



Endocarditis at a large community hospital with on-site cardiac surgery



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This paper is dedicated to the memory of Boris Fraiture, member of our endocarditis team and honoured colleague, who left us too early.

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ABSTRACT

Objective: Infective endocarditis (IE) is still a serious disease. The currently published EURO-ENDO registry showed a rate of surgery of 51.2% and a lower mortality in operated IE patients. We hypothesized differences between our data and the registry.

Methods: Retrospective single centre registry on the hospital course of patients with IE.

Results: In four years, 171 IE patients were treated at our hospital. Mean age of patients was 66.5 ± 13.8 years and 62.6% of patients were transferred from other hospitals. There were 85 (49.7%) patients with native valve IE (NVE), 53 (31%) with prosthetic valve IE (PVE) and 33 (19.3%) with either intra-cardiac device related IE ($n = 29$) or IE associated with central access lines ($n = 4$) (DRE). A total of 81.3% ($n = 139$) of patients were sent to cardiac surgery. Using a logistic regression model to analyse predictors of conservative instead of surgical therapy the only independent variables were: presence of large vegetation or abscesses (OR: 0.36, 95%CI 0.15–0.83; $p = 0.016$) and age (for each ten years) (OR: 1.61, 95%CI 1.11–2.32, $p = 0.01$). Hospital mortality was 21.6% ($n = 37/171$), with no difference ($p = 0.97$) between those who were operated (21.6%, $n = 30/139$) and those treated conservatively (21.9%, $n = 7/32$). Comparing those treated conservatively without an indication for surgery with those with an indication, mortality was 9.5% versus 45.5%, $p = 0.02$.

Conclusions: In this registry from a hospital with on-site cardiac surgery more than half of patients were referred. The rate of patients treated surgically was 81.3%. Hospital mortality was 21.6%, with no difference between operated and conservatively treated patients.

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1. Introduction

Infective endocarditis (IE) is one of the most serious infectious diseases with a still high hospital mortality, despite significant developments in diagnosis and therapy during the last decades [1–3].

The most significant developments were

- A clear strategy how to diagnose endocarditis using the modified Duke criteria [4], with implementation of new diagnostic tools besides transthoracic and transesophageal echocardiogra-

phy, such as cardiac multi-slice - computed tomography (MSCT) and ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) [3,5,6].

- The implementation of a multi-disciplinary endocarditis team, bringing together the expertise of different involved faculties in a formal way [3].
- The use of cardiac surgery in a timely fashion, which seems to be associated with a favourable clinical outcome [7–9].

However, these developments may be counterbalanced by an increasing age of the affected more often multimorbid patients, as well as the increase of prosthetic valve and device - related infections [2,10–12].

To determine the current care and outcomes of IE in Europe, the European society of cardiology (ESC) Endocarditis Registry (EURO-ENDO) was initiated, and the first results were recently published [13].

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Our institution, as well as 155 other hospitals, participated in the EURO-ENDO registry and included patients for one year, however we hypothesized differences between our data and the overall data from the registry, especially a higher rate of surgery as well as a potentially lower hospital mortality rate in patients treated conservatively.

Therefore, the aim of our study was to gather data from our institution over a longer time period using a similar data sheet as the EURO-ENDO registry and to compare our data to that of the EURO-ENDO registry.

2. Methods

We conducted a retrospective study, collecting data from our hospital database searching for German ICD code I33.0 = infective endocarditis (IE), irrespectively of the treating department and we screened the echocardiography as well as the cardiac surgery databases for IE patients. Then patient charts and discharge documents were gathered to verify the ICD codes. Only patients with definite endocarditis or possible endocarditis, considered and treated as endocarditis, according to the modified Duke criteria [3,4] were extracted. This is a retrospective study, relying only on hospital data. Therefore, no informed consent of patients was obtained.

An electronic database, similar to the data sheet of the EURO-ENDO registry [13,14], was created. Patient characteristics, concomitant diseases, laboratory and microbiological findings, echocardiographic data as well as data from other imaging tests performed at our hospital, clinical course, decision on surgical interventions and hospital mortality were entered.

2.1. Statistics

Absolute numbers and percentages as well as means (with standard deviation) or medians (with interquartile range) were computed to describe the patient population. Categorical values were compared by chi-square test and continuous variables were compared by two-tailed Wilcoxon rank sum test.

