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# The relationship between albuminuria and poor clinical outcomes in patients with infective endocarditis

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ABSTRACT

*Background:* We explored the impact of albuminuria on clinical outcomes in patients with infective endocarditis (IE).

*Methods:* Patients with IE were prospectively enrolled and divided into 3 groups based on albuminuria measured by qualitative dipstick at admission and were followed up for 1 y. Univariate and multivariate analysis were performed to evaluate the relationship between albuminuria and mortality.

*Results:* Nine-hundred seventy patients were divided into 3 groups: negative (urine dipstick negative) ($n = 694$), trace (urine dipstick trace) ($n = 150$) and positive (urine dipstick ≥ 1 + protein) ($n = 126$). In-hospital mortality increased with increasing albuminuria (5.2%, 8.0% and 17.5%, $p < 0.001$, for the negative, trace, and positive groups, respectively). Compared with negativity for albuminuria, positivity for albuminuria was an independent risk predictor for in-hospital death (OR = 2.79, 95% CI = 1.41–5.49; $p = 0.003$). The cumulative rate of one-year mortality was higher among albuminuria-positive patients than among albuminuria-negative patients. Multivariate Cox analysis demonstrated that albuminuria positivity was associated with one-year mortality (HR = 1.89, 95% CI = 1.17–3.04, $p = 0.010$).

*Conclusion:* Albuminuria was independently associated with in-hospital death in IE patients. Urine dipstick ≥ 1 + protein was linked to increased one-year mortality. As a simple and inexpensive marker, albuminuria measured by qualitative dipstick might be helpful for risk stratification in IE.



## 1. Introduction

Infective endocarditis (IE), which is characterized by microorganism accumulating in a heart valve, resulting in valve damage, may have a catastrophic outcome [1]. Although there have been advancements in diagnostic and therapeutic approaches for IE, this disease remains associated with high mortality both in-hospital and during long-term follow-up [2]. Therefore, earlier risk stratification could aid in making accurate clinical decisions that improve patient prognoses.

Albuminuria, which has been reported to be an index for both renal and systemic vascular disease, has been significantly associated with cardiovascular events in patients with and without diabetes mellitus [3]. In addition, albuminuria was found to be better than estimated glomerular filtration rate (eGFR) at identifying individuals who are at risk for accelerated GFR loss [4]. In one study, patients with heavy albuminuria (urine dipstick ≥ 2 +) were approximately 4 times more likely to develop acute kidney injury than patients without albuminuria after adjusting for eGFR < 60 ml/min/1.73 $m^2$ [5]. Current guidelines [6] note that renal failure has been established as a main factor influencing prognosis for IE. There exist limited data to elucidate the relationship between albuminuria and adverse prognosis in IE.

## 2. Methods

### 2.1. Patient enrollment and data collection

Patients definitively diagnosed with IE according to the modified Duke criteria [7] were prospectively enrolled between August 2008 and July 2015 at Guangdong General Hospital. The exclusion criteria were (1) age < 18 y; (2) several hospitalizations; (3) serious liver insufficiency; (4) cardiogenic shock; (5) end-stage renal disease or renal replacement therapy; (6) a diagnosis of IE after major cardiac surgery during hospitalization; and (7) no routine urine examination prior to surgery. Eventually, 970 patients were enrolled in this study (Fig. 1). This study was approved by the Guangdong General Hospital ethics committee. Written informed consent was gained before the procedure.

Early-morning urine samples were collected and measured at admission and prior to surgery. Urinary albumin was assessed by

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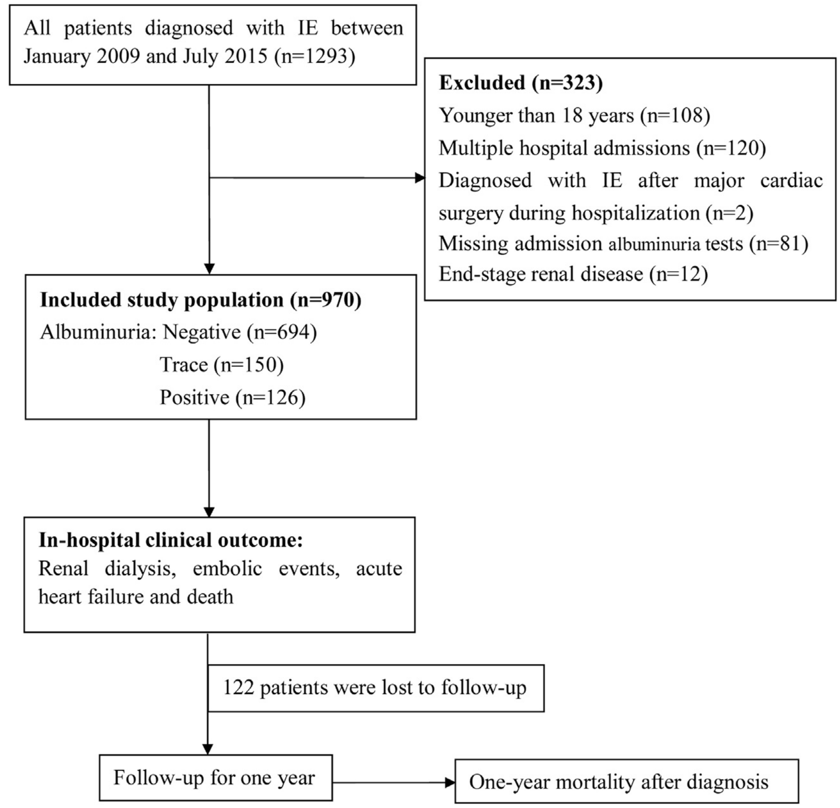


