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Evolution of epidemiological characteristics of infective endocarditis in Greece

Efthymia Giannitsioti[a,*], Angelos Pefanis[b], Charalampos Gogos[c], Alexandra Lekkou[c], Georgios N. Dalekos[d], Nikolaos Gatselis[d], Sara Georgiadou[d], Paraskevas Nikou[e], Agathi Vrettou[f], Angelos Rigopoulos[f], Christos Tryfonopoulos[g], Thomas Tsaganos[a], Emmanouil Karofilakis[a], Christos Psarrakis[a], Michail Argyriou[h], Panagiotis Gargalianos-Kakolyris[i], Georgios Adamis[i], Panagiota Lourida[i], Diamantis Kofteridis[j], Aggeliki Andrianaki[j], Chariclia Loupa[k], Evangelos Kostis[l], Dimitris Sinapidis[l], Styliani Sympardi[m], Nikolaos Alexiou[m], Ilias Karaiskos[n], Aikaterini Masgala[o], Efstratios Maltezos[p], Periklis Panagopoulos[p], Vasileios Sachpekidis[q], Constantinos Evdoridis[r], Nikolaos V. Sipsas[s], Georgios Daikos[t], Helen Giamarellou[n], On behalf of the Hellenic Society of Chemotherapy[1]

[a] Fourth Department of Internal Medicine, "Attikon" University General Hospital, National and Kapodistrian University of Athens (NKUA), Athens, Greece
[b] Department of Internal Medicine, "Sotiria" Hospital for Chest Diseases, Athens, Greece
[c] Department of Internal Medicine, Rio University Hospital, University of Patras, Rio, Greece
[d] Department of Internal Medicine, Larissa University Hospital, Faculty of Medicine, University of Thessaly, Larissa, Greece
[e] Department of Internal Medicine, Tripolis General Hospital, Tripolis, Greece
[f] Second Department of Cardiology, "Attikon" University General Hospital, NKUA, Athens, Greece
[g] Department of Informatics and Telecommunications, University of Peloponnese, Tripolis, Greece
[h] Cardiosurgical Department "Evangelismos" General Hospital, Athens, Greece
[i] First Department of Internal Medicine, "G. Gennimatas" General Hospital, Athens, Greece
[j] Department of Internal Medicine, University Hospital of Heraklion, Crete, Greece
[k] Department of Internal Medicine, "Amalia Fleming" Hospital, Athens, Greece
[l] Department of Clinical Therapeutics, "Alexandra" Hospital, NKUA, Athens, Greece
[m] First Department of Internal Medicine, "Thriassio" General Hospital, Elefsina, Attiki, Greece
[n] First Department of Internal Medicine - Infectious Diseases, "Hygeia" Hospital, Athens, Greece
[o] First Department of Internal Medicine, "Agia Olga" Hospital, Athens, Greece
[p] Department of Internal Medicine, University General Hospital of Alexandroupolis, Democritus University of Thrace, Alexandroupolis, Greece
[q] Second Cardiology Department "Papageorgiou" General Hospital, Aristotele University of Thessaloniki, Thessaloniki, Greece
[r] Cardiology Department, "Elpis" Hospital, Athens, Greece
[s] Pathophysiology Department, "Laikon" General Hospital of Athens, NKUA, Athens, Greece
[t] First Department of Internal Medicine, "Laikon "General Hospital of Athens, NKUA, Athens, Greece

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ABSTRACT

Objective: The clinical profile, management and outcome of infective endocarditis (IE) may be influenced by socioeconomic issues.
Methods: A nationwide prospective study evaluated IE during the era of deep economic crisis in Greece. Epidemiological data and factors associated with 60-day mortality were analyzed through descriptive statistics, logistic and Cox-regression models.
Results: Among 224 patients (male 72.3%, mean age 62.4 years), *Staphylococcus aureus* (n = 62;

* Corresponding author at: Internal Medicine and Infectious Diseases, Fourth Department of Internal Medicine, Athens University Medical School, NKUA, "Attikon" University General Hospital, Rimini 1, 12462, Chaidari, Athens, Greece.
E-mail addresses: gianiemi@hotmail.com, efthymia.giannitsioti@gmail.com (E. Giannitsioti).

[1] Collaborators: Konstantinos Pontikis, "Sotiria" Hospital for Chest Diseases, Athens; Ioannis Lioris, First Department of Internal Medicine, "Agia Olga" Hospital, Athens; Moysis Lelekis, Department of Internal Medicine, "Amalia Fleming" Hospital, Athens; Athanasios Trikkas, Cardiology Department, "Elpis" Hospital, Athens; Dimitrios Aggouras,Vasilios Kolias, Chris Rokkas Cardiac Surgery Department, "Attikon" University General Hospital, NKUA, Athens; Maria Nana-Anastasiou, Second Cardiology Department "Attikon" University General Hospital, NKUA Athens; Spiros Miyakis, Department of Internal Medicine, "Papageorgiou" General Hospital, University of Thessaloniki, Thessaloniki.

