Article

Infective Endocarditis in Diabetic Patients: A Different Profile with Prognostic Consequences

Maria Isabel Biezma 1, Patricia Muñoz 2,3, Sofía De la Villa 2,4, Mª Carmen Fariñas-Álvarez 4, Francisco Arnáiz de las Revillas 4, Encarnación Gutiérrez-Carretero 5, Aristides De Alarcón 5, Raquel Rodríguez-García 6, Jaume Llopis 7, Miguel Ángel Goenaga 8, Andrea Gutiérrez-Villanueva 9, Antonio Plata 10, Laura Vidal 11, Manuel Martínez-Sellés 1,12,*,† and on behalf of GAMES ‡

1 Escuela de Doctorado, Universidad Europea de Madrid, 28670 Madrid, Spain; mariabel.biezma@gmail.com
2 Servicio de Microbiología Clínica y Enfermedades Infecciosas, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, 28007 Madrid, Spain
3 CIBERES (CIBER Enfermedades Respiratorias)—Facultad de Medicina, Universidad Complutense de Madrid, 28040 Madrid, Spain
4 Servicio de Enfermedades Infecciosas, Hospital Universitario Marqués de Valdecilla, DIVAL (Instituto de Investigación Sanitaria Valdecilla), CIBER de Enfermedades Infecciosas-CIBERINFEC (CB21/15/00688), Instituto de Salud Carlos III, Universidad de Cantabria, 39008 Santander, Spain
5 Cardiac Surgery Service, CIBERCV (CIBER Enfermedades Cardiovasculares), Institute of Biomedicine of Seville (IBIS), University of Seville/CSIC/University Hospital Virgen del Rocío Seville, 41013 Seville, Spain
6 Servicio de Medicina Intensiva, Hospital Universitario Central de Asturias, Universidad de Oviedo, 33011 Oviedo, Spain
7 Department of Genetics, Microbiology and Statistics, University of Barcelona, 08007 Barcelona, Spain
8 Servicio de Enfermedades Infecciosas, Hospital Universitario Donostia, 20014 San Sebastian, Spain
9 Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Universitario Puerta de Hierro, 28222 Majadahonda, Spain
10 UGC Enfermedades Infecciosas, Microbiología y Medicina Preventiva, IBIMA (Instituto de Investigación Biomédica de Málaga), Hospital Regional Universitario de Málaga, 29010 Málaga, Spain
11 Servicio de Cardiología, Hospital Universitario Son Espases, 07120 Palma de Mallorca, Spain
12 Cardiology Department, Hospital General Universitario Gregorio Marañón, CIBERCV (CIBER Enfermedades Cardiovasculares), Universidad Complutense, 28040 Madrid, Spain

* Correspondence: mmssel@secardiologia.es
† GAMES members are listed in Acknowledgments.

Abstract: Background. Infective Endocarditis (IE) is a severe condition. Diabetes mellitus (DM) has been associated with a poor prognosis in other settings. Our aim was to describe the profile and prognosis of IE with and without DM and to analyze the prognostic relevance of DM-related organ damage. Methods. Retrospective analysis of the Spanish IE Registry (2008–2020). Results. The cohort comprised 5590 IE patients with a mean age of 65.0 ± 15.5 years; 3764 (67.3%) were male. DM was found in 1625 patients (29.1%) and 515 presented DM-related organ damage. DM prevalence during the first half of the study period was 27.6% vs. 30.6% in the last half, p = 0.015. Patients with DM presented higher in-hospital mortality than those without DM (521 [32.1%] vs. 924 [23.3%], p < 0.001) and higher one-year mortality (640 [39.4%] vs. 1131 [28.5%], p < 0.001). Among DM patients, organ damage was associated with higher in-hospital mortality than those without DM (521 [32.1%] vs. 924 [23.3%], p < 0.001) and one-year mortality (427 [48.0%] vs. 393 [35.4%], p < 0.001). Multivariate analyses showed an independent association of DM with in-hospital (odds ratio [OR] = 1.34, 95% confidence interval [CI]: 1.16–1.55, p < 0.001) and one-year mortality (OR = 1.38, 95% CI: 1.21–1.59, p < 0.001). Among DM patients, organ damage was independently associated with higher in-hospital (OR = 1.37, 95% CI: 1.06–1.76, p = 0.015) and one-year mortality (OR = 1.59, 95% CI = 1.26–2.01, p < 0.001) Conclusions. The prevalence of DM among patients with IE is increasing and is already above 30%. DM is independently associated with a poor prognosis, particularly in the case of DM with organ damage.

