Socio-Economic 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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ABSTRACT

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

Methods: The EurObservationalProgramme (EORP) of the European Society of Cardiology (ESC) EURO-ENDO 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 3 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%]).

Results: Group 3 patients were younger (median age [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 (HIV) 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 failure (13.6%; 11.1%; and 22.6%, respectively; p<0.001) and persistent fever (9.8%; 14.2%; 27.9%; 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).

Conclusions: Socio-economic 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.

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Keywords: Endocarditis, Socio-economic

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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 approximately 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 heterogenous, 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 randomised 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 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 inter-regional and socio-economic factors (including the implementation of ESC guidelines) that may impact on 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 socio-economic criteria.

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METHODS

Study design and data collection

The detailed methodology of the ESC-EORP EURO-ENDO registry - a prospective multi-centre 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 January 1st 2016 and March 31st 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, ^{18}F-FDG PET/CT), antibiotic therapy, complications, theoretical indications for surgery, and in-hospital mortality.[9]

In the present study, the resulting dataset was analysed on the basis of socio-economic characteristics. Individual nations were stratified based upon their economic performance during the fiscal year 2018 according to World Bank criteria [11] then grouped into the following categories: high income (Group 1), upper-middle income (Group 2) and lower-middle income (Group 3). 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

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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, chi-square 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 sub-divided according to socio-economic 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.

Demographic 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 lower-middle 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, 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 resynchronisation therapy [CRT] device). Conversely, smoking, intravenous drug use, and human immunodeficiency virus (HIV) infection were all more frequent (all p<0.001).

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Clinical, imaging and microbiological findings (Tables 2, 3, and 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 dyspnea) more frequently but general malaise was less common (all $p<0.001$, table 2), and 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 socio-economic 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 (whilst 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 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 - whilst methicillin-sensitive *Staphylococcus 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.

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DISCUSSION

This socio-economic analysis of the Euro-ENDO registry, the world's largest contemporary database of 3113 patients with IE, demonstrates that patients in lower-middle income countries, (A) are younger than their counterparts in high- and upper-middle income countries, with a lower frequency of diseases of affluence and ageing, (B) present later and are more likely to develop significant complications following hospital admission, (C) have a higher incidence of negative blood cultures and less frequent access to advanced cardiac imagIng (transoesophageal echocardiography, CT and PET), (D) undergo surgery less frequently, and (E) have higher mortality. These findings highlight an important socio-economic gradient influencing the clinical presentation and management of IE for the first time and emphasise the impact of limited access to healthcare resources on the outcome of this life-threatening condition.

Our observations suggest that variations in health seeking behavior (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 indirect consequence of socio-economic variation) strongly influenced

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the pathophysiological and microbiological phenotype of IE. Thus, the mitral and tricuspid valve IE were most common in lower-middle income countries, presumably reflecting greater prevalence 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 *Staphylococcus 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 approximately 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 5.7-35.8 cases per 100,000 people) remains unexplained and may relate to diagnostic definitions and coding.[14] Contributing factors in 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 intra-cardiac 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

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of the elderly). These demographic shifts further emphasize the strong association of rheumatic fever with poverty that requires the sustained attention of global health policy makers.

Previous attempts to determine geographical or socio-economic 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 health care-associated IE. *Staphyloccus 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, whilst 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 socio-economic status.

Study limitations

The EURO-ENDO registry presents a unique evaluation of the current features and treatment of IE and is the most extensive dataset available. Nevertheless, like all observational studies,

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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, whilst 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 dataset 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 adverse outcome of IE in patients from lower middle-income countries, these reflect an association rather than a systematic cause and effect relationship.

Summary and conclusion

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 socio-economic 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 dataset, 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

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resources, and greater adherence to international guidelines[12] are essential elements in attempts to address this global inequity.

