Importance of In-Hospital Prospective Registry and Infectious Endocarditis Heart Team to Monitor and Improve Quality of Care in Patients with Infectious Endocarditis

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Abstract: Aim: To investigate the value of prospective in-hospital registry data and the impact of an infectious endocarditis heart team approach (IEHT) on improvement in quality of care and monitor outcomes in hospitalized patients with IE. Methods: Between December 2014 and the end of 2019, 160 patients were hospitalized in one centre with the definite diagnosis of infectious endocarditis; outcome; quality of care

Keywords: infectious endocarditis; outcome; quality of care

1. Introduction

Infective endocarditis (IE) is a severe disease and is still associated with high morbidity and mortality [1–5]. Mortality rates vary considerably between different studies. In one of the latest largest registries, the Euro-Endo Registry, including possible and definite IE, in-hospital mortality was 17.1% [1]. Landmark guidelines in the field of IE report inhospital mortality rates between 15–30% [2,3]. In-hospital mortality is highly influenced
by the local integrated care pathway. Moreover, strategies aiming at improving care in patients with acute IE have the potential to impact mortality rates. Recent literature reports 30-day mortality of approximately 20%, whereas 1-year mortality reaches 40% [4,5].

Although the incidence of IE is low, between 3–10/100,000 per year, it increases with time despite improvements in diagnosis and treatment [6]. The complexity and heterogeneity of this disease coupled with the unabated mortality rate commits for a multidisciplinary integrated care pathway involving several specialties to pursue the best care for this fragile population. Current data on IE characteristics and impact of interventions on outcome remain scarce.

The aim of this study is (1) to demonstrate the value of in-hospital prospective data collection and an infectious endocarditis heart team approach (IEHT) decision-making pathway on the improvement in quality of care and outcomes in hospitalized patients with IE; and (2) to characterize the population of IE.

2. Material and Methods

2.1. Study Design

From December 2014, all patients hospitalized in the referral hospital OLV Aalst, Belgium, with the definite diagnosis of IE were included in a prospective registry (prespecified case report form). This registry from the Cardiovascular Centre OLV Aalst (CVCA) was created in accordance with the ethics committees of our institution. The need for written consent to participate in this research study was waived in view of its observational and anonymous nature. For this manuscript, patients entering the hospital between December 2014 and December 2019 were analysed. To be included, patients had to have the diagnosis of definite IE using the current ESC guidelines [2]. For each patient, a total of 225 variables was entered in this prospective database.

From January 2017, a multidisciplinary IEHT was organized. The IEHT was composed of cardiologists from the coronary care unit, cardiologists from the imaging and critical department, cardiac surgeons, microbiologists, neurologists, radiologists and specialists from nuclear medicine. They were all integrated in the management of the patients presenting with a suspicion of IE. From the introduction of the IEHT, all patients with a suspicion of IE were immediately admitted into the coronary care unit for close monitoring, and the IEHT was gathered the same day to decide the diagnostic and therapeutic pathways to follow for the next days, following the current ESC guidelines [2]. In the next days and weeks, patients’ clinical condition were discussed weekly in the heart team meetings. Patients were stratified into those treated following the recommendations of the IEHT and controls (i.e., patient management decided outside the structure of the IEHT before introduction of the IE heart team).

The objectives of the present study are: (1) to assess the impact of an intervention in the clinical care pathway (i.e., IEHT coupled with prospective data collection) on clinical outcomes; (2) to define patient’s characteristics and outcomes and place these results in perspective with the most recently published prospective registry data of the ESC-EORP EURO-ENDO registry and from other recent prospective registries [1,5,7–9].

For the evaluation of surgical indication in each case of IE, the recent ESC guidelines were used [2]. Cardiac device-related IE (CDRIE) was defined following the same ESC guidelines: an infection extending to the electrode leads, cardiac valve leaflets or endocardial surface [2]. All-cause death was assessed in-hospital, at 30 days, 6 months and 12 months. Length of stay was defined as the days from admission to discharge.

2.2. Data Collection and Statistical Methodology

Data were collected by a dedicated research nurse (MB) in cooperation with cardiologists, cardiac surgeons and microbiologists. Results of categorical variables were represented as counts and as proportions. Continuous variables were reported as medians with interquartile range (IQR) or means and standard deviations. For comparison of observed proportions in the different groups, chi-squared test with continuity corrections were used. For among-group comparison of continuous results, unpaired t tests or
Kruskal–Wallis non-parametric tests were used. In case of one sample testing of a variable on interval level, Wilcoxon rank sum test was performed. For time-to-event analysis, Kaplan–Meier survival curves were drawn. Differences in survival curves were analysed with logrank test. To compare differences in clinical outcomes between the period before and after the introduction of the registry and heart team approach, a propensity score matching was performed using a nearest neighbour. Patients were matched using 1:1 without replacement. Variables included in the propensity score were age, gender, diabetes, COPD, renal function (GFR) and presence of prosthetic valve (Figure A1). Cox regression models were used to assess independent predictors of mortality. Least square regression was used for the prediction of in-hospital length of stay. All results were considered statistically significant at \( p < 0.05 \) level. Data were analysed using R statistical software version 3.6.2 of the R Foundation for Statistical Computing, Vienna, Austria.

3. Results

A total of 160 patients with the definite diagnosis of IE were included in this study. In the same period, 27 patients had the diagnosis of possible IE and were not included in the present analysis.

3.1. Patient Characteristics and Comparison with Previous Registries

Patients’ characteristics are shown in Table 1. Median age was 72.5 y (62.75–80.00), diabetes was present in 33.1%, chronic kidney disease in 27.5%, COPD in 17.5%, and a history of ischaemic heart disease in 30.6%.