Keywords: infective endocarditis; diabetes mellitus; prognosis; in-hospital mortality; one-year mortality; organ damage
1. Introduction

Infective Endocarditis (IE) is a severe disease with high in-hospital mortality [1,2]. Almost one third of IE patients present diabetes mellitus (DM) [2–5]. DM has been associated with a poor prognosis in sepsis [6–8]. An association of DM with prognosis in IE patients has also been described [1,4]. However, DM is associated with advanced age, comorbidities, atypical clinical presentation, and longer IE diagnosis time, among other characteristics that have a strong prognostic influence in IE [2–5]. Due to that reason, the independent association of DM with IE mortality is unclear [3,4]. Some authors have suggested an independent association [1] while other data do not support it [3].

Our aim was to describe the profile and prognosis of IE with and without DM and to analyze the prognostic relevance of DM-related organ damage. We also studied the evolution of the yearly prevalence of DM in these patients.

2. Methods

The Spanish Collaboration on Endocarditis—GAMES (Grupo de Apoyo al Manejo de la Endocarditis Infectiosa en España)—is a national observational registry that has been previously described [9–11]. Multidisciplinary teams that compose this group, including infectious disease physicians, cardiologists, cardiac surgeons, microbiologists, echocardiographers, and other imaging specialists, prospectively completed standardized case report forms with information regarding IE episodes and follow-up data. A complete list of GAMES members is shown in Acknowledgments. IE patients were consecutively included at 38 Spanish hospitals between January 2008 and December 2020. Inclusion criteria were the diagnosis of definite or probable IE by modified Duke criteria [12]. IE management, including the decision to perform surgery and the type of surgery, was done by the local medical team following the 2009 and 2015 European Society of Cardiology recommendations [13]. DM was diagnosed based on the American Diabetes Association criteria [14]. DM-associated organ damage was considered to be present after analyzing clinical and laboratory techniques, as well as image data. For instance, renal disease with albuminuria and/or reduced glomerular filtration rate in the absence of signs or symptoms of other primary causes of kidney damage, neuropathy with loss of protective sensation, and neovascularization and/or vitreous/preretinal bleeding (in addition to non-proliferative retinopathy) [15].

This study complies with the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of participating centers.

Statistical Methods

Continuous variables are summarized as means ± standard deviations (SD) or medians, and interquartile ranges, when a normal distribution was not observed, as per the Kolmogorov−Smirnov goodness-of-fit test; categorical variables are expressed as numbers and percentages. Student’s t-test, Mann–Whitney U test, or paired t-test were used to compare continuous variables. Categorical variables were compared using the χ² test or Fisher’s exact test. Multivariable logistic regression analyses (backward selection) were performed to determine mortality predictors and to assess the independent association of DM, with and without organ damage, with mortality. All variables with p value < 0.10 in univariate analyses were included in the multivariable analyses. Statistical analysis was performed using SPSS, version 22.0 (IBM, Armonk, NY, USA).

3. Results

The cohort comprises 5590 IE patients with a mean age of 65.0 ± 15.5 years; 3764 (67.3%) were male. DM was found in 1625 patients (29.1%) and 515 presented DM-related organ damage (Figure 1).
Figure 1. Study overview. IE: infective endocarditis. DM: diabetes mellitus.

Figure 2 shows the yearly prevalence of DM during the study period. The prevalence of DM during the first half of the study period was 27.6% vs. 30.6% in the last half, \( p = 0.015 \).

![Graph showing yearly prevalence of diabetes](image)

Figure 2. Yearly prevalence of diabetes during the study period.

Table 1 shows the clinical characteristics of patients with and without DM. Compared with those without DM, DM patients presented more frequently advanced age, cardiac implantable electronic device location, nosocomial origin, cardiovascular and renal disease, and had a higher Charlson Comorbidity index. Mean age on the first 6.5 years of the study period was lower than in the last 6.5 years, both in the global population and in diabetic patients (65.0 ± 15.6 years vs. 66.2 ± 15.3 years, \( p = 0.004 \); 69.3 ± 11.2 vs. 71.0 ± 10.5, \( p = 0.003 \), respectively).
Table 1. Clinical characteristics of infective endocarditis (IE) according to the presence of diabetes mellitus (DM).