We compared patients who were operated to those who were treated conservatively. We also compared patients who died during hospital stay with those who survived. Parameters that showed a difference with a p-value of ≤ 0.1 were included in the multivariable model. Logistic regression analyses were performed to identify independent predictors of surgery as well as hospital mortality.

The Kaplan Meier method was used to visualize hospital survival rates until day 30 after admission. We calculated survival curves for patients with native IE, patients with prosthetic IE and patients with device-related IE. Additionally, we present Kaplan Meier curves for operated patients and conservatively treated patients and patients treated conservatively without an indication for surgery and those treated conservatively despite an indication for surgery.

P-values < 0.05 were considered significant. All p-values are results of two-tailed tests. The tests were performed using the SAS® statistical package, version 9.4 (Cary, North Carolina).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

3. Results

Between January 1, 2013 to December 31, 2016 171 patients with definite endocarditis (or possible endocarditis, considered and treated as endocarditis) were treated at our hospital. Almost 67.8% of patients were judged as definite endocarditis and 32.2% as possible endocarditis, considered, and treated as endocarditis.

There was an increase in the number of treated patients in those years (Table 1).

Patient characteristics and concomitant diseases are shown in Table 2. Mean age of patients was 66.5 ± 13.8 years (Median 69 years, Quartiles: 59/78 years). Most patients were males. Pulmonary diseases were present in 26.4% of patients and renal failure in 32.7% ($n = 56$) with another 3.5% ($n = 6$) being already on haemodialysis. 36.9% of patients had undergone a previous valve surgery, most patients with biological valve replacement and 6.4% of patients had received a transcatheter aortic valve implantation (TAVI).

A large proportion of patients (62.6%) were transferred from other hospitals for further diagnosis and therapy.

The most common clinical signs during hospital admission were fever (79.5%), unintended weight loss (21.6%) and dyspnoea (22.2%) and 17.5% presented with a cerebral ischemic event.

Most patients presented or were transferred with suspected IE (59.1%, $n = 101$), 5.8% ($n = 10$) with an elevated C-reactive protein of undetermined source and 34.5% ($n = 59$) for other reasons.

The endocarditis team was involved in diagnostic and therapeutic decisions in 95.9% of cases, and in all patients, who were operated later.

There were 85 (49.7%) patients with native valve IE (NVE), 53 (31%) with prosthetic valve IE (PVE) and 33 (19.3%) with either intra-cardiac device related IE ($n = 29$) or IE associated with central access lines ($n = 4$) (DRE).

Blood cultures were performed in each patient, with an average of 5.8 ± 0.7 pairs of cultures per patient. Per patient 80.1% of them were positive, with 97.8% showing Gram positive microorganisms, most of them being *Staphylococcus aureus* (21.2%) with another 2.2% of Methicillin resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecalis* (19.7%), *Staphylococcus epidermidis* (16.8%) and *Staphylococcus haemolyticus* (2.2%) (Table 3).

Leukocyte counts were 10.7/nl Median (8.0/nl; 14.2/nl) and C-reactive protein was 72.6 mg/l (32.6 mg/l; 153.8 mg/l) on admission (Table 3).

Echocardiography was the most frequently used imaging tool, with transthoracic echocardiography (TTE) being used in 100% and transesophageal echocardiography (TOE) being used in 95.3% of patients.

By TTE 54.4% of patients showed a normal left ventricular function, 21.6% a slightly reduced, 16.4% a moderate reduced and 7.6% a severely reduced left ventricular function. A comparison between TTE and TOE in the detection of vegetations and paravalvular abscesses is shown in Table 4. Overall TOE showed more pathological findings than TTE.

Additional imaging is either required to look for emboli (such as abdominal sonography, cranial or abdominal computed tomography (cCT/aCT) and nuclear magnetic resonance tomography (MRT)) or as additional imaging for the detection of IE such as cardiac multi-slice - computed tomography (caMSCT) and ^{18}F -flourodeoxyglucose positron emission tomography/computed tomography (PET-CT). caMSCT was not used at our institution during this time. The use and results of the other procedures performed at our hospital are shown in Table 5.