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methicillin-resistant *S. aureus* (MRSA) 33.8%) predominated in the young without impact on mortality (p = 0.593), whilst Enterococci (n = 36) predominated in the elderly. Complications of IE were associated with mortality: heart failure [OR 2.415 (95% CI: 1.159–5.029), p = 0.019], stroke [OR 3.206 (95% CI: 1.190–8.632), p = 0.018] and acute kidney injury [OR 2.283 (95% CI: 1.085–4.805), p = 0.029]. A 60-day survival benefit was solely related to cardiac surgery for IE during hospitalization [HR 0.386 (95% CI: 0.165–0.903), p = 0.028] and compliance with antimicrobial treatment guidelines [HR 0.487 (95% CI: 0.259–0.916), p = 0.026]. Compared with a previous country cohort study, history of rheumatic fever and native valve predisposition had declined, whilst underlying renal disease and right-sided IE had increased (p < 0.0001); HIV infection had emerged (p = 0.002). No difference in rates of surgery and outcome was assessed.

Conclusions: A country-wide survey of IE highlighted emergence of HIV, right-sided IE and predominance of MRSA in the youth during a severe socioeconomic crisis. Compliance with treatment guidelines promoted survival.

Introduction

Infective endocarditis (IE) is a potentially lethal disease with significant morbidity and mortality, even in the era of antimicrobial therapy and cardio-surgical interventions (Moreillon and Que, 2004; Hoen and Duval, 2013). Changing profiles of epidemiology, etiology, clinical presentation and outcome of IE are largely described via single or multi-center, nationwide or international collaborative, population-based cohort studies (Bin Abdulhak et al., 2014). The crude incidence of IE ranges between 1.5–11.6 cases/100,000 people (Hoen and Duval, 2013; Bin Abdulhak et al., 2014); however, it is reported to be higher in emerging populations (i.e. intravenous drug abuse (IVDA), human immunodeficiency virus (HIV), immunocompromised, and recipients of cardiac implantable devices) (Hoen and Duval, 2013; Tornos et al., 2005; Murdoch et al., 2009). Nosocomial and non-nosocomial healthcare-associated IE have significantly increased within the last few decades, bringing new concerns about diagnosis and treatment of the disease (Giamarellou, 2002). The epidemiological profile of IE has largely varied, not only among continents (Murdoch et al., 2009) but also within the same country between different time points (Tornos et al., 2005; Hoen et al., 2002; Selton-Suty et al., 2012; Olmos et al., 2017; Bruun Oestergaard et al., 2017). *Staphylococcus aureus* (*S. aureus*) is considered to be the leading pathogen in western countries, especially in healthcare-associated IE, elderly patients with comorbidities and left-sided IE (Hoen and Duval, 2013; Selton-Suty et al., 2012; Fowler et al., 2005). Cardiac surgery for IE is recommended upon indication, as reported by the current guidelines (Habib et al., 2015). Surgical intervention is classified as urgent, emergent and elective; however, the optimal timing for surgery is still debated (Hoen and Duval, 2013; Habib et al., 2015; Tleyjeh et al., 2008; Malhotra and Prendergast, 2012). Continuous epidemiological surveillance is an important tool for detecting a changing profile that can influence treatment and outcome of patients with IE (Moreillon and Que, 2004; Hoen and Duval, 2013). This nationwide cohort study was conducted in order to investigate the epidemiological trends, therapeutic management and prognosis of IE during an era of deep economic crisis.

Material and methods

Study schedule

A prospective, cohort study of patients with definite IE, according to the modified DUKE criteria (Li et al., 2000), was launched from January 2011 to December 2014. Sixteen medical institutions [university (n = 9), tertiary (n = 3) and regional (n = 4)] situated in different regions of Greece participated in the study. A case registration form per patient was completed by principal investigators and sub-investigators in each participating centre. Patients were evaluated after discharge during a hospital visit. The study was approved by each hospital's Ethics Committee.

Data collection

Demographics, comorbidities (i.e. diabetes mellitus, cardiac or renal disease, cirrhosis, rheumatologic diseases, HIV infection, malignancy) along with valve predisposition and history of IE were recorded. The presence of a prosthetic valve and/or a cardiac implantable device (implantable pacemakers/defibrillators) was also reported. Cases of IE were classified according to recent European Society of Cardiology (ESC) guidelines as healthcare-associated (both nosocomial and non-nosocomial), community-acquired and IVDA-related IE (Habib et al., 2015). Duration of symptoms of IE less or more than one month prior to diagnosis was assessed. Complications of the disease included peripheral embolization, stroke, heart failure (New York Heart Association — NYHA I-IV), valve abscess, vertebral osteomyelitis, acute kidney injury (AKI), and septic shock. Conventional blood cultures were taken in all cases, according to the DUKE criteria for IE (Li et al., 2000). Isolation and identification of pathogens from blood cultures and antimicrobial susceptibility were performed by standard methodology as per EUCAST recommendations (EUCAST, 2020). In cases of blood culture-negative infective endocarditis, blood serology or blood/valve PCR for pathogens implicated in IE was performed (Habib et al., 2015). Cardiac lesions compatible with IE (i.e. vegetations, abscess, severe valve regurgitation, prosthetic valve dehiscence) were assessed by transthoracic (TTE) and transesophageal (TEE) echocardiography according to ESC guidelines (Habib et al., 2015). Compliance with antimicrobial treatment was defined as the adherence to any antimicrobial schemas recommended by the ESC guidelines (Habib et al., 2015). Surgical indication was performed by the consultant cardiac surgeon in any case, based on clinical, microbiological and echocardiography findings during the evolution of the disease in accordance with ESC guidelines (Habib et al., 2015). The surgical procedure was performed during the index hospitalization for IE. The patients were followed up to 60 days after hospital admission.

