. This result suggested there was a threshold point of hemoglobin that predicted AKI. Therefore, we calculated the threshold point to be 10.5 g/dL based on the Youden index method.

We used the calculated threshold hemoglobin level to divide the patients into anemia (< 10.5 g/dL) and non-anemia (≥ 10.5 g/dL) groups. The baseline characteristics of the groups are shown in Table 1. The anemic patients had more underlying chronic kidney disease, non-hematologic and hematologic malignancies, and previously diagnosed anemia than the non-anemic patients. We then calculated the ORs for AKI in the anemia and non-anemia groups (Table 2). As a result, the risk of AKI was higher in the anemia group than in the non-anemia group irrespective of covariates. Although the albumin, electrolyte (sodium and potassium), and C-reactive protein were further adjusted (n = 1,187), the anemia group had a higher risk of AKI than the non-anemia group, as shown by the following results: OR, 1.65 (1.104-2.466); $P = 0.015$.

We next confirmed the relationship between anemia and AKI based on the AKI development time and severity (Table 2). First, we divided AKI cases into early (≤ 3 days) and late AKI (> 3 days) using the development time after ICU admission. We found that 90.3% of AKI developed within 3 days (i.e., early AKI). The other AKI cases (9.7%) developed after 4 days (i.e., late AKI). Although AKI occurred primarily in the early period, anemia predicted both early and late AKIs, as shown in Table 2. Although the mean hemoglobin values during the first three days were used, the anemia predicted late AKI with an unadjusted OR of 2.13 (1.415-3.208) and an adjusted OR of 1.75 (1.091-2.792); *P* values were < 0.001 and 0.020, respectively. Second, we examined the distributions of AKI stages in the anemia and non-anemia groups. The high AKI stages were more common in the anemia group [58.5% (stage 1), 27.8% (stage 2), and 13.7% (stage 3)] than in non-anemia group [73.0% (stage 1), 21.5% (stage 2), and

