ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2023) **9**, 85–96
https://doi.org/10.1093/ehjqcco/qcac012

ORIGINAL ARTICLE

Socioeconomic variations determine the clinical presentation, aetiology, and outcome of infective endocarditis: a prospective cohort study from the ESC-EORP EURO-ENDO (European Infective Endocarditis) registry

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Received 28 January 2022; revised 25 February 2022; accepted 7 March 2022; online publish-ahead-of-print 12 March 2022

Aims Infective endocarditis (IE) is a life-threatening disease associated with high mortality and morbidity worldwide. We sought to determine how socioeconomic factors might influence its epidemiology, clinical presentation, investigation and management, and outcome, in a large international multicentre registry.

Methods and results The EurObservational Programme (EORP) of the European Society of Cardiology EURO-ENDO (European Infective Endocarditis) registry comprises a prospective cohort of 3113 adult patients admitted for IE in 156 hospitals in 40 countries between January 2016 and March 2018. Patients were separated in three groups, according to World Bank economic stratification [group 1: high income (75.6%); group 2: upper-middle income (15.4%); group 3: lower-middle income (9.1%)]. Group 3 patients were younger [median age (interquartile range, IQR): group 1, 66 (53–75) years; group 2, 57 (41–68) years; group 3, 33 (26–43) years; $P < 0.001$] with a higher frequency of smokers, intravenous drug use, and human immunodeficiency virus infection (all $P < 0.001$) and presented later [median (IQR) days since symptom onset: group 1, 12 (3–35); group 2, 19 (6–54); group 3, 31 (12–62); $P < 0.001$] with a higher likelihood of developing congestive heart

[†] A complete list of the EURO-ENDO Investigators and National Coordinators is provided in Appendix 1.

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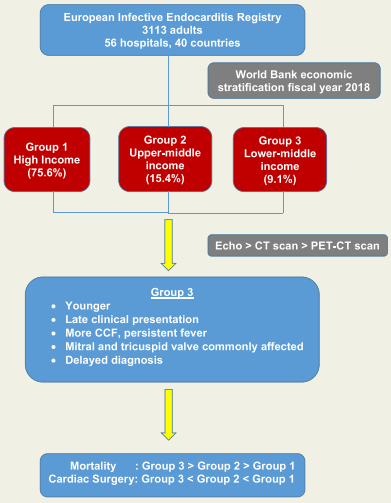
failure (13.6%, 11.1%, and 22.6%, respectively; $P < 0.001$) and persistent fever (9.8%, 14.2%, and 27.9%, respectively; $P < 0.001$). Among 2157 (69.3%) patients with theoretical indication for cardiac surgery, surgery was performed less frequently in group 3 patients (75.5%, 76.8%, and 51.3%, respectively; $P < 0.001$), who also demonstrated the highest mortality (15.0%, 23.0%, and 23.7%, respectively; $P < 0.001$).

Conclusion Socioeconomic factors influence the clinical profile of patients presenting with IE across the world. Despite younger age, patients from the poorest countries presented with more frequent complications and higher mortality associated with delayed diagnosis and lower use of surgery.

Graphical Abstract



Keywords Endocarditis • Socioeconomic

Introduction

Infective endocarditis (IE) remains prominent worldwide, with an estimated global incidence of 1.1 million cases in 2019.[1] Recent decades have witnessed advances in diagnosis, antimicrobial therapy, and access to life-saving surgery, yet IE still accounts for ~66 300 deaths and 1.7 million disability-adjusted life years per annum. Furthermore, the associated clinical challenges are substantial. Affected patients are older with multiple comorbidities,[2] virulent staphylococci are the most common cause in many high-income countries,[3] and healthcare-associated staphylococcal bacteraemia (a precursor to IE)[4] and antibiotic resistance[5] present a global challenge.

The clinical and microbiological characteristics of IE are highly heterogeneous, presenting difficulties for both researchers and clinicians. As a consequence, the evidence base for practice distilled within international guidelines is derived predominantly from specialist centre registries and observational cohort studies rather than randomized trials.[6,7] Delivery of high-level multidisciplinary care is difficult, even in first-world healthcare systems, and frequently impossible in the developing world.

The European Society of Cardiology (ESC) EurObservational Programme (EORP) of the EURO-ENDO (European Infective Endocarditis) (ESC-EORP EURO-ENDO) registry has provided a global overview of the contemporary epidemiology, investigation, management, and clinical outcomes of IE[8] but failed to differentiate interregional and socioeconomic factors (including the implementation of ESC guidelines) that may affect this life-threatening condition and influence overall patient outcomes. In this ancillary study, we therefore sought to determine regional variations in the prevalence, demography, presentation, access to diagnostic procedures and specialist care (including advanced imaging and surgery), and their consequence upon clinical outcomes of patients presenting with IE according to socioeconomic criteria.

