Temporal trends and patterns of infective endocarditis in a Chinese population: A territory-wide study in Hong Kong (2002–2019)

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Summary

Background The characteristics of infective endocarditis (IE) in Asians are poorly understood. Therefore, we aim to describe the epidemiological trends and clinical features of IE in Hong Kong.

Methods All patients with incident IE from 2002–2019 in a territory-wide clinical database in Hong Kong were identified. We studied the age- and sex-adjusted and one-year mortality of IE between 2002 and 2019 and identified significant contributors to 1-year all-cause death using the attributable fraction. We used propensity score and inverse propensity of treatment weighting to study the association of surgery with mortality.

Findings A total of 5139 patients (60.4 ± 18.2years, 37% women) were included. The overall incidence of IE was 4.9 per 100,000 person-year, which did not change over time ($P = 0.17$). Patients in 2019 were older and more comorbid than those in 2002. The one-year crude mortality rate was 30% in 2002, which did not change significantly over time ($P = 0.10$). Between 2002 and 2019, the rate of surgery increased and was associated with a 51% risk reduction in 1-year all-cause mortality (Hazard Ratio 0.49 [0.28–0.87], $P = 0.015$). Advanced age (attributable fraction 19%) and comorbidities (attributable fraction 15%) were significant contributors to death.

Interpretation The incidence of IE in Hong Kong did not change between 2002 and 2019. Patients with IE in 2019 were older and had more comorbidities than those in 2002. Mortality of IE remains persistently high in Hong Kong. Together, these data can guide public health strategies to improve the outcomes of patients with IE.

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Keywords: Infective endocarditis; Geographical variation; Epidemiology; Surgical intervention; Aging; Comorbidities

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Research in context

Evidence before this study

Infective endocarditis (IE) is associated with high mortality, posing an unresolved burden to our healthcare system. The epidemiological and clinical characteristics of IE are known to exhibit substantial geographical variability. We searched the Cochrane Library and PubMed for publications describing the epidemiology of IE published between Jan 1, 1990, and December 31, 2020, using the search terms "epidemiology", "incidence", "outcomes", and "infective endocarditis". No prior reports have comprehensively evaluated the characteristics of patients with IE in the Asian continent from both an epidemiological and clinical perspective. Furthermore, the effect of restriction of antibiotic prophylaxis on the incidence of IE, which has only been analysed previously only in Western cohorts, remains undefined in Asian populations.

Added value of this study

Our study provides important and novel evidence on the epidemiology and clinical characteristics of IE in a large, contemporary Chinese cohort based in Hong Kong. The overall incidence remained static over the past two decades and did not change following the restriction of antibiotic prophylaxis. While aging and the accompanying rise in comorbidities have been the major contributors to the dismal prognosis of IE, the burden has been further aggravated by the alarming rise in Methicillin-resistant *Staphylococcus aureus* (MRSA) endocarditis. The mortality and complication rate of IE remained irresistibly high, despite substantial survival benefits associated with surgical intervention and rising surgery rates over time.

Our study also provides insights into the geographical variation in the aetiology and microbiology of IE. While the proportion of prosthetic-valve endocarditis in Hong Kong appeared to be lower than that in the European and North American continent, the burden of drug abuse-related endocarditis and the associated *Staphylococcal* IE was greater in North America than in Hong Kong/European region.

Implications of all the available evidence

Patients with IE have evolved to be increasingly older with more comorbidities, which contributed to the persistently high mortality, highlighting the alarming public health burden of IE across the globe. The present study confirmed the applicability and generalizability of Western guidelines on antibiotic prophylaxis to a Chinese population where chronic rheumatic heart disease, a significant risk factor for IE, remains prevalent. The importance of surgical intervention was further reinforced, stressing the importance of following evidence-based recommendations and removing barriers to surgery. The unique characteristics of IE in an Asian population were revealed and evaluated comprehensively, providing important insights into the geographical disparities in epidemiological and clinical profiles of patients with IE, which may inform healthcare service planning and primary/secondary preventive intervention strategies.

Introduction

Infective endocarditis (IE) is prevalent and associated with high mortality, posing an unresolved burden to our healthcare system.[1,2] The epidemiological and clinical characteristics of IE are known to exhibit substantial geographical variability.[2–7] However, most studies were carried in North America and Europe.[1,4–6] Previous studies performed in Asia were either from a single centre or did not comprehensively assess changes in incidence, demographics, and outcomes.[8–12] The temporal changes in incidence, patient characteristics, and related mortality of IE, remain unknown in the Asian population.

Understanding the factors contributing to the dismal outcomes of IE is imperative to optimize public health intervention strategies, allocate healthcare resources and ultimately improve patient outcomes. Given the significant knowledge gaps in the epidemiology and characteristics of IE in an Asian population, the objectives of this study were to: (1) describe the patterns and temporal trends in incidence, comorbidities, microbiology, and outcomes spanning over 2 decades, and (2) identify the key contributors to death in IE patients in a large Chinese population.

Methods

Data source

This study used data from the Clinical Data Analysis Reporting System (CDARS), a territory-wide database developed by the Hong Kong Hospital Authority since January 1, 1993. The Hospital Authority is the sole public healthcare provider in Hong Kong, covering >80% of secondary and tertiary care in Hong Kong with a population of around 7.5 million.[13,14] Patients' clinical information, including demographics, diagnoses, blood tests, and surgical treatments, were prospectively recorded in CDARS. Previous high-quality population-based studies have validated the coding accuracy of CDARS.[13–15] The institutional review board of The University of Hong Kong and the West Cluster of Hong Kong Hospital Authority has approved this study (UW 20-819).

Participants

We included all patients aged 20 or above newly diagnosed with IE between January 1, 2002, and December 31, 2019. We adopted a look-back period of 9 years to minimize the risk of recurrent episodes of IE from

being defined as the incident episode. The diagnosis of IE was defined using *International Classification of Diseases 9* (*ICD-9*) codes (Appendix Table 1). In our validation exercise, there was a high diagnostic accuracy with a positive predictive value of 88.8% (95% confidence interval [CI] 84.8 to 92.9), which was comparable to that in previous studies[4,6] (Appendix Text 1).