Statistical analysis

Characteristics of the study population were summarized through means and SDs for continuous variables and absolute and relative (%) frequencies for categorical variables. Comparison of microbiological and surgical data as well as comparison of epidemiology of IE between this cohort and the previous one in the country were performed by two-sample T-tests and Chi-square tests (or Fisher's exact tests) for continuous and categorical

variables, respectively. Factors associated with cardiac surgery and predictors of mortality were assessed through logistic regression models. Probabilities of short-term, 60-day survival and the risk of death were modelled through stepwise Cox regression survival analysis. *P*-values <0.05 were considered statistically significant. All analyses were performed using IBM SPSS 22.0 statistics package.

Results

Clinical characteristics of patients with IE

A total of 224 cases of IE were eligible for analysis. Distribution of native valve endocarditis (n = 166), prosthetic valve endocarditis (PVE, n = 44) and cardiac implantable electronic device infective endocarditis (CIEDIE, n = 14) among university, tertiary non-university and regional hospitals is illustrated in Supplementary Figure S1. Most of the patients with PVE (70.5%) were seen at university hospital settings. Age-dependent clinical characteristics of the study population are highlighted in Table 1. Patients with IVDA IE were younger and more frequently had right-sided IE, whilst older patients with diabetes mellitus, cardiac disease and malignancy more frequently presented with healthcare-associated, left-sided IE. All patients living with HIV were aged <60 years (Table 1).

Microbiological data

The proportion of the number of positive vs the number of total blood cultures taken for the diagnosis of IE was abridged as a median of 2 (IQR 25–75: 2–3) vs 3 (IQR 25–75: 3–6). Pathogens detected by blood cultures are shown in Supplementary Table S1. *S aureus* predominated in patients aged <60 years ($p < 0.001$). Enterococci mostly affected patients aged >60 years ($p = 0.004$) who more frequently suffered from diabetes mellitus, malignancy and cardiac disease (Table 1). In summary, the main pathogens were distributed as follows: (i) *S. aureus*, n = 62 (methicillin-susceptible *S. aureus* (MSSA), n = 41; methicillin-resistant *S. aureus* (MRSA), n = 21); MRSA IE (33.8%) predominated in the younger patients, descending with age (41.7% in ages 18–32 vs 14.3% in ≥80 years). There was no difference in mortality between MRSA and MSSA cases (5/16, vs 11/41 $p = 1.0$); (ii) Streptococci, n = 48 (oral Streptococci n = 38, Group D Streptococci, n = 7, others, n = 3); (iii) Enterococci, n = 36 (*E. faecalis*, n = 30, *E. faecium*, n = 2, non-typable, n = 4); 30.6% of all strains were detected in those aged ≥80 years. There were two polymicrobial cases of IE. Blood cultures were negative in 39 patients (17.4%). Serology and/or PCR set the diagnosis of IE by *Coxiella burnetii* (n = 2) and *Legionella* spp. (n = 1).

Echocardiography diagnosis of IE

IE was documented by TTE (n = 77), TEE (n = 71) or both (n = 76). TEE was performed in all cases of PVE and CIEDIE. Echocardiography revealed lesions compatible with IE in mitral (n = 142), aortic (n = 111), tricuspid (n = 24), and pulmonary (n = 5) valves. Both aortic and mitral valve were affected in 70 cases. PVE accounted for 44 cases affecting mitral (n = 25), aortic (n = 29) and tricuspid (n = 4) valves, including 14 cases of multi-valvular involvement. Vegetations due to IE were found on the electrodes of 14 CIEDIE cases. Valve abscess was documented in 14 cases.

Table 1
Age-dependent characteristics of infective endocarditis.