|                          | No DM (3965) | DM (1625) | p   |
|--------------------------|--------------|-----------|-----|
| Age, years, median (IQR) | 67 (54–77)   | 72 (64–78) | <0.001 |
| Male Gender (%)          | 2679 (67.5)  | 1085 (66.7) | 0.564 |
| Nosocomial IE (%)        | 1041 (26.3)  | 535 (32.9)  | <0.001 |
| Health care-associated IE (%) | 306 (7.7) | 158 (9.7)  | 0.014 |
| Vegetation present (%)   | 2893 (73.0)  | 1150 (70.8) | 0.096 |
| New heart murmur (%)     | 1349 (34.0)  | 477 (29.3)  | 0.001 |
| Location (%)             |              |           |     |
| Aortic                   | 2060 (52.0)  | 830 (51.1)  | 0.551 |
| Mitral                   | 1688 (42.6)  | 670 (41.2)  | 0.356 |
| Tricuspid                | 215 (5.4)    | 79 (4.9)    | 0.394 |
| Pulmonary                | 71 (1.8)     | 8 (0.5)     | <0.001 |
| PM/ICD                   | 349 (8.8)    | 213 (13.1)  | <0.001 |
| Others                   | 113 (2.8)    | 37 (2.3)    | 0.229 |
| Multiple                 | 570 (14.4)   | 227 (14.0)  | 0.693 |
| Unknown                  | 66 (1.7)     | 24 (1.5)    | 0.613 |
| Native IE                | 2459 (62.0)  | 941 (57.9)  | 0.004 |
| Prosthetic IE            | 1213 (30.6)  | 528 (32.5)  | 0.164 |
| Comorbidities (%)        |              |           |     |
| Respiratory disease      | 668 (16.8)   | 379 (23.3)  | <0.001 |
| Coronary artery disease  | 877 (22.1)   | 625 (38.4)  | <0.001 |
| Heart failure            | 1179 (29.7)  | 691 (42.5)  | <0.001 |
| Peripheral arterial disease | 286 (7.2) | 315 (19.3)  | <0.001 |
| Stroke                   | 441 (11.1)   | 277 (17.0)  | <0.001 |
| Cancer                   | 642 (16.1)   | 254 (15.6)  | 0.604 |
| Renal disease            | 844 (21.3)   | 586 (36.1)  | <0.001 |
| Liver disease            | 370 (9.4)    | 163 (10.1)  | 0.443 |
| Congenital heart disease | 303 (7.6)    | 38 (2.3)    | <0.001 |
| Native heart valve disease | 1794 (45.2) | 773 (47.5)  | 0.113 |
| Age-adjusted Charlson score, median (IQR) | 4 (2–6) | 6 (5–8) | <0.001 |

IQR = Interquartile range; PM = Pacemaker; ICD = Implantable cardioverter defibrillator.

Staphylococcus and enterococcus etiology were more common among diabetics (Table 2). Table 3 shows the clinical outcome according to the presence of diabetes. Compared with those without DM, DM patients presented complications more frequently and had higher in-hospital and one-year mortality. Among diabetics, patients with DM-related organ damage were a high-risk population with a poor prognosis (Table 4 and Figure 3). Multivariate analyses showed an independent association of DM with in-hospital and one-year mortality (Table 5). In addition, among diabetics, organ damage was an independent predictor of mortality.

Table 2. Infective endocarditis etiology according to the presence of diabetes mellitus (DM).

| Etiology (%)                  | No DM (3965) | DM (1625) | p  |
|-------------------------------|--------------|-----------|----|
| *Staphylococcus aureus*       | 836 (21.1)   | 413 (25.4) | <0.001 |
| *Coagulase-negative staphylococcus* | 680 (17.2) | 322 (19.8) | 0.018 |
| *Enterococcus*                | 519 (13.1)   | 268 (16.5) | 0.001 |
| *Streptococcus*               | 1081 (27.3)  | 346 (21.3) | <0.001 |
| *Candida*                     | 68 (1.7)     | 20 (1.2)   | 0.187 |
| Other Fungi                   | 11 (0.3)     | 4 (0.2)    | 0.837 |
| Unknown                       | 345 (8.7)    | 112 (6.9)  | 0.025 |
| Anaerobe                      | 52 (1.3)     | 16 (1.0)   | 0.311 |
| Polymicrobial                 | 65 (1.6)     | 21 (1.3)   | 0.338 |
| Gram-negative bacteria        | 167 (4.2)    | 60 (3.7)   | 0.372 |
| Other etiologies              | 112 (2.8)    | 34 (2.1)   | 0.119 |
Table 3. Clinical Course according to the presence of diabetes mellitus (DM).

| Intracardiac complications (%) | No DM (3965) | DM (1625) | p   |
|--------------------------------|-------------|-----------|-----|
| Valve perforation              | 581 (14.6)  | 203 (12.4)| 0.035|
| Pseudoaneurysm                 | 248 (6.2)   | 90 (5.5)  | 0.308|
| Abscess                        | 639 (16.1)  | 283 (17.4)| 0.235|
| Fistula                        | 105 (2.6)   | 35 (2.1)  | 0.283|
| Vascular events (%)            | 340 (8.5)   | 98 (6.0)  | 0.001|
| Heart Failure (%)              | 1554 (39.1) | 699 (43.0)| 0.008|
| Persistent bacteremia (%)      | 402 (10.1)  | 204 (12.5)| 0.008|

| Central nervous system involvement (%) | No DM (3965) | DM (1625) | p   |
|----------------------------------------|-------------|-----------|-----|
| Vascular events (%)                    | 340 (8.5)   | 98 (6.0)  | 0.001|
| Heart Failure (%)                      | 1554 (39.1) | 699 (43.0)| 0.008|
| Persistent bacteremia (%)              | 402 (10.1)  | 204 (12.5)| 0.008|