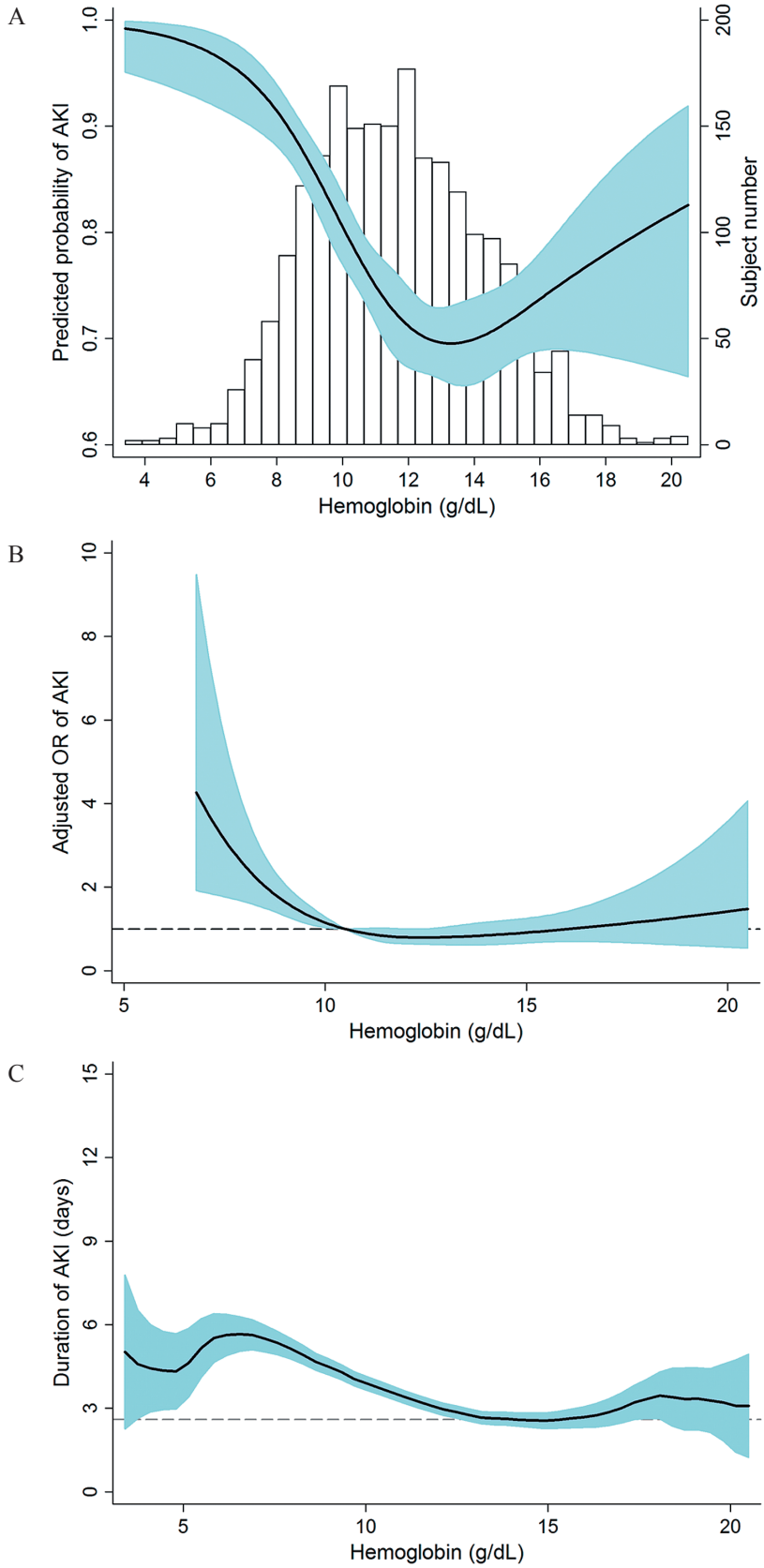

Fig. 1. Anemia and the risk of acute kidney injury (AKI).
Non-linear relationship between hemoglobin and the predicted probability of AKI (A), multivariable-adjusted odds ratio (OR) for AKI (B), or duration of AKI (C). Histogram in A indicates the subject number. Fitted line and 95% confidence interval are presented with solid line and shaded area, respectively.

Table 2. Risk analyses of acute kidney injury in the anemic patients compared with the non-anemic patients.

Outcome	Univariate		Multivariate[a]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Acute kidney injury	2.43 (1.926-3.074)	< 0.001	1.76 (1.349-2.291)	< 0.001
Early acute kidney injury	1.86 (1.525-2.279)	< 0.001	1.42 (1.128-1.781)	0.003
Late acute kidney injury[b]	2.53 (1.731-3.686)	< 0.001	1.83 (1.186-2.837)	0.006
Non-recovered AKI[c]	1.91 (1.541-2.361)	< 0.001	1.64 (1.296-2.083)	< 0.001

[a]Adjusted for age, sex, body weight, systolic/diastolic blood pressure, primary diagnosis, chronic kidney disease, diabetes mellitus, non-hematologic/hematologic malignancy, anemia, bleeding, need for mechanical ventilation, use of vasoactive and NSAID drugs, contrast media, and APACHE II score.
[b]Analysis is restricted to the patients without AKI development within 3 days (n = 651).
[c]Analysis is restricted to the AKI-developed patients (n = 1,655).
OR, odds ratio; CI, confidence interval; AKI, acute kidney injury.