Table 1. Patient characteristics.

| Registry | CVCA |
|----------|------|
| \( n \) hospitals | 1 |
| \( n \) countries | 1 |
| Data collection period | 2014–2019 |
| Cases included | Definite IE |
| **Demography:** | |
| \( N \) | 160 |
| Median age in years (IQR) | 72.50 (62.75 ± 80.00) |
| Age \( \geq \) 65 years | 112/160 (70%) |
| Age \( \geq \) 80 years | 44/160 (27.5%) |
| Females | 40/160 (25%) |
| **History of cardiovascular diseases:** | |
| Heart failure | 33/160 (20.6%) |
| Congenital disease | 13/160 (8.1%) |
| Ischaemic heart disease | 49/160 (30.6%) |
| Peripheral arterial disease | 28/160 (17.5%) |
| Previous endocarditis | 15/160 (9.4%) |
| Intra-cardiac device | 44/160 (27.6%) |
| Presence of prosthetic valve | 75/160 (46.9%) |
| **Risk factors and comorbidities:** | |
| Diabetes | 53/160 (33.1%) |
| Previous stroke/TIA | 14/160 (8.8%) |
| COPD/asthma | 28/160 (17.5%) |
| Chronic renal failure | 44/160 (27.5%) |
| Dialysis | 19/160 (11.9%) |
| HIV | 2/160 (1.2%) |
| Chronic liver disease | 13/160 (8.2%) |
| Cancer | 27/160 (16.9%) |
| Intravenous drug dependency | 3/160 (1.9%) |
| Intravenous catheter | 12/160 (7.5%) |
| Invasive procedure within 60 days | 43/160 (26.9%) |

Overview of basic study specifications, demography, cardiovascular disease history, risk factors and comorbidities in the CVCA.
Patient characteristics, clinical presentation, aetiology and comparison with contemporary IE registries are shown in Tables A1–A3. Staphylococcus (37.5%) was the most frequently encountered organism responsible for IE. Enterococcus, however, was almost as frequently present than streptococcus species (24.4%) in CVCA, representing 23.1% of all IE cases. This is higher compared to all other registries. From these 37 patients, 26 had a colonoscopy with resection of a polyp in 19 patients, unmasking 1 carcinoma, 2 high-grade, 3 moderate and 11 low-grade dysplasia.

Presence of a prosthetic valve IE (46.9%) and a cardiac electronic device (27.6%) were frequently present and more frequently compared to previous reports (Table A3). Similarly, prosthetic valve IE (43.8%) and CDRIE (16.9%) were more frequently encountered compared to EURO-ENDO (30.1% and 9.9%) and other registries. (Table A3) Whatever risk estimation tool is used, the risk profile of the CVCA IE registry was high. A Charlson comorbidity index not adjusted for age \(\leq 80\) was present in 32% of IE, Euroscore II \(\geq 10\) was present in 62.5% of IE, STS score \(\geq 4\) in 60.6%, KATZ ADL <4 in 50.6%, frailty score >4 in 59% and global risk assessment was high or prohibitive in 42% and 29.3% of IE patients [3,10–13] (Figure A2, Table A4). Entrance site and acquisition of IE (Table A5) and diagnostic details from the different imaging modalities (Table A6) are shown in the Appendix A. Transthoracic echocardiography (TTE) was less often performed (53%) and transoesophageal echocardiography (TOE) more often performed compared to other registries. PET-CT was more often performed (28.8%), but MDCT was less often performed (3.1%). The sensitivity of TTE, TOE and PET-CT were comparable between CVCA and other registries with a sensitivity of TTE in CVCA of 50%, of TOE 88% and of PET-CT of 66%. Valvular lesions and complications during the course of the intra-hospital observation are also detailed in the Appendix A (Tables A7 and A8).

### 3.2. Treatment and Clinical Outcomes

Surgery was performed in 82/160 (51.3%) patients in the CVCA registry comparable to the EURO-ENDO registry that reported 51.2% of IE patients undergoing surgery. The proportion of patients who needed surgery but in whom surgery was not performed were also comparable with 17.5% in CVCA and 18.1% in Euro-endo \((p > 0.05)\). In EURO-ENDO, more patients received a mechanical prosthesis compared to CVCA \((35.1\% \text{ versus } 3.1\%; p < 0.001)\). Despite this older age, repair was performed equally in CVCA versus EURO-ENDO \((11.1\% \text{ versus } 19.5\%; p > 0.05)\) (Table 2).

### Table 2. Treatment.

| Registry                  | CVCA     | EURO-ENDO | ICE-PCS | RIEI       | Fernández-Hidalgo et al. Hospital Universitari Vall d’Hebron, Spain |
|---------------------------|----------|-----------|---------|-----------|---------------------------------------------------------------------|
| **Treatment type:**       |          |           |         |           |                                                                      |
| Indication for surgery    | 110/160  | 2160/3115 | 1335/2769 | 422/677  | *                                                                   |
| Surgery performed         | 82/160   | 1596/3116 | 1335/2769 | 422/677  | 174/438 (39.7%) *                                                   |
| **Type of surgery performed:** |         |           |         |           |                                                                      |
| Mechanical prosthesis     | 5/81 (3.1%) | 560/1596 (35.1%) | 1335/2769 | 422/677 | 318/438 (72.6%) \*                                                 |
| Bioprosthesis             | 61/81 (75.3%) | 817/1596 (51.2%) | 1335/2769 | 422/677 | 135/438 (30.8%) ***                                                |
| Repair                    | 9/81 (11.1%) | 311/1596 (19.5%) | 1335/2769 | 422/677 | 36/438 (8.2%) ***                                                  |
| Surgery indicated but not performed | 28/160 (17.5%) | 564/3115 (18.1%) | 1335/2769 | 422/677 | 144/438 (32.8%) ***                                                |
| Medical treatment (surgery not indicated) | 50/160 (31.3%) | 955/3115 (30.6%) | 1335/2769 | 422/677 | 161/438 (36.8%)                                                   |

Comparison of the IE treatment in the five studies. Cells markings with asterisks represents the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions. Reported significance levels for pairwise comparison between OLV Hospital and each of the four other registries individually are the following: No asterisk marking given for \(p \geq 0.05\), * for \(p < 0.05\) and *** for \(p < 0.001\).

