

## Retrospective Study

# Clinical outcomes in patients with native valve infective endocarditis and diabetes mellitus

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**Institutional review board**

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## Abstract

### BACKGROUND

There is a lack of data on the clinical outcomes in patients with native valve infective endocarditis (NVIE) and diabetes mellitus (DM).

### AIM

To investigate (1) trends in the prevalence of DM among patients with NVIE; and (2) the impact of DM on NVIE outcomes.

### METHODS

We identified 76385 with NVIE from the 2004 to 2014 National Inpatient Sample, of which 22284 (28%) had DM. We assessed trends in DM from 2004 to 2014 using the Cochrane Armitage test. We compared baseline comorbidities, microorganisms, and in-patients procedures between those with *vs* without DM. Propensity match analysis and multivariate logistic regression were used to investigate study outcomes in in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block.

### RESULTS

database in the United States. Informed patient consent is not required.

**Conflict-of-interest statement:**

Authors declare no conflict of interests for this article.

**Data sharing statement:**

Data that support the findings of this study are publicly available at <https://www.hcup-us.ahrq.gov/db/nation/nis/nisdb/documentation.jsp>.

**Open-Access:**

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Crude rates of DM increased from 22% in 2004 to 30% in 2014. There were significant differences in demographics, comorbidities and NVIE risk factors between the two groups. *Staphylococcus aureus* was the most common organism identified with higher rates in patients with DM (33.1% vs 35.6%;  $P < 0.0001$ ). After propensity matching, in-hospital mortality (11.1% vs 11.9%;  $P < 0.0001$ ), stroke (2.3% vs 3.0%;  $P < 0.0001$ ), acute heart failure (4.6% vs 6.5%;  $P = 0.001$ ), cardiogenic shock (1.5% vs 1.9%;  $P < 0.0001$ ), septic shock (7.2% vs 9.6%;  $P < 0.0001$ ), and atrioventricular block (1.5% vs 2.4%;  $P < 0.0001$ ), were significantly higher in patients with DM. Independent predictors of mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, *Staphylococcus aureus*, and older age.

**CONCLUSION**

There is an increasing prevalence of DM in NVIE and it is associated with poorer outcomes. Further studies are crucial to identify the clinical, and sociodemographic contributors to this trend and develop strategies to mitigate its attendant risk.

**Key Words:** Infective endocarditis; Native valve infective endocarditis; Diabetes mellitus; Valvular heart disease; Cardiovascular disease; National Inpatient Sample

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**Core Tip:** In this observational study, we found increasing prevalence rates for diabetes mellitus (DM) among patients with native valve infective endocarditis (NVIE) from 2004–2014. There were significant differences in risk factors, microbiology, and inpatient procedures between patients with DM compared to those without DM. DM was associated with mortality, acute heart failure, stroke, atrioventricular block, septic shock, and cardiogenic shock. Independent predictors of in-hospital mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, *Staphylococcus aureus*, and older age.

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**INTRODUCTION**

Despite advancements in management strategies, infective endocarditis (IE) is associated with high mortality rates ranging from 10%-26% and an estimated five-year survival rate of 60%-70%<sup>[1-4]</sup>. Also, IE carries a significant long term morbidity risk with high rates of stroke (24%), and heart failure (49%)<sup>[1-4]</sup>. One of the challenges associated with IE management is identifying patients at increased risk of complications. While current guidelines recommend active surveillance, early stratification can help identify patients who may benefit from further intervention.

We have seen an increase in hospitalization from native valve infective endocarditis (NVIE) in the United States [from 155151 (2002-2006) to 195300 (2012-2016)]<sup>[5]</sup>. This is likely related to increased risk factors such as drug abuse, advanced age, and diabetes mellitus (DM)<sup>[5-9]</sup>. There is a paucity of data on the outcomes of NVIE in DM patients. Previous studies looking at DM and IE have been limited by single-center experiences, sample size and analyses that combine NVIE and prosthetic valve infective endocarditis (PVIE)<sup>[9-16]</sup>. In this study, using a well-characterized database, we investigated trends in the prevalence of DM among patients with NVIE; and the impact of DM on in-hospital mortality, acute heart failure, stroke, septic shock, cardiogenic shock, and atrioventricular block.