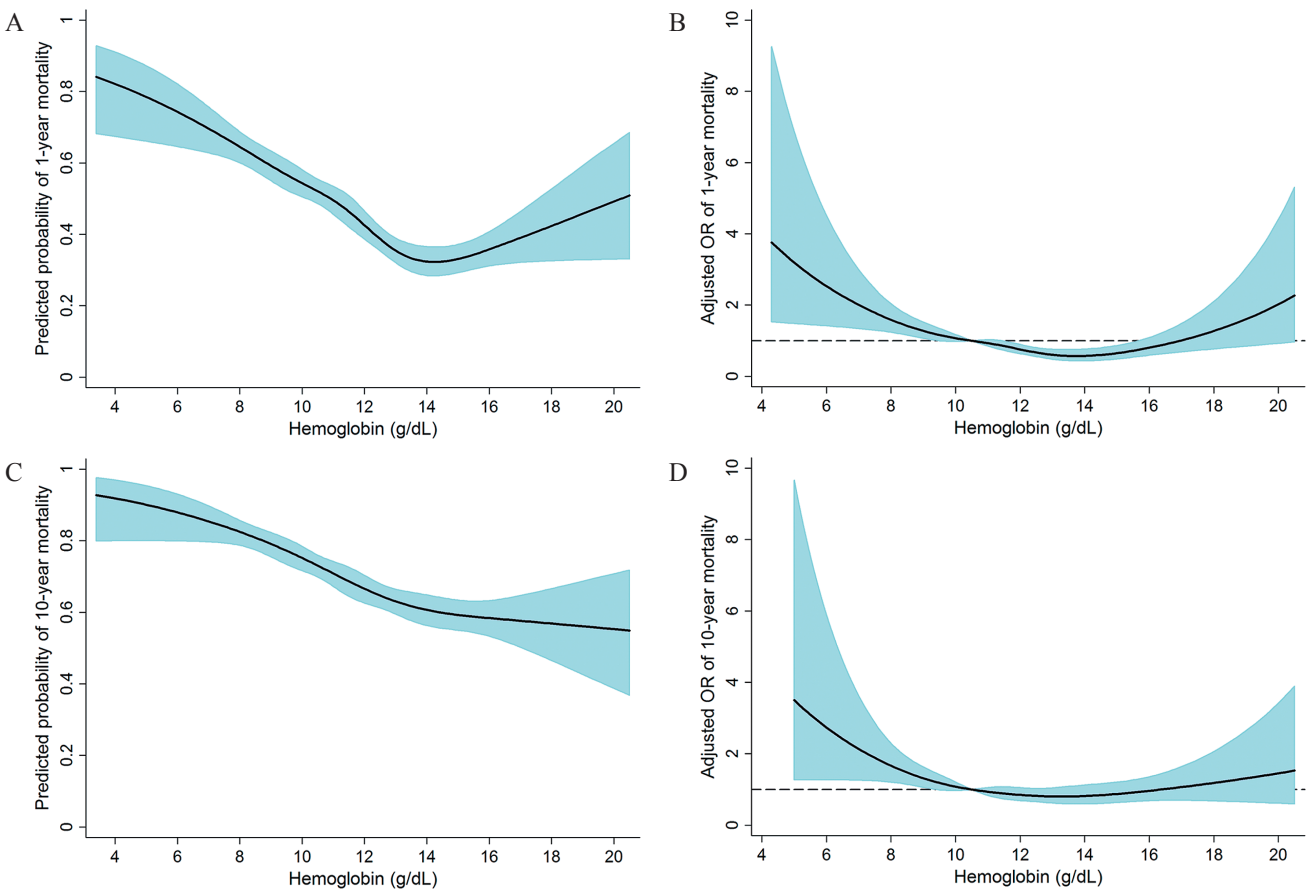

Fig. 2. Effects of anemia on mortality.
Non-linear relationship between hemoglobin and the predicted probability of mortality (A, C) or multivariable-adjusted odds ratio (OR) for mortality (B, D), based on the 1-year (A, B) or 10-year (C, D) timeframe. Fitted line and 95% confidence interval are presented with solid line and shaded area, respectively.

5.5% (stage 3)]; $P < 0.001$. AKI recovery was also affected by the presence of anemia because the AKI patients with anemia had worse recovery than those without anemia (Table 2).