We extracted demographic information (age, sex), aetiology of IE, comorbidities, predisposing factors for IE, clinical course during hospitalization, blood culture and sensitivity testing information, mode of acquisition, and information on death (death status and date) for each patient with IE. Appendix Table 1 shows the *ICD-9* codes used for defining the comorbidities. We categorized the aetiology of IE as native-valve endocarditis, prosthetic-valve endocarditis, cardiac device-related endocarditis, or drug abuse-related endocarditis (Appendix Figure 1).[6] Appendix Table 1 and Appendix Figure 2 show the *ICD-9* codes and the hierarchical allocation algorithm for the acquisition mode. Acquisition mode categories included community-acquired endocarditis and healthcare-associated IE.[6] We categorized healthcare-associated IE further into non-nosocomial endocarditis and nosocomial endocarditis.[6] Appendix Figure 3 shows the hierarchical allocation algorithm for classifying the groups of causative organisms based on blood culture results directly obtained during hospitalization (not based on *ICD-9* codes).

The primary outcome was 1-year all-cause mortality. Other outcomes of interest include 30-day all-cause mortality. Patient follow-up was censored at the date of death, or end of the study (December 31, 2020). Mortality rate was estimated by dividing the total number of deaths at follow-up by the total number of patients and was reported in %.

Statistical analysis

The crude incidence of IE was calculated by dividing the number of patients with incident IE in each year by the total population of Hong Kong.[16] To account for changes in age and sex in the population, direct standardization was applied with the population in 2002 as the reference. To evaluate the temporal trends in the incidence of IE, Poisson regression analysis adjusted for age and sex was performed. To allow for over-dispersion, a scaling factor (quasi-Poisson) was used.[4] Subgroup analyses of the incidence according to age group and sex were performed. Trends in incidence were assessed by annual percentage change (APC). An interrupted time-series analysis was used to evaluate the change in the incidence of IE after implementing new antibiotic prophylaxis guidelines in 2007.[4,6,17] A sensitivity analysis using 2008[18] and 2009[19] as the year of guideline revision was performed. The incidence was reported per 100,000 person-year.

Baseline characteristics (demographics, comorbidities including the modified Charlson Comorbidity Index [CCI],[20] aetiology of IE, predisposing factors, causative organism, mode of acquisition) were summarized by 6 calendar year groups. For descriptive analysis, continuous variables were reported as means ± standard deviations (mean ± SD), while categorical variables were reported as proportions out of the total number of IE cases. Trends in baseline patient characteristics were evaluated using Log-Linear Poisson regression and the APC was reported; linear regression was used to evaluate the trends in patient age and CCI.[6]

A propensity score approach was employed to evaluate the mortality rate between patients with and without surgical intervention. Variables that were considered prognostically significant or those that influenced treatment selection, including age, sex, hospital/centre cluster, comorbidities, aetiology, microbiology, and mode of acquisition, were included as covariates and logistically regressed to the probability of receiving surgery using covariate balancing propensity score.[21,22] An inverse propensity of treatment weighting (IPTW) was used, which allowed a pseudo-population to be created through assigning individuals with weights that corresponded to the inverse of their probability of receiving treatment given observed covariates. The differences in the prevalence of covariates were considered insignificant if the standardized mean difference (SMD) was ≤0.10. A Cox proportional-hazards model was used to evaluate the relative risk of 1-year all-cause death in patients who received surgical intervention compared to those who did not. The "doubly-robust estimation", where covariates used in calculating the propensity score were further adjusted for in the Cox model, was performed to minimise confounding.[21] To account for potential immortal time bias, the time from diagnosis of IE to performing surgery was considered and was incorporated as a time-dependent covariate in an extended Cox model.[23] To ensure non-violation of the proportionality and linearity of covariates assumption, we inspected the Schoenfeld residuals and Martingale residuals, respectively. To quantify the effect size, we reported the omega squared (ω^2) for surgical intervention.

To evaluate the trends in outcomes, multivariable Cox regression was performed, adjusted for age, sex, baseline comorbidities, aetiology of IE, mode of acquisition, causative organism, and surgical intervention. Using a hazard risk approach, an attributable fraction analysis was performed to evaluate the contribution of age, CCI, comorbidities, causative organism, aetiology, mode of acquisition, and surgical intervention to 1-year all-cause death. The details through which the attributable fractions and the corresponding 95% CI were calculated are shown in Appendix Text 2.

All statistical tests for temporal trends were performed using individual years as a continuous variable,

instead of calendar year groups. All tests were 2-tailed, and statistical significance was defined as $P < 0.05$. Statistical analyses were performed using R (v4.0.4) with the "*survival*", "*CBPS*", and "*AF*" packages.

Role of funding source

The funding source of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all data.

Results

Study population and Incidence

A total of 5139 patients (age 60.4 ± 18.2 years; 1918 [37.3%] women) had incident IE from 2002 to 2019 (Table 1).

The overall incidence of infective endocarditis was 4.9 (95% CI 4.8 to 5.1) cases per 100,000 person-year. The incidence of IE was reported in 5.1 (95% CI 4.8 to 5.4) cases per 100,000 person-year between 2002 and 2005. The most recent incidence of IE was recorded as 5.4 (95% CI 5.1 to 5.7) cases per 100,000 person-year between 2016 and 2019. After adjustment for age and sex, the incidence did not significantly change over time (APC 2.0%, 95% CI −0.7 to 4.8, $P = 0.17$). Appendix Figure 4 and Appendix Table 2 show the trends in age- and sex-standardized incidence in the overall population by age group and sex. The incidence in men (6.7 per 100,000 person-year) was nearly twice that in women (3.4 per 100,000 person-year). Interrupted time series analysis did not demonstrate a significant change in the incidence of IE (relative risk of change 0.86, 95% CI 0.70 to 1.06, $P = 0.18$) (Figure 1) following the revision of guidelines on antibiotic prophylaxis in 2007. Sensitivity analysis using 2008 and 2009 as the year of implementation of guidelines showed consistent results (Appendix Table 3).

Aetiology

Most patients with IE in Hong Kong had native-valve endocarditis (92.3%) and the proportion remained stable over time (APC 0.0%, 95% CI −0.2 to 0.1, $P = 0.86$). The proportion of drug abuse-related endocarditis decreased (APC −6.7%, 95% CI −11.6 to −1.7, $P = 0.011$). For prosthetic-valve endocarditis, although the increase from 2002–2019 was non-significant (APC 1.2%, 95% −0.8 to 3.3, $P = 0.23$), there was a surge from 2014–2019 (APC 11.3%, 95% CI 0.7 to 23.2, $P = 0.037$).