Methods

Study design and data collection

The detailed methodology of the ESC-EORP EURO-ENDO registry—a prospective multicentre observational study of patients presenting with definite or possible IE to hospitals around the world—has already been reported.[9] In brief, consecutive patients greater than 18 years of age presenting with IE were enrolled during a 2-year period between 1 January 2016 and 31 March 2018. The main inclusion criteria were a diagnosis of definite IE (or possible IE considered and treated as IE) based on the ESC 2015 IE diagnostic criteria.[6] All patients provided informed consent for data collection that was grouped as follows: demographics, Charlson index,[10] clinical, biological, microbiological, and imaging findings (echocardiography, CT scan, leucocyte scintigraphy, fluorodeoxyglucose F18-positron emission tomography (^{18}F-FDG PET)/CT), antibiotic therapy, complications, theoretical indications for surgery, and in-hospital mortality.[9]

In this study, the resulting data set was analysed on the basis of socioeconomic characteristics. Individual nations were stratified based upon their economic performance during the fiscal year 2018 according to World Bank criteria[11] and then grouped into the following categories:

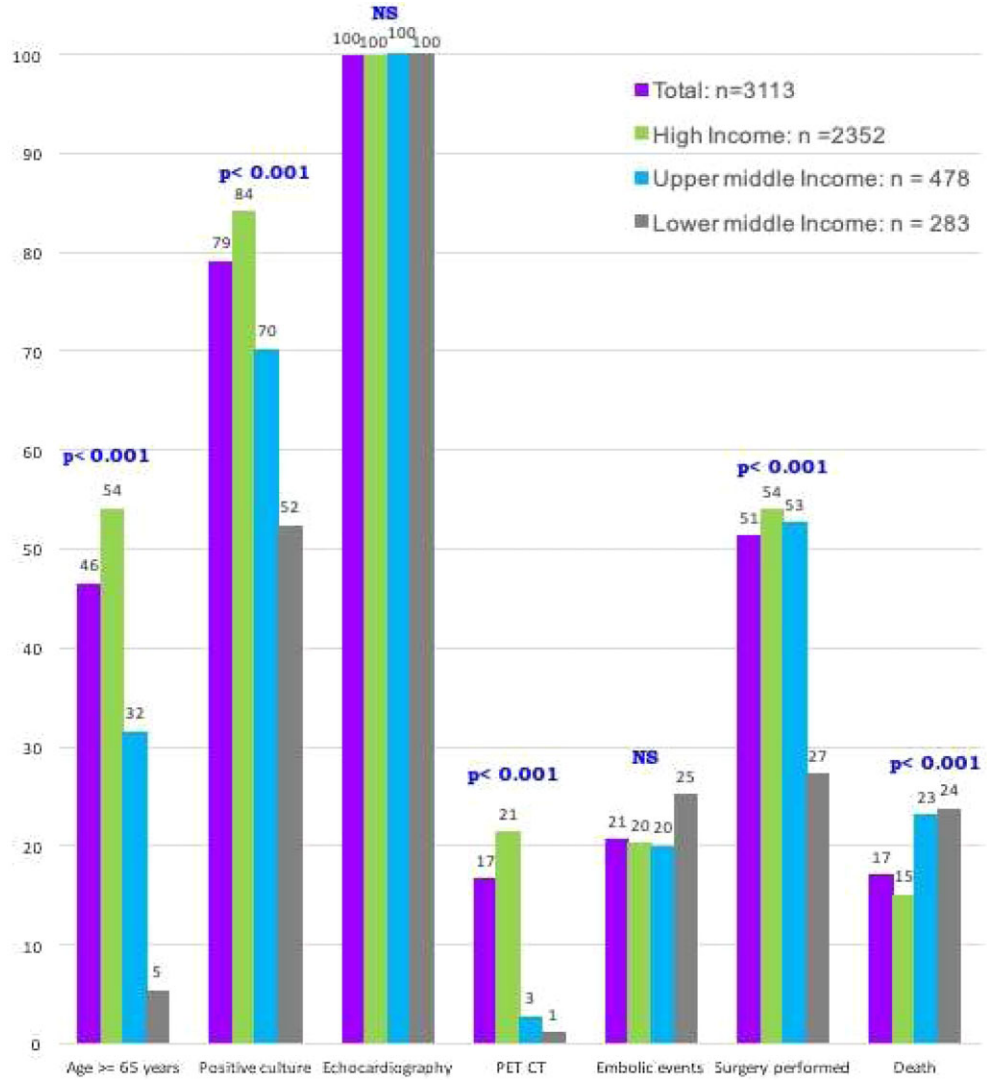


Figure 1 Variations in clinical, imaging, and outcome characteristics according to socioeconomic grouping.

high income (group 1), upper-middle income (group 2), and lower-middle income (group 3) *Figure 2*. No patients were enrolled from low-income countries.

National coordinators, in conjunction with local centres or participating centres, managed the approvals of national or regional ethics committees or institutional review boards, according to local regulations.

Data management and statistical analysis

Pre-assembled data from the ESC-EORP EURO-ENDO registry were used for this ancillary study and all patients enrolled with possible or definite IE included in analyses. Continuous variables are reported as mean ± SD or median with interquartile range (IQR), and categorical variables as counts and percentages. Univariate analysis was applied to both continuous and categorical variables and group comparisons made using non-parametric analysis (Kruskal–Wallis test, χ^2 test, or Fisher's exact test, as appropriate). Overall results are presented and stratified according to World Bank economic stratification (high vs. upper-middle vs. lower-middle income).