Effects of anemia and acute kidney injury on mortality

During the follow-up period (max. 10.7 years), the mortality rate of the patients was 63.1 per 100,000 patient-days. The hemoglobin level was significantly related to the mortality rate based on the predicted probability (Fig. 2A, C) and the ORs (Fig. 2B, D). This relationship remained consistent for both the short-term (i.e., 1-year) and long-term (i.e., 10-year) mortality rates. We measured the cumulative mortality rates according to the presence of anemia and AKI (Fig. 3). The data showed the overall mortality curves to be separated by anemia and AKI ($P < 0.001$).

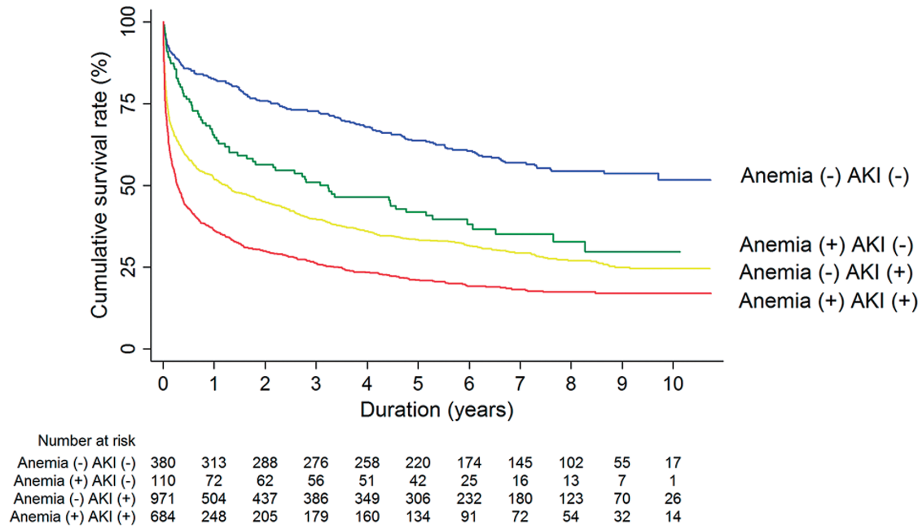

Fig. 3. Kaplan-Meier survival curves according to the presence of anemia or AKI.

Table 3. Risk of all-cause mortality according to the anemia and acute kidney injury.

Group	Subject no. (%)	Univariate		Multivariate[a]	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Non-anemia, non-AKI	380 (17.7)	1 (Reference)		1 (Reference)	
Anemia, non-AKI	110 (5.1)	1.78 (1.347-2.349)	< 0.001	1.40 (1.053-1.851)	0.020
Non-anemia, AKI	971 (45.3)	2.38 (2.007-2.817)	< 0.001	1.79 (1.500-2.131)	< 0.001
Anemia, AKI	684 (31.9)	3.38 (2.842-4.028)	< 0.001	2.21 (1.835-2.662)	< 0.001
Non-anemia, recovered AKI	737 (44.5)	1 (Reference)		1 (Reference)	
Anemia, recovered AKI	426 (25.7)	1.32 (1.139-1.518)	< 0.001	1.17 (1.010-1.358)	0.036
Non-anemia, non-recovered AKI	234 (14.1)	4.75 (4.042-5.581)	< 0.001	4.03 (3.413-4.748)	< 0.001
Anemia, non-recovered AKI	258 (15.6)	4.51 (3.856-5.281)	< 0.001	4.07 (3.446-4.806)	< 0.001
Non-anemia, AKI stage 1	709 (42.8)	1 (Reference)		1 (Reference)	
Anemia, AKI stage 1	400 (24.2)	1.36 (1.170-1.569)	< 0.001	1.21 (1.036-1.402)	0.016
Non-anemia, AKI stage 2	209 (12.6)	3.38 (2.851-4.004)	< 0.001	2.97 (2.499-3.533)	< 0.001
Anemia, AKI stage 2	190 (11.5)	3.18 (2.665-3.789)	< 0.001	3.02 (2.519-3.624)	< 0.001
Non-anemia, AKI stage 3	53 (3.2)	4.98 (3.724-6.671)	< 0.001	5.05 (3.736-6.825)	< 0.001
Anemia, AKI stage 3	94 (5.7)	4.29 (3.410-5.400)	< 0.001	3.56 (2.781-4.550)	< 0.001
Non-anemia, short duration of AKI	855 (51.7)	1 (Reference)		1 (Reference)	
Anemia, short duration of AKI	510 (30.8)	1.35 (1.185-1.526)	< 0.001	1.19 (1.045-1.361)	0.009
Non-anemia, long duration of AKI	116 (7.0)	1.48 (1.187-1.834)	< 0.001	1.40 (1.124-1.749)	0.003
Anemia, long duration of AKI	174 (10.5)	1.95 (1.631-2.324)	< 0.001	1.67 (1.385-2.008)	< 0.001