Variables	Total (n, %)	Age <60 years (n, %)	Age >60 years (n, %)	*p*
Male	162 (73.2)	65 (76.5)	97 (69.8)	0.356
BMI >25.5 kg/m^2	65 (29)	19 (22.4)	46 (33.1)	0.096
Comorbidities	165 (73.7)	42 (49.4)	123 (88.5)	<0.001
Diabetes mellitus	48 (21.4)	8 (9.4)	40 (28.8)	0.001
Cardiac disease	61 (27.2)	13 (15.3)	48 (34.5)	0.002
Malignancy	25 (11.2)	3 (3.5)	22 (15.8)	0.004
Renal disease	50 (22.3)	16 (18.8)	34 (24.5)	0.409
Hemodialysis	11 (4.9)	3 (3.5)	8 (5.8)	0.540
Cirrhosis	3 (1.3)	1 (1.2)	2 (1.4)	1.0
Rheumatologic disease	5 (2.2)	2 (2.4)	3 (2.2)	1.0
HIV infection	10 (4.5)	10 (11.8)	0	<0.001
History of IE	20 (8.9)	10 (11.8)	10 (7.2)	0.334
Native valve predisposition	38 (17)	13 (15.3)	25 (18)	0.714
PVE	44 (19.6)	12 (14.1)	32 (23)	0.120
CIED IE	14 (6.3)	4 (4.7)	10 (7.2)	0.576
IVDA IE	24 (10.7)	24 (28.2)	0	<0.001
Healthcare IE	45 (20.1)	12 (14.1)	33 (23.7)	0.088
Community-acquired IE	155 (69.2)	49 (57.6)	106 (76.3)	0.005
Right-sided IE	41 (18.3)	24 (28.2)	17 (12.2)	0.004
Left-sided IE	183 (81.7)	61 (71.8)	122 (87.8)	0.004
Staphylococcus aureus	62 (27.7)	39 (45.9)	23 (16.5)	<0.001
Enterococcus spp.	36 (16.1)	6 (7.1)	30 (21.6)	0.004
Oral Streptococci	38 (17)	17 (20)	21 (15.1)	0.363
Candida spp.	8 (3.6)	3 (3.5)	5 (3.6)	1.0
BCN IE	39 (17.4)	12 (14.1)	27 (19.4)	0.366
Complications of IE				
Heart failure	95 (42.4)	33 (38.8)	62 (44.6)	0.407
Stroke	27 (12.1)	10 (11.8)	17 (12.2)	1.0
Peripheral embolization	47 (21)	27 (31.8)	20 (14.4)	0.002
AKI	93 (41.5)	28 (32.9)	65 (46.8)	0.051
Septic shock	15 (6.7)	5 (5.9)	10 (7.2)	0.789
Valve abscess	14 (6.3)	3 (3.5)	11 (7.9)	0.259
Cardiac surgery for IE	54 (24.1)	28 (32.9)	26 (18.7)	0.024
Rx guidelines for IE[a]	165 (73.7)	63 (74.1)	102 (73.4)	1.0

Abbreviations: IE, infective endocarditis; PVE, prosthetic valve endocarditis; CIED, cardiac implantable electronic device; IVDA, intravenous drug abuse; BCN, blood culture negative; AKI, acute kidney injury.
[a] Compliance with European Society of Cardiology guidelines for antimicrobial treatment of infective endocarditis.

Management of IE and outcomes

Antimicrobial treatment for IE was given in accordance with the European guidelines (Habib et al., 2015) in 165 patients (73.6%). Prior to IE diagnosis, empirical antibiotics for fever as the main symptom were administered in 109 patients (48.6%). Among patients with an indication for surgical treatment for IE (n = 122), 54 underwent cardiac surgery within the time frame of the study (44%). Overall, 24.1% of the entire cohort of patients (n = 224) were surgically treated compared with 75.9% (n = 170) who were only medically treated by antibiotics. Patients with advanced age, comorbidities and those with lower compliance with antimicrobial treatment also presented significantly reduced surgical rates (Table 2). Mortality was significantly higher in patients with heart failure from IE who were not operated vs those who underwent surgical treatment (42.4% vs 17.2%, p = 0.02). Overall mortality in this cohort reached 22.7% (n = 51). Logistic regression analysis for factors influencing the in-hospital outcome is shown in Table 3. Briefly: mortality was induced by complications of IE: heart failure [OR 2.415 (95% CI: 1.159-5.029), p = 0.019], stroke [OR 3.206 (95% CI: 1.190-8.632), p = 0.018] and AKI [OR 2.283 (95% CI: 1.085-4.805), p = 0.029]. All patients with septic shock died.

In the 60-day Cox regression stepwise survival analysis, the performed cardiac surgery [HR 0.386 (95% CI: 0.165–0.903), p = 0.028] and compliance with antimicrobial treatment guidelines [HR 0.487 (95% CI: 0.259–0.916), p = 0.026] were the only predictors of survival, as depicted in Figures 1 and 2 (analysis of data in Supplementary Table S2).

Median time from hospital admission to surgery was 16 days (range 1–58). Mean (±SD) time between the indication and surgical operation was 15.8 (±11.2) days. Moreover, patients who underwent cardiac surgery within the first 7 days (n = 12) survived 100% compared with 83% of those who were operated on later. If both cardiac surgery upon indication and compliance with antimicrobial treatment guidelines were applied, survival reached 89%. If none of these two cornerstones of treatment were followed, 45% of patients survived ($p < 0.001$).

Table 4 illustrates a comparison of epidemiological data between the current study and a previous country cohort (Giannitsioti et al., 2007). Native valve predisposition along with a history of rheumatic fever or cirrhosis declined, whilst renal disease as an underlying comorbidity emerged. Moreover, right-sided IE (RSIE) was more frequently detected in the current cohort. Emerging HIV infection was not detected in the previous cohort (2000–2004). Overall, a diagnostic delay was assessed in the current study, as symptoms of IE lasting <1 month before diagnosis fell from 70.8% in the previous cohort to 60.3% in the current one. Compared with the 2000–2004 survey, *S. aureus* emerged as the leading cause of IE (p = 0.014). Complications of IE, surgical treatment and mortality rates did not significantly differ between the two cohorts (Table 4).