Table 4. Main differences seen in patients with diabetes according to the presence of diabetes-related organ damage.

| Organ Damage (515) | No Organ Damage (1110) | p   |
|--------------------|------------------------|-----|
| Nosocomial IE (%)  | 330 (29.7)             | 205 (39.8) | <0.001|
| Health care-associated IE (%) | 67 (6.0) | 91 (17.7) | <0.001|
| Native IE (%)      | 617 (55.6)             | 324 (62.9) | 0.005|
| Prosthetic IE (%)  | 392 (35.3)             | 136 (26.4) | <0.001|
| Coronary artery disease (%) | 394 (35.4) | 231 (44.8) | <0.001|
| Heart failure (%)  | 428 (38.5)             | 263 (51.0) | <0.001|
| Perivascular arterial disease (%)    | 116 (10.4)           | 199 (38.4) | <0.001|
| Stroke (%)         | 168 (15.1)             | 109 (21.1) | 0.003|
| Cancer (%)         | 197 (17.7)             | 57 (11.0)  | 0.001|
| Renal disease (%)  | 267 (24.1)             | 319 (61.9) | <0.001|
| Age-adjusted Charlson score, median (IQR) | 6 (4–7) | 8 (6–9) | <0.001|
| Staphylococcus aureus (%) | 219 (19.7) | 194 (37.7) | <0.001|
| Streptococcus (%)   | 278 (25.0)             | 68 (13.2)  | <0.001|
| Cardiac Surgery (%) | 523 (47.1)            | 184 (35.7) | <0.001|
| In-hospital mortality (%) | 321 (28.9) | 200 (38.8) | <0.001|
| One-year mortality (%) | 393 (35.4) | 247 (48.0) | <0.001|

IQR = Interquartile range.

Table 5. Independent predictor of mortality. (A) All population, in-hospital mortality. (B) All population, one-year mortality. (C) Diabetics, in-hospital mortality. (D) Diabetics, one-year mortality.

| OR (95% CI) | p   |
|-------------|-----|
| Diabetes    | 1.4 (1.2–1.6) | <0.001|
| Age (years) | 1.02 (1.02–1.03) | <0.001|
| Female sex  | 1.3 (1.1–1.5) | 0.001|
| Heart failure | 2.6 (2.3–3.0) | <0.001|
| Renal disease | 2.2 (1.9–2.5) | <0.001|
| Sepsis      | 2.1 (1.7–2.5) | 0.005|
| S. aureus   | 1.4 (1.2–1.7) | 0.002|
Table 5. Cont.

| (B)                              | OR (95% CI)       | p     |
|----------------------------------|-------------------|-------|
| Diabetes                         | 1.4 (1.2–1.6)     | <0.001|
| Age (years)                      | 1.02 (1.02–1.03)  | <0.001|
| Female sex                       | 1.17 (1.02–1.34)  | 0.027 |
| Heart failure                    | 2.4 (2.1–2.8)     | <0.001|
| Renal disease                    | 2.0 (1.8–2.3)     | <0.001|
| Sepsis                           | 2.0 (1.7–2.4)     | <0.001|
| Cardiac surgery not done         | 1.3 (1.1–1.5)     | 0.005 |
| *S. aureus*                      | 1.3 (1.1–1.5)     | 0.002 |

| (C)                              | OR (95% CI)       | p     |
|----------------------------------|-------------------|-------|
| Diabetes-related organ damage    | 1.4 (1.1–1.8)     | 0.01  |
| Age (years)                      | 1.02 (1.01–1.03)  | 0.007 |
| Female sex                       | 1.4 (1.1–1.8)     | 0.01  |
| Heart failure                    | 3.2 (2.5–4.1)     | <0.001|
| Renal disease                    | 2.3 (1.8–2.9)     | <0.001|
| Sepsis                           | 1.8 (1.3–2.4)     | <0.001|
| *S. aureus*                      | 1.4 (1.1–1.9)     | 0.01  |

| (D)                              | OR (95% CI)       | p     |
|----------------------------------|-------------------|-------|
| Diabetes-related organ damage    | 1.6 (1.3–2.0)     | <0.001|
| Age (years)                      | 1.02 (1.01–1.03)  | <0.001|
| Female sex                       | 1.32 (1.04–1.67)  | 0.024 |
| Heart failure                    | 2.7 (2.1–3.3)     | <0.001|
| Renal disease                    | 2.1 (1.7–2.6)     | <0.001|
| Sepsis                           | 1.7 (1.3–2.3)     | <0.001|

OR = Odds ratio; CI = Confidence Interval.

