ANNALS OF MEDICINE
2025, VOL. 57, NO. 1, 2482023
https://doi.org/10.1080/07853890.2025.2482023

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Risk factors of infective endocarditis-associated acute kidney injury: benefits of low-dose amikacin and surgery

SanXi Ai[a]*, XinPei Liu[b]*, Nan Zhao[c], Qi Miao[b], Yan Qin[a] and XueMei Li[a]

[a]Department of Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [b]Department of Cardiac Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [c]Department of Medical Research, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

ABSTRACT

Objective: Acute kidney injury (AKI) is a frequent presentation in patients with infective endocarditis (IE), and is associated with poor outcomes. The primary aim of the study was to determine the risk factors for AKI in patients with IE.

Methods: A retrospective study was conducted in a tertiary hospital in China from August 2012 to April 2022. The primary outcome was AKI. Logistic regression was used to identify risk factors for AKI.

Results: A total of 594 patients with IE were included, of which 256 (43.1%) experienced AKI. The following variables were found to be independent risk factors for AKI: hypertension (OR 1.96, $p=0.011$), *Staphylococcus aureus* infection (OR 2.69, $p=0.008$), heart failure (OR 5.99, $p<0.001$), shock (OR 5.93, $p=0.015$) and hematuria (OR 2.38, $p<0.001$). The use of low-dose amikacin (400 mg daily) was associated with a lower incidence of AKI (OR 0.38, $p<0.001$). Among patients with IE complicated by heart failure, surgery was associated with a lower incidence of AKI (OR 0.21, $p=0.010$).

Conclusion: AKI is common in IE. Hypertension, *Staphylococcus aureus* infection, heart failure, shock and hematuria are risk factors of IE-associated AKI, whereas low-dose amikacin is a protective factor. Surgery is a protective factor of AKI in the setting of IE complicated by heart failure.

KEY MESSAGES

What is already known on this topic

- AKI is a common complication of IE, but the risk factors of IE-associated AKI were only described in a few small studies.

What the study adds

- Low-dose amikacin is a protective factor of AKI in patients with IE.
- Surgery is a protective factor of AKI among patients with IE and heart failure.

How this study might affect research, practice or policy

- The study expands the understanding of the role of amikacin and surgery in IE-associated AKI.

ARTICLE HISTORY

Received 16 August 2023
Revised 28 October 2023
Accepted 11 February 2025

KEYWORDS

Acute kidney injury; risk factor; amikacin; infective endocarditis; surgery

Introduction

IE is a potentially lethal disease associated with serious complications and substantial mortality. AKI is a common complication of IE, which was reported to occur in 40–66% of cases [1–4]. AKI is associated with poor prognosis and chronic kidney disease in patients with IE [4–6], with a non-negligible economic burden and worsening quality of life.

Patients with IE are exposed to multiple risk factors of AKI, including immune-mediated glomerulonephritis, renal infarction, heart failure, shock, cardiac surgery and nephrotoxic agents. There are a few studies investigating the risk factors for IE-associated AKI with inconsistent results, possibly due to differences in study populations, limitations in methods and relatively small sample sizes (112–276 cases) [1–4,7,8].

Antibiotics and surgery are the major treatments for IE [9]. The association of nephrotoxic antibiotics (mainly vancomycin and aminoglycosides) with IE-associated AKI has been evaluated in previous studies which did not demonstrate a clear association [1–4,7,8]. IE

CONTACT Yan Qin qinyan@pumch.cn Department of Nephrology, Peking Union Medical College Hospital, No. 1 Shuaifuyuan, Dongcheng District, Beijing, China

*SanXi Ai and XinPei Liu contributed equally to this work.

complicated by heart failure is a strong indication for surgery which is associated with reduced mortality. However, the association between surgery and AKI in patients with IE and heart failure has not been evaluated previously.

The aim of the study was to describe the incidence of AKI in patients with IE, and to identify the risk factors for AKI.

Materials and methods

Patient selection and data collection

This was a retrospective observational cohort study. Between August 2012 and April 2022, all consecutive adult patients hospitalized in Peking Union Medical College Hospital (Beijing, China), a tertiary hospital with wide experience in medical and surgical treatment of IE, for an acute episode of possible or definite IE were included. IE was diagnosed according to the modified Duke criteria [10]. The patients on chronic dialysis and patients with incomplete files were excluded. The study was approved by the institutional review board of Peking Union Medical College Hospital (K4039). Verbal informed consent for participation has been obtained from patients. The study adhered to the Declaration of Helsinki.