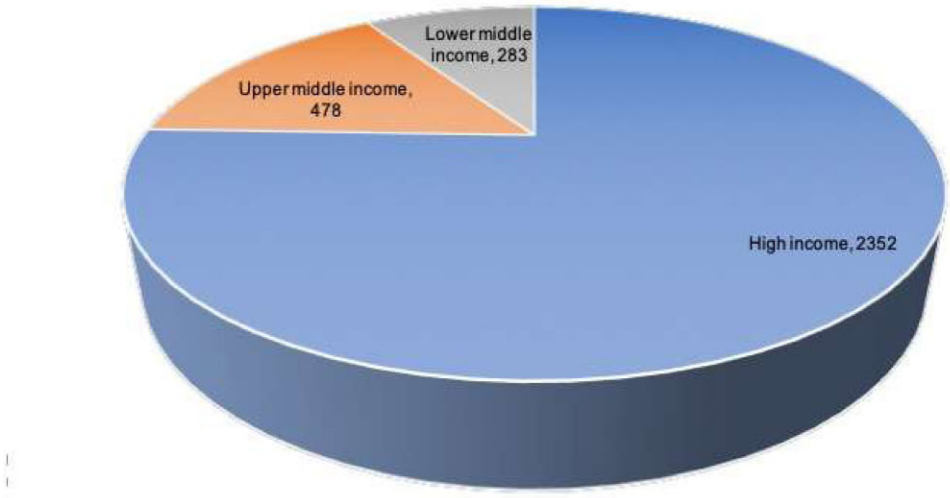
A two-sided *P*-value <0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 3113 patients with IE were enrolled at 156 centres from 40 countries in this ancillary study of the EURO-ENDO registry and subdivided according to socioeconomic distribution [group 1: high income (75.6%); group 2: upper-middle income (15.4%); group 3: lower-middle income (9.1%)]. These distributions and the number of patients enrolled in each nation are illustrated in *Figure 1*.

Demographics and patients' medical history (*Table 1*)

Stratification according to national economic performance demonstrated marked variation in demographic and clinical characteristics with a consistent gradient between high, upper-middle, and



High Income	2352
UAE	6
Austria	21
Belgium	130
Canada	60
Czech Republic	173
Germany	132
Spain	292
France	459
UK	73
Greece	63
Croatia	49
Israel	21
Italy	262
Japan	63
Korea Republic of	31
Lithuania	40
Luxembourg	36
Malta	3
New Caledona	77
Netherland	137
Norway	8
Poland	39
Portugal	59
Argentina	55
Saudi Arabia	27
Singapore	26

Upper middle Income	478
Brazil	129
Ecuador	5
Iran	152
Montenegro	12
Romania	11
Serbia	68
Russian Federation	38
Turkey	63

Lower middle Income	283
Egypt	189
India	24
Moldova Republic	12
Pakistan	55
Tunisia	2
Uzbekistan	1

Figure 2 Demonstrating infective endocarditis pattern between various regions included in the study. The number in brackets defines the number of cases from that region.

lower-middle income countries. Patients in group 3 were younger ($P < 0.001$), with a lower frequency of diseases of affluence and ageing (ischaemic heart disease, atrial fibrillation, diabetes mellitus, heart failure, chronic obstructive pulmonary disease (COPD)/asthma, chronic renal failure, and cancer: all $P < 0.001$), and lower frequency of implantable cardiac devices. No patients from lower-middle income countries had an implantable defibrillator [ICD; or cardiac resynchronization therapy (CRT) device]. Conversely, smoking, intravenous drug use, and human immunodeficiency virus (HIV) infection were all more frequent (all $P < 0.001$).

Clinical, imaging, and microbiological findings (*Tables 2–4*)

Group 3 patients presented later with IE than their counterparts in groups 1 and 2. They reported specific symptoms (fever, cough, chest pain, and dyspnoea) more frequently but general malaise was less common (all $P < 0.001$, *Table 2*), and they were more likely to present with a lower blood pressure, higher heart rate, and evidence of congestive heart failure. Although rates of cardiogenic and septic shock and abscess formation were similar in all three