Figure 3. Kaplan–Meier survival according to the presence of diabetes mellitus (DM) and DM-related organ damage.
4. Discussion

Our data show that the prevalence of DM among patients with IE is increasing and about 30% of patients with IE have DM. Diabetics had a poor prognosis, particularly in the case of DM with organ damage. Compared with non-diabetics, diabetic patients had comorbidities more frequently, mainly cardiovascular and renal disease. Diabetics also had a high-risk profile with more nosocomial and healthcare-related IE and more frequent \textit{S. aureus} etiology. As expected, diabetics had a poor prognosis. Even after correcting for confounding factors, the association of DM with in-hospital and one-year mortality remained significant.

The prevalence of DM in the general population is increasing [16]. In our country the prevalence of DM in the general population aged 65–75 years increased from 17% in 2006 to 21% in 2017 [17]. Our study also found a similar trend in IE patients. Previous authors have suggested an increase in DM prevalence in IE patients [3,5]. Abe et al. [5] found a prevalence of 22% in 2004 that increased to 30% in 2014. The reasons that explain the increase in the prevalence of DM are unknown. Population aging may play a role. In our sample, the mean age on the last half of the study period was higher than in the first half, and this was also true in diabetic patients.

Although some previous studies suggested an association of DM with IE mortality [1,4], others did not identify DM as a prognostic factor [18–24]. The independent association of DM with prognosis is unclear and a significant age interaction could be a confounding factor [4]. On the other hand, even prediabetes has been associated with a higher mortality risk [25,26]. Although no previous studies have focused on the prognostic implications of DM-related organ damage, DM has been associated with higher rates of heart and renal failures [26] and more advanced DM stages, such as longer DM duration, insulin-treated DM [25], and higher Diabetes Complications Severity Index [27], which have been related to higher IE risk and a poor prognosis.

The relation of DM with the prognosis of IE might have several explanations. DM is associated with endothelial dysfunction which can promote stronger bacterial adhesion [28,29]. In addition, diabetics have an impaired immune response [30] and more common bacteremia with aggressive bacteria such as \textit{S. aureus} [31]. Moreover, diabetics have defects of neutrophil activities [32–34]. Immune system dysfunction due to chronic low-grade inflammation seen in DM favors micro-organism growth, a process that contributes to sepsis progression [6–8].

Our work could have relevant clinical implications. Due to the poor prognosis of IE in diabetics, it might be reasonable to consider earlier and more aggressive treatments and interventions in these patients, particularly in those with previous DM-related organ damage. Close follow-up and correct glycaemia control might improve the outcome.

The limitations of this study should be noted. The retrospective design justifies that relevant variables such as type of DM, DM duration, level of glycated hemoglobin, presence of diabetic cardiomyopathy, and DM-therapy were not collected systematically. Local medical teams were responsible for IE management, including deciding on surgery, and any judgements may have been influenced by factors not registered in this study. Finally, cause of death during follow-up was not available for a large number of patients.

In any case, our data come from a large national database and show a clear association of DM with IE prognosis. Moreover, ours is the first study to compare the prognosis of IE in diabetics with and without organ damage.

5. Conclusions

The prevalence of DM among patients with IE is increasing and is already above 30%. DM is independently associated with a poor prognosis, particularly in the case of DM with organ damage.
Author Contributions: Conceptualization, M.M.-S.; Formal analysis, M.I.B. and M.M.-S.; Investigation, P.M., S.D.I.V., M.C.E.-A., F.A.d.I.R., E.G.-C., A.D.A., R.R.-G., J.L., M.A.G., A.G.-V., A.P., L.V. and M.M.-S.; Supervision, M.M.-S.; Writing—original draft, M.I.B.; Writing—review & editing, M.I.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Comunidad de Madrid (protocol code18/07, approval date 11 January 2008).

Informed Consent Statement: Informed consent was obtained from all subjects.

Data Availability Statement: Data available under request from SEICAV.