**Fig. 1.** Flow diagram of the study population.

qualitative dipstick, using an Aution Max AX-4280 analyzer or an Aution Max AX-4030 analyzer. Fasting venous blood was collected after hospital admission, and blood indices were measured accordingly. Blood samples were also collected from at least 3 different venipuncture sites for blood culture. Patients were subjected to echocardiography within 24 h of admission. Left ventricular ejection fraction (LVEF) was determined using Simpson's biplane method. The largest vegetation size was recorded. We also evaluated the heart function of these patients on admission. eGFR was calculated using the 4-variable Modification of Diet in Renal Disease equation for Chinese patients [8].

*2.2. Follow-up and endpoints*

Telephone interviews were performed every three months after discharge for a total of 1 y. The primary endpoint was in-hospital mortality, and the secondary endpoints were in-hospital major adverse clinical events (MACEs,including all-cause mortality, embolic events, renal dialysis and acute heart failure) and 1-y mortality. Follow-up time was defined as the time from diagnosis to death or the follow-up deadline.

*2.3. Statistical analyses*

Statistical analyses were performed using SPSS software, vers19.0. Patients were divided into 3 groups based on albuminuria: the negative group (urine dipstick negative), the trace group (urine dipstick trace), and the positive group (urine dipstick ≥ 1 + protein). Continuous data are expressed as means ± SD or as medians and interquartile ranges and were compared using variance analysis or the Wilcoxon rank-sum test. Categorical data are presented as percentages and compared using a $\chi^2$ test or Fisher's exact test. Age, prior valvular surgery, eGFR < 90 ml/min/1.73 $m^2$, LVEF, and surgical treatment were used in multivariable logistic regression analysis to detect risk factors for in-hospital death. The Kaplan-Meier survival method was used, and cumulative 1-y mortality was compared across groups using a log-rank test. Multivariate Cox regression analyses were also conducted. A 2-tailed *P*-value ≤ 0.05 was regarded as significant.

## 3. Results

*3.1. Baseline clinical characteristics*

This study included 970 patients (69.8% men; age, 44 ± 15 y) who were divided into 3 groups based on albuminuria measured at admission: the negative ($n = 694$), trace ($n = 150$) and positive ($n = 126$) groups. Patients in the trace and positive groups were more likely to exhibit NYHA class III–IV status (31.8% vs 42.7% vs 42.1%, $p = 0.008$) and to have developed multiple vegetation sites (8.7% vs 20.3% vs 16.5%, $p < 0.001$). Among the groups, a trend towards a lower incidence of surgical intervention as albuminuria increased was observed (72.6% vs 72.7% vs 57.1%, $p = 0.002$). Lower eGFR was detected in albuminuria-positive patients relative to other patients (107.7 ± 38.5 vs 102.7 ± 40.5 vs 74.2 ± 38.2, $p < 0.001$) .

In-hospital mortality increased with increasing albuminuria (5.2%, 8.0% and 17.5%, $p < 0.001$, for the negative, trace, and positive groups, respectively). Similar results were observed for MACEs (18.7%, 27.3% and 38.1%, $p < 0.001$, respectively) (Table 1).

The association between clinical characteristics and in-hospital mortality was explored by dividing patients into 2 groups based on the occurrence of in-hospital death (Table 2). Comparisons of patients with in-hospital death and other patients indicated that the former patients were older (53.4 ± 15.2 vs. 43.7 ± 15.0 y, $p < 0.001$) and more likely to have a history of valvular surgery (21.4% vs. 5.8%, $p < 0.001$). The rate of NYHA class III–IV status was increased in patients with in-hospital mortality. In addition, eGFR and LVEF were significantly lower in patients with in-hospital mortality. Compared with patients who underwent surgery, patients who did not receive surgical treatment were more likely to suffer in-hospital death (30.0% vs. 73.8%, $p < 0.001$).