Table 1 Demography and patient medical history

	Total (*n* = 3113)	High income (*n* = 2352)	Upper-middle income (*n* = 478)	Lower-middle income (*n* = 283)	*P*-value
Demographics					
Age (mean ± SD)	59.26 ± 18.03	62.89 ±16.28	54.88 ±17.53	36.50 ±14.10	<0.001
Age [median (IQR)]	63.0 (46.0–73.0)	66.0 (53.0–75.0)	57.0 (41.0–68.0)	33.0 (26.0–43.0)	<0.001
Age ≥65 years	1443/3113 (46.4%)	1277/2352 (54.3%)	151/478 (31.6%)	15/283 (5.3%)	<0.001
Age ≥80 years	375/3113 (12.0%)	342/2352 (14.5%)	31/478 (6.5%)	2/283 (0.7%)	<0.001
History of cardiovascular diseases					
Heart failure	661/2837 (23.3%)	513/2076 (24.7%)	115/478 (24.1%)	33/283 (11.7%)	<0.001
Congenital disease	365/3111 (11.7%)	255/2350 (10.9%)	80/478 (16.7%)	30/283 (10.6%)	0.002
Ischaemic heart disease	620/2894 (21.4%)	514/2133 (24.1%)	93/478 (19.5%)	13/283 (4.6%)	<0.001
Atrial fibrillation	765/2915 (26.2%)	657/2154 (30.5%)	82/478 (17.2%)	26/283 (9.2%)	<0.001
Hypertrophic cardiomyopathy	63/2837 (2.2%)	45/2076 (2.2%)	18/478 (3.8%)	0/283	<0.001
Known valve murmur	970/2837 (34.2%)	659/2076 (31.7%)	233/478 (48.7%)	78/283 (27.6%)	<0.001
Device therapy					
No	2578/3113 (82.8%)	1891/2352 (80.4%)	411/478 (86.0%)	276/283 (97.5%)	<0.001
Pacemaker	325/3113 (10.4%)	281/2352 (11.9%)	37/478 (7.7%)	7/283 (2.5%)	
ICD (defibrillator)	125/3113 (4.0%)	107/2352 (4.5%)	18/478 (3.8%)	0/283	
CRT-D (with ICD)	70/3113 (2.2%)	60/2352 (2.6%)	10/478 (2.1%)	0/283	
CRT-P (pacing only)	15/3113 (0.5%)	13/2352 (0.6%)	2/478 (0.4%)	0/283	
Risk factors					
Previous stroke/TIA	340/2857 (11.9%)	246/2100 (11.7%)	71/474 (15.0%)	23/283 (8.1%)	0.017
Arterial hypertension	1499/3108 (48.2%)	1253/2348 (53.4%)	215/477 (45.1%)	31/283 (11.0%)	<0.001
COPD/asthma	317/3108 (10.2%)	279/2348 (11.9%)	28/477 (5.9%)	10/283 (3.5%)	<0.001
Chronic renal failure	551/3110 (17.7%)	432/2349 (18.4%)	99/478 (20.7%)	20/283 (7.1%)	<0.001
Dialysis	163/551 (29.6%)	107/432 (24.8%)	44/99 (44.4%)	12/20 (60.0%)	<0.001
HIV	31/3035 (1.0%)	21/2281 (0.9%)	1/475 (0.2%)	9/279 (3.2%)	0.001
Diabetes mellitus	704/3109 (22.6%)	590/2349 (25.1%)	97/477 (20.3%)	17/283 (6.0%)	<0.001
Cancer	359/3085 (11.6%)	324/2335 (13.9%)	30/468 (6.4%)	5/282 (1.8%)	<0.001
Smoking	756/2935 (25.8%)	547/2197 (24.9%)	103/456 (22.6%)	106/282 (37.6%)	<0.001
Intravenous drug dependency	212/3064 (6.9%)	124/2312 (5.4%)	23/474 (4.9%)	65/278 (23.4%)	<0.001
Immunosuppressive treatment	104/2837 (3.7%)	79/2076 (3.8%)	18/478 (3.8%)	7/283 (2.5%)	0.573
Long corticotherapy	127/2837 (4.5%)	109/2076 (5.3%)	12/478 (2.5%)	6/283 (2.1%)	0.003
Intravenous catheter	250/3101 (8.1%)	175/2343 (7.5%)	60/476 (12.6%)	15/282 (5.3%)	<0.001
Charslon index					
N	2631	1997	439	195	
Mean ± SD	3.48 ±2.91	3.83 ±2.93	2.93 ±2.72	1.20 ±1.75	<0.001
Median (IQR)	3.0 (1.0–5.0)	3.0 (2.0–5.0)	2.0 (1.0–4.0)	1.0 (0.0–1.0)	<0.001

COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack.

socioeconomic groups, embolic complications were more frequent in group 3 (principally driven by an excess of pulmonary embolism).

Transthoracic echocardiography was more frequently used as an isolated investigation in group 3 (while transoesophageal imaging, CT, and PET-CT were used less often) and echocardiographic abnormalities were more frequently detected. The mitral and tricuspid valves were most commonly affected in group 3, whereas aortic valve IE and device-related IE were more common in group 1 (*Table 3*). *Streptococcus viridans* and methicillin-resistant *Staphylococcus aureus* were the most frequent causative agents in group 3—and culture-negative cases were also more common in this setting—while methicillin-sensitive *S. aureus* IE was more common in group 1 (*Table 3*).

Complications and clinical outcomes (*Table 4*)

Group 3 patients were more likely to develop congestive heart failure and persistent fever for greater than 7 days following hospital admission. Among 2157 (69.3%) patients with theoretical indication for cardiac surgery, surgical intervention was undertaken less frequently despite these clear indications (often because of patient refusal) and mortality was highest in this group.