Microbiology

Staphylococcus aureus (1,205, 23.4%) and *Streptococci* (1125, 21.5%) were the most common organisms (Table 1). The proportion of culture-negative (APC 0.1%, 95% CI −0.6 to 0.8, $P = 0.74$), *Staphylococcal* (APC 0.2%, 95% CI −0.7 to 1.2, $P = 0.63$), and *Streptococcal* (APC 0.5%, 95% CI −0.5 to 1.4, $P = 0.36$) endocarditis did not change over time (Table 1). Notably, there was significantly increasing trend in Methicillin-resistant *Staphylococcus aureus* (MRSA), with an APC of 4.2% (95% CI 1.9 to 6.6, $P = 0.00043$).

Age and comorbidity profile

The mean age of patients with IE increased significantly (APC 1.0%, 95% CI 0.8 to 1.1, $P < 0.0001$). The CCI increased (APC 3.1%, 95% CI 2.1 to 4·1, $P < 0.0001$), and the prevalence of individual comorbidities increased significantly from 2002 to 2019 (Table 1). Chronic rheumatic heart disease prevalence decreased significantly over time (APC −3.3%, 95% CI −4.7 to −1.8, $P < 0.0001$).

Surgical intervention

Overall, 901 patients (17.5%) underwent surgery. The rate of surgical intervention significantly increased (APC 1.4%, 95% CI 0.3 to 2.6, $P = 0.016$). Those who received surgery were younger and less comorbid than those who did not. For both the surgical and non-surgical cohorts, baseline covariates were well-balanced upon IPTW (Appendix Table 4). There were 131 and 1,511 deaths among patients who received ($N = 901$) and did not receive ($N = 4,238$), and the crude 1-year mortality rates were 14.5% and 35.7%, respectively. Surgical intervention was associated with a 51% adjusted-risk reduction in 1-year all-cause mortality (Hazard ratio [HR] 0.49, 95% CI 0.28 to 0.87, $P = 0.015$) (Figure 2). The ω^2 was 0.029 for surgical intervention. The proportionality and linearity of covariates assumptions of the Cox model were not violated. There was a null association between surgery and negative control outcome (spondylitis) (HR 0.65, 95% CI 0.31 to 1.37, $P = 0.25$).

Outcomes

The crude all-cause mortality rate at 1 year increased from 30% in 2002–2007 to 32% in 2014–2019 (APC 0.7%, 95% CI −0.1 to 1.4, $P = 0.087$). After adjustment for confounding factors (age, sex, comorbidities, aetiology, mode of acquisition, and causative organism), there was a trend of reduction in mortality rate (APC −1.1%, 95% CI −2.0 to −0.1, $P = 0.029$). Interestingly, after further adjustment for surgical intervention, there was no significant trend (APC −0.8%, 95% CI −1.7 to 0.2, $P = 0.10$).

Attributable fraction analysis

Table 2 shows the proportion of 1-year all-cause deaths attributable to demographics, comorbidities, aetiology,