Mortality at 30 days was 19.4%, at 90 days 30.6%, at 180 days 34.4% and at 1 year 37.5% (Figure 1).
In-hospital mortality was non-significantly higher in medically treated patients compared to patients undergoing surgery (Figure 2). The medically treated group was divided into a first group of patients who should have been operated conforming to the guidelines but were not (i.e., considered inoperable by the heart team or refusal by the patient or family) and a second group of patients medically treated conforming to the guidelines. Mortality in the first group was high while mortality in the second group was comparable to surgically treated patients (Figure 2, Table 3).

Figure 1. Overall survival curve of the CVCA registry 2014–2019.

Figure 2. Cont.
In-hospital mortality was non-significantly higher in medically treated patients compared to patients undergoing surgery (Figure 2). The medically treated group was divided into a first group of patients who should have been operated conforming to the guidelines but were not (i.e., considered inoperable by the heart team or refusal by the patient or family) and a second group of patients medically treated conforming to the guidelines. Mortality in the first group was high while mortality in the second group was comparable to surgically treated patients (Figure 2, Table 3).

Figure 2. Survival curves of the CVCA registry. Panel 1: Patients grouped according medical or surgical treatment. Panel 2 patients grouped in one surgical and two medical treatment groups. Group I = medically treated patients conforming to the guidelines; Group II = surgically treated patients conforming to the guidelines; Group III = medically treated group who should have been operated, conforming to the guidelines, but were not operated (considered inoperable, refusal by the patient...).

Table 3. Risk and outcome.

| Registry                          | OLV Hospital | EURO-ENDO | ICE-PCS | RIEI | Hospital Universitari Vall d’Hebron, Spain |
|----------------------------------|--------------|-----------|---------|------|-------------------------------------------|
| **Risk assessments:**            |              |           |         |      |                                           |
| Median EuroSCORE                 | 13.3 (6.2–24.0) | 3.0 (2.0–13.3) *** | 12.9 (6.2–22.3) | 11.7 (6.0–16.7) | 9.9 (6–13) *** |
| Median EuroSCORE when surgery performed | 12.5 (6.2–22.3) | 10.9 (5.2–24.9) *** | 10.9 (5.2–18.8) | 10.9 (5.0–22.3) | 10.9 (5.0–18.8) *** |
| Median EuroSCORE when surgery indicated but not performed (RQR) | 17.6 (9.5–26.7) | 17.8 (9.5–26.7) | 16.9 (9.5–13.8) | 16.9 (9.5–13.8) | 16.9 (9.5–13.8) |
| Subjects with definite Modified Duke criteria | 61 (40.0%) | 532/930 (57.1%) *** | 386/658 (58.6%) *** | 530/1120 (47.4%) *** | 530/1120 (47.4%) *** |
| Median EuroSCORE prosthetic IE (RQR) | 9.0 (5.2–18.8) | 9.0 (5.2–18.8) | 9.0 (5.2–18.8) | 9.0 (5.2–18.8) | 9.0 (5.2–18.8) |
| Median EuroSCORE native IE (RQR) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) |
| Median EuroSCORE device-related IE (RQR) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) | 10.0 (11.1–27.9) |
| **Mortality:**                    |              |           |         |      |                                           |
| In-hospital mortality             | 46/160 (28.7%) | 532/930 (57.1%) *** | 490/2774 (18.0%) *** | 93/677 (13.7%) *** | 125/677 (28.5%) |
| In-hospital mortality prosthetic IE | 18/70 (25.7%) | 107/195 (55.9%) | 187/939 (19.9%) | 187/939 (19.9%) | 187/939 (19.9%) |
| In-hospital mortality native IE    | 19/93 (20.2%) | 286/1764 (16.2%) ** | 286/1764 (16.2%) ** | 286/1764 (16.2%) ** | 286/1764 (16.2%) ** |
| In-hospital mortality device-related IE | 9/27 (33.3%) | 47/208 (22.4%) * | 47/208 (22.4%) * | 47/208 (22.4%) * | 47/208 (22.4%) * |
| Cumulative 1-month mortality      | 50/160 (31.4%) | 107/195 (55.9%) | 107/195 (55.9%) | 107/195 (55.9%) | 107/195 (55.9%) |
| Cumulative 6-month mortality      | 55/160 (34.4%) | 107/195 (55.9%) | 107/195 (55.9%) | 107/195 (55.9%) | 107/195 (55.9%) |
| Cumulative 1-year mortality       | 60/160 (37.5%) | 107/195 (55.9%) | 107/195 (55.9%) | 107/195 (55.9%) | 107/195 (55.9%) |

Overview of risk assessment and mortality outcome reported in the five studies. Cells markings with asterisks represents the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions and of the one-sample Wilcoxon rank sum tests for the medians. Reported significance levels for pairwise comparison between OLV Hospital and each of the four other registries individually are the following: No asterisks marking given for p ≥ 0.05, * for p < 0.05, ** for p < 0.01 and *** for p < 0.001.

3.3. Impact of an Infective Endocarditis Heart Team and Prospective Data Collection

Overall, 92 patients were managed following the recommendations of the IEHT and were compared with 68 controls. Baseline clinical characteristics, aetiology, risk estimation and type of IE were comparable between groups, except for frailty, which was higher in the IEHT group (5.9% vs 3.8%, p < 0.001) (Table 4). The observed that length of stay (LOS) tended to be shorter in patients treated following the IEHT approach (36.1 ± 25.2 days vs 44.40 ± 32 days, p = 0.0828). In a multivariate analysis, an IEHT decision-making approach was independently associated with a shorter LOS in hospital (−10.3 days, 95% CI: −20 to −0.5; p = 0.04).
Table 4. Baseline clinical characteristics, aetiology, risk assessment and type of IE: IEHT approach versus standard care.