Acknowledgments: The authors of this manuscript are grateful for the collaboration of the researchers of the GAMES: Hospital Costa del Sol, (Marbella): Fernando Fernández Sánchez, Mariam Noureddine, Gabriel Rosas, Javier de la Torre Lima; Hospital Universitario de Cruces, (Bilbao): Roberto Blanco, María Victoria Boado, Marta Campaña Lázzaro, Alejandro Crespo, Josune Goikoetxea, José Ramón Iuretaygoiena, Josu Iruzun Zuazabal, Leire López-Soria, Miguel Montejo, Javier Nieto, David Rodrigo, Regina Rodríguez, Yolanda Vitoria, Roberto Vocos; Hospital Universitario Virgen de la Victoria, (Málaga): Mª Victoria García López, Radka Ivanova Georgieva, Guillermo Ojeda, Isabel Rodríguez Ballón, Josefa Ruiz Morales; Hospital Universitario Donostia-Policíncula Gipuzkoa, (San Sebastián): Ana María Cuende, Tomás Echeverría, Ana Fuerte, Eduardo Gaminde, Miguel Ángel Goenga, Pedro Idigoras, José Antonio Iribarren, Alberto Izaguirre Yarza, Xabier Kortajarena Urkola, Carlos Reviejo; Hospital General Universitario de Alicante, (Alicante): Rafael Carrasco, Vicente Climent, Patricio Llamas, Esperanza Merino, Joaquín Plazas, Sergio Reus; Complejo Hospitalario Universitario A Coruña, (A Coruña): Nemesio Álvarez, José María Bravo-Ferrer, Laura Castelo, José Cuenca, Pedro Linares, Enrique Riceguez, María Rodríguez Mayo, Efrén Sánchez, Dolores Sousa Requejo; Complejo Hospitalario Universitario de Huelva, (Huelva): Francisco Javier Martínez; Hospital Universitario de Canarias, (Canarias): Mª del Mar Alonso, Beatriz Castro, Teresa Delgado Melian, Javier Fernández Sarabia, Dacíl García Rosado, Julia González González, Juan Calzadilla, Lissette Lorenzo de la Peña, Alina Pérez Ramirez, Pablo Prada Arrondo, Fermin Rodríguez Moreno; Hospital Regional Universitario de Málaga, (Málaga): Antonio Plata Ciezar, José Mª Regueira Iglesias; Hospital Universitario Central Asturias, (Oviedo): Víctor Asensi Álvarez, Carlos Costas, Jesús de la Hera, Jonnathan Fernández Suárez, Lisardo Iglesias Fraile, Víctor León Arguero, José López Menéndez, Pilar Mencia Bajo, Carlos Morales, Alfonso Moreno Torrico, Carmen Palmolo, Begona Paya Martínez, Ángeles Rodríguez Esteban, Raquel Rodríguez García, Mauricio Telenti Assenso; Hospital Clinic-IDIBAPS, Universidade de Barcelona, (Barcelona): Manuel Almela, Juan Ambrosioni, Manuel Azqueta, Mercé Brunet, Marta Bodro, Ramón Cartañá, Carlos Falces, Guillermina Fita, David Fuster, Cristina García de la María, Delia García-Pares, Marta Hernández-Meneses, Jaume Llopis Pérez, Francesc Marco, José M. Miró, Asunción Moreno, David Nicolás, Salvador Ninot, Eduardo Quintana, Carlos Paré, Daniel Pereda, Juan M. Pericás, José L. Pomar, José Ramírez, Irene Rovira, Elena Sandolvo, Marta Sitges, Dolores Soy, Adrián Téllez, José M. Tolosana, Bárbara Vidal, Jordi Vila; Hospital General Universitario Gregorio Marañón, (Madrid): Iván Adán, Javier Bermejo, Emilio Bouza, Daniel Celemín, Gregorio Cuerpo Caballer, Antonia Delgado Montero, Ana García Mansilla, Mª Eugenia García Leoni, Victor González Ramallo, Martha Kestler Hernández, Amaia Mari Hualde, Mercedes Marín, Manuel Martínez-Sellés, Patricia Muñoz, Cristina Rincón, Hugo Rodríguez-Abelea, Marta Rodríguez-Créixems, Blanca Pinilla, Angel Pinto, Mariaela Valerio, Pilar Vázquez, Eduardo Verde Moreno; Hospital Universitario La Paz, (Madrid): Isabel Torrenueva, Belén Loeches, Alejandro Martín Quiro, Mar Moreno, Ulises Ramírez, Verónica Rial Bastón, María Romero, Araceli Saldaña; Hospital Universitario Marqués de Valdecilla, (Santander): Jesús Agüero Balbin, Carlos Armíñanzas Castillo, Ana Arnaiz, Francisco Arnaiz de las Revillas, Manuel Cobo Blauestegui, María Carmen Farinas, Concepción Fariñas-Alvarez, Rubén Gómez Izquierdo, Iván García, Claudia González Rico, Manuel Gutiérrez-Cuadra, José Gutiérrez Diez, Marcos Pajaron, José Antonio Parra, Ramón Teira, Jesús Zarauza; Hospital Universitario Puerta de Hierro, (Madrid): Jorge Calderón Parra, Marta Cobo, Fernando Dominguez, Alberto Forteza, Pablo García Pavia, Jesús González, Ana Fernández Cruz, Elena Muñez, Antonio Ramos, Isabel Sánchez Romero; Hospital Universitario Ramón y Cajal, (Madrid): Tomasa Centella, José Manuel Hermida, José Luis Moya, Pilar Martín-Davila, Enrique Navas, Enrique Oliva, Alejandro del Río, Jorge Rodríguez-Roda Stuart, Soledad Ruiz; Hospital Universitario Virgen de las Nieves, (Granada): Carmen Hidalgo Tenorío; Hospital Universitario
