The Association of Erythropoietin Levels and Long-term Outcomes following Severe Acute Kidney Injury: A *Post-hoc* Analysis of Hormonal Status in Post-AKI Survivors (HAKI Study)

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Background

Acute kidney injury (AKI) survivors are at an increased risk of chronic kidney disease (CKD), end-stage kidney disease, and mortality. Little is known about the effect of erythropoietin (EPO), major hormone producing by fibroblast-like cell in a kidney, in post-AKI setting. We aimed to investigate the role of EPO as a predictor of long-term outcomes in post-severe AKI survivors.

Methods

We performed a retrospective analysis of post-AKI cohort conducted between August 2018 to December 2021. Adults who survived from severe AKI stage 2-3 were enrolled into the study. Measurement of EPO level was obtained at the first visit of post-AKI clinic (1 month after hospital discharge). Primary outcome was the mortality at 12 months. Secondary outcomes included kidney replacement therapy (KRT), persistent kidney dysfunction, incidence of CKD, progression of CKD, the amount of albuminuria, and anemia status at 12 months.

Results

Eighty-two patients were enrolled into the study. Median EPO level was significant higher in non-survivors than survivors, 33.85 (16.2, 50.7) vs 12 (7.9, 21.7), p = 0.001.

Table 1. Demographic data

	Total (n = 82)
Male, n (%)	40 (48.8)
Mean age, year	64.3 ± 16.8
Underlying disease	
Diabetes mellitus, n (%)	42 (51.2)
Hypertension, n (%)	60 (73.2)
CKD, n (%)	50 (61.0)
Liver disease, n (%)	8 (9.8)
Coronary artery disease, n (%)	19 (23.2)
Congestive heart failure, n (%)	30 (36.6)
Cerebrovascular disease, n (%)	13 (15.9)
Malignancy, n (%)	10 (12.2)
AKI staging	
Stage 2 AKI	31 (37.8)
Stage 3 AKI	51 (62.2)
Cause of AKI	
Renal hypoperfusion	5 (6.1)
Sepsis	23 (28.1)
Nephrotoxic	8 (9.8)
Cardiorenal syndrome	26 (31.7)
Liver disease	4 (4.9)
Obstructive uropathy	4 (4.9)
Systemic disease	3 (3.7)
Pregnancy	3 (3.7)
Contrast-induced	5 (6.1)
Ischemic	8 (9.8)
Other	1 (1.2)

	Total (n = 82)
Cause of AKI	
Baseline serum creatinine (mg/dL)	1.41 (0.91, 2.49)
Baseline GFR (mL/min/1.73 m^2)±	42.13 (22.47, 83.64)
Discharge creatinine (mg/dL)±	1.68 (1.04, 2.89)
Discharge GFR (mL/min/1.73 m^2)±	35.89 (20.45, 55.52)
KRT during admission, n (%)	45 (54.9)
KRT dependence at discharge date, n (%)	9 (10.1)
Hemoglobin (g/dL)#	10.5 (1.8)
Hematocrit (%)#	32.3 (5.5)
EPO (mU/mL)±	12.6 (8.1, 22.6)
Log EPO#	1.2 (0.4)
Log EPO±	1.1 (0.9, 1.4)

Abbreviation: AKI, acute kidney injury; CKD, chronic kidney disease; EPO, erythropoietin; GFR, glomerular filtration rate; IQR, interquartile range; KRT, kidney replacement therapy; LR+, positive likelihood ratio; LR-, negative likelihood ratio; SD, standard deviation; UACR, urine albumin-to-creatinine ratio

* Data excluded patients with RRT or death

Mean (SD)

± Median (IQR)

$ Wilcoxon's rank sum test (Mann-Whitney U test)

Results

EPO level predicted mortality with an area under the receiver operating characteristic (ROC) curve of 0.72. Multivariable analysis adjusted with severity of AKI, cause of AKI, co-morbidities, and baseline kidney function demonstrated that high EPO level associated with higher mortality (p = 0.018). The best cut-off EPO level was 16.2 mU/mL (sensitivity 83.3%, specificity 61.8%). The high-level group had significantly higher mortality compared with low-level group (14.7% vs 2.1%, p = 0.042). Hematocrit level was significantly lower in high-level group compared with low-level group at 12 months (33.4±1.4% vs 36.5±1.0%, p = 0.038).