Characteristics	Overall	2002–2007	2008–2013	2014–2019	APC (95% CI)	*P*-value*
N	5139	1603	1628	1908		
Incidence, cases per 100,000 person-year						
Overall	4.9 (4.8 to 5.1)	5.0 (4.7 to 5.2)	4.7 (4.5 to 4.9)	5.1 (4.9 to 5.4)	2.0 (−0.7 to 4.8)	0.17
Male	6.7 (6.5 to 7.0)	6.6 (6.2 to 7.0)	6.4 (6.0 to 6.8)	7.1 (6.7 to 7.5)	1.9 (−0.2 to 4.0)	0.095
Female	3.4 (3.2 to 3.6)	3.4 (3.2 to 3.7)	3.2 (3.0 to 3.5)	3.5 (3.3 to 3.8)	−4.4 (−9.1 to 0.3)	0.089
Demographic						
Age, mean ± SD, years	60.4 ± 18.2	56.8 ± 18.3	60.2 ± 18.0	63.8 ± 17.6	1.0 (0.8 to 1.1)	< 0.0001†
20–39, n (%)	845 (16.4)	344 (21.5)	271 (16.6)	230 (12.1)	−4.6 (−5.7 to −3.5)	< 0.0001
40–59, n (%)	1634 (31.8)	574 (35.8)	541 (33.2)	519 (27.2)	−2.3 (−3.1 to −1.6)	< 0.0001
60–79, n (%)	1800 (35.0)	511 (31.9)	549 (33.7)	740 (38.8)	1.9 (1.2 to 2.7)	< 0.0001
≥80, n (%)	860 (16.7)	174 (10.9)	267 (16.4)	419 (22.0)	5.4 (4.2 to 6.7)	< 0.0001
Female, n (%)	1918 (37.3)	588 (36.7)	610 (37.5)	720 (37.7)	0.0 (−0.2 to 0.2)	0.96
Aetiology of IE, n (%)						
Native-valve endocarditis	4744 (92.3)	1474 (92)	1510 (92.8)	1760 (92.2)	0.0 (−0.2 to 0.1)	0.86
Prosthetic-valve endocarditis	324 (6.3)	103 (6.4)	92 (5.7)	129 (6.8)	1.2 (−0.8 to 3.3)	0.23
Cardiac device-related endocarditis	20 (0.4)	6 (0.4)	6 (0.4)	8 (0.4)	0.9 (−7.1 to 9.8)	0.83
Drug abuse-related endocarditis	51 (1.0)	20 (1.2)	20 (1.2)	11 (0.6)	−6.7 (−11.6 to −1.7)	0.011
Comorbidities, n (%)						
Charlson Comorbidity Index, mean ± SD	0.84 ± 1.57	0.67 ± 1.31	0.88 ± 1.70	0.96 ± 1.64	3.1 (2.1 to 4.1)	< 0.001†
Hypertension	962 (18.7)	215 (13.4)	314 (19.3)	433 (22.7)	4.1 (3.0 to 5.3)	< 0.0001
Heart failure	846 (16.5)	241 (15.0)	256 (15.7)	349 (18.3)	1.8 (0.6 to 3.0)	0.0025
Myocardial infarction	190 (3.7)	33 (2.1)	45 (2.8)	103 (5.4)	8.8 (5.8 to 12.0)	< 0.0001
Peripheral vascular disease	234 (4.6)	49 (3.1)	93 (5.7)	92 (4.8)	2.8 (0.3 to 5.3)	0.026
Cerebrovascular disease	541 (10.5)	144 (9.0)	164 (10.1)	233 (12.2)	2.3 (0.8 to 3.9)	0.0031
Cardiac dysrhythmia	948 (18.4)	239 (14.9)	292 (17.9)	417 (21.9)	3.3 (2.2 to 4.5)	< 0.0001
Diabetes	595 (11.6)	140 (8.7)	200 (12.3)	255 (13.4)	3.5 (2.0 to 5.0)	< 0.0001
Chronic pulmonary disease	309 (6.0)	81 (5.1)	108 (6.6)	120 (6.3)	1.8 (−0.3 to 3.9)	0.095
Impaired renal function	427 (8.3)	96 (6.0)	140 (8.6)	191 (10.0)	4.2 (2.4 to 6.0)	< 0.0001
Chronic rheumatic heart disease	576 (11.2)	221 (13.8)	183 (11.2)	172 (9.0)	−3.3 (−4.7 to −1.8)	< 0.0001
Malignancy	303 (5.9)	69 (4.3)	92 (5.7)	142 (7.4)	5.4 (3.2 to 7.7)	< 0.0001
HIV infection	6 (0.1)	0 (0)	2 (0.1)	4 (0.2)	22.0 (3.5 to 52.6)	0.038
Predisposing factor, n (%)						
Congenital heart disease	127 (2.5)	41 (2.6)	46 (2.8)	40 (2.1)	−0.9 (−4.1 to 2.4)	0.58
Congenital heart disease repaired with prosthetic material	11 (0.2)	4 (0.2)	4 (0.2)	3 (0.2)	−2.2 (−12.8 to 9.5)	0.69
Prosthetic valve replacement or valve repair with prosthetic material	254 (4.9)	91 (5.7)	66 (4.1)	97 (5.1)	0.1 (−2.1 to 2.4)	0.93
Acquired valve disease	706 (13.7)	220 (13.7)	221 (13.6)	265 (13.9)	0.4 (−0.9 to 1.7)	0.58
Hypertrophic cardiomyopathy	22 (0.4)	5 (0.3)	8 (0.5)	9 (0.5)	3.4 (−4.5 to 12.3)	0.42
Causative organism, n (%)						
Culture-negative	1818 (35.4)	559 (34.9)	573 (35.2)	686 (36.0)	0.1 (−0.6 to 0.8)	0.74
Staphylococcus aureus	1205 (23.4)	367 (22.9)	393 (24.1)	445 (23.3)	0.2 (−0.7 to 1.2)	0.63
MRSA	233 (4.5)	55 (3.4)	72 (4.4)	106 (5.6)	4.2 (1.9 to 6.6)	0.00043
MSSA	972 (18.9)	312 (19.5)	321 (19.7)	339 (17.8)	−1.0 (−1.5 to −0.4)	0.00040
Other *staphylococci*	173 (3.4)	64 (4.0)	51 (3.1)	48 (2.5)	−1.7 (−4.4 to 1.1)	0.23
Streptococci	1125 (21.9)	346 (21.6)	347 (21.3)	432 (22.6)	0.5 (−0.5 to 1.4)	0.36
Enterococci	155 (3.0)	46 (2.9)	48 (2.9)	61 (3.2)	1.0 (−2.0 to 4.0)	0.53
Other microorganisms	335 (6.5)	113 (7.0)	102 (6.3)	120 (6.3)	−1.0 (−2.9 to 0.9)	0.31
Mixed microorganisms	328 (6.4)	108 (6.7)	114 (7.0)	106 (5.6)	−1.5 (−3.5 to 0.4)	0.12
Mode of acquisition, n (%)						
Community-acquired endocarditis	4420 (86.0)	1371 (85.5)	1400 (86.0)	1649 (86.4)	0.0 (−0.2 to 0.2)	0.98
Healthcare-associated	719 (14.0)	232 (14.5)	228 (14.0)	259 (13.6)	−0.0 (−1.3 to 1.3)	0.98
Non-nosocomial endocarditis	378 (7.4)	120 (7.5)	117 (7.2)	141 (7.4)	0.4 (−0.9 to 1.7)	0.55
Nosocomial endocarditis	341 (6.6)	112 (7.0)	111 (6.8)	118 (6.2)	−0.4 (−1.9 to 1.0)	0.55

***Table 1*: Patient characteristics from 2002 through 2019, overall and trends by years.**

Abbreviations in Table 1: APC, annual percentage change; CI, confidence intervals; SD, standard deviation; IE, infective endocarditis; HIV, human immunodeficiency virus; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-sensitive *Staphylococcus aureus*.

* *P*-values were calculated with 2-tailed log-linear Poisson regression, unless otherwise specified.

† *P*-value was calculated with linear regression.

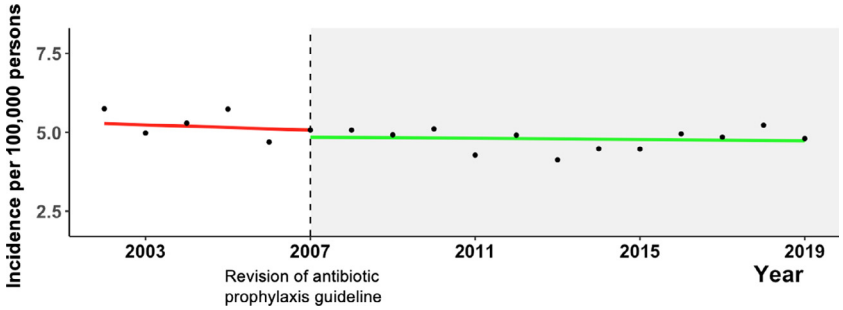


Figure 1. Overall incidence per 100,000 persons by year of hospitalization (black dots), in relation to the introduction of antibiotic prophylaxis guidelines.