| Baseline characteristics               | IEHT Approach | Standard Care | p Value |
|----------------------------------------|---------------|---------------|---------|
| **Baseline characteristics**           |               |               |         |
| Age 6/69.5 (sd: 13.3)                  | 71.0 (sd: 11.8)| 0.4710        |
| Gender (male) 66/92 (71.7%)            | 54/68 (79.4%) | 0.3558        |
| Diabetes 33/92 (35.9%)                 | 20/68 (29.4%) | 0.4914        |
| COPD 16/92 (17.6%)                    | 12/68 (17.4%) | 0.9999        |
| GFR 52.1 (sd: 28.7)                   | 54.1 (sd: 25.7)| 0.6393        |
| Previous cardiac surgery 44/92 (47.8%)| 36/68 (52.9%) | 0.6314        |
| Previous coronary artery disease 25/92| 24/68 (35.3%) | 0.3534        |
| Stroke 8/92 (8.7%)                    | 6/68 (8.8%)  | 0.9999        |
| Peripheral arterial disease 13/92 (14.1%)| 15/68 (22.1%)| 0.2738        |
| LVEF < 50% 23/92 (25.0%)              | 10/68 (14.7%)| 0.1835        |
| Degenerative Valve Disease 54/92 (58.7%)| 35/68 (51.5%)| 0.4542        |
| Previous endocarditis 9/92 (9.8%)     | 6/68 (8.8%)  | 0.9999        |
| Cancer 14/92 (19.1%)                  | 13/68 (15.2%)| 0.6616        |
| **Aetiology**                          |               |               |         |
| Streptococcus viridans 8/92 (8.7%)    | 9/68 (13.2%) | 0.5082        |
| Staphylococcus aureus 27/92 (29.4%)   | 20/68 (29.3%)| 0.9999        |
| Enterococcus 18/92 (19.6%)            | 19/68 (27.9%)| 0.2925        |
| **Risk Assessment**                    |               |               |         |
| Charlson index (not age related) 82.7 (sd: 21.4) | 81.1 (sd: 27.3) | 0.6745 |
| Frailty score 5.6 (sd: 1.8)           | 3.8 (sd: 2.5) | 0.0001        |
| Euroscore II 16.7 (sd: 12.6)          | 17.4 (sd: 16.7)| 0.7535        |
| KATZ score 3.2 (sd: 2.1)              | 3.4 (sd: 2.3) | 0.6216        |
| Global Risk score 1.8 (sd: 0.8)       | 2.1 (sd: 0.9) | 0.0879        |
| **IE Type:**                           |               |               |         |
| Prosthetic 38/92 (41.3%)              | 32/68 (47.1%)| 0.1610        |
| Native 34/92 (37.0%)                  | 29/68 (42.6%)|               |
| Device-related 20/92 (21.7%)          | 7/68 (10.3%) |               |

Overview of basic characteristics, demography, cardiovascular disease history, risk factors and comorbidities before propensity score matching: IEHT approach versus standard care.

Table 5 shows unadjusted and adjusted mortality after propensity score matching between patients treated under IEHT and controls. There was no difference in in-hospital mortality. However, after propensity matching, mortality at 6 months and 1 year tended to be lower in patients managed by the IEHT (23.5% IEHT vs 36.8% controls, \( p = 0.0926 \) and 26.5% IEHT vs. 41.2% controls, \( p = 0.0699 \), respectively). Figure 3 shows survival curves of patients with definite IE managed by the IEHT and controls.

Table 5. Outcome IEHT approach versus standard care.

| Unadjusted mortality | Standard Care | p Value |
|----------------------|---------------|---------|
| In-hospital mortality | 28.3%         | 29.4%   | 0.8737 |
| 30 days mortality    | 20.7%         | 20.7%   | 0.8104 |
| 180 days mortality   | 32.6%         | 36.8%   | 0.5843 |
| 1 year mortality     | 34.8%         | 41.2%   | 0.4089 |

Comparison of mortality data In-hospital, after 30 days, after 180 days, after 1 year between IEHT approach and standard care unadjusted and after propensity score matching.


4. Discussion

From our prospective in-hospital registry of IE, we can conclude that compared with contemporary literature, our population with IE: 1) is at higher risk, has more enterococcus IE probably related to older age, has more PVE and CDRIE, is detected with similar sensitivity compared to other centres by echo and PET, is as frequently operated, has a 30-day and 1-year mortality comparable with mortality rates mentioned in current literature. Mortality was high in those patients treated medically, although surgery was theoretically indicated. 2) The introduction of IEHT led to a reduction in LOS with a trend towards reduction in mortality. These results demonstrate that an in-hospital registry for IE and a multidisciplinary approach can be used as a management tool to evaluate and improve the quality of care of patients with IE.

Benchmarking medical management of every disease starts with precise characterization of the population studied. These characteristics of patients with IE can vary depending on several hospital and environmental aspects. Comparison of our population with the most recent published registries illustrate that our patients were older, had more frequent diabetes, COPD, chronic kidney disease and prosthetic valves or electronic devices [1,5,7–9].
This resulted in a high-risk population documented by high-risk scores (i.e., STS, Euroscore II, Charlson co-morbidity, Katz score, frailty and global risk score). All the patient characteristics associated with poor outcome mentioned in the latest guidelines were more frequently present in the CVCA registry: older age, prosthetic valve IE, diabetes mellitus, comorbidity (e.g., frailty, renal, or pulmonary disease) [2]. These high-risk characteristics must be acknowledged in the comparison of outcome with other registries.

The microbiological findings of our IE population are mostly in line with current literature [14–17]. In developed countries, IE patients are older and IE cases are more frequently related to health-care facilities. Prosthetic valves and CIED devices have replaced rheumatic disease as the main risk factor for IE [2,14–16]. In parallel, staphylococcus has replaced streptococcus as the most frequently isolated pathogen.

Staphylococcus aureus is also in CVCA, the most frequently encountered organism responsible for 37.5% of IE, followed by Streptococcus IE (24.4%). Enterococcus, however, is almost as frequently present as Streptococcus species (23.1%). This is higher compared to all other registries. This can probably be explained by the older age of the CVCA registry and is illustrated by the frequent finding of a digestive entrance place (multiple polyps and cancer). In CVCA registry, IE was frequently health care related (40%) with an important representation of non-nosocomial health care related IE that can be explained by the old age of this population living frequently in residential care centres.