Table 2. EPO level at various cut-off values for predicting 12-month mortality

EPO level cut-off (mU/mL)	Sensitivity (%)	Specificity (%)	LR+	LR-
10.1	83.33	35.53	1.29	0.47
16.2	**83.33**	**61.84**	**2.18**	**0.27**
22.3	50.00	75.00	2.00	0.67

Fig 1. Area under the ROC curve of EPO level ≥16.2 mU/mL for 12-month mortality

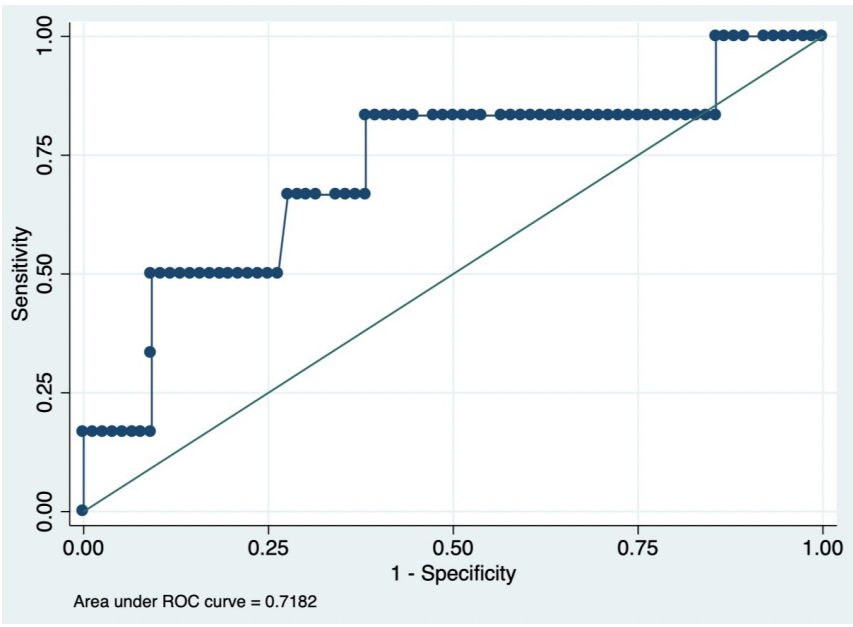

Table 3. Outcomes at 12 months follow up

	Univariable analysis			Multivariable analysis	
	EPO level <16.2 mU/mL (n = 48)	EPO level ≥16.2 mU/mL (n = 34)	p-value	Odds ratio (95% CI)	p-value
Primary outcome					
Death, n (%)	1 (2.1)	5 (14.7)	**0.042**	0.25 (0.03-0.34)	**0.018**
Secondary outcomes					
KRT, n (%)	6 (12.5)	3 (8.8)	0.441	0.10 (0.10-0.37)	0.433
Persistent AKI, n (%)	5 (10.4)	4 (11.8)	0.559	0.11 (0.01-0.22)	0.060
Serum creatinine (mg/dL)*	1.53 (0.25)#	1.85 (0.25)#	0.132$	0.06 (0.01-0.12)	0.070
eGFR (mL/min/1.73 m2)*	59.42 (5.28)#	48.27 (6.92)#	0.138$	0.01 (0.01-0.02	0.566
New CKD, n (%)*	7/43 (16.3)	2/29 (6.9)	0.210	0.21 (0.14-0.56)	0.244
CKD progression, n (%)*	12/43 (27.9)	12/29 (41.4)	0.175	0.15 (0.10-0.39)	0.240
UACR (mg/g)	780.6 (380.9)#	647.4 (238.0)#	0.253$	0.01 (0.01-0.02)	0.802
Hemoglobin (g/dL)#	12.1 (0.3)	11.2 (0.5)	0.073	0.04 (0.01-0.11)	0.146
Hematocrit (%)#	36.5 (1.0)	33.4 (1.4)	**0.038**	1.04 (0.29-1.81)	**0.008**

Conclusions

Plasma EPO appears to be a useful marker for predicting long-term outcome in AKI patients who survived from severe AKI.