[a]Adjusted for age, sex, body weight, systolic/diastolic blood pressure, primary diagnosis, chronic kidney disease, diabetes mellitus, non-hematologic/hematologic malignancy, anemia, bleeding, need for mechanical ventilation, use of vasoactive and NSAID, contrast media, and APACHE II score.
HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury.

Compared with the patients without anemia and AKI, the patients with anemia, AKI, or both diseases had 1.4, 1.8, and 2.2 fold increased mortality risk, respectively, after adjusting for covariates (Table 3). For the in-hospital mortality outcome, the trend was similar to the above results, as following adjusted ORs: 1.11 (0.509-2.413) in anemia and non-AKI group ($P = 0.796$); 3.71 (2.374-5.796) in non-anemia and AKI group ($P < 0.001$); and 4.54 (2.865-7.179) in anemia and AKI group ($P < 0.001$).

We further examined the effect of anemia on mortality according to AKI severity (Table 3, Fig. 4). Anemia separated the survival curves of patients with recovered AKI and stage 1 AKI (Fig. 4A, B). The survival curves were also separated based on the presence of anemia when the

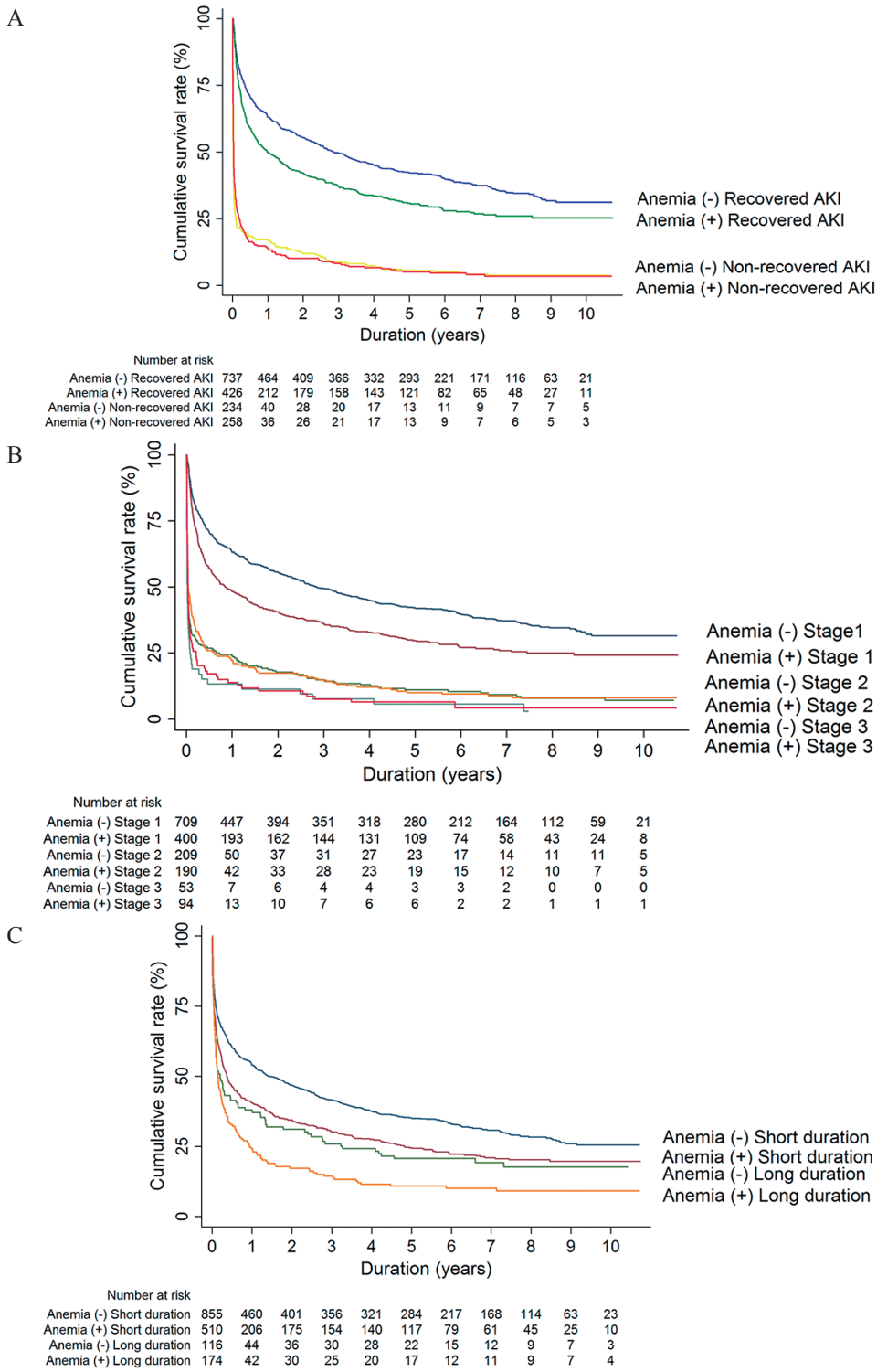

Fig. 4. Survival curves according to the presence of anemia and the severity of AKI. The severity of AKI was categorized by recovery (A), stage (B), or duration (C).

duration of AKI was divided into short duration (< 8 days) and long duration (≥ 8 days) groups (Fig. 4C). The HR results showed similar patterns, and anemia separately increased the HRs for mortality in each AKI group (Table 3).