PVE (43.8%) and CDRIE (16.9%) represent a larger group of IE patients in the CVCA registry compared to other current registries [1,5,7–9]. This can be explained by the fact that within a developed country, the hospital is a referral centre for valvular heart disease. Patients that were operated on (valve surgery) or had device implants in the hospital are also referred to the CVCA when complications occur. This aspect must be considered when evaluating the outcome of IE patients since mortality is higher in PVE and CDRIE compared to native valve IE.

TTE was less often performed in the CVCA registry, which is due to the fact that TTE is often already performed by the referral hospital and exams are available when the patients arrive in the CVCA. TEE and PET-CT were frequently performed and the more frequent use of PET-CT in the CVCA registry results probably also in the less frequently performed MDCT. The diagnostic yield of these imaging techniques was comparable with other registries. Since not one of these techniques is the holy grail, multi-modality imaging is key in the diagnosis of IE [18].

The CVCA registry counts less culture negative IE (3.8%), illustrating the high performance of microbiological detection of IE. The microbiological team is active in the hospital, working with the different departments when blood cultures are positive, while sensible physicians actively perform complementary imaging techniques or perform supplementary blood cultures in patients with unexplained infections.

Complications are similar in CVCA and other current registries [1,5,7–9]. Surgery was performed in 82/160 (51.3%) patients in the CVCA registry, also comparable with the other registries. The proportion of patients who needed surgery but in whom surgery was not performed (18.1%) is also comparable. Less mechanical valves are implanted in the CVCA registry, probably linked to older age. Despite this older population, valve repair was performed as frequently as in the recent EURO-ENDO registry, illustrating the efforts of the surgical department to repair valves in IE when possible.

Mortality of IE in CVCA in-hospital was 28.7%, at 30 days 19.4%, at 90 days 30.6%, at 180 days 34.4% and at 1 year 37.5%. These results are consistent with current literature. In-hospital mortality is difficult to compare between studies and registries since it depends on the regional health care organization (early versus late discharge; early versus late referral to other care facilities). Therefore, 30-day and 1-year mortality should also be used as reliable metrics. The 30-day mortality of 19.4% was comparable, with most publications reporting mortality rates of 10–30% [4,19]. A 1-year mortality of 37.5% is also comparable with literature, reporting rates of 21–40% [5,8,9,18]. CVCA mortality rate cannot be compared with the EURO-ENDO registry since only in-hospital mortality was reported (17.1%).
1-month mortality is missing in the other registries but the 1-year mortality of the RIEI registry was 16.7% and 37.8% in the study of Hidalgo et al [8,9]. Comparison of outcomes of IE between prospective studies and registries remains difficult, but considering the high-risk profile of the CVCA population and the inclusion of only definite IE cases (EURO-ENDO [1] and Hidalgo et al. [9] included possible and definite IE), outcome in the CVCA registry compares favourably with other data.

Patients treated medically or surgically following the guidelines have the same favourable outcome. Contrarily, patients treated medically, although the guidelines indicate surgical treatment, have a dramatic high mortality. This finding is consistent with the EURO-ENDO registry [1].

Linked to the high mortality of IE and the multi-system involvement in most patients with IE, current guidelines encourage an organized multidisciplinary approach for these patients, including cardiologists, cardiac surgeons, cardiac anaesthetists, neurologists, microbiologists and intensive care physicians and the use of clinical pathways integrating the existing guidelines [2,19,20]. Although the heart team has already functioned many years in the hospital, we organized an IEHT in 2017, implementing a multidisciplinary approach with a focus on early recognition with acute close monitoring in the cardiac intensive care unit, early multidisciplinary decision-making using current guidelines and close follow-up in the heart team during the course of the hospitalization. The prospective registry enables us to compare the current outcome of patients with IE before the introduction of the IEHT (year 2014–2016) with the period with IEHT (2017–2019). We found an important reduction of the LOS of more than 8 days. An IEHT decision-making approach was independently associated with a shorter length of stay in-hospital. This can be explained by the early decision making within the IEHT. We observed a tendency towards a better outcome with IEHT (1-year mortality decreases from 41.2% to 34.8%) despite a higher frailty in the IEHT group. After propensity score matching, 1-year mortality decreased from 41.2% before IEHT to 26.5% with IEHT ($p = 0.0699$), illustrating, besides the impact on the LOS, the potential benefit of an early multidisciplinary approach on outcomes.

Future perspectives: Considering the great proportion of PVE and CDRIE in our CVCA registry, prophylactic measurements to prevent this deadly disease should be encouraged. Supplementary tools to instruct our patients with prosthetic valves and electronic devices to follow rigorously prophylactic measures against IE will be introduced. The multidisciplinary approach will be continued within the IEHT with a special attention to the group of patients in whom surgery would be denied in contradiction with the guidelines. This will be challenging due to the older age and the frailty of our population. Finally, patients will be followed in the valve clinic after hospital discharge, knowing the still high mortality in this population.

5. Limitations

The major limitation of this single-centre study is the low number of patients. However, a complete dataset of current prospective obtained data in 160 patients with long-term follow-up enhances the knowledge in the domain of IE in which data are still scarce.

6. Conclusions

We can conclude from our CVCA registry that in-hospital prospective registration of data in IE patients permits to characterize the particular IE patient population of the hospital, which is a high-risk population in CVCA and which can differ significantly from other published registries. These differences can have a major impact on the interpretation of the outcome. In-hospital prospective registration of IE patients is the only way to monitor the effect of interventions to lower mortality in this disease. Implementation of IEHT resulted in an important decrease in the LOS with a non-significant trend for lower mortality.
Overview of basic study specifications, demography, cardiovascular disease history, risk factors and comorbidities in the five samples. Cell markings with asterisks represent the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions and of the one-sample Wilcoxon rank sum tests for the medians. Reported significance levels for pairwise comparison between OLV Hospital and each of the four other registries individually are the following: no asterisks marking given for