Epidemiological, clinical and laboratory data were retrospectively collected based on medical charts.

Outcome measure and definitions

The primary outcome was AKI during the course of IE. We applied the Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define and stage AKI. AKI was defined as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h or to 1.5 times baseline within the prior 7 days [11]. Baseline serum creatinine was sought in each patient's medical records prior to the admission for IE. When unavailable, the lowest serum creatinine during follow-up was used.

Chronic kidney disease was defined by an eGFR < 60 ml/min/1.73m^2 at baseline. We estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration equation [12]. Heart failure was defined by NHYA classification III or IV. The diagnosis and classification of heart failure was determined by the referred physicians.

Candidate variables

We identified candidate variables from a review of literature, including patient-related, disease-related, and treatment-related variables. Patient-related variables included age (dichotomized as ≤ or >65 years), gender, hypertension, diabetes, and chronic kidney disease. Disease-related variables included valve status (native or prosthetic), location of IE (left- or right-sided), microorganisms, hematuria, shock, heart failure, and embolism. Treatment-related variables included vancomycin, aminoglycosides, contrast agents, and cardiac surgery. Only factor exposure present before AKI onset was analyzed.

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median (interquartile range [IQR]) and were compared using Student's *t*-test or Mann-Whitney U tests based on the normality of data. Categorical variables were reported as *n* (%) and were compared by χ^2 test or Fisher exact test as appropriate. Due to few missing data, cases with missing data were deleted.

To identify the risk factors associated with AKI, we first explored the potential associations by univariable logistic regression. Multivariable logistic regression was further performed by entering the variables with a significance level $p < 0.10$ in the univariable analysis after testing for collinearity. We hypothesized that surgery might reduce the risk of AKI in patients with heart failure by correcting heart failure which is a recognized risk factor for AKI. Therefore, we conducted subgroup analyses in patients with or without heart failure.

All analyses were performed using SPSS version 26. Two-sided *p* values of less than 0.05 were considered statistically significant.

Results

Characteristics of patients with IE

Characteristics of patients with IE are presented in Table 1. A total of 630 consecutive adult patients with an active episode of IE were screened. Among them, 36 were excluded (16 because of chronic dialysis before IE, 20 because of incomplete files). A total of 594 patients were included in the study with a median age of 47 (IQR 33–58) years. Male patients numbered 392 (66.0%). Only 9 (1.5%) patients had background chronic kidney disease.

The median time between onset of symptoms and diagnosis of IE was 2 (IQR 1.0–4.5) months. Right-sided IE was presented in 104 (17.5%) patients. Prosthetic valves were involved in 42 (7.1%) patients. *Streptococcus viridans* were the most common microorganisms (42.3%), followed by *Staphylococcus aureus* (11.4%). Among the 68 patients with *Staphylococcus aureus* infection, antimicrobial resistance data were available

Table 1. Characteristics of patients with IE.

	All patients ($n=594$)	No AKI ($n=338$)	AKI ($n=256$)	p Value
Age (years)	47 (33–58)	44 (31–55)	52 (40–60)	<0.001
Age > 65 years	68 (11.4%)	29 (8.6%)	39 (15.2%)	0.012
Male	392 (66.0%)	216 (63.9%)	176 (68.8%)	0.217
Comorbidities				
Hypertension	140 (23.6%)	61 (18.0%)	79 (30.9%)	<0.001
Diabetes	54 (9.1%)	25 (7.4%)	29 (11.3%)	0.099
Chronic kidney disease	9 (1.5%)	2 (0.6%)	7 (2.7%)	0.044
Right-sided IE	104 (17.5%)	59 (17.5%)	45 (17.6%)	0.969
Prosthetic valve	42 (7.1%)	15 (4.4%)	27 (10.5%)	0.004
Microorganisms				
Staphylococcus aureus	68 (11.4%)	21 (6.2%)	47 (18.4%)	<0.001
Streptococcus viridans	251 (42.3%)	170 (50.3%)	81 (31.6%)	<0.001
Other microorganisms	142 (23.9%)	82 (24.3%)	60 (23.4%)	0.816
Culture negative	133 (22.4%)	65 (19.2%)	68 (26.6%)	0.034
Complications of IE				
Heart failure	181 (30.5%)	42 (12.4%)	139 (54.3%)	<0.001
Shock	33 (5.6%)	3 (0.9%)	30 (11.7%)	<0.001
Embolism	308 (51.9%)	160 (47.3%)	148 (57.8%)	0.011
Renal embolism	17 (2.9%)	11 (3.3%)	6 (2.3%)	0.510
Hematuria (missing data = 29)	297 (52.6%)	136 (41.8%)	161 (67.1%)	<0.001
Nephrotoxic agents				
Vancomycin[a]	221 (37.2%)	119 (35.2%)	102 (39.8%)	0.247
Amikacin[a]	316 (53.2%)	234 (69.2%)	82 (32.0%)	<0.001
Contrast media[a]	341 (57.4%)	210 (62.1%)	131 (51.2%)	0.007
Surgery[a]	360 (60.6%)	241 (71.3%)	119 (46.5%)	<0.001