Discussion

This socioeconomic analysis of the Euro-ENDO registry, the world's largest contemporary database of 3113 patients with IE,

Table 2 Clinical presentation

	Total (*n* = 3113)	High income (*n* = 2352)	Upper-middle income (*n* = 478)	Lower-middle income (*n* = 283)	*P*-value
Location of endocarditis					
Aortic	1514/3056 (49.5%)	1206/2299 (52.5%)	212/474 (44.7%)	96/283 (33.9%)	<0.001
Mitral	1284/3056 (42.0%)	923/2299 (40.1%)	221/474 (46.6%)	140/283 (49.5%)	0.002
Tricuspid	349/3056 (11.4%)	195/2299 (8.5%)	65/474 (13.7%)	89/283 (31.4%)	<0.001
Pulmonary	74/3056 (2.4%)	37/2299 (1.6%)	26/474 (5.5%)	11/283 (3.9%)	<0.001
ICD/PM	333 / 3056 (10.9%)	284/2299 (12.4%)	42/474 (8.9%)	7/283 (2.5%)	<0.001
Location of endocarditis					
Left IE	2449/3008 (81.4%)	1885/2262 (83.3%)	365/463 (78.8%)	199/283 (70.3%)	
Right IE	301/3008 (10.0%)	157/2262 (6.9%)	66/463 (14.3%)	78/283 (27.6%)	
Time since first symptoms (days)					
N	3000	2255	467	278	
Mean ± SD	34.64 ±70.94	30.37 ± 55.01	44.32 ± 118.47	52.99 ± 74.90	<0.001
Median (IQR)	14.0 (4.0–40.0)	12.0 (3.0–35.0)	19.0 (6.0-54.0)	30.5 (12.0-62.0)	<0.001
Symptoms					
Fever	2380/3065 (77.7%)	1699/2304 (73.7%)	410/478 (85.8%)	271/283 (95.8%)	<0.001
Cough	522/3065 (17.0%)	296/2304 (12.8%)	118/478 (24.7%)	108/283 (38.2%)	<0.001
Dizziness	331/3065 (10.8%)	216/2304 (9.4%)	80/478 (16.7%)	35/283 (12.4%)	<0.001
Chest pain	248/3065 (8.1%)	156/2304 (6.8%)	48/478 (10.0%)	44/283 (15.5%)	<0.001
Shortness of breath	1016/3065 (33.1%)	608/2304 (26.4%)	237/478 (49.6%)	171/283 (60.4%)	<0.001
General non-well-being	1557/3065 (50.8%)	1130/2304 (40.0%)	315/478 (65.9%)	112/283 (39.6%)	<0.001
Signs					
SBP (mmHg)					
N	2702	1953	467	282	
Mean ± SD	120.36 ± 21.13	122.28 ± 21.56	118.02 ± 19.57	110.94 ± 17.38	<0.001
Heart rate (beats/min)					
N	2676	1949	468	259	
Mean ± SD	88.42 ± 18.93	86.87 ± 19.12	89.04 ± 17.56	98.95 ± 16.30	<0.001
Cardiac murmur	2005/3109 (64.5%)	1414/2348 (60.2%)	372/478 (77.8%)	219/283 (77.4%)	<0.001
Congestive heart failure	846/3113 (27.2%)	621/2352 (26.4%)	125/478 (26.2%)	100/283 (35.3%)	0.007
Cardiogenic shock	63/2837 (2.2%)	48/2076 (2.3%)	10/478 (2.1%)	5/283 (1.8%)	0.914
Septic shock	203/3112 (6.5%)	154/2351 (6.6%)	31/478 (6.5%)	18/283 (6.4%)	1.000
Complications on admission					
Abscess	363/3113 (11.7%)	272/2352 (11.6%)	52/478 (10.9%)	39/283 (13.8%)	0.465
Embolic events	791/3113 (25.4%)	591/2352 (25.1%)	101/478 (21.1%)	99/283 (35.0%)	<0.001

PM, pacemaker

demonstrates that patients in lower-middle income countries (1) are younger than their counterparts in high- and upper-middle income countries, with a lower frequency of diseases of affluence and ageing, (2) present later and are more likely to develop significant complications following hospital admission, (3) have a higher incidence of negative blood cultures and less frequent access to advanced cardiac imaging (transoesophageal echocardiography, CT, and PET), (4) undergo surgery less frequently, and (5) have higher mortality. These findings highlight an important socioeconomic gradient influencing the clinical presentation and management of IE for the first time and emphasize the impact of limited access to healthcare resources on the outcome of this life-threatening condition.