All patients with IE were treated with antibiotics, either guided by the results of the blood cultures or by an empirical antibiotic therapy.

81.3% ($n = 139$) of patients were sent to cardiac surgery. Bio-prosthetic valve replacement was performed in 76.3% (106/139), retrieval of infected pacemakers, defibrillators or central lines in 20.8% (29/139), debridement of the infected valve in 10.8% (15/139), valve reconstruction in 9.4% (13/139) and mechanical valve replacement in 3.6% (5/139). A valve replacement by implantation of a conduit was performed in 3.6% (5/139).

Table 1
Patients with endocarditis between 2013 until 2016.

| Year | Number of patients (n = 171) | % |
|------|------------------------------|------|
| 2013 | 21 | 12.3 |
| 2014 | 45 | 26.3 |
| 2015 | 37 | 21.6 |
| 2016 | 68 | 39.8 |

Table 2
Patient characteristics and clinical presentation.

| | Total (n = 171) |
|---|-----------------|
| Age (years) | 66.5 ± 13.8 |
| Women | 25.1% (n = 43) |
| Concomitant diseases | |
| Chronic obstructive pulmonary disease (COPD) | 11.1% (n = 19) |
| • Pneumonia | 11.1% (n = 19) |
| • Diabetes mellitus | 26.9% (n = 46) |
| • Hyperlipidaemia | 29.2% (n = 50) |
| • Renal failure | 32.7% (n = 56) |
| • Renal failure on haemodialysis | 3.5% (n = 6) |
| Risk groups | |
| • Previous endocarditis | 6.4% (n = 11) |
| • Previous dental procedures | 3.5% (n = 6) |
| • Intravenous drug abuse | 2.3% (n = 4) |
| • Congenital heart disease | 1.8% (n = 3) |
| • HIV | 0.6% (n = 1) |
| Previous valve replacements/interventions | 36.9% (n = 63) |
| • Bioprosthetic aortic valve replacement | 19.3% (n = 33) |
| • Mechanical aortic valve replacement | 3.5% (n = 6) |
| • Bioprosthetic mitral valve replacement | 5.3% (n = 9) |
| • Mechanical mitral valve replacement | 1.8% (n = 3) |
| • Mitral valve reconstruction | 0% (n = 0) |
| • Bioprosthetic tricuspid valve replacement | 0.6% (n = 1) |
| • Transcatheter aortic valve replacement (TAVI) | 6.4% (n = 11) |
| Clinical presentation | |
| • Fever >38 °C | 79.5% (n = 136) |
| • Not intended loss of weight | 21.6% (n = 37) |
| • Dyspnoea | 22.2% (n = 38) |
| • Acute/progressive heart failure | 18.1% (n = 31) |
| • Stroke/transient ischemic attack | 17.5% (n = 30) |
| • Presumptive new heart murmur | 8.8% (n = 15) |
| • Peripheral emboli | 4.7% (n = 8) |
| • Splenomegaly | 2.3% (n = 4) |
| • Oslefs nodes | 1.2% (n = 2) |
| • Janeway's lesions | 1.2% (n = 2) |

Table 3
Microbiology findings and laboratory results.

| | |
|--|--------------------|
| Gram positive strains | 97.8% (134/137) |
| • Staphylococcus aureus | 21.2% (29/137) |
| • Methicillin-resistant staphylococcus aureus (MRSA) | 2.2% (3/137) |
| • Enterococcus faecalis | 19.7% (27/137) |
| • Staphylococcus epidermidis | 16.8% (23/137) |
| • Staphylococcus haemolyticus | 2.2% (3/137) |
| Gram negative strains | 2.2% (3/137) |
| • Escherichia coli | 0.7% (1/137) |
| • Aggregatibacter actinomycetem comitans | 0.7% (1/137) |
| • Serratia marcescens | 0.7% (1/137) |
| Laboratory results | |
| • leukocytes (/nl) (Median/Quartiles) | 10.7 (8.0; 14.2) |
| • C-reactive protein (CRP) (mg/l) (Median/Quartiles) | 72.6 (32.6; 153.8) |
| • procalcitonin (PCT) (ng/ml) (Median/Quartiles) | 3.7 (1.2; 6.6) |