AKI: acute kidney injury; IE: infective endocarditis; [a]management present before AKI onset.

for 51 patients, among whom 15 had methicillin-resistant *Staphylococcus aureus*. Blood cultures were negative in 133 (22.4%) patients. Before the occurrence of AKI, a total of 181 (30.5%) patients had symptoms of heart failure (NHYA functional class III or IV) and 33 (5.6%) patients had shock. Three hundred and eight patients (51.9%) had systemic embolism, including 17 (2.9%) with renal infarction.

Urinalysis was performed in 565 (95.1%) patients, which revealed hematuria in 297 (52.6%) patients and proteinuria in 166 (29.4%). Among the patients with hematuria, 51.9% had urine sediment analysis which revealed a predominance of dysmorphic erythrocytes in 89.5% of patients, suggesting glomerulonephritis. Kidney biopsy was performed in six patients, which revealed glomerulonephritis in five and acute interstitial nephritis in one.

All patients received antibiotics. The kind of aminoglycosides used in our center was amikacin and the dosing regimen was 400 mg once daily which was lower than the standard dosage. Dosage of vancomycin was adjusted according to therapeutic drug monitoring. During hospitalization, a total of 459 (77.3%) patients underwent cardiac surgery which was performed before AKI in 360 (60.6%) patients. The median time from diagnosis and surgery was 11 (IQR 6–19) days.

Incidence of AKI

As shown in Figure 1, a total of 256 (43.1%) patients presented with AKI, including 114 (19.2%) at AKI stage 1, 56 (9.4%) at stage 2, and 86 (14.5%) at stage 3. A total of 53 (8.9%) patients required renal replacement therapy during hospitalization.

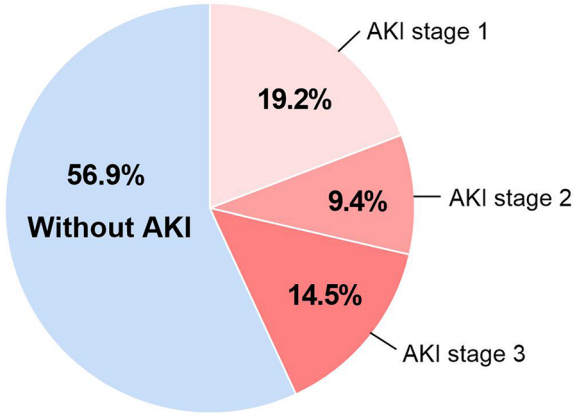

Figure 1. Incidence of AKI.

Forty-five (7.6%) patients died during their hospital stay. Mortality was significantly higher in patients with AKI compared to those without (14.8% vs 2.1%, $p<0.001$, univariable analysis).

Risk factors for AKI

The variables associated with AKI with a significance level $p<0.10$ in the univariable analysis were: age, hypertension, diabetes, chronic kidney disease, prosthetic valve infection, microorganisms, heart failure, shock, embolism, hematuria, amikacin, contrast media, and surgery (Table 1).

In the multivariable analysis, a total of 565 patients were included because 29 patients were excluded due to missing hematuria data. In the multivariable logistic regression model built with all the variables with a p value < 0.10 in the univariable analysis, hypertension (OR 1.96, $p=0.011$), *Staphylococcus aureus* (OR 2.69, $p=0.008$), heart failure (OR 5.99, $p<0.001$), shock (OR 5.93, $p=0.015$), hematuria (OR 2.38, $p<0.001$), and amikacin (OR 0.38, $p<0.001$) were independently associated with AKI (Table 2; Figure 2). No association between surgery and AKI was observed in the overall population of IE (OR 0.93, $p=0.755$).

Table 2. Risk factors for AKI in patients with IE.