- **p < 0.05**
- *p < 0.01*
- ***p < 0.001***

### Table A1. Patient characteristics (CVCA and other registries).

| Registry            | CVCA       | EURO-ENDO  | ICE-PCS     | RII        | Fernández-Hidalgo et al. Hospital Universitari Vall d’Hebron, Spain |
|---------------------|------------|------------|-------------|------------|------------------------------------------------------------------|
| N countries         | 1          | 40         | 1           | 1          | 1                                                                |
| N hospitals         | 1          | 156        | 56          | 17         | 1                                                                |
| Data collection period | 2014–2019 | January 2016–March 2018 | 2000–2005 | 2007–2010 | 2008–2011 |

#### Demographic Data

- **Age:**
  - Median age in years (IQR): 72.30 (62.75–80.80) for CVCA, 63.0 (54.0–73.0) for EURO-ENDO, 57.9 (43.2–71.8) for ICE-PCS, 65.34 (49.60–74.39) for RII, and 66.4 (51.8–74.9) for Fernández-Hidalgo et al.
  - 26.9% of CVCA patients are aged 60 years or older, compared to 27.0% of EURO-ENDO, 25.3% of ICE-PCS, 25.3% of RII, and 25.3% of Fernández-Hidalgo et al.

- **Sex:**
  - 25% of CVCA patients are female, compared to 31.1% of EURO-ENDO, 32.0% of ICE-PCS, 27.3% of RII, and 34.9% of Fernández-Hidalgo et al.

#### History of Cardiovascular Diseases

- **Invasive procedures within 60 days:** 26.9% of CVCA patients, compared to 27.0% of EURO-ENDO, 25.3% of ICE-PCS, 25.3% of RII, and 25.3% of Fernández-Hidalgo et al.

#### Risk Factors and Comorbidities

- **Diabetes mellitus:** 33.1% of CVCA patients, compared to 16.0% of EURO-ENDO, 17.1% of ICE-PCS, 22.6% of RII, and 13.5% of Fernández-Hidalgo et al.

#### Clinical Presentation

- **Fever:** 59.4% of CVCA patients, compared to 77.7% of EURO-ENDO, 96.0% of ICE-PCS, 83.9% of RII, and 82.5% of Fernández-Hidalgo et al.

#### Table A2. Clinical presentation.

| Registry            | CVCA       | EURO-ENDO  | ICE-PCS     | RII        | Fernández-Hidalgo et al. Hospital Universitari Vall d’Hebron, Spain |
|---------------------|------------|------------|-------------|------------|------------------------------------------------------------------|
| Clinical assessment: |
| First sign to admission < 1 month | 141/160 (88.1%) | 308/368 (83.9%) | 280/316 (88.5%) | 316/677 (46.9%) | 170/438 (38.8%) |
| Transformed from other centers | 45/160 (28.1%) | 283/366 (77.1%) | 266/287 (92.8%) | 266/677 (39.1%) | 163/438 (37.5%) |
| Increased C-reactive protein | 139/160 (89.4%) | 383/366 (105.1%) | 263/250 (82.0%) | 263/677 (39.1%) | 155/438 (35.1%) |
| New murmur or worsening old murmur | 40/160 (25.0%) | 280/316 (88.5%) | 266/287 (92.8%) | 266/677 (39.1%) | 163/438 (37.5%) |

#### Summary

The clinical onset and assessments reported in the five studies. Cell markings with asterisks represent the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions. Reported significance levels for pairwise comparison between OLV Hospital and each of the four other registries individually are the following: no asterisks marking given for p > 0.05, * for p < 0.05, ** for p < 0.01 and *** for p < 0.001.
### Table A3. Type and etiology of IE.

| Registry          | CVCA                  | EURO-ENDO             | ICE-PCS               | RIEI                   | Fernández-Hidalgo et al. Hospital Universitari Vall d'Hebron, Spain |
|-------------------|-----------------------|-----------------------|-----------------------|------------------------|---------------------------------------------------------------------|
| Type IE:          |                       |                       |                       |                        |                                                                     |
| Native valve      | 63/160 (39.4%)        | 1764/3116 (56.6%) *** | 1901/2626 (72.2%) *** | 445/677 (65.7%) ***    | 327/485 (67.9%) ***                                                 |
| Prosthetic valve  | 70/160 (43.8%)        | 939/3116 (30.1%) ***  | 583/2626 (22.1%) ***  | 126/677 (18.9%) ***    | 103/485 (21.3%) ***                                                 |
| Intra-cardiac device related | 27/160 (16.9%)        | 308/3116 (9.9%)      | 372/2626 (7.0%) ***  |                        |                                                                     |
| Staphylococci     |                       |                       |                       |                        |                                                                     |
| Positive blood culture | 154/160 (96.3%)      | 261/3116 (83.0%) *** | 492/2671 (72.7%) *** |                        |                                                                     |
| Streptococci      | 39/160 (24.4%)        | 163/438 (37.2%) **   |                       |                        |                                                                     |
| Staphylococcus aureus | 1/160 (0.6%)          | 162/2781 (6.0%) **   |                       |                        |                                                                     |
| Prophylactic drug  |                       |                       |                       |                        |                                                                     |
| Perioperative     |                       |                       |                       |                        |                                                                     |
| Native valve      | 63/160 (39.4%)        | 1764/3116 (56.6%) *** | 1901/2626 (72.2%) *** | 445/677 (65.7%) ***    | 327/485 (67.9%) ***                                                 |
| Prosthetic valve  | 70/160 (43.8%)        | 939/3116 (30.1%) ***  | 583/2626 (22.1%) ***  | 126/677 (18.9%) ***    | 103/485 (21.3%) ***                                                 |
| Intra-cardiac device related | 27/160 (16.9%)        | 308/3116 (9.9%)      | 372/2626 (7.0%) ***  |                        |                                                                     |
| CardiacDevice     |                       |                       |                       |                        |                                                                     |
| Related           | 27/160 (16.9%)        | 308/3116 (12.4%)      | 445/2781 (17.0%) *    |                        |                                                                     |
| Enterococci       | 32/160 (19.7%)        | 165/2781 (6.0%)      | 57/677 (11.6%)       |                        |                                                                     |
| Staphylococci     | 5/160 (3.1%)          | 60/2781 (2.2%)       | 44/677 (6.4%)        |                        |                                                                     |
| Other-staphylococci | 1/160 (0.6%)          | 162/2781 (6.0%) **   |                       |                        |                                                                     |
| Gram-negative rods (GNR) | 3/160 (1.9%)          | 86/2461 (3.5%)       | 19/438 (4.3%)        |                        |                                                                     |
| HACEK group       | 1/160 (0.6%)          | 44/2781 (1.6%)       | 6/677 (1.2%)         |                        |                                                                     |
| Fungi/yeast       |                       |                       |                       |                        |                                                                     |
| Polymicrobial     | 4/160 (2.5%)          | 28/2781 (1.0%)       |                        |                        |                                                                     |
| Culture negative  | 6/160 (3.8%)          | 310/2781 (11.1%) *** |                        |                        |                                                                     |