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DISCLOSURE

None for all authors

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Figure 1

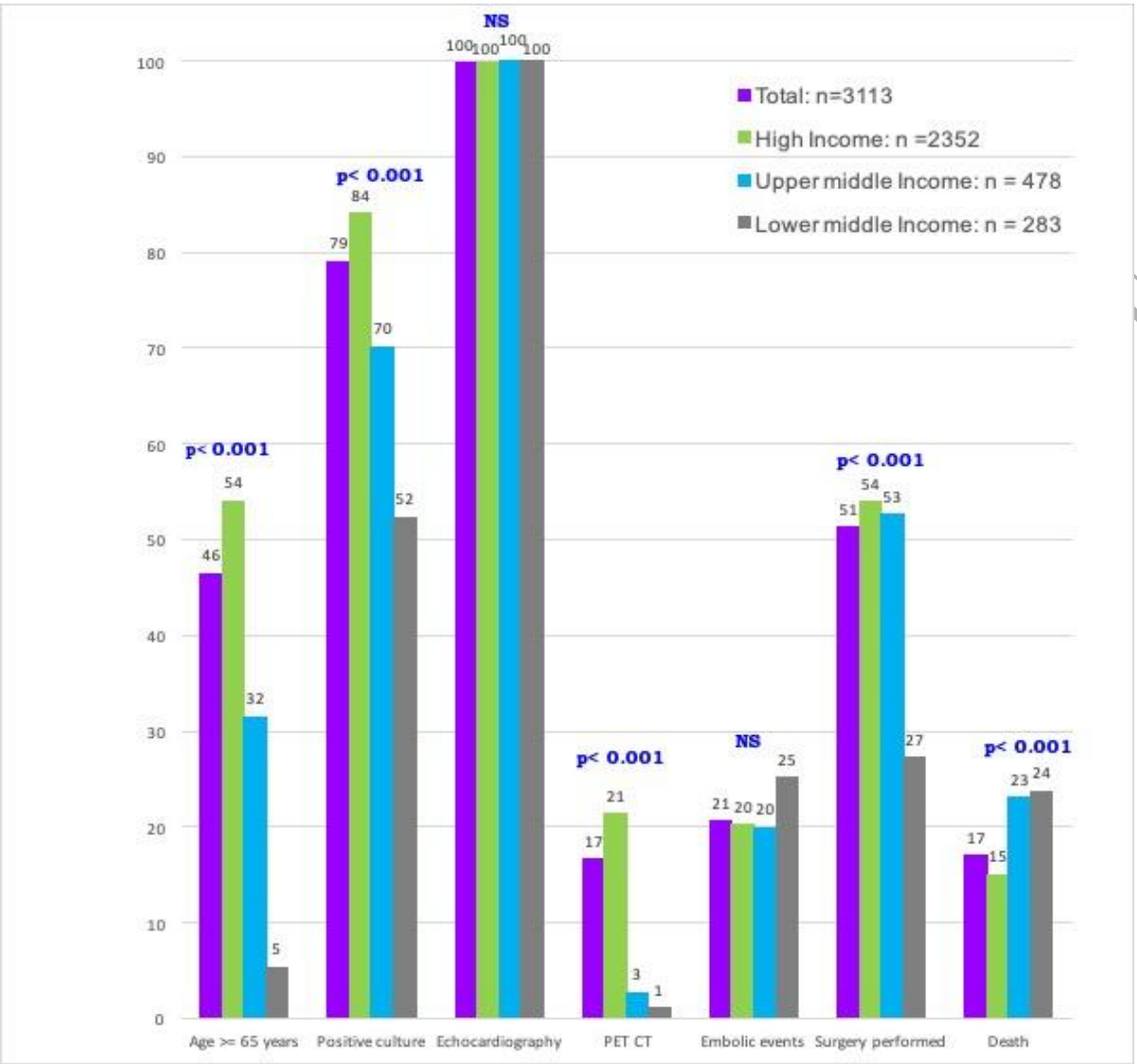

Figure 1: Variations in clinical, imaging, and outcome characteristics according to socio-economic grouping.

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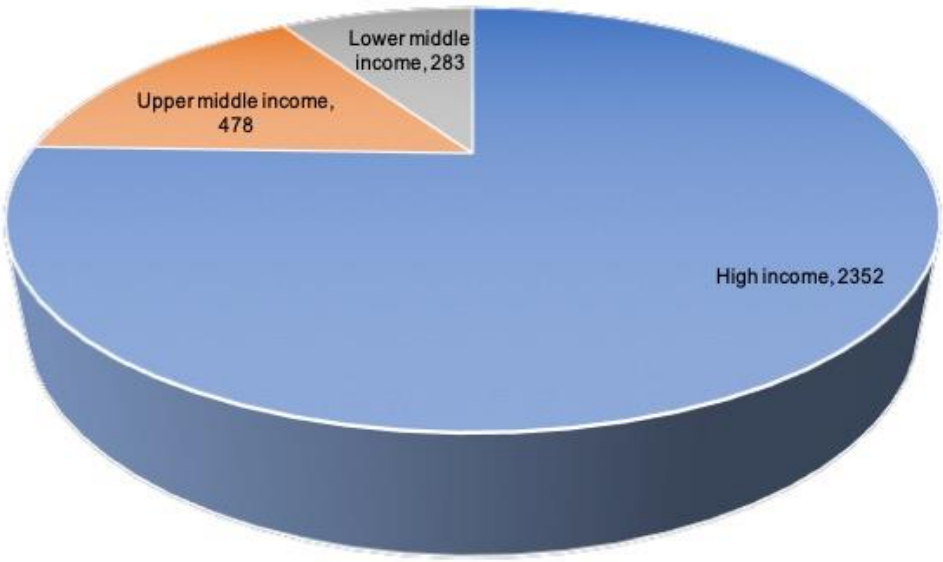
Figure 2



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
Eqypt	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. Number in bracket defines number of cases from that region.

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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
Charslons 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

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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-wellbeing	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/mn)					
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

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TABLE 3. Microbiological finding 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 Staphylococcus 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
Transesophageal 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%)	
Pseudoaneurysm					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 1 criteria 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

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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
Acure 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 etiology	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 etiology	12 / 105 (11.4%)	9 / 90 (10.2%)	3 / 15 (20.0%)		

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Appendix 1

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