Discussion

This study revealed a changing epidemiological profile of IE during an era of economic crisis. The impact of socioeconomic twisting conditions on the epidemiology, treatment and outcome of IE is unclear as data are sparse (Bin Abdulhak et al., 2014; Murdoch et al., 2009; Bruun Oestergaard et al., 2017). In Greece, unmet healthcare needs increased after the enactment of austerity measures (Zavras et al., 2016). For the first time in the country, this study systematically revealed a co-existence of HIV infection and IVDA IE. HIV infection among IVDA had dramatically increased (1600%) during the time of economic crisis as a result of the decline in gross domestic product, immigration waves, and network transmission (Paraskevis et al., 2013). According to data from other countries, the outcome of patients with IVDA IE is independent of the presence of HIV infection (Miró et al., 2002; Fernández Guerrero et al., 2009). In the current cohort, IVDA IE rates (10%) corroborated the international tendency (Gray et al., 2018) and was increasing compared with previous country studies (Giannitsioti et al., 2007; Loupa et al., 2004). Moreover, it revealed a decline in rheumatic fever and native valve predisposition for IE within one decade (from 2000–2004 to 2011–2014) (Giannitsioti et al., 2007) and from a previous cohort (Loupa et al., 2004), whilst underlying renal disease in patients with IE had increased. End-stage renal disease is a well-described risk factor for IE and relevant increased mortality (Ludvigsen et al., 2016).

Regarding microbiology of IE, *S. aureus* did not predict mortality in the current cohort, which is a finding directly confronting already published data. In wealth-income countries, *S. aureus* has been classified as the main pathogen of IE in the elderly, with

Table 2
Surgery vs only medical treatment for infective endocarditis.

Total n = 224	Surgery for IE n = 54 (24.1)	Only medical treatment n = 170 (75.9)	p
Age >60 years	26 (48.1)	113 (66.5)	0.024
Male/female	39/15 (72.2)/(27.8)	123/47 (72.4)/(27.6)	1.0
BMI >25 kg/m^2	10 (18.5)	55 (32.4)	0.059
Comorbidities	34 (63)	131 (77.1)	0.051
Staphylococcus aureus	11 (20.4)	51 (30.0)	0.221
Oral Streptococci	10 (18.5)	28 (16.5)	0.684
Enterococci	8 (14.8)	28 (16.5)	0.835
Candida spp.	3 (5.6)	5 (2.9)	0.403
BCN IE	13 (24.1)	26 (15.3)	0.152
Healthcare IE	15 (27.8)	30 (17.6)	0.120
PVE	10 (18.5)	34 (20)	1.0
CIED IE	5 (9.3)	9 (5.3)	0.334
Left-sided IE	46 (85.2)	137 (80.6)	0.547
Heart failure	29 (53.7)	66 (38.8)	0.059
Peripheral embolization	12 (22.2)	35 (20.6)	0.848
Stroke	8 (14.8)	19 (11.2)	0.477
Septic shock	0	15 (8.8)	0.025
AKI	25 (46.3)	68 (40)	0.432
Valve abscess	7 (13)	7 (4.1)	0.046
Rx guidelines for IE[a]	46 (85.2)	119 (70)	0.033

Abbreviations: IE, infective endocarditis; PVE, prosthetic valve endocarditis; CIED, cardiac implantable electronic device; AKI, acute kidney injury.
[a] Compliance with European Society of Cardiology guidelines for antimicrobial treatment of infective endocarditis.

Table 3
Predictors of mortality in patients with infective endocarditis.