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## MATERIALS AND METHODS

### Study design

Our data source was the National In-patient Sample (NIS) 2004–2014, a subset of the Healthcare Cost Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ)<sup>[17,18]</sup>. Briefly, NIS and HCUP are the largest all-payer inpatient database in the United States. The database contains a 20% stratified sample of all discharges from United States hospitals representing the United States population and accounts for 90% of all hospitalizations<sup>[18]</sup>. It includes information on demographics, hospital characteristics, up to 25 diagnostic and procedure codes based on the International Classification of Diseases 9<sup>th</sup> revision, Clinical Modification (ICD-9-CM), and outcomes based on patient discharge records.

### Study population, variables and outcomes

We queried NIS 2004–2014 using ICD-9-CM codes to identify patients age 18 and above, who were hospitalized with the primary diagnosis of acute or subacute IE. To limit the sample to NVIE, we excluded patients with a prior history of valve replacement and cardiac devices (Figure 1). The algorithm has been validated<sup>[9]</sup>. The cohort was then divided into those with and without DM. Demographics associated with each diagnosis were identified from NIS, and associated comorbidities were extracted from AHRQ<sup>[17,18]</sup>. This allows the identification of comorbidities that were present before admission. Other variables that could impact study outcomes, such as the type of organism and inpatient procedures, were included in the analysis. The primary endpoint was to investigate the impact of DM on in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock and atrioventricular block in those with NVIE. All clinical characteristics were defined using ICD-9-CM codes (Supplementary Table 1).

### Statistical analysis

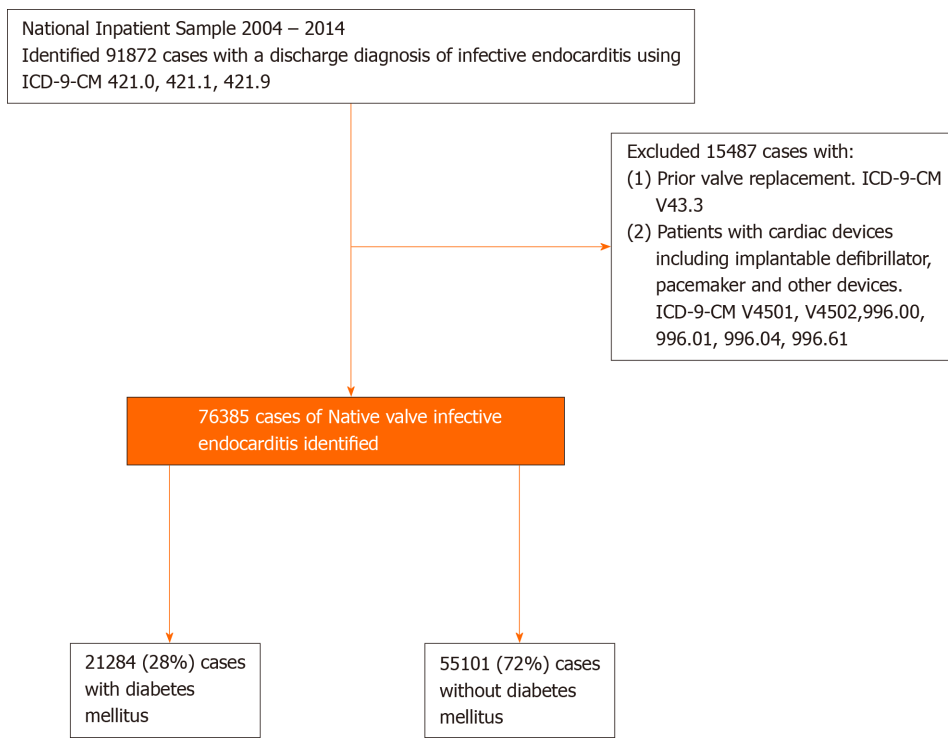
IBM SPSS V.25 was used for statistical analysis. Statistical significance was defined as  $P < 0.05$ . We compared baseline characteristics, organisms involved, and inpatient procedures between patients with DM compared to those without DM. Chi-square was used for categorical variables, while an independent student *t*-test was used for continuous variables. We performed trend analysis using the Cochran-Armitage test to evaluate the temporal trends in the prevalence of DM in patients with NVIE.