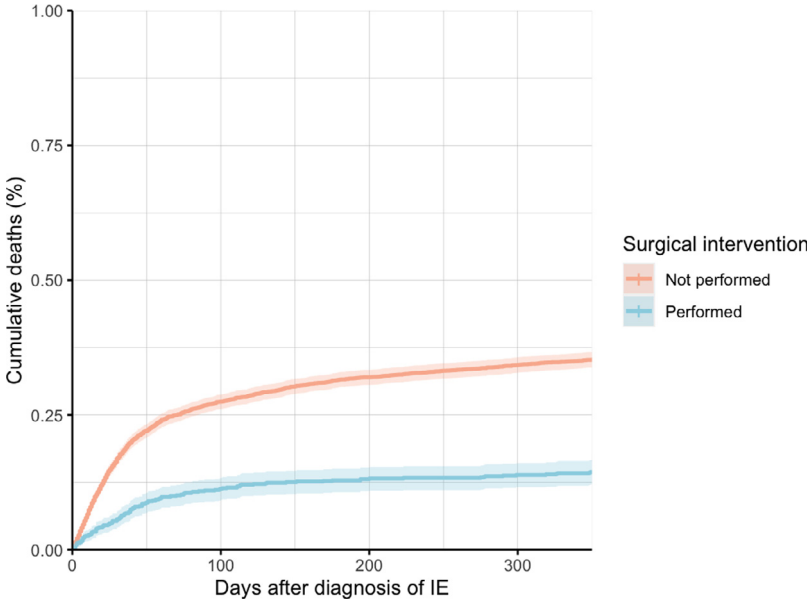


Figure 2. Survival curves for 1-year mortality in patients who received vs did not receive surgical intervention. The shaded areas represent the 95% Confidence Intervals.

mode of acquisition, the microbiology of IE, and surgical intervention. Age ≥ 60 years (19.2%, 95% CI 14.5 to 23.9) and CCI ≥ 1 (14.6%, 95% CI 11.6 to 18.5) had the highest attributable fractions of all risk factors considered. Other major contributors to 1-year death included impaired renal function (attributable fraction 1.8%, 95% CI 0.5 to 3.2, $P = 0.0089$) and MRSA endocarditis (attributable fraction 3.4%, 95% CI 2.5 to 4.3, $P < 0.0001$). The attributable fraction of surgery was −7.9% (95% CI −9.5 to −6.4, $P < 0.0001$).

Discussion

Our study has three significant findings. First, the incidence of IE in Hong Kong remained stable in the past two decades and was not influenced by the revision of antibiotic prophylaxis guidelines. Second, patients with IE in Hong Kong are increasingly older, with more comorbidities and an increasing burden of MRSA endocarditis, which were important determinants of IE-related mortality. Third, surgical intervention was associated with reduced 1-year all-cause mortality. Our data highlight that, despite an increasing surgical rate and the associated lower risk of death, the prognosis of IE remains poor in Hong Kong.

IE remains a significant challenge to global cardiovascular health.[2] In Hong Kong, the incidence of IE remained stable in the past two decades, which is in line with studies from other regions and previous Asian studies carried out in China.[4,6,10,24,25] For example, a previous North American study reported a stable trend incidence of 7.8 per 100,000 person-year in 2013.[6] A recent Scottish study also identified a static incidence with a rate of 8.1 per 100,000 person-year in 2014.[4] We confirmed that the incidence of IE did not change following the restriction of antibiotic prophylaxis,