Variables	Death n = 51 (22.8%)	Survival n = 173 (77.2%)	Univariate OR (95% CI)	p	Multivariate Adjusted OR (95% CI)	p
Age >60 years[a]	39 (76.5)	100 (57.8)	***2.373 (1.162–4.845)***	***0.021***		
Male/female	37/14 (72.5)/(27.5)	125/48 (72.3)/(27.7)	*1.015 (0.504–2.042)*	*1.0*		
BMI >25.5 kg/m^2	16 (31.4)	49 (28.3)	*1.157 (0.587–2.278)*	*0.726*		
Comorbidities[a]	46 (90.2)	119 (68.8)	***4.175 (1.571–11.094)***	***0.002***		
- Diabetes mellitus	10 (19.6)	38 (22.0)	*0.866 (0.397–1.889)*	*0.847*		
- Cardiac disease	24 (47.1)	37 (21.4)	***3.267 (1.690–6.316)***	***0.001***		
- Renal disease	16 (31.4)	34 (19.7)	*1.869 (0.928–3.765)*	*0.087*		
Hemodialysis	5 (9.8)	6 (3.5)	*3.025 (0.884–10.359)*	*0.131*		
- Malignancy	9 (17.6)	16 (9.2)	*2.103 (0.868-5.094)*	*0.126*		
- Cirrhosis	1 (2.0)	2 (1.2)	*1.710 (0.152–19.251)*	*0.541*		
- HIV	2 (3.9)	8 (4.6)	*0.842 (0.173-4.095)*	*1.0*		
- Rheumatologic disease	2 (3.9)	3 (1.7)	*2.313 (0.376–14.235)*	*0.320*		
Clinical features of IE						
Duration of symptoms <1 month	35 (68.6)	100 (57.8)	*1.547 (0.822–3.102)*	*0.194*		
Heart failure[a]	33 (64.7)	62 (35.8)	***3.282 (1.708–6.306)***	***<0.001***	***2.415 (1.159–5.029)***	***0.019***
Stroke[a]	11 (21.6)	16 (9.2)	***2.698 (1.162–6.266)***	***0.026***	***3.206 (1.190–8.632)***	***0.021***
Peripheral emboli[a]	5 (9.8)	42 (24.3)	***0.339 (0.126–0.909)***	*0.030*		
Vertebral osteomyelitis	3 (5.9)	10 (5.8)	*1.019 (0.270–3.851)*	*1.0*		
AKI[a]	31 (60.8)	62 (35.8)	***2.775 (1.460–5.275)***	***0.002***	***2.283 (1.085–4.805)***	***0.030***
Predisposition of IE						
History of IE	3 (5.9)	17 (9.8)	*0.574 (0.161–2.041)*	*0.577*		
Native valve predisposition	9 (17.6)	29 (16.8)	*1.064 (0.467–2.423)*	*0.835*		
Pathogens of IE						
BCN IE	8 (15.7)	31 (17.9)	*1.173 (0.502–2.742)*	*0.835*		
Staphylococcus aureus	16 (31.4)	46 (26.6)	*1.262 (0.639–2.493)*	*0.593*		
Enterococcus spp.[a]	13 (25.5)	23 (13.3)	***2.231 (1.036–4.807)***	***0.050***		
Oral Streptococci	6 (11.8)	32 (18.5)	*0.588 (0.231–1.495)*	*0.297*		
Candida spp.	3 (5.9)	5 (2.9)	*2.100 (0.484–9.105)*	*0.386*		
Cardiac ECHO of IE						
LSIE/RSIE[3]	44/7 (86.3)/(13.7)	139/34 (80.3)/(19.7)	*0.650 (0.269–1.570)*	*0.413*		
Multi-valvular IE	16 (31.4)	54 (31.2)	*1.007 (0.514-1.975)*	*1.0*		
PVE	15 (29.4)	29 (16.8)	*2.069 (1.005–4.261)*	*0.069*		
CIED IE	1 (2.0)	13 (7.5)	*0.246 (0.031–1.929)*	*0.199*		
Valve abscess[a]	7 (13.7)	7 (4.0)	***3.773 (1.257–11.324)***	***0.020***		
Community-acquired IE	33 (64.7)	122 (70.5)	*0.766 (0.396–1.484)*	*0.491*		
Healthcare IE[a]	15 (29.4)	30 (17.3)	*1.986 (0.967–4.078)*	*0.073*		
IVDA IE[6]	3 (5.9)	21 (12.1)	*0.452 (0.129–1.583)*	*0.303*		
Cardiac surgery for IE[a]	7 (13.7)	47 (27.2)	*0.426 (0.180–1.013)*	*0.062*	***0.304 (0.107–0.863)***	***0.026***
Rx guidelines for IE[a,b]	32 (62.7)	133 (76.9)	***0.507 (0.260–0.989)***	***0.049***	***0.416 (0.189–0.915)***	***0.029***

Abbreviations: AKI, acute kidney injury; IE, infective endocarditis; BCN, blood culture negative; ECHO, echocardiography; LSIE, left-sided infective endocarditis; RSIE, right-sided infective endocarditis; PVE, prosthetic valve endocarditis; CIED, cardiac implantable electronic device; IVDA, intravenous drug abuse.
[a] Variables included in the multivariate logistic statistical model.
[b] Compliance with European Society of Cardiology guidelines for antimicrobial treatment of infective endocarditis.

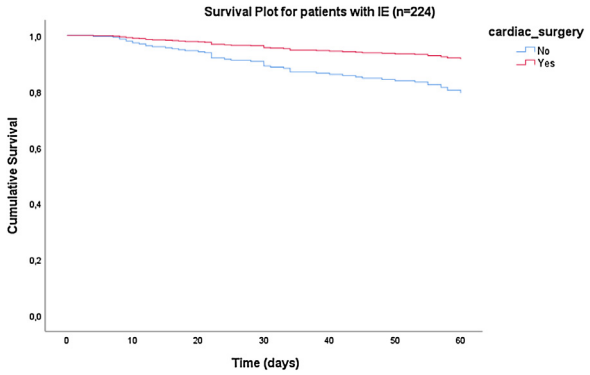

Figure 1. Patients who receive cardiac surgery during hospitalization presented a 60-day survival benefit in the cox-regression analysis [HR 0.386 CI95%: 0.165–0.903, $p = 0.028$).

comorbidities and healthcare-associated infection bearing an in-hospital mortality around 30% (Selton-Suty et al., 2012; Bruun Oestergaard et al., 2017; Gálvez-Acebal et al., 2010; Durante-Mangoni et al., 2008; Hase et al., 2015; DeSimone et al., 2015; Le Moing et al., 2015). The paradox of the current study was not the predominance of *S. aureus* in the IVDA patients (Le Moing et al., 2015), but the lack of impact of *S. aureus* on short-term mortality. MRSA prevailed in younger patients, with IE reflecting either community-acquired MRSA or pre-colonization by nosocomial MRSA due to prior hospitalizations, especially among IVDAs; however, relevant data were not available. Moreover, MRSA was not more lethal than MSSA, as previously reported (Hill et al., 2008). Even if *S. aureus* was the leading cause of IE in the current cohort, a potential correlation between *S. aureus* IE and the patients' socioeconomic conditions that might influence the incidence of bacteremia, as previously reported, could not be evaluated (Bruun Oestergaard et al., 2017).