Variables	OR	95% CI	*p* Value
Age >65 years	1.20	0.62–2.32	0.592
Hypertension	1.96	1.17–3.30	0.011
Diabetes	1.33	0.67–2.63	0.421
Chronic kidney disease	1.26	0.21–7.46	0.803
Prosthetic valve	0.86	0.38–1.95	0.710
Microorganisms[a]			0.043
Staphylococcus aureus	2.69	1.29–5.62	0.008
Other microorganisms	1.51	0.88–2.58	0.135
Culture negative	1.61	0.94–2.77	0.084
Heart failure	5.99	3.71–9.67	<0.001
Shock	5.93	1.42–24.88	0.015
Embolism	1.22	0.80–1.87	0.362
Hematuria	2.38	1.56–3.65	<0.001
Amikacin	0.38	0.25–0.59	<0.001
Contrast media	0.85	0.54–1.34	0.488
Surgery	0.93	0.57–1.50	0.755

AKI: acute kidney injury; IE: infective endocarditis; [a]dummy variable with *Streptococcus viridans* as a reference.

We performed an analysis of interaction between surgery and heart failure which revealed a p value of 0.001. Multivariable logistic regression analyses were performed in subgroups according to heart failure. Chronic kidney disease was excluded in the regression model because the number of patients with chronic kidney disease and without AKI was zero in the subgroup of heart failure. Among patients with heart failure (Figure 3), surgery (OR 0.21, $p=0.010$) and amikacin were independently associated with AKI (OR 0.22, $p=0.005$). Whereas in patients without heart failure, the risk factors of AKI were similar to those identified in the overall population of IE, and no associations were observed between surgery and AKI (Table 3).

Discussion

The present study investigated the incidence and risk factors of AKI in a largest cohort of IE to date. We confirmed a high incidence of AKI (43.1%) in patients with IE and its association with in-hospital mortality. We identified hypertension, *Staphylococcus aureus*, heart failure, shock and hematuria to be risk factors of AKI.