Additionally, both anemia and AKI increased the length of hospital stay as following median results: 15 days (IQR, 8 to 33 days) in non-anemia and non-AKI group (reference); 21 days (IQR, 11 to 41 days) in anemia and non-AKI group (P = 0.003); 22 days (IQR, 10 to 45 days) in non-anemia and AKI group (P < 0.001); and 21 days (IQR, 11 to 44 days) in anemia and AKI group (P < 0.001).

Discussion

Anemia and AKI are both important health issues due to the associated morbidity and mortality. However, their potential relationship remains unclear in critically ill patients. With this regard, this study has several clinical implications. We first demonstrated the relationship based on multiple aspects such as AKI stages, duration, and recovery. We further identified the hemoglobin threshold for detecting an increased risk of AKI. Lastly, anemia discriminated and increased the predictability of AKI on long-term mortality. We believe the robust relationships between anemia, AKI, and mortality may be immediately applicable to the current clinical practice.

In normal physiologic responses, the kidney receives approximately 20-25 percent of the blood from cardiac output (Brezis and Rosen 1995). This is the highest need throughout the body in relation to organ weight. As a pathologic response, the anemia directly reduces the delivery of oxygen. Because AKI frequently develops in the ischemic conditions, anemia can be one of reasons for the high incidence of AKI in hospital-admitted patients (i.e., 1 in 5 adults and 1 in 3 children patients) (Susantitaphong et al. 2013). Previous studies in several clinical settings (Karkouti et al. 2009; Legrand et al. 2013; Sickeler et al. 2014) and our ICU results support the relationship between anemia and AKI. Thus, it is helpful to monitor serum hemoglobin or anemia to prevent worse outcomes of AKI.