Enterococcus spp. has been emerging in Greece since the 2000–2004 population study, with a double incidence compared with international IE cohorts (Habib et al., 2019; McDonald et al., 2005; Olaison and Schadewitz, 2002; Olmos et al., 2017). Moreover, in the past country cohort, enterococcal IE was more healthcare than community acquired (30.9% vs 16.3%, $p = 0.05$) (Giannitsioti et al., 2007). In the present study, enterococcal IE predominated in the elderly who also presented with healthcare-associated IE. Therefore, enterococcal IE is a timeless frequently persistent pathogen of IE in the country and should be taken into account in the initial empirical antimicrobial treatment of the disease prior to

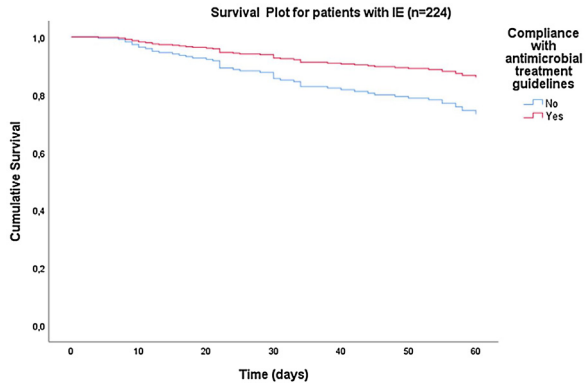

Figure 2. Compliance with antimicrobial treatment guidelines significantly promoted 60-day survival in Cox-regression analysis. HR: 0.487 (CI95%: 0.259–0.916), $p = 0.026$.

microbiological documentation. Moreover, contrary to other studies (Fernández Guerrero et al., 2007; Chirouze et al., 2013), the current findings suggest that enterococcal IE could be even more lethal than *S. aureus* IE. Perhaps this is due to the advanced age of patients with enterococcal IE, which can bear high rates of complications from the disease.

Overall, mortality exceeded the international average (Murdoch et al., 2009) and was strongly predicted by complications of IE, especially the detrimental effect of heart failure, AKI and stroke, as already described (Moreillon and Que, 2004; Hoen and Duval, 2013; Tornos et al., 2005; Murdoch et al., 2009; Olmos et al., 2017; Fowler et al., 2005; Miró et al., 2002; Ludvigsen et al., 2016; Gálvez-Acebal et al., 2010; Hase et al., 2015; Habib et al., 2019; Kiefer et al., 2011; Oliver et al., 2017; Vikram et al., 2003; Gabbieri et al., 2008; Buchholtz et al., 2009). Surprisingly, peripheral embolization did not reduce survival in the current cohort, perhaps due to a relative predilection for patients with RSIE who usually present a more favorable outcome than those with left-sided IE (Miró et al., 2002; Habib et al., 2019). Valve abscess showed only a non-significant trend towards mortality, which was contrary to previous data (Murdoch et al., 2009; Gálvez-Acebal et al., 2010; Habib et al., 2019; Kiefer et al., 2011). Furthermore, the current study did not confirm that diabetes mellitus had adversely influenced the outcome (Selton-Suty et al., 2012; Kiefer et al., 2011; Aksoy et al., 2007).

Cardiac surgery within the index hospitalization time was performed upon indication in <50% of the current patients compared with >70% of patients from international cohorts (McDonald et al., 2005; Chu et al., 2015). A population country study in the USA showed lower rates of surgery for IE in regional than referral centers (DeSimone et al., 2015). This is a recognized potential bias of the conflicting results in IE studies (Chu et al., 2015; Gálvez-Acebal et al., 2014). Comparable low rates of cardiac surgery for IE were observed in the 2000–2004 cohort study (Giannitsioti et al., 2007). Moreover, mortality of IE remained high in both periods, and did not corroborate the significant fall within decades that was detected in other countries (Selton-Suty et al., 2012; Olmos et al., 2017). A reluctance for surgery, despite relevant indication, was documented in the critically ill, elderly and patients with *S. aureus* IE (Chu et al., 2015; Gálvez-Acebal et al., 2014). However, in the current cohort, *S. aureus* was not a predictor against surgery for IE, directly confronting data from more than 1200 patients operated for IE (Chu et al., 2015). The relatively low rates of surgery cannot be directly correlated with the sustained increased mortality. Moreover, the optimal timing for performing early surgery for IE is still unknown. Overall, the largest propensity-based studies indicate that early surgery reduces mortality, especially in native valve endocarditis (Hoen and Duval,

Table 4
Epidemiological trends of infective endocarditis between two periods before and during the economic crisis.