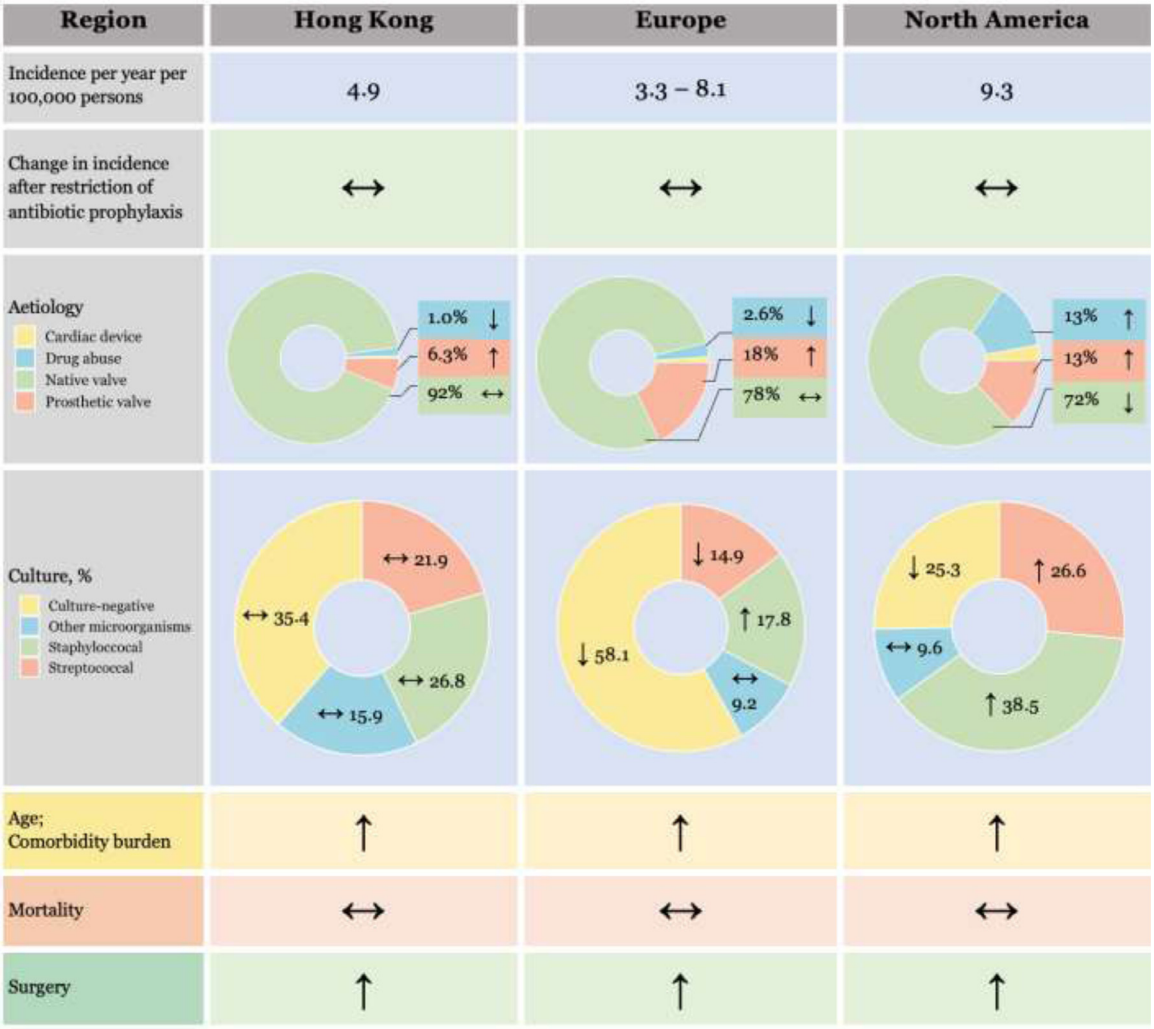
Variable	Prevalence, %	HR (95% CI), *P*-value	Attributable fraction, % (95% CI), *P*-value
Demographics			
Age (≥ 60 years)	51.8%	1.57 (1.40 to 1.75), < 0.0001	19.2 (14.5 to 23.9), < 0.0001
Sex (Female)	37.3%	0.91 (0.82 to 1.01), 0.072	−2.8 (−5.7 to 0.2), 0.064
Comorbidities			
CCI (≥ 1)	32.6%	1.64 (1.43 to 1.88), < 0.0001	14.6 (10.6 to 18.5), < 0.0001
Hypertension	18.7%	1.10 (0.97 to 1.25), 0.14	1.7 (−0.5 to 4.0), 0.13
Diabetes	11.6%	1.00 (0.87 to 1.16), 0.94	0.0 (−1.5 to 1.6), 0.95
Myocardial infarction	3.7%	0.91 (0.73 to 1.13), 0.40	−0.3 (−1.1 to 0.4), 0.37
Peripheral vascular disease	4.6%	1.09 (0.89 to 1.34), 0.41	0.4 (−0.4 to 1.2), 0.40
Cerebrovascular disease	10.5%	1.02 (0.88 to 1.17), 0.82	0.2 (−1.2 to 1.5), 0.82
Chronic pulmonary disease	6.0%	1.00 (0.84 to 1.20), 0.96	0.0 (−1.0 to 1.1), 0.96
Malignancy	5.9%	1.15 (0.96 to 1.37), 0.14	0.8 (−0.2 to 1.9), 0.12
Congenital heart disease	2.5%	0.46 (0.30 to 0.72), 0.00068	−1.1 (−1.7 to −0.6), < 0.0001
Impaired renal function	8.3%	1.24 (1.05 to 1.47), 0.012	1.8 (0.5 to 3.2), 0.0089
Rheumatic heart disease	11.2%	1.00 (0.85 to 1.19), 0.97	0.0 (−1.4 to 1.5), 0.97
Characteristics of IE			
Aetiology of IE (non-native)	7.7%	0.97 (0.79 to 1.19), 0.75	−0.2 (−1.4 to 1.0), 0.72
Mode of acquisition (Healthcare-associated)	14.0%	1.15 (1.02 to 1.31), 0.028	1.8 (0.2 to 3.4), 0.025
Microbiology			
Culture-negative	35.4%	1.05 (0.95 to 1.17), 0.35	1.5 (−1.6 to 4.7), 0.34
MRSA	4.5%	2.08 (1.74 to 2.47), < 0.0001	3.4 (2.5 to 4.3), < 0.0001
Surgical intervention			
Surgery (performed)	17.5%	0.45 (0.38 to 0.54), < 0.0001	−7.9 (−9.5 to −6.4), < 0.0001

***Table 2*: Results from attributable fraction analysis.**
Abbreviations used in Table 2: HR, Hazard Ratio; 95% CI, 95% Confidence Interval; CCI, Charlson Comorbidity Index; IE, infective endocarditis; MRSA, Methicillin-resistant Staphylococcus aureus.

extending the applicability and generalizability of Western guidelines[17–19] to a Chinese population where chronic rheumatic heart disease, a significant risk factor for IE, remains prevalent. In contrast, previous British and Spanish studies identified an increase in IE incidence.[5,26] However, these studies analysed the crude incidence rates, which are more susceptible to changes in population size and composition, and they did not exclude recurrent cases of IE, leading to possible overestimation. Importantly, these studies did not formally test the temporal change using interrupted time series analysis.[4,6,27] Therefore, these previous results might not necessarily reflect the actual difference in incidence. Notably, we found an alarming increase in prosthetic-valve endocarditis, which is expected to further increase with expanding indications for valvular replacements and transcatheter valvular interventions.[28] Together, these data highlight that IE remains a persistent global burden, which may increase in future years.

Several characteristics of IE are unique to our Hong Kong population (Central illustration 1). Consistent with previous Asian observational studies conducted in Japan and China,[10,12] majority of our cohort had native-valve endocarditis (92%), possibly due to a higher prevalence of chronic rheumatic heart disease.[7] In the United States, native-valve endocarditis was only present in ~70% of cases.[6] Only 6% of our Asian cohort had prosthetic-valve endocarditis, which is lower compared to Europe (12%) and North America (20%).[5,6] Compared with 13% in the United States[6] and 3% in Spain,[5] only 1% of IE cases in Hong Kong were related to drug abuse, similar to that reported in previous Asian studies.[10] The incidence of drug abuse-related endocarditis, associated with *Staphylococcal* IE, increased in North America, but not in Asia/Europe, which might be explained by the ongoing "opioid crisis" in the United States.[29] Nevertheless, the definition for IE cases differed between the current and previous studies. Future global collaborative research with a unified definition for IE is needed to better evaluate the possible geographical differences, in order to inform healthcare service planning and primary/secondary preventive intervention strategies.

IE's 1-year case mortality rate did not improve in our study, confirming previous results from other regions.[5,6] Therefore, it is essential to understand factors contributing to worse outcomes. We found that age, CCI, impaired renal function, healthcare-associated IE, and MRSA were the most significant factors contributing to increased mortality. The combination of an ageing population with more comorbidities and an increasing incidence of MRSA infections poses a



Central illustration 1. Geographical differences in characteristics of infective endocarditis.