There is substantial mortality in critically ill patients (Zimmerman et al. 2013). Long-term mortality has received recent attention because more patients now survive the ICU and require critical care to maintain a high quality of life (Jackson et al. 2012; Luangasanatip et al. 2013). The present data also highlighted the long-term mortality associated with anemia and AKI. As a result, anemia separated the relationship between AKI and mortality over 10 years. Additionally, patients with both anemia and AKI had a higher mortality risk than the counterpart groups. This may be because both anemia and AKI aggravate organ dysfunction or delay of organ recovery (Cilley et al. 1991; Basile et al. 2012). Anemia can have both direct and indirect effects on mortality; in the context of indirect effect, anemia may increase the severity of AKI and worsen the mortality rate. Nevertheless, the present observational design could not clarify the underlying mechanisms for the causal relationships between anemia, AKI, and mortality. Future follow-up studies should determine the direct cause of mortality to solve these complex relationships.

The strengths of the present study include the large sample size, statistical robustness, and the long-term follow-up. Although the data are informative, this study has some limitations. First, the study design involved observing correlations, and this precludes conclusions based on causality. However, the main aim of the present study was to determine the relationship itself. Thus, the current design does not significantly hamper this aim. Second, we did not consider the direct cause of anemia and mortality because of the retrospective nature of the database. Additionally, we did not collect some important data, such as change in hemoglobin levels and other possible confounding factors (e.g., duration of drug use). Although the present study could not address these issues, it will form the basis of later studies without these limitations.

Anemia and AKI are related and increase the long-term mortality of critically ill patients. Current ICU outcomes remain suboptimal. Thus, it is important to monitor these two conditions in both ICU-admitted and ICU-surviving patients. Future follow-up studies will evaluate the underlying mechanisms of relationship between anemia and AKI. Additionally, new data should reveal when to correct the anemia of critically ill patients to attain a personalized treatment approach and better survival outcomes.

Acknowledgments

This work was supported from the grant (No. 2013R1A1A1012689) from the National Research Foundation of Korea.

Conflict of Interest

The authors declare no conflict of interest.

References

Anand, I., McMurray, J.J., Whitmore, J., Warren, M., Pham, A., McCamish, M.A. & Burton, P.B. (2004) Anemia and its relationship to clinical outcome in heart failure. *Circulation*, **110**, 149-154.

Basile, D.P., Anderson, M.D. & Sutton, T.A. (2012) Pathophysiology of acute kidney injury. *Compr. Physiol.*, **2**, 1303-1353.

Brezis, M. & Rosen, S. (1995) Hypoxia of the renal medulla: its implications for disease. *N. Engl. J. Med.*, **332**, 647-655.

Chertow, G.M., Burdick, E., Honour, M., Bonventre, J.V. & Bates, D.W. (2005) Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.*, **16**, 3365-3370.

Cilley, R.E., Scharenberg, A.M., Bongiorno, P.F., Guire, K.E. & Bartlett, R.H. (1991) Low oxygen delivery produced by anemia, hypoxia, and low cardiac output. *J. Surg. Res.*, **51**, 425-433.

Clermont, G., Acker, C.G., Angus, D.C., Sirio, C.A., Pinsky, M.R. & Johnson, J.P. (2002) Renal failure in the ICU: comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. *Kidney Int.*, **62**, 986-996.

Corwin, H.L., Gettinger, A., Pearl, R.G., Fink, M.P., Levy, M.M., Abraham, E., MacIntyre, N.R., Shabot, M.M., Duh, M.S. & Shapiro, M.J. (2004) The CRIT Study: anemia and blood transfusion in the critically ill: current clinical practice in the United States. *Crit. Care Med.*, **32**, 39-52.

du Cheyron, D., Parienti, J.J., Fekih-Hassen, M., Daubin, C. & Charbonneau, P. (2005) Impact of anemia on outcome in critically ill patients with severe acute renal failure. *Intensive Care Med.*, **31**, 1529-1536.

