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Title:
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Date:
2021-05-01

Citation:
Ye, X. T., Buratto, E., Dimitriou, J., Yaftian, N., Wilson, A., Darby, J. & Newcomb, A. (2021). Right-Sided Infective Endocarditis: The Importance of Vegetation Size. Heart Lung and Circulation, 30 (5), pp.741-750. https://doi.org/10.1016/j.hlc.2020.09.927.

Heart, Lung and Circulation (2021) **30**, 741–750
1443-9506/20/$36.00
https://doi.org/10.1016/j.hlc.2020.09.927

ORIGINAL ARTICLE

Right-Sided Infective Endocarditis: The Importance of Vegetation Size

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Received 19 May 2020; received in revised form 6 September 2020; accepted 9 September 2020; online published-ahead-of-print 30 January 2021

Background Right-sided infective endocarditis (IE) carries favourable prognosis compared to left-sided IE. However, the prognostic significance of vegetation size in right-sided IE is less well defined. This study reports the clinical, microbiological, and echocardiographic findings associated with right-sided IE and examines the predictors of adverse outcomes.

Methods Consecutive adults admitted with isolated right-sided IE at an Australian tertiary referral centre between June 1999 and May 2017 were retrospectively reviewed. Patients were stratified according to intravenous drug user (IVDU) status. Culprit organisms, sepsis severity, treatment regimens, inpatient complications, and vegetation size were recorded. Hospital survivors were followed mean 6.9±4.8 years for late mortality and IE recurrence.

Results Of 318 consecutive cases of IE, 60 (19%) were isolated right-sided IE and included in this study. Forty-three (43) (72%) patients were current IVDUs, who were younger and more likely to have hepatitis. The majority (90%) of patients were medically managed with multi-agent antimicrobial regimens (median three agents) for a total duration of median 91 days. In-hospital mortality was 3% (2/60). Septic emboli were found in 82% (49/60) of patients, were significantly more common among IVDUs but were not related to vegetation size. Survival after hospital discharge was 100% at 1 year, 96% at 3 years, and 89% at 5 years. Vegetation size >2 cm, chronic kidney disease, and Pitt bacteraemia score were independent predictors of all-cause late mortality. Freedom from IE recurrence was 93% at 1 year, 87% at 3 years, and 84% at 5 years. Vegetation >2.5 cm, prisoner status, and multivalvular IE involvement conferred higher risks of recurrence.

Conclusions Patients with right-sided IE and small vegetations do well with medical management and this should continue to be the preferred strategy. However, those with large vegetations have poorer late outcomes and may require more aggressive treatment and closer follow-up.

Keywords Infective endocarditis • Right-sided • Recurrence • Mortality

Introduction

Right-sided infective endocarditis (IE) accounts for approximately 10% of all IE cases and portends a relatively benign prognosis as compared to left-sided IE [1]. Intravenous drug use is the leading cause of right-sided IE in the Western world and is increasingly prevalent amidst the current opioid epidemic [2]. However, other predisposing factors remain prevalent, including intracardiac devices, central venous catheter (CVC), arteriovenous fistula for dialysis, and

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Read at the 68th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand, 11-13 December 2020.

underlying cardiac anomalies. To date, the few studies of right-sided IE have focussed predominantly on intravenous drug users (IVDUs) [3,4], patients managed surgically [5,6], or patients with isolated tricuspid valve (TV) IE [7,8], which may be subject to selection bias. Furthermore, few studies have evaluated prognostic factors for right-sided IE. Studies of IVDUs have suggested that vegetation size and fungal aetiology may be predictors of poor outcome [3,4], but limited data is available beyond the initial admission. Whether such prognostic factors also predict long-term adverse sequelae is unclear. We therefore retrospectively reviewed predisposing factors, clinical, microbiological, and echocardiographic parameters in order to identify risk factors for all-cause mortality and IE recurrence in a consecutive cohort of patients treated for right-sided IE over an 18-year period.

Methods

Patient Selection

This study was undertaken at an Australian public tertiary referral centre located in an inner-city area with high rates of IVDUs [9]. Consecutive presentations of right-sided IE between June 1999 and May 2017, including patients transferred from peripheral hospitals, were retrospectively analysed. Patients were identified from hospital records using the International Classification of Diseases (ICD-10), where "acute and subacute infective endocarditis" (I33.0) was listed as the principal or associated diagnosis. Patients were included if they had isolated IE involving the tricuspid valve, pulmonary valve, or implantable devices in the right-sided chambers of the heart. All met modified Duke criteria for having definite IE or possible IE as determined by the infectious diseases team [10]. Patients with concurrent left-sided IE as evident on echocardiography were excluded.

Data Collection

Data were retrospectively collected from paper and electronic medical records. Active IVDU was defined as IVDU within 3 months prior to admission. Chronic lung disease was defined as lung disease that required long-term use of bronchodilators or steroids. Immunosuppressed patients were those who took immunosuppressing drugs within 3 months prior to admission and/or received chemotherapy within 6 months. For all patients, the presence of sepsis on admission was retrospectively determined by the "quick" Sequential Organ Failure Assessment (qSOFA) [11] and the Systemic Inflammatory Response Syndrome (SIRS) [12] criteria. The Pitt bacteraemia score was calculated using clinical information on admission as an indicator of sepsis severity [13]. For patients admitted to the intensive care unit (ICU), the SOFA score [14] and the Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score [15] were calculated retrospectively. Antimicrobial agents that were prescribed based on the susceptibility of the target organism or those used for more than 1 week were recorded.

Diagnosis of IE

The diagnosis of IE was made according to the modified Duke criteria [10]. Organisms were identified from blood culture or specimens obtained during surgical intervention. Polymicrobial infections were identified when more than one organism was isolated.