Legends for Central Illustration:

- An increasing trend (in the proportion of endocarditis due to a specific aetiology/causative organism, age and comorbidity burden, and rate of surgery) is denoted by "↑"
- A decreasing trend (in the proportion of endocarditis due to a specific aetiology/causative organism) is denoted by "↓"
- A static trend (in the incidence of infective endocarditis after the restriction of antibiotic guidelines, in the proportion of endocarditis due to a specific aetiology/causative organism, and mortality rate) was denoted by "↔"

Data from Europe were obtained from:

- Shah ASV, McAllister DA, Gallacher P, Astengo F, Rodríguez Pérez JA, Hall J, et al. Incidence, Microbiology, and Outcomes in Patients Hospitalized With Infective Endocarditis. Circulation. 2020;141(25):2067–77. (for Incidence, Change in incidence after restriction of antibiotic prophylaxis, Culture, and Mortality)
- Olmos C, Vilacosta I, Fernández-Pérez C, Bernal JL, Ferrera C, García-Arribas D, et al. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). J Am Coll Cardiol. 2017;70(22):2795–804. (for Incidence, Aetiology, Age, Comorbidity burden, and Surgery)

Data from North America were obtained from:

- Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in Infective Endocarditis in California and New York State, 1998–2013. JAMA. 2017;317(16):1652–60.

substantial challenge to future treatment of IE and complicates management.[30] In addition, hospital-acquired endocarditis significantly impaired survival. Ageing populations forebode a rising number of hospitalizations in Hong Kong and other regions. Therefore, strategies to reduce the risk of endocarditis secondary to healthcare procedures are urgently needed to alleviate the burden of IE. Increasing hospitalizations and comorbidities might also contribute to the widespread use of broad-spectrum antibiotics, hastening the emergence of bacterial resistance.[2] By using real-time patient-level culture and sensitivity testing information retrieved directly from microbiology laboratories, our study quantified the jeopardizing rise of MRSA. The mandated use of vancomycin might give rise to adverse effects clinically and accelerate the emergence of Vancomycin-resistant *Staphylococcus aureus*.[31] Accordingly, surveillance by a concerted international effort with accurate information on culture and antimicrobial resistance is imperative to ascertain the burden of risk factors and evaluate the effectiveness of interventions.

Our results reinforced the importance of surgical intervention, as part of the treatment for IE. Although the association between surgery and lower risk of death requires further corroborations, our findings suggested that surgical intervention might have neutralized the adverse effects conferred by advanced age and comorbidities, thus contributing to the static trend in mortality. Using real-world patient data, our study further supports the guideline recommendations to perform valvular surgery when indicated.[32,33] Nevertheless, mortality in the total population remained high. Patient/surgeon's refusal, high-risk factors such as those with complications, and resources unavailability might be the reasons for not performing surgery in those who are indicated.[34] These results stress the importance of following evidence-based recommendations and removing barriers to surgery.

Strengths and limitations

The current study results are best valued in light of the sampling strategy and the comprehensiveness of information. First, we retrieved complete blood culture information and sensitivity testing results for all patients included in the present study, ensuring the accuracy of the information on causative organisms and avoiding potential reporting bias due to reliance on *ICD* codes to obtain microbiology information. Second, CDARS is a well-validated real-world territory-wide database with accurate information on diagnoses and outcomes, and high-quality studies utilizing CDARS have been published previously.[13–15] As such, our study is likely to be accurate and with minimal selection bias and high generalizability. Third, our study used a minimum look-back period of 9 years to ensure that only the first diagnosis of IE cases were included, ensuring the accuracy in evaluating the epidemiology, comorbidity profile, and outcomes.[6] Fourth, the temporal trends in comorbidity profiles in IE patients have not been comprehensively reviewed previously. The present study evaluated such trends, incorporating CCI as well as a broad range of comorbidities. Fifth, to the authors' knowledge, in this largest Asia-based study to date, we captured high-quality clinical, epidemiological, and microbiological data, which enabled us to generate timely insights into the geographical differences of endocarditis. Notably, the intrinsic limitations (such as selection bias and lack of information on incidence/patient characteristics) present in previous Asian studies[8–12] were absent in the current study. Sixth, we have validated the accuracy of ICD-9 codes used in the present study with a comparable positive predictive value with previous studies.[4,6]

Nevertheless, there are several limitations to our study. Similar to previous studies,[4,6] we were unable to retrieve information on any dental procedure/antibiotic prophylaxis and whether endocarditis was present at the time of hospital admission. Patient presentation/symptoms and echocardiographic data were not available in CDARS, which is a recognized limitation in many of these population-based databases.[4–6] As a result, patients might have had an undiagnosed endocarditis in the previous admission which potentially may wrongly classify as health care-associated endocarditis. Indications for surgery, including vegetation size and regurgitant severity, were not available in CDARS (as echocardiographic data were not available). We therefore could not evaluate the exact surgical indications in association with death. The association between surgery and outcomes might also be prone to residual confounding. Although CDARS (run by public hospitals) might not be able to capture IE patients presenting to private hospitals and the incidence might be under-estimated, in this locality, most IE cases at the private hospitals were referred and managed in the public hospitals and could be included in CDARS. Further, all diagnostic codings in CDARS were based on *ICD-9* codes instead of *ICD-10* codes; nevertheless, our validation exercise and previous studies showed high coding accuracy.[14] The rate of culture-negative endocarditis (35.4%) in our study was similar to prior studies,[4,35] although it was higher compared with others (25.3%).[6] The observed differences could be attributed to geographical variation in microbiological profiles, which merits future evaluation. As our study defined IE cases differently from other studies, caution needs to be taken when comparing the results between studies.

Conclusion

We found that the incidence of IE remained stable between 2002 and 2019 in Hong Kong and was not influenced by the revision of antibiotic prophylaxis guidelines. Over time, patients with IE are increasingly

older and more comorbid. Notably, the burden of MRSA endocarditis increased, together leading to a dismal prognosis. Despite rising surgery rates and associated lower risk of death, the mortality of IE remained high. Taken together, our findings provide important insights into the geographical disparities in epidemiological and clinical profiles of patients with IE, with several important implications for health policymakers, researchers, and clinicians.

Contributors

Concept and design: HLL, JT, KT, CSPL, KHY.

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Critical revision of the manuscript for important intellectual content: All authors.

Obtained funding: KHY.

Supervision: CSPL, KHY.

Final approval of the version to be published: All authors.