We compared the incidence of in-hospital mortality, stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block. Descriptive statistics were reported in frequencies with percentages for categorical variables, while continuous variables were reported in mean, standard deviation, median, and 25<sup>th</sup> and 75<sup>th</sup> percentiles. To limit selection bias, we employed propensity score methodology to match hospitalizations with NVIE patients who had DM *vs* those without any DM at a 1:1 ratio. The nearest neighbor technique was adopted to match each case to control, which is closest to the calculated propensity score, with a caliper width of 0.1. The propensity score was calculated from the following 26 matching variables: Age, sex, race, atrial fibrillation, tobacco use disorder, valvular heart disease, hypothyroidism, chronic kidney disease, obesity, hypertension, congestive heart failure, chronic lung disease, hyperlipidemia, hemodialysis, chronic liver disease, peripheral artery disease, coronary artery disease, drug abuse, pulmonary hypertension, human immunodeficiency virus, congenital heart disease, history of cardiac transplant, rheumatic heart disease, staphylococcus aureus, other staphylococcus, viridians, streptococci, enterococci, group A streptococci, group B streptococci, group G streptococci, and gram-negative bacteremia. Multivariate logistic regression was then used to estimate the adjusted odds ratio of the study outcome in those with DM compared to those without DM.

Binomial regression was used to identify variables in the demographics, comorbidities, and microbiology that were associated with mortality. All significant variables were then incorporated into a multivariate logistic regression model to determine the predictors of in-hospital mortality.

## RESULTS

We identified 76385 patients with NVIE. Among these patients, 21284 (28%) had DM. The mean age of patients with DM was significantly higher ( $63.4 \pm 14$  *vs*  $58.2 \pm 19$ ;  $P < 0.0001$ ). The most predominant race was White American, and they were less likely to



**Figure 1** Flow chart of our study design. ICD-9-CM: International Classification of Diseases 9<sup>th</sup> revision, Clinical Modification.

have DM compared to African, Hispanics, Asians, and Native Americans (Table 1). Patients with DM had higher rates of comorbidities, including hypertension, congestive heart failure, dyslipidemia, obesity, coronary artery disease, and pulmonary hypertension compared to those without DM (Table 1). The crude rates of DM in patients with NVIE significantly increased from 22% in 2004 to 30% in 2014;  $P < 0.0001$  (Figure 2).

In terms of the infective organism involved, patients with DM had higher rates of staphylococcus aureus (35.6% vs 33.1%;  $P < 0.0001$ ), other staphylococcus organisms (6.7% vs 5.4%;  $P < 0.0001$ ), enterococci (7.6% vs 6.5%;  $P < 0.0001$ ), group B streptococci (1.6% vs 1.3%;  $P < 0.0001$ ), and gram-negative organisms (4.8 vs 3.8;  $P < 0.0001$ ) (Table 2). For inpatient procedures, DM patients were less likely to undergo surgical valve replacement (8.2% vs 10.6%;  $P < 0.0001$ ) (Table 3).

After propensity matching rates of stroke (2.4% vs 1.5%;  $P < 0.0001$ ), acute heart failure (6.5% vs 4.6%;  $P = 0.001$ ), atrioventricular block (6.5% vs 4.6%;  $P < 0.0001$ ), septic shock (9.6% vs 7.2%;  $P < 0.0001$ ), cardiogenic shock (1.9% vs 1.5%;  $P < 0.0001$ ), and in-hospital mortality (11.9% vs 11.1%;  $P < 0.0001$ ), were significantly higher in patients with DM and NVIE, compared to those with NVIE alone. The multivariate logistic regression followed similar trends (Table 4). Predictors of in-hospital mortality in patients with NVIE and DM included hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age (Table 5).