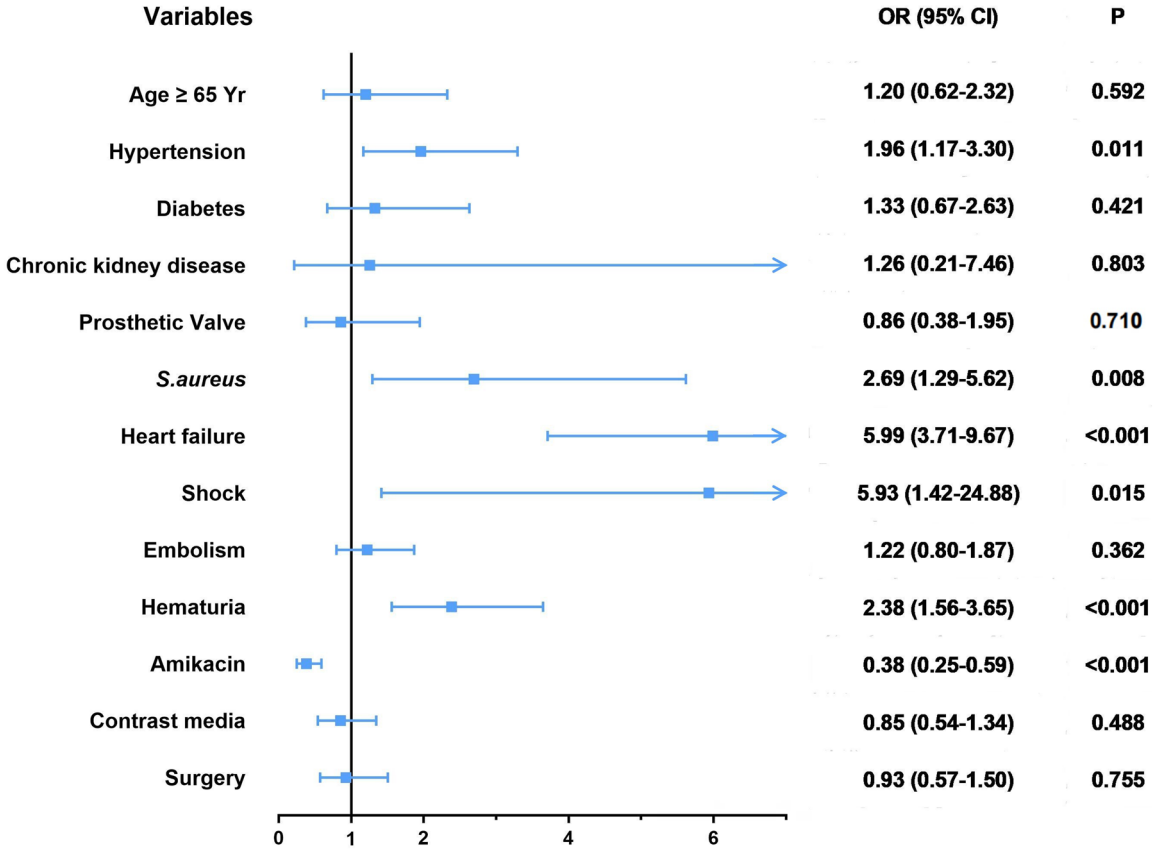

Figure 2. Forest plot of risk factors for AKI in patients with IE.

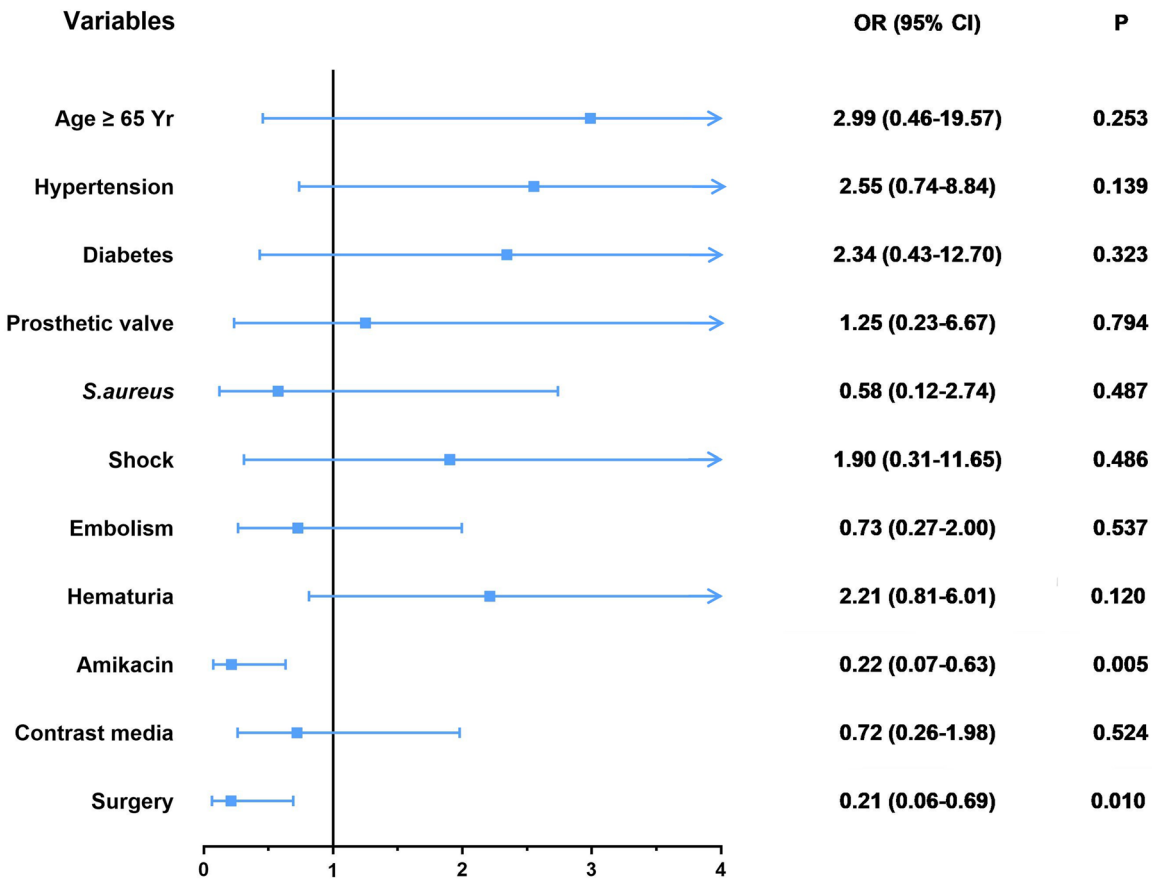

Figure 3. Forest plot of risk factors for AKI in patients with IE complicated by heart failure.

Table 3. Risk factors for AKI in IE patients with or without heart failure.