Using a logistic regression model to analyse predictors of conservative instead of surgical therapy the only independent variables were: presence of large vegetation or abscesses (OR: 0.36, 95%CI 0.15–0.83; p = 0.016) and age (for each ten years) (OR: 1.61, 95%CI 1.11–2.32, p = 0.01)

Hospital mortality was 21.6% (n = 37/171), with no difference (p = 0.97) between those who were operated (21.6%, n = 30/139)

Table 4
Echocardiographic findings.

| | Transthoracic echo (TTE) n = 171 | Transesophageal echo (TOE) n = 163 |
|------------------------|-------------------------------------|------------------------------------|
| Aortic valve | | |
| • Vegetations | 39.8% (68/171) | 50.3% (82/163) |
| • Paravalvular abscess | 4.7% (8/171) | 14.1% (23/163) |
| Mitral valve | | |
| • Vegetations | 28.1% (48/171) | 35.6% (58/163) |
| • Paravalvular abscess | 0.0% | 1.8% (3/163) |
| Tricuspid valve | | |
| • Vegetations | 5.3% (9/171) | 8.6% (14/163) |
| • Paravalvular abscess | 0.0% | 0.0% |

Table 5
Use and results of additional imaging procedures.

| | Use of procedures | Pathological results |
|--------------------------|-------------------|----------------------|
| cCCT | 33/171 (19.3%) | 78.8% (n = 26) |
| Cranial or vertebral MRT | 32/171 (18.7%) | 100% (n = 32) |
| PET-CT | 10/171 (5.8%) | 90% (n = 9) |
| aCT | 29/171 (17%) | 83% (n = 24) |
| • Liver | | 10% (n = 3) |
| • Spleen | | 52% (n = 15) |
| • Kidney | | 28% (n = 8) |
| Abdominal sonography | 20/171 (11.7%) | 80% (n = 16) |
| • Liver | | 5% (n = 1) |
| • Spleen | | 75% (n = 15) |
| • Kidney | | 15% (n = 3) |

cCCT = cranial computed tomography, MRT = magnetic resonance tomography, PET-CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography, aCT = abdominal computed tomography.

and those treated only by antibiotics (conservatively) 21.9% (n = 7/32). Comparing those treated conservatively without an indication for surgery with those with an indication, mortality was 9.5% versus 45.5%, p = 0.02. In patients with NVE hospital mortality was 23.5% (20/85), with PVE 20.8% (11/53) and DRE 18.2% (6/33).

Using a logistic regression model to analyse predictors of mortality the only independent variables were: higher CRP values (OR: 1.01, 95%CI 1.0–1.01; p < 0.001) and the presence of large vegetation or abscesses (OR: 3.09, 95%CI 1.05–9.10; p = 0.04). Negative blood cultures (OR: 2.35, 95%CI 0.91–6.08, p = 0.08) did not reach statistical significance.

Survival rates of all patients, patients with NVE, PVE and DRE are shown in Fig. 1. Survival rates of patients treated with cardiac surgery and patients treated conservatively as well as patients treated conservatively without an indication for surgery and patients treated conservatively despite an indication for surgery are shown in Figs. 2 and 3.

4. Discussion

The recently published EURO-ENDO endocarditis registry with 3116 adult patients from 156 hospitals in 40 countries gives an overview of current clinical presentation, diagnostic procedures, and management of IE in Europe. However, as stated by the authors, there were big differences in almost all features between countries and participating hospitals [13].

Although we participated in the EURO-ENDO registry, we expected differences between results at our hospital, being a referral centre for IE with on-site cardiac surgery, and those of the European registry.