## DISCUSSION

In this observational study, we found increasing prevalence rates for DM among patients with NVIE from 2004–2014. There were significant differences in risk factors, microbiology, and in-patient procedures between patients with DM compared to those without DM. DM was associated with mortality, acute heart failure, stroke, atrioventricular block, septic shock, and cardiogenic shock. Independent predictors of in-hospital mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age. Compared to other studies that have investigated the clinical outcomes of DM in IE patients<sup>[9-16]</sup>. We had a robust sample size. Also, the analyses in these studies combined NVIE and PVIE. It is essential to stratify because the clinical course, management, and outcomes significantly differ<sup>[19-21]</sup>. Lastly, we identified the independent predictors of mortality.

The overall prevalence of DM was 28%, and the crude rates of DM significantly

**Table 1** Baseline characteristics of primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014

Demographics and Co-morbidities	NVIE		
	No DM (%)	DM (%)	P value
Age (yr), mean (SD)	58.2 ± 19	63.37 ± 14	< 0.0001
Gender			< 0.0001
Male	58.4	55.6	
Female	41.6	44.4	
Race			< 0.0001
White	71.9	62.5	
Black	15.9	20.0	
Hispanic	7.1	11.2	
Asian	1.8	2.4	
Native Americans	0.6	1.0	
Other	2.7	2.9	
Co-morbidities			
Tobacco abuse	14.8	9.0	< 0.0001
Hypothyroidism	6.2	9.6	< 0.0001
Hyperlipidemia	11.5	25.1	< 0.0001
Valvular heart diseases	21.6	19.0	< 0.0001
Chronic kidney disease	3.8	7.9	< 0.0001
Obesity	1.8	7.2	< 0.0001
Congestive heart failure	26.2	34.2	< 0.0001
Chronic liver disease	9.3	12.4	< 0.0001
Hypertension	39.1	64.8	< 0.0001
HIV	2.6	0.9	< 0.0001
Atrial fibrillation	18.9	22.4	< 0.0001
Pulmonary hypertension	5.8	6.5	< 0.0001
Coronary artery disease	14.2	29.7	< 0.0001
Peripheral artery disease	2.4	5.5	< 0.0001
Hemodialysis	15.0	27.8	< 0.0001
History of cardiac arrest	0.0	0.1	0.011
History of drug abuse	11.9	3.8	< 0.0001
Congenital heart disease	1.8	0.8	< 0.0001
Rheumatic heart disease	11.8	9.6	< 0.0001

DM: Diabetes mellitus; HIV: Human immunodeficiency virus; SD: Standard deviation; NVIE: Native valve infective endocarditis.

increased from 2004–2014. It should be mentioned that there has been a parallel increase in the prevalence of DM in the United States, which had been attributed to increased risk factors such as obesity, sedentary lifestyle, enhanced detection, and increased longevity<sup>[22,23]</sup>. A study demonstrated an increased prevalence from 7.7% in 1999–2000 to 13.3% in 2015–2016 among United States adults<sup>[24]</sup>. In another study using the national health and nutrition examination survey, the prevalence increased from 9.8% in 1988–1994 to 12.4% in 2011–2012, across all age, sex, and racial groups<sup>[25]</sup>.

The clinical profile of NVIE patients with DM was different compared to those without DM. DM patients had higher rates of comorbidities, and IE risk factors such as

**Table 2 Infective organisms identified in primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014**

Infective organisms	NVIE		
	No DM (%)	DM (%)	P value
Staphylococcus aureus	33.1	35.6	< 0.001
Other staphylococcus	5.4	6.7	< 0.001
Viridans streptococci	18.6	15.5	< 0.001
Enterococci	6.5	7.6	< 0.001
Pneumococcus	0.5	0.4	0.11
Group A streptococci	0.7	0.5	0.003
Group B streptococci	1.3	1.6	< 0.001
Group C streptococci	0.1	0.1	0.44
Group G streptococci	0.2	0.2	0.87
Gram negative	3.8	4.8	< 0.001
Anaerobes	0.4	0.3	0.82
Fungemia	0.2	0.2	0.81

DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

**Table 3 Inpatient procedures in primary hospitalizations for native valve infective endocarditis by diabetes mellitus in the United States from 2004–2014**