Our observations suggest that variations in health-seeking behaviour (evidenced by frequent refusal of surgery), lack of preventive screening, and limited access to healthcare resources impeding the implementation of international guideline recommendations[6] (evidenced by infrequent use of TOE, CT, and PET and low rates of surgery) in lower-middle income countries directly impact on patterns of disease presentation and clinical outcome.[12] Patients in lower-middle income countries demonstrated far more frequent echocardiographic abnormalities than those in wealthier settings (presumably reflecting presentation at a more advanced stage of disease) and were far more likely to develop congestive heart failure septic shock and persistent fever for greater than 7 days following hospital admission as a consequence of their late presentation. Similarly, national demographics and patterns of endemic disease (both an indirect consequence of socioeconomic variation) strongly influenced the pathophysiological and microbiological phenotype of IE. Thus, the mitral and tricuspid valve IE was most common in lower-middle income countries, presumably reflecting greater prevalence

Table 3 Microbiological findings and imaging features

	Total ($n = 3113$)	High income ($n = 2352$)	Upper-middle income ($n = 478$)	Lower-middle income ($n = 283$)	*P*-value
Positive blood cultures	2458/3113 (79.0%)	1975/2352 (84.0%)	335/478 (70.1%)	148/283 (52.3%)	<0.001
Methi-S *Staphylococcus aureus*	593/2458 (24.1%)	514/1975 (26.0%)	53/335 (15.8%)	26/148 (17.6%)	<0.001
Methi-R *S. aureus*	177/2458 (7.2%)	107/1975 (5.4%)	28/335 (8.4%)	42/148 (28.4%)	<0.001
Methi-S staph coagulase negative	163/2458 (6.6%)	107/1975 (5.4%)	39/335 (11.6%)	17/148 (11.5%)	<0.001
Methi-R staph coagulase negative	150/2458 (6.1%)	104/1975 (5.3%)	37/335 (11.0%)	9/148 (6.1%)	<0.001
Streptococcus viridans	304/2458 (12.4%)	249/1975 (12.6%)	30/335 (9.0%)	25/148 (16.9%)	0.037
Enterococcus	389/2458 (15.8%)	315/1975 (15.9%)	60/335 (17.9%)	14/148 (9.5%)	0.051
Streptococcus bovis	162/2458 (6.6%)	139/1975 (7.0%)	16/335 (4.8%)	7/148 (4.7%)	0.228
Gram-negative bacillus	86/2458 (3.5%)	63/1975 (3.2%)	15/335 (4.5%)	8/148 (5.4%)	0.193
Echocardiography					
Transthoracic echocardiography	2791/3108 (89.8%)	2075/2347 (88.4%)	441/478 (92.3%)	275/283 (97.2%)	<0.001
Transoesophageal echocardiography	1806/3108 (58.1%)	1394/2347 (59.4%)	286/478 (59.8%)	126/283 (44.5%)	<0.001
Vegetations					<0.001
Yes	2258/3108 (72.7%)	1619/2347 (69.0%)	373/478 (78.0%)	266/283 (94.0%)	
Doubtful	171/3108 (5.5%)	151/2347 (6.4%)	16/478 (3.3%)	4/283 (1.4%)	
Abscess					0.389
Yes	323/3108 (10.4%)	244/2347 (10.4%)	45/478 (9.4%)	34/283 (12.0%)	
Doubtful	56/3108 (1.8%)	48/2347 (2.0%)	5/478 (1.0%)	3/283 (1.1%)	
Pseudo-aneurysm					0.001
Yes	108/3108 (3.5%)	77/2347 (3.3%)	28/478 (5.9%)	3/283 (1.1%)	
Doubtful	6/3108 (0.2%)	3/2347 (0.1%)	1/478 (0.2%)	2/283 (0.7%)	
Fistula					0.424
Yes	52/3108 (1.7%)	43/2347 (1.8%)	7/478 (1.5%)	2/283 (0.7%)	
Doubtful	6/3108 (0.2%)	4/2347 (0.2%)	2/478 (0.4%)	0/283	
New prosthetic dehiscence					0.646
Yes	105/3108 (3.4%)	78/2347 (3.3%)	17/478 (3.6%)	10/283 (3.5%)	
Doubtful	9/3108 (0.3%)	6/2347 (0.3%)	1/478 (0.2%)	2/283 (0.7%)	
At least one criterion above					<0.001
Yes	2443/3108 (78.6%)	1766/2347 (75.2%)	404/478 (84.5%)	273/283 (96.5%)	
Doubtful	151/3108 (4.9%)	134/2347 (5.7%)	15/478 (3.1%)	2/283 (0.7%)	
Pericardial effusion	267/2832 (9.4%)	149/2071 (7.2%)	77/478 (16.1%)	41/283 (14.5%)	<0.001
18FDG PET/CT scan					
PET scan performed	518/3113 (16.6%)	502/2352 (21.3%)	13/478 (2.7%)	3/283 (1.1%)	<0.001
Positive PET/CT	361/518 (69.7%)	348/503 (69.2%)	10/12 (83.3%)	3/3 (100.0%)	
Doubtful PET/CT	52/518 (10.0%)	51/503 (10.1%)	1/12 (8.3%)	0/3	
Multislice computed tomography					
Multislice computed tomography	1656/3113 (53.2%)	1332/2352 (56.6%)	241/478 (50.4%)	83/283 (29.3%)	<0.001
Perivalvular extension	101/1647 (6.1%)	76/1323 (5.7%)	17/241 (7.1%)	8/83 (9.6%)	0.259
Extra cardiac lesions	798/1655 (48.2%)	607/1331 (45.6%)	129/241 (53.5%)	62/83 (74.7%)	<0.001

18FDG PET, fluorodeoxyglucose F18-positron emission tomography.

of rheumatic heart disease, whereas aortic valve IE was more common in high-income countries, presumably as a consequence of degenerative aortic valve disease in an older population where there was also a higher prevalence of atherosclerotic risk factors. Similarly, methicillin-sensitive *S. aureus* IE was also more common in high-income countries, reflecting the greater prevalence of device-related IE.