Declaration of interests

JT received speaker fees from Boehringer Ingelheim, Daiichi Sankyo and Roche diagnostics, consultancy fees from Us2.ai, is Stockholder of Us2.ai and owns a patent (US-10702247-B2) unrelated to the present work. CSPL is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Abbott, Actelion, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai. All other authors declare no conflict of interest.

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Data sharing statement

The participant data cannot be made available as CDARS is an anonymous database. Study protocol and statistical analysis plan will be made available upon reasonable request to the corresponding author immediately following publication to anyone wishes to access the data.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100417.

References

1 Weir MA, Slater J, Jandoc R, Koivu S, Garg AX, Silverman M. The risk of infective endocarditis among people who inject drugs: a retrospective, population-based time series analysis. *CMAJ*. 2019;191(4):E93–E99.

2 Yang X, Chen H, Zhang D, Shen L, An G, Zhao S. Global magnitude and temporal trend of infective endocarditis, 1990–2019: results from the global burden of disease study. *Eur J Prev Cardiol*. 2021. https://doi.org/10.1093/eurjpc/zwab184.

3 Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. *Arch Intern Med*. 2009;169(5):463–473.

4 Shah ASV, McAllister DA, Gallacher P, et al. Incidence, microbiology, and outcomes in patients hospitalized with infective endocarditis. *Circulation*. 2020;141(25):2067–2077.

5 Olmos C, Vilacosta I, Fernández-Pérez C, et al. The evolving nature of infective endocarditis in spain: a population-based study (2003 to 2014). *J Am Coll Cardiol*. 2017;70(22):2795–2804.

6 Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York State, 1998–2013. *JAMA*. 2017;317(16):1652–1660.

7 Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982–3021.

8 Kim JH, Lee HJ, Ku NS, et al. Infective endocarditis at a tertiary care hospital in South Korea. *Heart*. 2021;107(2):135–141.

9 Angsutararux T, Angkasekwinai N. Cumulative incidence and mortality of infective endocarditis in Siriraj hospital-Thailand: a 10-year retrospective study. *BMC Infect Dis*. 2019;19(1):1062.

10 Wu Z, Chen Y, Xiao T, Niu T, Shi Q, Xiao Y. Epidemiology and risk factors of infective endocarditis in a tertiary hospital in China from 2007 to 2016. *BMC Infect Dis*. 2020;20(1):428.

11 Shih CJ, Chu H, Chao PW, et al. Long-term clinical outcome of major adverse cardiac events in survivors of infective endocarditis: a nationwide population-based study. *Circulation*. 2014;130(19):1684–1691.

12 Kiriyama H, Kaneko H, Itoh H, et al. Surgical treatment for infective endocarditis in the ageing society: a nationwide retrospective study in Japan. *Open Heart*. 2021;8(1). https://doi.org/10.1136/openhrt-2021-001627.

13 Ren QW, Yu SY, Teng TK, et al. Statin associated lower cancer risk and related mortality in patients with heart failure. *Eur Heart J*. 2021;42(32):3049–3059.

14 Lau WC, Chan EW, Cheung CL, et al. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. *JAMA*. 2017;317(11):1151–1158.

15 Lau WCY, Cheung CL, Man KKC, et al. Association between treatment with apixaban, dabigatran, rivaroxaban, or warfarin and risk for osteoporotic fractures among patients with atrial fibrillation: a population-based cohort study. *Ann Intern Med*. 2020;173(1):1–9.

16 Census and Statistics Department, The Government of Hong Kong Special Administrative Region. Retrieved from https://www.censtatd.gov.hk/en/.

17 Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American heart association: a guideline from the American heart association rheumatic fever, endocarditis, and Kawasaki disease committee, council on cardiovascular disease in the young, and the council on clinical cardiology, council on cardiovascular surgery and anesthesia, and the

quality of care and outcomes research interdisciplinary working group. *Circulation*. 2007;116(15):1736–1754.
18 Richey R, Wray D, Stokes T. Prophylaxis against infective endocarditis: summary of NICE guidance. *BMJ*. 2008;336(7647):770–771.
19 Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the task force on the prevention, diagnosis, and treatment of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for infection and cancer. *Eur Heart J*. 2009;30(19):2369–2413.
20 Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682.
21 Simon TG, Duberg AS, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of aspirin with hepatocellular carcinoma and liver-related mortality. *N Engl J Med*. 2020;382(11):1018–1028.
22 Nägele MP, Barthelmes J, Ludovici V, et al. Retinal microvascular dysfunction in heart failure. *Eur Heart J*. 2018;39(1):47–56.
23 Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.
24 Bikdeli B, Wang Y, Kim N, Desai MM, Quagliarello V, Krumholz HM. Trends in hospitalization rates and outcomes of endocarditis among medicare beneficiaries. *J Am Coll Cardiol*. 2013;62(23):2217–2226.
25 Desimone DC, Tleyjeh IM, Correa de Sa DD, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American heart association's endocarditis prevention guidelines. *Circulation*. 2012;126(1):60–64.
26 Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. *Lancet*. 2015;385(9974):1219–1228.
27 Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299–309.
28 Sedrakyan A, Dhruva SS, Sun T, Mao J, Gaudino MFL, Redberg RF. Trends in use of transcatheter aortic valve replacement by age. *JAMA*. 2018;320(6):598–600.
29 Pericàs JM, Llopis J, Athan E, et al. Prospective cohort study of infective endocarditis in people who inject drugs. *J Am Coll Cardiol*. 2021;77(5):544–555.
30 Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. *Lancet*. 2015;385(9967):540–548.
31 Galar A, Weil AA, Dudzinski DM, Muñoz P, Siedner MJ. Methicillin-resistant staphylococcus aureus prosthetic valve endocarditis: pathophysiology, epidemiology, clinical presentation, diagnosis, and management. *Clin Microbiol Rev*. 2019;32(2).
32 Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the american heart association. *Circulation*. 2015;132(15):1435–1486.
33 Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36(44):3075–3128.
34 Chu VH, Park LP, Athan E, et al. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the international collaboration on endocarditis. *Circulation*. 2015;131(2):131–140.
35 Kadri AN, Wilner B, Hernandez AV, et al. Geographic trends, patient characteristics, and outcomes of infective endocarditis associated with drug abuse in the United States from 2002 to 2016. *J Am Heart Assoc*. 2019;8(19):e012969.