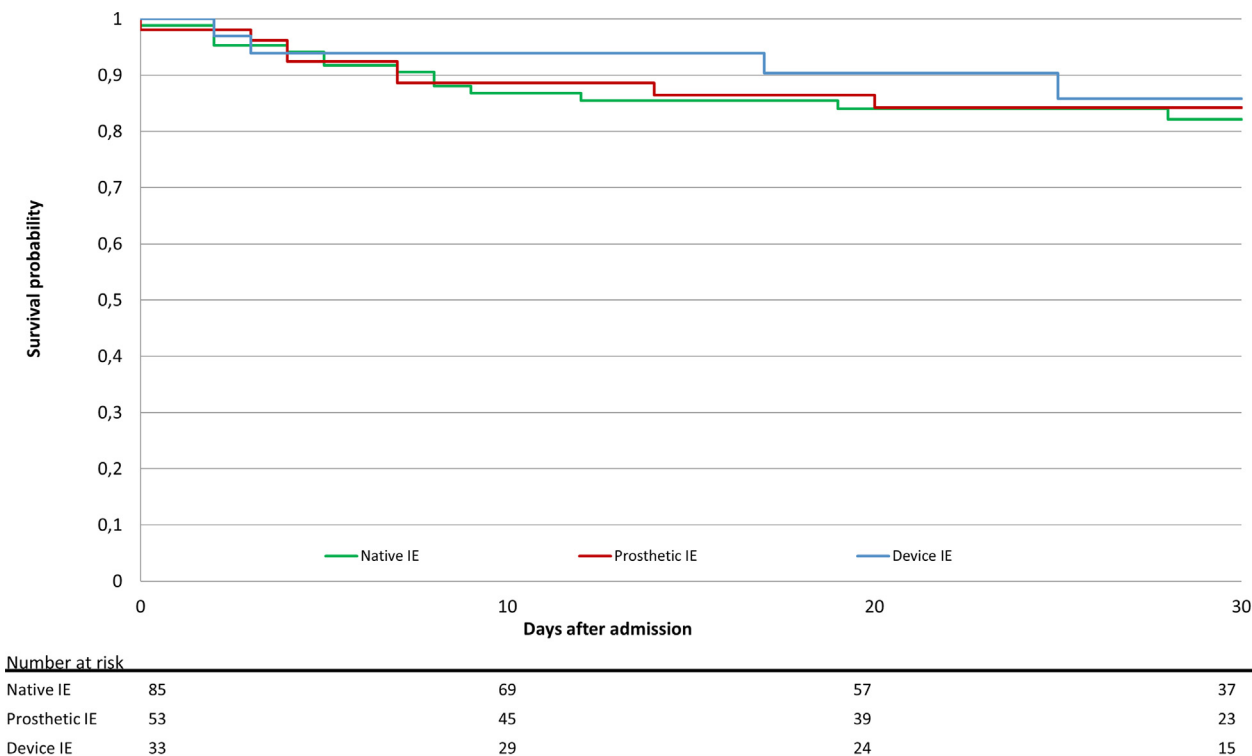


Fig. 1. Kaplan-Meier survival curves of patients with native valve IE, prosthetic valve IE and device related IE.