Virgen Macarena, (Sevilla): Manuel Almedro Delia, Omar Araji, José Miguel Barquero, Román Calvo Jambrina, Marina de Cueto, Juan Gálvez Acebal, Irene Méndez, Isabel Morales, Luis Eduardo López-Cortés; Hospital Universitario Virgen del Rocío, (Sevilla): Aristides de Alarcón, Emilio García, Juan Luis Haro, José Antonio Lepe, Francisco López, Rafael Luque; Hospital San Pedro, (Logroño): Luis Javier Alonso, Pedro Azcárate, José Manuel Azcona Gutiérrez, José Ramón Blanco, Antonio Cabrera Villegas, Lara García-Alvarez, José Antonio Oteo, Mercedes Sanz; Hospital de la Santa Creu i Sant Pau, (Barcelona): Natividad de Benito, Mercè Gurguí, Cristina Pacho, Roser Pericas, Guillem Pons; Complejo Hospitalario Universitario de Santiago de Compostela, (A Coruña): M. Álvarez, A. L. Fernández, Amparo Martínez, A. Prieto, Benito Regueiro, E. Tijeira, Marino Vega; Hospital Santiago Apóstol, (Vitoria): Andrés Canut Blasco, José Cordero Mollar, Juan Carlos Gainzarain Arana, Oscar García Uriarte, Alejandro Martín López, Zurifiñe Ortiz de Zárate, José Antonio Urturi Matos; Hospital SAS Linea de la Concepción, (Cádiz): García-Dominguez Gloria, Sánchez-Porto Antonio; Hospital Clínico Universitario Virgen de la Arrixaca (Murcia): José Mª Arribas Leal, Elisa García Vázquez, Alicia Hernández Torres, Ana Blázquez, Gonzalo de la Morena Valenzuela; Hospital de Txagorritxu, (Vitoria): Angel Alonso, Javier Abarburu, Felicitas Elena Calvo, Anai Moreno Rodríguez, Paola Tarabini-Castellani; Hospital Virgen de la Salud, (Toledo): Eva Heredero Gálvez, Carolina Maicas Bellido, José Largo Pau, Mª Antonia Sepúlveda, Pilar Toledano Sierra, Sadaf Zafar Iqbal-Mirza; Hospital Rafael Méndez, (Lorca-Murcia): Eva Cascales Alcolea, Ivan Keituwa Yañez, Julián Navarro Martínez, Ana Peláez Ballesta; Hospital Universitario San Cecilio (Granada): Eduardo Moreno Escobar, Alejandro Peña Monje, Valme Sánchez Cabrera, David Vinuesa García; Hospital San Lázaro (Palma de Mallorca): María Arrizabalaga Asenjo, Carmen CIFuentes Luna, Juana Núñez Morcillo, Mª Cruz Pérez Seco, Aroa Villoslada Gelabert; Hospital Universitario Miguel Servet (Zaragoza): Carmen Aured Guallar, Nuria Fernández Abad, Pilar García Mangas, Marta Matamala Adell, Mª Pilar Palacán Ruiz, Juan Carlos Porres; Hospital General Universitario Santa Lucía (Cartagena): Begoña Alcaraz Vidal, Nazaret Cobos Trigueros, María Jesús Del Amor Espín, José Antonio Giner Caro, Roberto Jiménez Sánchez, Amaya Jimeno Almazán, Alejandro Ortiz Freire, Monserrat Viqueira González; Hospital Universitario Son Espases (Palma de Mallorca): Pere Pericás Ramis, Mª Ángeles Ribas Blanco, Enrique Ruiz de Goepgui Bordes, Laura Vidal Bonet; Complejo Hospitalario Universitario de Albacete (Albacete): Mª Carmen Bellón Munera, Elena Escríbano Garayzabal, Antonia Tercero Martínez, Juan Carlos Segura Luque; Hospital Universitario Terrassa: Cristina Badía, Lucía Boix Palop, Mariona Xercavins, Sónia Ibars; Hospital Universitario Negrín (Gran Canaria): Eloy Gómez Nebreda, Italia Horcajada Herrera, Irene Menduiña Gallego; Complejo Hospitalario Universitario Insular Materno Infantil (Las Palmas de Gran Canaria): Héctor Marrero Santiago, Isabel de Miguel Martínez, Elena Pisos Álamo; Hospital Universitario 12 de Octubre (Madrid): Carmen Díaz Pedrecho, Fernando Chaves, Santiago de Cossío, Francisco López Medrano, Mª Jesús López, Javier Solera, Jorge Solis; Hospital Universitari Bellvitge (Barcelona): Carmen Ardanuy, Guillermo Cuervo Requena, Sara Grillo, Alejandro Ruiz Majoral.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Lin, C.J.; Chua, S.; Chung, S.Y.; Hang, C.L.; Tsai, T.H. Diabetes mellitus: An independent risk factor of in-hospital mortality in patients with infective endocarditis in a new era of clinical practice. *Int. J. Environ. Res. Public Health* **2019**, *16*, 2248. [CrossRef] [PubMed]