Overview of the infective endocarditis type and etiology reported in the five studies. Cell markings with asterisks represent the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions. Reported significance levels for pairwise comparison between OLV Hospital and each of the five other registries individually are the following: No asterisk marking given for \( p \geq 0.05 \), * for \( p < 0.05 \), ** for \( p < 0.01 \) and *** for \( p < 0.001 \).

### Table A4. Risk scores in CVCA registry.

| Prophylactic IE | Native IE | Cardiac Device Related IE | Significance Level of \( p \)-Value | Overall |
|-----------------|-----------|---------------------------|-------------------------------------|---------|
| \( n = 70 \)    | \( n = 63 \) | \( n = 27 \)             |                                     | \( n = 160 \) |
| Median EuroSCORE (IQR) | 19.0 (11.1–27.5) | 8.6 (3.2–18.8) | 9.0 (5.2–16.3) | *** | 13.3 (6.2–24.0) |
| Median STS score (only calculated for aortic or mitral valve surgeries) | 8.6 (5.7–17.8) | 6.6 (3.8–13.5) | 6.8 (4.8–24.6) | | 7.5 (4.2–15.9) |
| Global risk score >= 2 | 49 (70.0%) | 44 (69.8%) | 21 (77.8%) | | 114 (71.3%) |
| Median Charlson comorbidity index-not age related (IQR) | 96.0 (90.2–98.3) | 90.2 (77.5–98.3) | 90.2 (53.4–95.9) | * | 90.2 (77.4–98.3) |
| Median Katz score (IQR) | 4.0 (2.0–5.0) | 3.0 (1.0–5.0) | 4.0 (2.0–5.8) | | 3.0 (2.0–5.0) |
| Median frailty score (IQR) | 4.5 (3.0–6.0) | 6.0 (4.0–7.0) | 5.0 (4.0–6.0) | | 5.0 (3.0–7.0) |

Risk score in the different groups of IE. Median values are shown. No asterisks marking given for \( p >= 0.05 \), * for \( p < 0.05 \) and *** for \( p < 0.001 \).

### Table A5. Entrance site and acquisition.

| Registry          | CVCA                  | EURO-ENDO             | ICE-PCS               | RIEI                   | Fernández-Hidalgo et al. Hospital Universitari Vall d’Hebron, Spain |
|-------------------|-----------------------|-----------------------|-----------------------|------------------------|---------------------------------------------------------------------|
| Entrance site:    |                       |                       |                       |                        |                                                                     |
| Oral/dental       | 16/160 (10%)          | (9.8%)                |                       |                        |                                                                     |
| Digestive         | 39/160 (24.4%)        | (6.3%) ***            |                       |                        |                                                                     |
| Gentilaurinary    | 7/160 (4.4%)          | (4.5%)                |                       |                        |                                                                     |
| Skin              | 33/160 (20.6%)        |                       |                       |                        |                                                                     |
| Acquisition:      |                       |                       |                       |                        |                                                                     |
| Community-acquired | 92/160 (57.5%)        | 2046/3116 (65.7%) *   | 1975/2781 (71.0%) *** | 425/677 (62.8%)        | 327/485 (67.9%) ***                                                 |
| Healthcare related | 64/160 (40%)          | 1027/3116 (33.0%)     | 640/2781 (23%) ***    | 160/677 (23.6%) ***    | 135/438 (30.8%) *                                                  |
| Nosocomial         | 15/160 (9.4%)         | 624/3116 (19.5%) **   | 390/2781 (14.0%)      | 76/677 (11.2%)         |                                                                     |
| No-nosocomial healthcare related | 49/160 (30.6%)        | 403/3116 (12.9%) ***  | 250/2781 (9.0%) ***   | 84/677 (12.4%) ***     |                                                                     |
| Unknown           | 4/160 (2.5%)          | 43/3116 (1.4%)        | 167/2781 (6.0%)       | 92/677 (13.6%) ***     |                                                                     |

Comparison of the IE entrance site and acquisition reported in the five studies. Cell markings with asterisks represent the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions. Reported significance levels for pairwise comparison between CVCA and other registries. No asterisks marking given for \( p >= 0.05 \), * for \( p < 0.05 \), ** for \( p < 0.01 \) and *** for \( p < 0.001 \).
### Table A6. Diagnostic Imaging.

| Registry                  | CVCA          | EURO-ENDO     | ICE-PCS       | RIEI          | Fernández-Hidalgo et al. Hospital Universitari Vall d’Hebron, Spain |
|---------------------------|---------------|---------------|---------------|---------------|---------------------------------------------------------------------|
| **Clinical imaging**      |               |               |               |               |                                                                     |
| Cardiac echo performed    | 151/160 (94.4%) | 3111/3116 (99.8%)*** |               | 640/677 (94.5%)*** |                                                                     |
| TTE performed             | 85/160 (53%)   | 2793/3111 (89.8%)*** |               | 478/677 (70.6%)*** |                                                                     |
| TEE performed             | 148/160 (92.5%) | 1808/3111 (58.1%)*** |               | 478/677 (70.6%)*** |                                                                     |
| TEE positive              | 42/85 (49.4%)  |               | 395/640 (62.0%)*** |               |                                                                     |
| PET CT performed          | 130/148 (87.8%)|               | 447/476 (93.5%)*** |               |                                                                     |
| Leucocyte scintigraphy    | 46/160 (28.8%) | 518/3116 (16.6%)*** |               |               |                                                                     |
| MDCT                      | 5/160 (3.1%)   | 1656/3116 (53.1%)*** |               |               |                                                                     |
| **Clinical imaging in the five studies.** |               |               |               |               |                                                                     |
| Cell markings with asterisks represent the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions. Reported significance levels for pairwise comparison between OLV Hospital and each of the four other registries individually are the following: no asterisk marking given for \( p \geq 0.05 \) and *** for \( p < 0.001 \). |