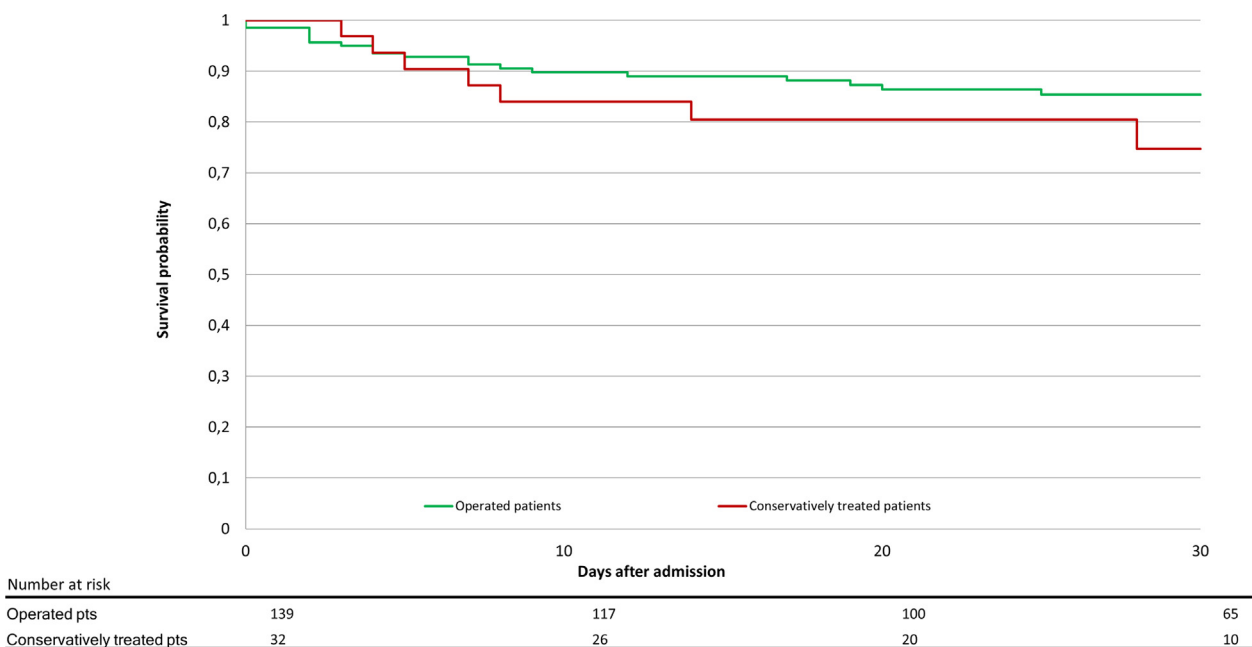


Fig. 2. Kaplan-Meier survival curves of patients treated with cardiac surgery and patients treated conservatively.

The main diverging findings are: 1) the high rate of device-related IE, 2) the huge number of patients treated surgically and 3) the loss of difference in mortality between operated and conservatively treated patients under these circumstances.

Our patients were almost 7 years older (66.5 vs 59.3 years), renal failure was more present (32.7% vs 17.8%) and we had a high proportion (36.9%) of previous valve replacement/interventions patients compared to the EURO-ENDO registry [13].

The rates of NVE and PVE were comparable, but we had an almost twice higher rate of DRE (19.3% vs 9.9%) [13]. This may be caused by the fact that our institution is a certified centre of extraction of devices by the German cardiac society. In accordance with previous registries, the data show an increase of DRE over time [2,10,15].

The clinical presentation was similar as was the proportion of positive blood cultures (80.1% vs 79%) with predominantly staphy-