	With heart failure ($n=164$)			Without heart failure ($n=401$)		
Variables	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Age >65 years	2.99	0.46–19.57	0.253	1.02	0.46–2.30	0.955
Hypertension	2.55	0.74–8.84	0.139	2.15	1.15–4.01	0.016
Diabetes	2.34	0.43–12.70	0.323	1.42	0.63–3.17	0.397
Prosthetic valve	1.25	0.23–6.67	0.794	0.65	0.21–2.01	0.457
Microorganisms[a]			0.084			0.002
Staphylococcus aureus	0.58	0.12–2.74	0.487	4.57	1.97–10.61	<0.001
Other microorganisms	0.54	0.15–1.94	0.348	1.98	1.07–3.66	0.029
Culture negative	3.44	0.93–12.69	0.064	1.10	0.55–2.22	0.787
Shock	1.90	0.31–11.65	0.486	20.32	2.14–193.03	0.009
Embolism	0.73	0.27–2.00	0.537	1.52	0.92–2.50	0.101
Hematuria	2.21	0.81–6.01	0.120	2.50	1.52–4.13	<0.001
Amikacin	0.22	0.07–0.63	0.005	0.45	0.27–0.74	0.002
Contrast media	0.72	0.26–1.98	0.524	0.86	0.49–1.49	0.580
Surgery	0.21	0.06–0.69	0.010	1.47	0.81–2.67	0.208

AKI: acute kidney injury; IE: infective endocarditis; [a]dummy variable with *Streptococcus viridans* as a reference.

For the first time, our study suggested a beneficial role of low-dose amikacin and surgery in IE-associated AKI.

We identified hypertension as a risk factor for AKI in patients with IE. Hypertension is a recognized risk factor for AKI [13,14]. Such an association could be attributed to a high susceptibility to AKI due to the frequent occurrence of chronic kidney injury and heart disease in hypertensive patients. In previous studies, advanced age, diabetes and chronic kidney disease were found to be associated with IE-associated AKI [2,4,7]. In our study, a trend toward a higher incidence of AKI with these variables was noted, but statistical significance in the multivariable analysis was not reached, possibly due to the small numbers of patients with advanced age, diabetes or chronic kidney disease in our cohort.

In agreement with a previous study [4], we observed an association between *Staphylococcus aureus* infection and AKI in patients with IE. The association may be explained by the greater severity of IE due to

Staphylococcus aureus infection [15]. Consistent with precious studies [4,8], heart failure and shock were also found to be risk factors for AKI in our cohort. The association could be attributed to decreased renal perfusion pressure (pre-renal injury) caused by heart failure and shock.

IE-associated glomerulonephritis is well-recognized and is primarily an immune-mediated glomerular injury triggered by infection. In our cohort, hematuria was present in 52.6% of patients with a predominance of dysmorphic erythrocytes, suggesting a high prevalence of glomerulonephritis. However, the role of glomerulonephritis in IE-associated AKI has been poorly assessed because urinalysis results were not available in most studies [1–3,7,8]. In our study, urinalysis data were available in most patients and hematuria was found to be a risk factor of AKI. Our finding is in line with the study from Tokarski et al. who observed a relationship between immune manifestation and IE-associated AKI [4]. In their study, patients with AKI showed a significantly higher prevalence of hematuria than those without AKI, but hematuria data were missing in 26% of patients.

Vancomycin and aminoglycosides are well-known nephrotoxic agents. The association between vancomycin and IE-associated AKI was found in one small study [8], but this was not confirmed in larger studies [2–4,7]. The association of aminoglycosides with IE-associated AKI was not found in previous studies [2–4,7,8]. Concomitant use of aminoglycosides and vancomycin was identified as a risk factor for IE-associated AKI in Ritchie's study [2], but it was not confirmed in another study [4]. The lack of a clear association between vancomycin or aminoglycosides and IE-associated AKI may be explained by the double-edged sword effects. Although vancomycin or aminoglycosides are potentially nephrotoxic, they have important roles in antimicrobial treatment of IE [9], through which they may reduce the risk of AKI. Moreover, their nephrotoxic effects are related to drug dosage, dosing interval, treatment duration and combined use of the two drugs [16–19]. Thus risk of drug-induced nephrotoxicity can be reduced through optimizing therapeutic regimens such as once daily administration of aminoglycosides rather than multiple daily doses [19].