IE remains prominent worldwide, with a persistently high mortality despite advances in care, and accounts for ~66 300 deaths and 1.7 million disability-adjusted life years per annum. Global prevalence has increased by 44% since 1990,[1] and this change has been most apparent in middle-income countries (possibly as a consequence of the increased availability of cardiac imaging and microbiological investigation). Global incidence increased by 39% (from 9.9 to 13.8 cases per 100 000 people) between 1990 and 2017, and reached 1.1 million cases in 2019,[1] with more detailed assessment suggesting that this increase was most prominent in the past decade.[13] Wide variation between and within countries (varying from 5.7 to 35.8 cases per 100 000 people) remains unexplained and may relate to diagnostic definitions and coding.[14] Contributing factors in

Table 4 Complications and clinical outcomes

	Total ($n = 3113$)	High income ($n = 2352$)	Upper-middle income ($n = 478$)	Lower-middle income ($n = 283$)	*P*-value
Complications under therapy					
Embolic events	641/3113 (20.6%)	475/2352 (20.2%)	95/478 (19.9%)	71/283 (25.1%)	0.151
Pulmonary	171/641 (26.7%)	101/475 (21.3%)	37/95 (38.9%)	33/71 (46.5%)	<0.001
Cerebral	283/641 (44.1%)	229/475 (48.2%)	36/95 (37.9%)	18/71 (25.4%)	<0.001
Renal	58/641 (9.0%)	54/475 (11.4%)	2/95 (2.1%)	2/71 (2.8%)	<0.001
CHF	436/3113 (14.0%)	319/2352 (13.6%)	53/478 (11.1%)	64/283 (22.6%)	<0.001
Septic shock	287/3113 (9.2%)	198/2352 (8.4%)	51/478 (10.7%)	38/283 (13.4%)	0.014
Acute renal failure	548/3113 (17.6%)	408/2352 (17.3%)	104/478 (21.8%)	36/283 (12.7%)	0.004
Persistent fever (>7 days)	350/2837 (12.3%)	203/2076 (9.8%)	68/478 (14.2%)	79/283 (27.9%)	<0.001
Acute MI	8/342 (2.3%)	2/220 (0.9%)	4/79 (5.1%)	2/43 (4.7%)	0.034
Pulmonary embolism	13/342 (3.8%)	1/220 (0.5%)	3/79 (3.8%)	8/43 (18.6%)	<0.001
Theoretical Indication of cardiac surgery	2157/3112 (69.3%)	1680/2352 (71.4%)	327/477 (68.6%)	150/283 (53.0%)	<0.001
Indication					
Haemodynamic	996/2157 (46.2%)	731/1680 (43.5%)	191/327 (58.4%)	74/150 (49.3%)	<0.001
Embolic	693/2157 (32.1%)	545/1680 (32.6%)	110/327 (33.6%)	38/150 (25.3%)	0.164
Infectious	1384/2157 (64.2%)	1038/1680 (61.8%)	242/327 (74.0%)	104/150 (69.3%)	<0.001
Cardiac surgery performed	1596/2157 (74.0%)	1268/1680 (75.5%)	251/327 (76.8%)	77/150 (51.3%)	<0.001
In left IE	1301/1766 (73.7%)	1040/1392 (74.7%)	197/258 (76.4%)	64/116 (55.2%)	<0.001
In right IE	110/170 (64.7%)	72/99 (72.7%)	27/40 (67.5%)	11/31 (35.5%)	0.001
In ICD/PM IE	170/192 (88.5%	144/163 (88.3%)	24/26 (92.3%)	2/3 (66.7%)	0.308
In missing aetiology	15/29 (51.7%)	12/26 (46.2%)	3/3 (100.0%)		
Death	529/3113 (17.0%)	352/2352 (15.0%)	110/478 (23.0%)	67/283 (23.7%)	<0.001
Death in left IE	435/2449 (17.8%)	302/1885 (16.0%)	88/365 (24.1%)	45/199 (22.6%)	<0.001
Death in right IE	43/301 (14.3%)	15/157 (9.6%)	8/66 (12.1%)	20/78 (25.6%)	0.005
Death in ICD/PM	39/258 (15.1%)	26/220 (11.8%)	11/32 (34.4%)	2/6 (33.3%)	0.002
Death in missing IE aetiology	12/105 (11.4%)	9/90 (10.2%)	3/15 (20.0%)		

CHF, congestive heart failure; MI, myocardial ischemia; PM, pacemaker

high-income countries include prolonged life expectancy in some regions (IE is more common in the elderly), improved survival resulting from early access to diagnostic cardiac imaging and cardiac surgery, higher numbers of patients with intracardiac devices and prosthetic valves, and higher rates of intravenous drug use.[15,16] Conversely, societal impact is greatest in low-income countries, particularly those with a high prevalence of rheumatic heart disease (Oceania, India, South Asia, and sub-Saharan Africa).[17] This observation is even more evident given the fact that patients with IE in low middle-income countries were substantially younger than those in their high-income counterparts (where IE is now substantially a disease of the elderly). These demographic shifts further emphasize the strong association of rheumatic fever with poverty that requires the sustained attention of global health policymakers.