Inpatient procedures	NVIE		
	No DM (%)	DM (%)	P value
Surgical valve replacement	12.3	9.2	< 0.001
Aortic valve replacement	6.5	5.1	< 0.001
Mitral valve replacement	5.0	3.7	< 0.001
Tricuspid valve replacement	0.1	0.1	0.43
Pulmonary valve replacement	0.7	0.3	< 0.001

Surgical valve replacement, included aortic valve replacement, mitral valve replacement, tricuspid valve replacement and pulmonary valve replacement. DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

older age, and hemodialysis. They were less likely to have structural heart disease (valvular heart disease and congenital heart disease) and intravenous drug abuse (Table 1). Several other studies have reported similar findings<sup>[8,10,12-14]</sup>. We also found significant differences in the organisms involved. DM patients had higher rates of staphylococcus species, enterococci, and gram-negative microorganisms. This is also consistent with prior studies and likely due to increased health care utilization in DM patients, exposing them to nosocomial infections and immune dysfunctions, rendering them more susceptible to skin and soft tissue infections<sup>[16,26]</sup>.

There are a couple of explanations for the poor outcomes among NVIE patients with DM. First, they are more likely to have staphylococcus aureus infections. Staphylococcus aureus tends to stick and multiply on heart valves, promoting vegetation, abscess formation, mechanical complications, and mortality<sup>[27-29]</sup>. Secondly, IE is characterized by an immunologic response that leads to immune complex formation; the exaggerated immunologic response in DM patients likely contributed to poor outcomes noted in this study<sup>[30]</sup>. Finally, lower rates of life-saving procedures such a surgical valve replacement, as demonstrated in this study, and higher rates of comorbidities in DM patients are other explanations.

Current IE management strategies center around presumed patient mortality risk. Generally, low-risk patients can be safely managed with antibiotics. At the same time,



**Table 4 Association between diabetes mellitus and outcomes of hospitalizations for native valve infective endocarditis after propensity matching**

NVIE						
	No DM (%)	DM (%)	aOR	Lower CI	Upper CI	P value
In-hospital mortality	11.1	11.9	1.2	1.1	1.4	< 0.0001
Acute heart failure	4.6	6.5	1.2	1.1	1.3	0.001
Stroke	2.3	3.0	1.3	1.1	1.5	< 0.0001
Atrioventricular block	1.5	2.4	1.5	1.3	1.5	< 0.0001
Septic shock	7.2	9.6	1.2	1.1	1.3	< 0.0001
Cardiogenic shock	1.5	1.9	1.4	1.2	1.6	< 0.0001

aOR: Adjusted odds ratio; CI: Confidence interval; DM: Diabetes mellitus; NVIE: Native valve infective endocarditis.

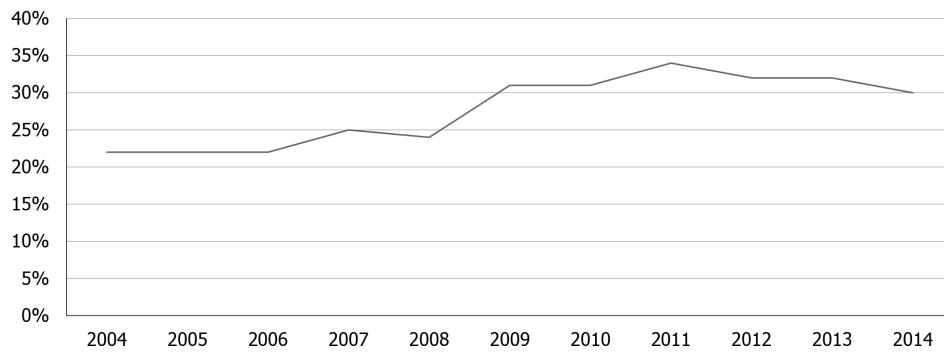
**Table 5 Logistic regression analysis for predictors of in hospital mortality among patients with native valve infective endocarditis and diabetes mellitus**