Variables, n (%)	Cohort A (2000–2004)	Cohort B (2011–2014)	*p*
Demographics of IE			
Age >60 years	124 (63.6)	139 (62.1)	0.762
Male/female	126/69 (64.6)/(35.4)	162/62 (72.3)/(27.7)	0.092
Symptoms lasting <1 month before diagnosis	138 (70.8)	135 (60.3)	0.031
Comorbidities	117 (60)	165 (73.5)	0.003
Diabetes mellitus	39 (20)	48 (21.4)	0.809
Renal failure	7 (3.6)	50 (22.3)	<0.001
Cardiovascular diseases	73 (37.4)	61 (27.2)	0.028
Malignancy	18 (9.2)	25 (11.2)	0.629
Cirrhosis	11 (5.6)	3 (1.3)	0.026
HIV infection	0	10 (4.5)	0.002
Predisposition of IE			
History of IE	19 (9.7)	20 (8.9)	0.866
History of rheumatic fever	28 (14.4)	16 (7.1)	0.024
Native valve IE predisposition	77 (39.5)	38 (17.0)	<0.001
Healthcare IE	42 (21.5)	45 (20.1)	0.719
IVDA IE	14 (7.2)	24 (10.7)	0.235
Echo diagnosis			
PVE	42 (21.5)	44 (19.6)	0.716
Right/left-sided IE	13/182 (6.7)/(93.3)	41/183 (18.3)/(81.7)	<0.001
Microbiology of IE			
BCN IE	37 (19)	39 (17.4)	0.704
Viridans streptococci	40 (20.5)	38 (17.0)	0.380
Staphylococcus aureus	34 (17.4)	62 (27.7)	0.014
Enterococci	38 (19.5)	36 (16.1)	0.372
Candida spp.	3 (1.5)	8 (3.6)	0.233
Complications of IE			
Heart failure of IE	67 (34.4)	95 (42.4)	0.108
Embolization of IE	66 (33.8)	65 (29.0)	0.293
Treatment outcome			
Cardiac surgery	53 (28.3)	54 (24.1)	0.367
Mortality	39 (23.4)	51 (22.8)	0.904

Abbreviations: IE, infective endocarditis; PVE, prosthetic valve endocarditis; IVDA, intravenous drug abuse; BCN, blood culture negative.

2013; Tleyjeh et al., 2008; Kiefer et al., 2011; Vikram et al., 2003; Gabbieri et al., 2008; Aksoy et al., 2007; Chu et al., 2015; Gálvez-Acebal et al., 2014; Lalani et al., 2010). Variations in population cohorts, definition of timing of surgery and methods of statistical analysis cannot allow safe considerations (Tleyjeh et al., 2008; Malhotra and Prendergast, 2012; Bannay et al., 2011).

This study showed that very early cardiac surgery (within 7 days from indication during the index hospitalization) led to 100% survival. Despite the small size, the results were in accordance with large epidemiological international cohorts, which demonstrated that early surgery confers a survival benefit and absolute risk reduction of death compared with solely medically treated patients (Chu et al., 2015; Lalani et al., 2010; Ohara et al., 2013; Wang et al., 2019; Werner et al., 2003). Even if older patients were slower in undergoing surgery for IE, their chances of survival increased following the operation (Durante-Mangoni et al., 2008; Oliver et al., 2017; Østergaard et al., 2018). Moreover, the current results corroborate a previous study on patients with heart failure from IE who survived following surgery compared with those only medically treated (Giannitsioti et al., 2007). Cardiac surgery for IE should be individualized in the context of an integrated management of patients with IE by the 'endocarditis team' (Hoen and Duval, 2013; Habib et al., 2015; Malhotra and Prendergast, 2012; Habib et al., 2019). The current study also evaluated the role of physicians' compliance with antimicrobial treatment guidelines (Habib et al., 2015). Adherence to guideline-driven antimicrobial treatment for IE was >70% compared with the 58% rate reported by a multi-center survey (Tissot-Dupont et al., 2017). The current study demonstrated that if both adequate antimicrobial treatment and early cardiac surgery for IE upon indication were applied, mortality fell to approximately 10%. Therefore, this study highlights the necessity of adherence with current guidelines for the treatment of IE. Moreover, the reduction in pre-diagnostic empirical antimicrobial administration from 70% in the 2000–2004 registry (Giannitsioti et al., 2007) to 48.6% in the present cohort, while far from being ideal, is encouraging towards a prompt diagnosis of the disease. Rates of blood-culture-negative IE affecting adequate antimicrobial treatment increased in parallel with raised antimicrobial consumption prior to diagnosis of IE (Lamas et al., 2016; Werner et al., 2003).

This study had certain limitations. There was a lack of long-term follow-up of participants; therefore, delayed surgical treatment for IE or relapse of the disease affecting long-term mortality could not be evaluated. Moreover, factors associated with restrain from surgery, despite relevant indication, were not fully explored. Although the previous cohort was the largest in the country, it had not incorporated the variables of the current study; therefore, any comparison should be mentioned with caution.

However, this study succeeded in demonstrating not only an evolving profile of the disease, but also the significant degree of adherence to diagnostic and treatment guidelines in Greece, despite the deep economic crisis. Mortality was not worse compared with previous data, as it could have been hypothesized in the light of reduced healthcare resources during the study period.

In conclusion, this study did not confirm the classical risk factors of adverse outcome in IE as diabetes mellitus, *S. aureus* and peripheral embolization; on the contrary, Enterococci emerged and was sustained as a significant factor of mortality. Emerging HIV infection, IVDA and RSIE along with predominance of *S. aureus* — mostly MRSA — in the youth might partly explain this differentiation from other international reports. Only compliance with guidelines for antimicrobial treatment and cardiac surgery upon indication significantly promoted 60-day survival. These results highlighted the importance of adherence to the current guidelines for diagnosis and treatment of IE and the need for a continuous epidemiological survey of the changing profile of IE as a useful tool towards adequate management of the disease.

Ethical approval

The study received Ethical approval by the Hospital Scientific and Administrative Committee.

Informed consent

Each participant gave written informed consent for the study.

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Conflict of interest

No conflict of interest to be declared by all authors.

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.ijid.2021.03.009.

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