In line with most previous studies, we found no association between vancomycin and AKI. In contrast to previous studies, low-dose amikacin was associated with a lower incidence of IE-associated AKI in our cohort. Several reasons can be proposed to explain this difference. First, short duration and few combined use of amikacin and vancomycin in our cohort may reduce the risk of amikacin-induced nephrotoxicity. Second, the dose of amikacin administrated in our center was 400 mg per day, which was significantly lower than the standard dosage (15 mg/kg per day) [20]. According to our experience, amikacin at this lower dosage had significantly lower rates of adverse events compared to the standard dosage while maintaining efficacy (unpublished data). Our finding is supported by the observation that low-dose amikacin (6.5–8.9 mg/kg) is associated with reduced toxicity while maintaining efficacy in the treatment of multidrug-resistant tuberculosis [21,22]. Finally, the predominance of young patients with a low prevalence of comorbidities in our cohort may lead to a low susceptibility to drug-induced nephrotoxicity.

Previous studies showed that early surgery management could decrease the risk of stroke and death in patients with IE [23,24]. Heart failure (NYHA class III or IV) occurs in approximately one-third of patients with IE and is a major prognostic factor in IE [25,26]. Among patients with IE complicated by heart failure, early surgery has been associated with reduced mortality and is strongly recommended in current guidelines [25,27]. Heart failure in IE results predominantly as a consequence of valvular regurgitation. Although cardiac surgery is per se a risk factor for AKI, on the other hand, it may reduce the risk of AKI through correcting heart failure by repairing valvular regurgitation. Previous studies found no association between surgery and AKI in the overall population with IE [2,4,8], consistent with the findings in our study. However, subgroup analyses in our study showed benefits of surgery on AKI development among patients with heart failure. Our findings suggest that the renal benefits of surgery outweighing its risks to kidney in patients with heart failure. This is a novel finding because, as far as we are aware, this is the first study showing the beneficial role of surgery in AKI in the setting of IE complicated by heart failure.

Our study has several limitations. First, it was a retrospective study. Data was retrospectively collected and urinalysis data were missing in 29 patients. Second, the patients were hospitalized in a tertiary center, which might limit the external validity because patients with less severe disease were likely not referred to the tertiary center. Finally, patients in our cohort were relatively young with a relatively low prevalence of *Staphylococcus aureus* infection. Our results may not be generalized to other populations with advanced age and a predominance of *Staphylococcus aureus* infection.

Conclusions

AKI is common in IE and is associated with poor outcomes. The study identified low-dose amikacin as a

protective factor for AKI, suggesting the benefits of low-dose amikacin outweighing its risks for IE-associated AKI. For the first time, the study revealed a beneficial role of surgery for AKI among patients with IE and heart failure, adding new evidence to the benefits of surgery in IE. The study may contribute to a better knowledge of risk factors for IE-associated AKI.

Authors contributions

SanXi Ai: Design, data analysis, and draft the article. XinPei Liu: Design, data acquisition and analysis. Nan Zhao: Statistical analysis, revise the article. Qi Miao, Yan Qin and XueMei Li: Design and revise the article. All authors have read and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the National Natural Sciences Foundation of China Grants [81970621 to Dr. Y Q], National High Level Hospital Clinical Research Funding [2022-PUMCH-B-020 and 2022-PUMCH-D-002] and The National Key Research and Development Program of China [2022YFC2703100].

ORCID

Yan Qin http://orcid.org/0000-0003-4729-6673

Data availability statement

The data in the current study are available from the corresponding author on reasonable request.

References

[1] Legrand M, Pirracchio R, Rosa A, et al. Incidence, risk factors and prediction of post-operative acute kidney injury following cardiac surgery for active infective endocarditis: an observational study. Crit Care. 2013;17(5):R220. doi: 10.1186/cc13041.

[2] Ritchie BM, Hirning BA, Stevens CA, et al. Risk factors for acute kidney injury associated with the treatment of bacterial endocarditis at a tertiary academic medical center. J Chemother. 2017;29(5):292–298. doi: 10.1080/1120009X.2017.1296916.

[3] Ortiz-Soriano V, Donaldson K, Du G, et al. Incidence and cost of acute kidney injury in hospitalized patients with infective endocarditis. J Clin Med. 2019;8(7):927. doi: 10.3390/jcm8070927.

[4] Von Tokarski F, Lemaignen A, Portais A, et al. Risk factors and outcomes of early acute kidney injury in infective endocarditis: a retrospective cohort study. Int J Infect Dis. 2020;99:421–427. doi: 10.1016/j.ijid.2020.08.022.