	95%CI			P value
	OR	Lower	Upper	
Age (yr)				
18-65	REF	REF	REF	REF
> 65	1.02	1.02	1.02	< 0.001
Hypertension	0.56	0.50	0.62	< 0.0001
Atrial fibrillation	1.17	1.05	1.31	0.006
Tobacco abuse	0.74	0.61	0.90	0.003
Hyperlipidemia	0.69	0.61	0.78	< 0.0001
Congestive heart failure	1.34	1.22	1.48	< 0.0001
Chronic liver disease	1.51	1.19	1.92	0.001
Staphylococcus aureus	1.25	1.13	1.39	< 0.0001
Hemodialysis	2.04	1.83	2.27	< 0.0001

CI: Confidence interval; OR: Odds ratio; REF: Reference.

aggressive intervention such as valve replacement is recommended for those at high risk of mortality, suffering from, acute heart failure, large vegetation, and mechanical complications such as valvular dysfunction, and perivalvular abscess<sup>[31-34]</sup>. These recommendations stem from observational studies demonstrating mortality benefit<sup>[31-34]</sup>. In this study, odds for in-hospital mortality was 20% higher in DM patients compared to those without DM. Staphylococcus aureus was highly prevalent among patients with DM, and it was significantly associated with mortality. Several other studies have linked staphylococcus aureus to death, likely due to severe valvular damage and complications<sup>[4,27,28,34]</sup>. Early surgery should be considered in NVIE secondary to staphylococcus aureus, especially in DM patients, due to severe valve destruction and increased mortality.

Other predictors of mortality among DM patients in this study include congestive heart failure, hemodialysis, and atrial fibrillation. This suggests that prevention and aggressive management of comorbid conditions in DM patients could potentially decrease associated NVIE mortality. NVIE is characterized by bacteremia, bacteria colonization, adhesion on cardiac valves and vegetation formation<sup>[35]</sup>. Immune dysfunction, micro- and macro-angiopathies, and decreased bactericidal activity of the gastrointestinal and genitourinary system make DM patients more susceptible to infections<sup>[36]</sup>. Tight glycemic control, vaccination, and adequate skin care will help reduce bacteremia and NVIE in DM patients.



Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Diabetes mellitus	22%	22%	22%	25%	24%	31%	31%	34%	32%	32%	30%

**Figure 2** Trends in the prevalence of diabetes mellitus among patients with infective endocarditis.  $P < 0.0001$ .

Some limitations of our study should also be noted. First, data on glycemic control and management of DM were not available. It is well known that strict glycemic control can improve the clinical outcome in patients with DM<sup>[4]</sup>. Secondly, the study lacked information on clinical variables such as echocardiographic features, vegetation size, and antimicrobials therapy, all of which might impact clinical outcomes<sup>[4]</sup>.

## CONCLUSION

Among patients with NVIE, DM is associated with increased mortality and complications. This is likely due to higher rates of staphylococcus bacteremia, underlying comorbidities, and immune dysfunction. Further studies should focus on prevention and management strategies among DM patients with NVIE.

## ARTICLE HIGHLIGHTS

### Research background

There is a lack of data on the clinical outcomes in patients with native valve infective endocarditis (NVIE) and diabetes mellitus (DM).

### Research motivation

Previous studies looking at DM and infective endocarditis (IE) have included analyses that combine NVIE and prosthetic valve IE.

### Research objectives

In this study, aim to investigate the temporal trends in the prevalence of DM in NVIE and investigate the impact of DM on NVIE outcomes.

### Research methods

The National Inpatient Sample 2004–2014 was queried. Cochrane Armitage test was used for trend analysis. Propensity match scoring and multivariate logistic regression were used to investigate study outcomes (Supplementary Table 2).

### Research results

We identified 76385 patients with NVIE, of which 21284 (28%) had DM. Patients with DM had more comorbidities, were more likely to have staphylococcus infection, and less likely to undergo surgical valve replacement. In-hospital mortality, and IE related complications such as stroke, acute heart failure, cardiogenic shock, septic shock, and atrioventricular block, were significantly higher in patients with DM. Independent predictors of mortality in NVIE patients with DM include hemodialysis, congestive heart failure, atrial fibrillation, staphylococcus aureus, and older age.



### Research conclusions

There is an increasing prevalence of DM in NVIE and it is associated with poorer outcomes.

### Research perspectives

Further studies are crucial to identify the clinical, and sociodemographic contributors to this trend and develop strategies to mitigate its attendant risk.

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