Previous attempts to determine geographical or socioeconomic variation in the clinical and microbiological characteristics of IE and their impact on outcomes have been limited. The International Collaboration on Endocarditis (ICE) prospectively assembled data on a cohort of 2781 adults with definite IE admitted to 58 hospitals in 25 countries across the world (North America: $n = 597$, 21%; South America: $n = 254$, 9%; Europe: $n = 1213$, 44%; elsewhere: $n = 717$, 26%) between 2000 and 2005.[2] The median age of the cohort was 58 years and the majority (72%) had native valve IE. Patients from North America were more likely to have diabetes mellitus, chronic intravenous access, or renal failure requiring haemodialysis, and a correspondingly higher frequency of healthcare-associated IE. *Staphylococcus aureus* was the most common organism in all regions with the exception of South America, where viridans group streptococci were predominant. The frequency of *Streptococcus bovis* IE was much higher in Europe and South America, and HACEK organisms relatively uncommon in North America, while the majority of *Coxiella burnetii* and *Bartonella* infections were identified in Europe. Although minor geographic variations in management were noted, there was no obvious impact on outcome, with an overall in-hospital mortality of 18%. However, patients were predominantly enrolled from specialist centres in economically advantaged nations and there was no attempt to stratify findings according to socioeconomic status.

Study limitations

The EURO-ENDO registry presents a unique evaluation of the current features and treatment of IE and is the most extensive data set available. Nevertheless, like all observational studies, there are inevitable limitations. Participation was voluntary. Furthermore, in common with other registries of this type, large specialist centres (with advanced imaging and cardiac surgical facilities) were

over-represented. Importantly, the number of enrolled patients was relatively small from some regions, while others (notably sub-Saharan Africa) were absent. Regrettably, no patients were enrolled from low-income countries where rheumatic heart disease is most prevalent. The registry data set is therefore unlikely to be a true population-based sample and our findings may not be applicable in other settings. This is of particular importance when considering factors that may determine clinical outcomes in low-income countries with sparse medical resources. However, we believe that the large number of enrolled patients, high quality of CRF completion, and representation of a wide range of specialist and non-specialist centres in many countries around the world outweigh these limitations. Furthermore, although we identified numerous clinical characteristics that may have contributed to the adverse outcome of IE in patients from lower middle-income countries, these reflect an association rather than a systematic cause-and-effect relationship.

Conclusions

This ancillary analysis of data from the Euro-ENDO registry, the largest and most comprehensive accumulation of patients with IE to date, demonstrates a steep socioeconomic gradient influencing the clinical presentation, aetiology, investigation, management, and outcome of this rare yet threatening condition across the world. Late presentation and lower use of surgery are associated with more frequent complications and higher mortality in the poorest countries. Although low-income countries were not represented within the data set, extrapolation of the findings suggests a high likelihood of even poor management and worse outcomes in this setting. Education programmes aimed at both patients and clinicians, focused investment programmes targeting strategic allocation of healthcare resources, and greater adherence to international guidelines[12] are essential elements in attempts to address this global inequity.

Acknowledgements

The authors thank the EORP Oversight Committee and Registry Executive and Steering Committees. The project management (study launch, data collection and coordination, data management, and statistical analyses) was conducted by the EURObservational Research Programme (EORP), European Society of Cardiology, Sophia Antipolis, France: Rachid Mir Hassaine and Clara Berle as clinical project managers; Emanuela Fiorucci as project officer; Viviane Missiamenou and Florian Larras as data managers; and Cécile Laroche as the statistical project lead. Overall activities were coordinated and supervised by Doctor Aldo P. Maggioni (EORP Scientific Coordinator). The authors give special thanks to the EACVI (European Association of CardioVascular Imaging) and to the ESC Working Group on Valvular Heart Disease for their support.

Funding

Abbott Vascular Int. (2011–21), Amgen Cardiovascular (2009–18), AstraZeneca (2014–21), Bayer AG (2009–18), Boehringer Ingelheim (2009–19), Boston Scientific (2009–12), the Bristol Myers Squibb and Pfizer Alliance (2011–19), Daiichi Sankyo Europe GmbH (2011–20), the Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014–17), Edwards (2016–19), Gedeon Richter Plc. (2014–16), Menarini Int. Op. (2009–12), MSD–Merck & Co. (2011–14), Novartis Pharma AG (2014–20), ResMed (2014–16), Sanofi (2009–11), Servier (2009–21), and Vifor (2019–22).

Conflict of interest: None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Appendix 1

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