[5] Buchholtz K, Larsen CT, Hassager C, et al. In infectious endocarditis patients mortality is highly related to kidney function at time of diagnosis: a prospective observational cohort study of 231 cases. Eur J Intern Med. 2009;20(4):407–410. doi: 10.1016/j.ejim.2008.12.017.

[6] Alonso-Valle H, Fariñas-Alvarez C, García-Palomo JD, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. J Thorac Cardiovasc Surg. 2010;139(4):887–893. doi: 10.1016/j.jtcvs.2009.05.042.

[7] Conlon PJ, Jefferies F, Krigman HR, et al. Predictors of prognosis and risk of acute renal failure in bacterial endocarditis. Clin Nephrol. 1998;49(2):96–101.

[8] Gagneux-Brunon A, Pouvaret A, Maillard N, et al. Acute kidney injury in infective endocarditis: a retrospective analysis. Med Mal Infect. 2019;49(7):527–533. doi: 10.1016/j.medmal.2019.03.015.

[9] Baddour LM, Wilson WR, Bayer AS, et al. in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from. Circulation. 2015;132(15):1435–1486. doi: 10.1161/CIR.0000000000000296.

[10] Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633–638. doi: 10.1086/313753.

[11] Summary of recommendation statements. Kidney Int Suppl. 2012;2(1):8–12.

[12] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612. doi: 10.7326/0003-4819-150-9-200905050-00006.

[13] Hsu CY, Ordoñez JD, Chertow GM, et al. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int. 2008;74(1):101–107. doi: 10.1038/ki.2008.107.

[14] James MT, Grams ME, Woodward M, et al. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis. 2015;66(4):602–612. doi: 10.1053/j.ajkd.2015.02.338.

[15] Selton-Suty C, Célard M, Le Moing V, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. Clin Infect Dis. 2012;54(9):1230–1239. doi: 10.1093/cid/cis199.

[16] Bosso JA, Nappi J, Rudisill C, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. Antimicrob Agents Chemother. 2011;55(12):5475–5479. doi: 10.1128/AAC.00168-11.

[17] Buchholtz K, Larsen CT, Hassager C, et al. Severity of gentamicin's nephrotoxic effect on patients with infective endocarditis: a prospective observational cohort study of 373 patients. Clin Infect Dis. 2009;48(1):65–71. doi: 10.1086/594122.

[18] Goetz MB, Sayers J. Nephrotoxicity of vancomycin and aminoglycoside therapy separately and in combination. J Antimicrob Chemother. 1993;32(2):325–334. doi: 10.1093/jac/32.2.325.

[19] Barza M, Ioannidis JP, Cappelleri JC, et al. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ. 1996;312(7027):338–345. doi: 10.1136/bmj.312.7027.338.

[20] Pérez-Blanco JS, Sáez Fernández EM, Calvo MV, et al. Evaluation of current amikacin dosing recommendations and development of an interactive nomogram: the role of albumin. Pharmaceutics. 2021;13(2):264. doi: 10.3390/pharmaceutics13020264.

[21] van Altena R, Dijkstra JA, van der Meer ME, et al. Reduced chance of hearing loss associated with therapeutic drug monitoring of aminoglycosides in the treatment of multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2017;61(3):e01400-16. doi: 10.1128/AAC.01400-16.

[22] Sabur NF, Brar MS, Wu L, et al. Low-dose amikacin in the treatment of multidrug-resistant Tuberculosis (MDR-TB). BMC Infect Dis. 2021;21(1):254. doi: 10.1186/s12879-021-05947-6.

[23] Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation. 2010;121(8):1005–1013. doi: 10.1161/CIRCULATIONAHA.109.864488.

[24] Kang D-H, Kim Y-J, Kim S-H, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012;366(26):2466–2473. doi: 10.1056/NEJMoa1112843.

[25] Kiefer T, Park L, Tribouilloy C, et al. Association between valvular surgery and mortality among patients with infective endocarditis complicated by heart failure. JAMA. 2011;306(20):2239–2247. doi: 10.1001/jama.2011.1701.

[26] Bohbot Y, Habib G, Laroche C, et al. Characteristics, management, and outcomes of patients with left-sided infective endocarditis complicated by heart failure: a substudy of the ESC-EORP EURO-ENDO (European infective endocarditis) registry. Eur J Heart Fail. 2022;24(7):1253–1265. doi: 10.1002/ejhf.2525.

[27] Otto CM, Nishimura RA, Bonow RO, et al. ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143(5):e35–e71.