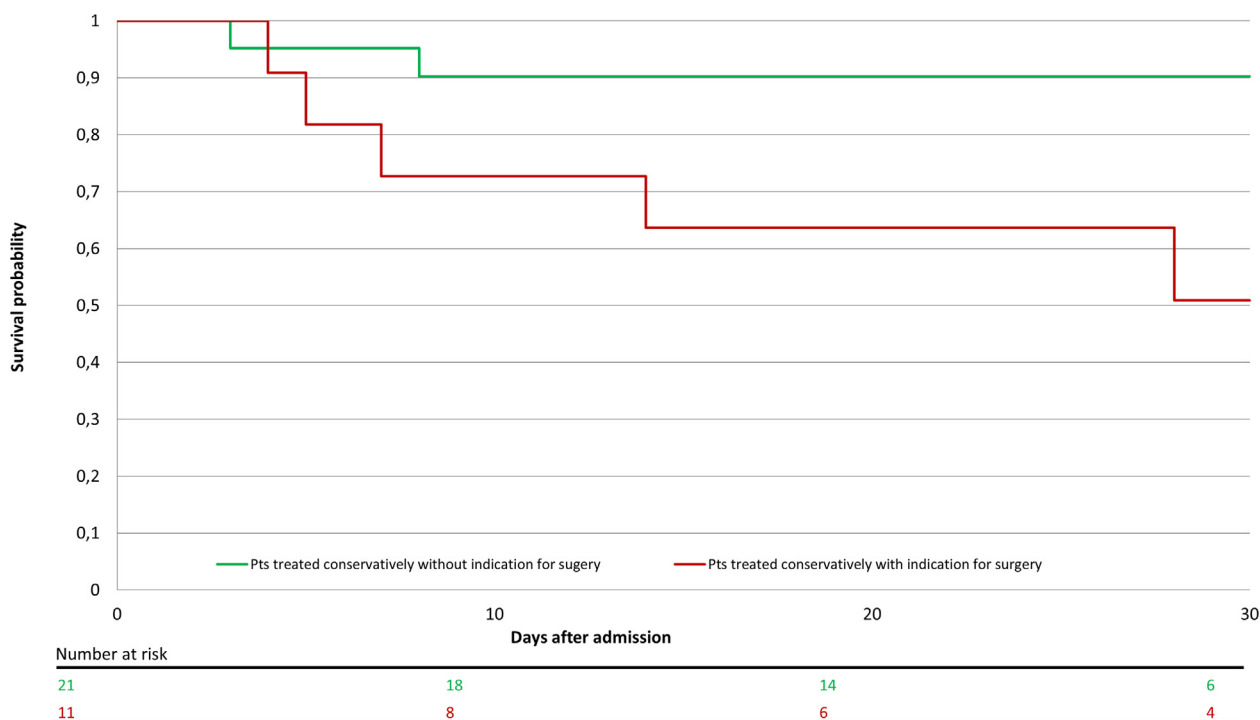


Fig. 3. Kaplan-Meier survival curves of patients treated conservatively without an indication for surgery and patients treated conservatively despite an indication for surgery.

lococci in more than 40% of patients. Also, the rates of enterococci were similar high on both registries (19.7% vs 15.8%) [13].

More than half (62.6%) of our IE patients were transferred from other hospitals either for further diagnosis or for treatment. Both seems to be reliable, for our cardiological department is a reference centre for other hospitals for further diagnosis of IE in uncertain cases as well as our cardiac surgery department is the target of other hospitals in cases of IE to send to. Therefore, surgery was performed in 95 out of 107 (88.8%) transferred IE patients compared to 44 out of 64 (68.8%) of not transferred IE patients ($p < 0.001$). Unfortunately, we cannot compare these data to that from the EURO-Endo registry, because as mentioned in the limitations section, transferral status was not gathered [13]. This is also true for most other multi-centre registries on IE [2,10,12]. However, referral carries the risk of bias regarding patient selection and diagnosis and treatment choices [16].

TTE and TOE are the most important diagnostic tools besides blood cultures for the diagnosis of IE. The recent ESC endocarditis guidelines advise to perform TOE even if TTE is already diagnostic for IE to quantify the exact length of the vegetations and to detect complications, such as paravalvular abscesses [3]. Given this background, the 100% use of TTE and the 95.3% use of TOE in our series seems to get pretty close to this. The rates are higher than those registered in the EURO-ENDO registry (90% and 58%) [13]. As known before, TOE is superior to TTE concerning detection rates of vegetations, their measurement as well as the detection of complications, thus, contributing to potentially higher operation rates.

On the other side, the use of other diagnostic tools, for example cranial and abdominal CT and cranial MRT seem to be rather low given the advice of the ESC guidelines to do so [3]. However, this may in part be due to the high transferral rate of patients, where some diagnostic work-up may have been done already in the hospital of primary presentation.

Although our hospital owns a PET-CT, we were restrictive in its use (5.8% of patients). This is much lower than the 16.6% use in EURO-ENDO. However, we normally do first a second TOE in cases

where the first one does not give a clear diagnosis, leaving PET-CT only as back-up diagnostic tool in persisting unclear situations.

Cardiac surgery was performed in 81.3% of our patients. This is much higher than the observed rate of 40–50% in most registries [2,10,15], and still considerably higher than the 51.2% rate in EURO-ENDO. However, in EURO-ENDO [13] the authors suggested, that the theoretical rate of indications to surgery (mainly heart failure, uncontrolled infection, prevention of emboli) would have been 69.3%, which is closer to our rate and almost identical to the operation rate of IE patients who were not transferred (68.8%). Another factor contributing to this high rate may be the high referral rate in our registry, indicating a selection of referred patients (younger, clear indication for surgery, ...). This is supported by our multivariable analysis of predictive factors for conservative therapy instead of surgery, which found only two independent factors: presence of large vegetation or abscesses (OR: 0.36, 95%CI 0.15–0.83; $p = 0.016$) and age (for each ten years) (OR: 1.61, 95%CI 1.11–2.32, $p = 0.01$). The Median age of operated patients was 67 years compared to 78 years ($p < 0.001$) in conservatively treated patients. All patients sent to surgery were beforehand discussed by our endocarditis team, which also may have contributed to the observed high rate. Furthermore, our 10% higher rate of DRE also may have contributed to the high surgical rate, for DRE are almost ever advised and sent to surgery [3].