### Table A7. Valvular lesions in CVCA registry.

| Aortic Valve | Mitral Valve | Tricuspid Valve | Pulmonal Valve |
|--------------|--------------|-----------------|----------------|
| Prosthetic   | 56           | 22              | 3              | 0              |
| Vegetation   | 66/160 (41.3%) | 55/160 (34.4%) | 14/160 (8.8%)  | 1/160 (0.6%)   |
| Vegetation median size in mm (IQR) | 10.0 (7.0–13.0) | 12.5 (9.0–20.0) | 16.0 (10.0–20.0) | 18 (18.0–18.0) |
| Vegetation range in mm | 2–35 | 3–50 | 6–25 | – |
| Valve regurgitation >= 3/4 | 33 | 27 | 16 | 1 |
| Leaflet perforation | 9 | 17 | 3 | 0 |
| Periannular abscess | 28 | 5 | 0 | 0 |
| Periannular pseudoaneurysm | 3 | 2 | 0 | 0 |
| Prosthetic valve dehiscence | 12 | 4 | 1 | 0 |
| Prosthetic valve obstruction | 2 | 0 | 0 | 0 |

### CVCA diagnostic imaging results.

### Table A8. Complications.

| Registry                  | CVCA          | EURO-ENDO     | ICE-PCS       | RIEI          | Fernández-Hidalgo et al. Hospital Universitari Vall d’Hebron, Spain |
|---------------------------|---------------|---------------|---------------|---------------|---------------------------------------------------------------------|
| **Complications (at admission or while under treatment):** |               |               |               |               |                                                                     |
| Congestive heart failure  | 19/160 (11.9%) | 1280/3116 (40.3%)*** |               | 301/677 (44.5%)*** | 285/438 (65.8%)                                                                     |
| Intraatrial abscess       | 31/160 (19.4%) | 556/3116 (17.8%)*** |               | 386/2707 (14.0%)*** | 77/677 (11.4%)*** 84/438 (19.1%)                                                                     |
| New conduction abnormality| 42/160 (26.2%) | 499/3116 (16.0%)*** |               | 217/2689 (8.0%)*** |                                                                     |
| Persistent positive blood cultures | 21/160 (13.1%) | 433/3116 (13.4%)*** |               | 253/2689 (9.4%)*** |                                                                     |
| Pulmonary embolism        | 10/160 (6.2%)  | 364/3116 (11.7%)*** |               |               |                                                                     |
| Intramural haemorrhage    | 5/160 (3.1%)   | 120/3116 (3.9%)*** |               |               |                                                                     |
| Vascular embolism         | 54/160 (33.8%) | 1429/3116 (45.8%)*** |               | 106/2781 (38.6%)*** | 57/677 (8.4%)*** 89/438 (20.3%)                                                                     |
| Cardiac embolism          | 36/160 (22.5%) | 635/3116 (20.3%)*** |               |               |                                                                     |
| Stroke/TIA                | 30/160 (18.8%) | 403/3116 (12.9%)*** |               | 402/2727 (17.3%)*** |                                                                     |
| Splanic/Renal embolism/ Spontaneous | 14/160 (8.1%) | 752/3116 (24.3%)*** |               |               |                                                                     |
| Septic shock              | 33/160 (20.6%) | 494/3116 (15.9%)*** |               |               |                                                                     |
| **Valvular assessment:**  |               |               |               |               |                                                                     |
| Vegetation present        | 134/160 (83.8%) | 2406/3116 (77.0%)** |               | 605/677 (90.2%)** |                                                                     |
| AV                        | 66/160 (41.3%) | 1031/2741 (38.0%) |               |               |                                                                     |
| MV                        | 55/160 (34.4%) | 1125/2741 (41.0%) |               |               |                                                                     |
| TV                        | 14/160 (8.8%)  | 321/2741 (11.8%) |               |               |                                                                     |
| PV                        | 1/160 (0.6%)   | 29/2741 (1.0%) |               |               |                                                                     |
| Paravalvular abscess      | 31/160 (19.3%) | 355/3116 (11.3%)** |               | 77/677 (11.4%)** |                                                                     |
| Prosthetic valve complication | 57/160 (35.6%) | 518/2781 (18.2%)** |               |               |                                                                     |
| Aortic valve affected     | 77/160 (48.1%) | 402/2781 (46.0%)** |               |               |                                                                     |
| Mitral valve affected     | 65/160 (41.6%) | 402/2781 (46.0%)** |               |               |                                                                     |
| Tricuspid valve affected  | 21/160 (13.1%) | 314/2781 (11.4%)** |               |               |                                                                     |
| Pulmonary valve affected  | 1/160 (0.6%)   | 314/2781 (11.4%)** |               |               |                                                                     |
| **Valvular assessment:**  |               |               |               |               |                                                                     |

**Overview of IE complications and valvular assessments reported in the five studies.** Cell markings with asterisks represents the statistical significance levels of the two-sample Pearson’s chi-squared tests for the observed proportions. Reported significance levels for pairwise comparison between OLV Hospital and each of the four other registries individually are the following: no asterisk marking given for \( p > = 0.05 \), * for \( p < 0.05 \), ** for \( p < 0.01 \) and *** for \( p < 0.001 \).
Figure A1. Figure with covariate balance before and after propensity score matching.

Figure A2. Risk scores of patients with IE from CVCA registry. Added vertical red line represents discrimination boundaries for elevated risk of mortality.
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