2. Olmos, C.; Vilacosta, I.; Fernández-Pérez, C.; Bernal, J.L.; Ferrera, C.; García-Arribas, D.; Pérez-García, C.; San Román, J.A.; Maroto, L.; Macaya, C.; et al. The evolving nature of infective endocarditis in Spain. A population-based study (2003 to 2014). *J. Am. Coll. Cardiol.* **2017**, *70*, 2795–2804. [CrossRef] [PubMed]

3. De Miguel-Yanes, J.M.; Jiménez-García, R.; Hernández-Barrera, V.; de Miguel-Diez, J.; Méndez-Bailón, M.; Muñoz-Rivas, N.; Pérez-Farínós, N.; López-de-Andrés, A. Infective endocarditis according to type 2 diabetes mellitus status: An observational study in Spain, 2001–2015. *Cardiovasc. Diabetol.* **2019**, *18*, 161–174. [CrossRef] [PubMed]

4. Benvenega, R.M.; De Rosa, R.; Silverio, A.; Matturro, R.; Zambrano, C.; Masullo, A.; Mastrogiavanni, G.; Soriente, L.; Ascoli, R.; Citro, R.; et al. Infective endocarditis and diabetes mellitus: Results from a single-center study from 1994 to 2017. *PLoS ONE* **2019**, *14*, e0223710. [CrossRef]

5. Abe, T.; Eyituoyo, H.O.; De Allie, G.; Olanipekun, T.; Efooe, V.S.; Olaoosibewan, K.; Mather, P. Clinical outcomes in patients with native valve infective endocarditis and diabetes mellitus. *World J. Cardiol.* **2021**, *13*, 11–20. [CrossRef]

6. Frydrych, L.M.; Biau, G.; O’Lone, D.E.; Ward, P.A.; Delano, M.J. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. *J. Leukoc. Biol.* **2018**, *104*, 525–534. [CrossRef]

7. Costantini, E.; Carlin, M.; Porta, M.; Brizzi, M.F. Type 2 diabetes mellitus and sepsis: State of the art, certainties and missing evidence. *Acta Diabetol.* **2021**, *58*, 1139–1151. [CrossRef]
30. Delamaire, M.; Maugendre, D.; Moreno, M.; Le Gof, M.C.; Allannic, H.; Genetet, B. Impaired leucocyte functions in diabetic patients. *Diabet. Med.* 1997, 14, 29–34. [CrossRef]

31. Chirillo, F.; Bacchion, F.; Pedrocco, A.; Scotton, P.; De Leo, A.; Rocco, F.; Valfrè, C.; Olivari, Z. Infective endocarditis in patients with diabetes mellitus. *J. Heart Valve Dis.* 2010, 19, 312–320.

32. Alba-Loureiro, T.C.; Munhoz, C.D.; Martins, J.O.; Cerchiaro, G.A.; Scavone, C.; Curi, R.; Sannomiya, P. Neutrophils function and metabolism in individuals with diabetes mellitus. *Braz. J. Med. Res.* 2007, 40, 1037–1044. [CrossRef] [PubMed]

33. Leonidou, L.; Mouzaki, A.; Michalaki, M.; DeLastic, A.L.; Kyriazopoulou, V.; Bassaris, H.P.; Gogos, C.A. Cytokine production and hospital mortality in patients with sepsis-induced stress hyperglycemia. *J. Infect.* 2007, 55, 340–346. [CrossRef] [PubMed]

34. Ahmad, R.; Haque, M. Oral health messiers: Diabetes mellitus relevance. *Diabetes Metab. Syndr. Obes.* 2021, 14, 3001–3015. [CrossRef] [PubMed]