6.4% ($n = 11$) of our patients had previous transcatheter aortic valve replacement (TAVI). Those TAVI patients were significantly less often sent to surgery than non TAVI patients: 9.1% (1/11) versus 86.3% (138/160) treated conservatively; $p < 0.001$). However, due to the low numbers of TAVI patients, we could not include them into the multivariable regression analysis. This low operation rate is also supported by data from the literature. Amat-Santos et al. for a large multi-centre registry [17] reported an 11% (6/53 patients) valve intervention rate (4 operations and 2 valve-in-valve interventions) for IE after TAVI; Summers et al. on behalf of the Placement of Aortic Transcatheter Valve (PARTNER) investigators [18] reported a 4.7% intervention rate in TAVI associated IE (5

of 107 patients) and Bjursten et al. for a nationwide registry in Sweden [19] reported an 1.9% operation rate (2 of 107 patients). However, with the changing profile of TAVI patients, increasingly switching to intermediate and even low surgical risk patients, one can expect higher surgical rates for TAVI associated IE in the future.

Hospital mortality was 23.5% in patients with NVE, 20.8% in PVE and 18.2% in DRE. This is almost identical with the observation from the EURO-ENDO registry, where no differences in mortality rates between the types of IE were found [13].

In the EURO-ENDO registry surgery was significantly associated with lower hospital mortality, even after adjustment for confounding parameters (OR = 0.63, 95%CI: 0.43 – 0.92; p = 0.0169). Thus, suggesting a causal effect of surgery when indicated. These data are supported by randomized data [8].

With the high surgical rate in our registry, we found no significant association of surgery with hospital mortality (adjusted OR = 1.14, 95%CI: 0.88 – 3.39; p = 0.82). Therefore, we would hypothesize that, if surgery is performed in nearly all appropriate indications, outcome can be mitigated towards patients treated conservatively. However, this group of patients still reflects two different subgroups with quite different outcomes: Those without a surgical indication and those with an indication. Comparing those treated conservatively without an indication for surgery with those with an indication, mortality was 9.5% versus 45.5%, p = 0.02. For all patients treated conservatively with a “theoretical” indication for surgery were seen by the endocarditis team, surgery was not a real option for these patients. They simply reflect those patients for whom just supportive care seems to be appropriate.

5. Conclusions

In this single centre registry from a hospital with on-site cardiac surgery we found significant differences compared to the EURO-ENDO registry: more than half of patients were referred and 81.3% of patients were treated surgically. Hospital mortality was 21.6% with no difference between operated and conservatively treated patients. However, conservatively treated patients consist of two totally different groups with different mortality, those without an indication for surgery and those in whom surgery although indicated is not a real option.

6. Limitations

An inherent limitation of all registry data is, that treatment effects cannot be taken as a simple result of treatment alone, but also of selection of treatments by doctors. Therefore, one should be cautious in the interpretation of the effects of surgery.

In contrast to the prospective EURO-ENDO registry, this is a retrospective registry. However, we are sure to have gathered all patients with IE because we looked for the relevant ICD code, irrespective of the department which cared for the patient.

Given the high proportion of transferred patients some investigations performed at the transferring hospital were not repeated. This may explain the low use of some investigations.

Furthermore, our sample size of 171 IE patients is far smaller than that of the EURO-ENDO registry. Nevertheless, we collected data over a 4-year period, with an average of 43 patients per year, indicating a high-volume hospital.

Currently, we only have data on the hospital course of the patients at our institution. We plan to perform a follow-up.

Funding

No funds, grants or other support was received.

Availability of data and material

The authors grant access to all relevant data and material.

Ethical standards

This is a retrospective study, relying only on hospital data. Therefore, no informed consent of patients was obtained.

Patient and Public involvement statement

There was no patient or public involvement in our study.

Contributorship statement

Ralf Zahn has planned and reported the work described in the article.

Philippe M. Barth has conducted the work and was involved in the report of the article.

Caroline Kilkowski, Boris Fraiture, Ann-Katrin Karcher, René Brüttsch, Ralph Winkler, Thomas Kleemann, Steffen Schneider, Dorothée Sutor, Udo Weisse and Falk-Udo Sack were all involved in the planning, conduction and reporting the work of the article.

Steffen Schneider did the statistical analyses.

Ralf Zahn is responsible for the overall content as guarantor.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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