Jackson, J.C., Ely, E.W., Morey, M.C., Anderson, V.M., Denne, L.B., Clune, J., Siebert, C.S., Archer, K.R., Torres, R., Janz, D., Schiro, E., Jones, J., Shintani, A.K., Levine, B., Pun, B.T., et al. (2012) Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Crit. Care Med.*, **40**, 1088-1097.

Karkouti, K., Wijeysundera, D.N., Yau, T.M., Callum, J.L., Cheng,

D.C., Crowther, M., Dupuis, J.Y., Fremes, S.E., Kent, B., Laflamme, C., Lamy, A., Legare, J.F., Mazer, C.D., McCluskey, S.A., Rubens, F.D., et al. (2009) Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation*, **119**, 495-502.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int. Suppl.*, **2**, 1-138.

Knaus, W.A., Draper, E.A., Wagner, D.P. & Zimmerman, J.E. (1985) APACHE II: a severity of disease classification system. *Crit. Care Med.*, **13**, 818-829.

Legrand, M., Pirracchio, R., Rosa, A., Petersen, M.L., Van der Laan, M., Fabiani, J.N., Fernandez-gerlinger, M.P., Podglajen, I., Safran, D., Cholley, B. & Mainardi, J.L. (2013) Incidence, risk factors and prediction of post-operative acute kidney injury following cardiac surgery for active infective endocarditis: an observational study. *Crit. Care*, **17**, R220.

Luangasanatip, N., Hongsuwan, M., Lubell, Y., Limmathurotsakul, D., Teparrukkul, P., Chaowarat, S., Day, N.P., Graves, N. & Cooper, B.S. (2013) Long-term survival after intensive care unit discharge in Thailand: a retrospective study. *Crit. Care*, **17**, R219.

Metnitz, P.G., Krenn, C.G., Steltzer, H., Lang, T., Ploder, J., Lenz, K., Le Gall, J.R. & Druml, W. (2002) Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit. Care Med.*, **30**, 2051-2058.

Sickeler, R., Phillips-Bute, B., Kertai, M.D., Schroder, J., Mathew, J.P., Swaminathan, M. & Stafford-Smith, M. (2014) The risk of acute kidney injury with co-occurrence of anemia and hypotension during cardiopulmonary bypass relative to anemia alone. *Ann. Thorac. Surg.*, **97**, 865-871.

Susantitaphong, P., Cruz, D.N., Cerda, J., Abulfaraj, M., Alqahtani, F., Koulouridis, I. & Jaber, B.L. (2013) World incidence of AKI: a meta-analysis. *Clin. J. Am. Soc. Nephrol.*, **8**, 1482-1493.

Turney, J.H. (1996) Acute renal failure: a dangerous condition. *JAMA*, **275**, 1516-1517.

Vincent, J.L., Baron, J.F., Reinhart, K., Gattinoni, L., Thijs, L., Webb, A., Meier-Hellmann, A., Nollet, G. & Peres-Bota, D. (2002) Anemia and blood transfusion in critically ill patients. *JAMA*, **288**, 1499-1507.

Ympa, Y.P., Sakr, Y., Reinhart, K. & Vincent, J.L. (2005) Has mortality from acute renal failure decreased? A systematic review of the literature. *Am. J. Med.*, **118**, 827-832.

Youden, W.J. (1950) Index for rating diagnostic tests. *Cancer*, **3**, 32-35.

Zakai, N.A., Katz, R., Hirsch, C., Shlipak, M.G., Chaves, P.H., Newman, A.B. & Cushman, M. (2005) A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. *Arch. Intern. Med.*, **165**, 2214-2220.

Zimmerman, J.E., Kramer, A.A. & Knaus, W.A. (2013) Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit. Care*, **17**, R81.