Transthoracic echocardiography (TTE) reports were retrospectively reviewed to identify locations of endocardial involvement, size of vegetations, valvular and ventricular functions. Data were collected from the first TTE performed during admission, or preferentially from the first transoesophageal echocardiography (TOE) performed if available. If information was missing from the first report, then subsequent reports were reviewed. Vegetation sizes were recorded if available, with the largest dimension on multiple views recorded. The presence of abscess was determined on echocardiography or surgery. Right ventricular (RV) systolic function was measured by visual estimation and tricuspid annular plane systolic excursion (TAPSE), with dysfunction defined as TAPSE <16 mm [16].

Clinical Outcomes

In-hospital complications and mortality were recorded from medical records of the index admission. Septic emboli were embolic phenomena deemed unlikely to be the primary source of infection and were identified from radiology reports. Follow-up of hospital survivors were obtained through medical record review and correspondence with referral hospitals, general practitioners, or other last known points of clinical contact. Recurrence of IE was defined as re-presentation to a health service (any public hospital in Victoria) with a diagnosis of IE. We classified recurrence as "relapse" if the causative organisms were consistent between episodes and the recurrence occurred within 6 months of the index admission, or "reinfection" otherwise. Survival status at the last clinical contact was recorded. All-cause mortality and IE recurrence were the primary endpoints of clinical outcomes.

Statistical Analysis

Continuous variables were reported as mean±standard deviation and compared between groups using the Wilcoxon rank-sum test. Categorical variables were reported as frequencies and percentages and compared using the Fisher's exact test. Cox regression analysis was performed to evaluate predictors of mortality and disease recurrence. Time-related outcomes were estimated using the Kaplan-Meier method. Variables with at least moderate evidence against the null hypothesis ($p<0.10$) in univariable analysis were included in multivariable analysis, after excluding collinearity with Fisher's exact test or Wilcoxon rank-sum test. Data were analysed using Stata version 14 (StataCorp, College Station, TX, USA). Statistical significance was $p<0.05$.

Ethics Approval

Ethics approval for this study was granted by our institution's human research ethics committee (QA 048/18). The requirement for informed consent was waived due to the retrospective nature of the study.

Results

Patient Characteristics

Out of 318 consecutive adults admitted with IE during the study period, 60 (19%) had isolated right-sided IE and were included in the present study. Twelve (12) (4%) patients had concurrent left-sided IE and were excluded. Overall, the cohort aged 41.3±16.4 years and 40% were female (Table 1). The predisposing risk factors for IE were active IVDU in 43 patients (72%), intracardiac devices (pacemaker or defibrillator leads) in 11 patients (18%), CVCs in three patients (5%), and others/non-identified in three patients (5%). The three patients with CVCs had health care-associated infection, including two with central lines for haemodialysis and one

Table 1 Patient characteristics based on history of intravenous drug use.

	All Patients (n=60)	IVDU (n=43)	Non-IVDU (n=17)	P-value
Age (yr)	41.3±16.4	35.0±9.5	57.1±19.5	<0.001
Female	24 (40.0)	18 (41.9)	6 (35.3)	NS
Transferred from peripheral hospital	30 (50.0)	18 (41.9)	12 (66.6)	0.08
Cardiovascular history				
Cardiac implantable device	11 (18.3)	0 (0.0)	11 (64.7)	<0.001
Congestive heart failure	5 (8.3)	1 (2.3)	4 (23.5)	0.020
Previous IE	6 (10.0)	6 (14.0)	0 (0.0)	NS
Previous cardiac surgery	5 (8.3)	0 (0.0)	5 (29.4)	0.001
Prosthetic valve	1 (1.6)	0 (0.0)	1 (5.9)	NS
Congenital heart disease	5 (8.3)	2 (4.7)	3 (17.6)	NS
Comorbidities and risk factors				
Chronic lung disease	10 (16.7)	10 (23.3)	0 (0.0)	0.049
Current smoker	36 (60.0)	33 (78.7)	3 (17.6)	<0.001
CKD	3 (5.0)	0 (0.0)	3 (17.6)	0.02
Hypertension	9 (15.0)	1 (2.3)	8 (47.1)	<0.001
Diabetes	8 (13.3)	2 (4.6)	6 (35.3)	<0.01
Chronic vascular access	3 (5.0)	0 (0.0)	3 (17.6)	0.02
Hepatitis	38 (63.3)	37 (86.0)	1 (5.9)	<0.001
Immunosuppressed	3 (5.0)	0 (0.0)	3 (17.6)	0.02
Malignancy	3 (5.0)	1 (2.3)	2 (11.8)	NS
Psychiatric conditions	21 (35.0)	20 (46.5)	1 (5.9)	<0.01
Social history				
Homeless	8 (13.3)	7 (16.2)	1 (5.9)	NS
Unemployed	28 (46.7)	27 (62.8)	1 (5.9)	<0.001
Lacked family support	24 (40.0)	19 (44.2)	5 (29.4)	NS
Prisoner	7 (11.7)	7 (16.3)	0 (0.0)	NS
Sepsis severity on admission				
Met SIRS criteria	48 (80.0)	37 (86.0)	11 (64.7)	0.08
Met qSOFA criteria	24 (40.0)	19 (44.2)	5 (29.4)	NS
Pitt bacteraemia score	1.7±1.6	1.8±1.7	1.3±1.2	NS
Biochemistry on admission				
Haemoglobin (g/L)	109±22	107±23	114±17	NS
White cell count ($\times 10^9$/L)	13.3±6.7	13.9±6.7	11.7±6.7	NS
Platelet count ($\times 10^9$/L)	186±174	175±172	212±182	NS
Creatinine (μmol/L)	134±182	102±71	215±315	0.03
Bilirubin total (μmol/L)	24±25	24±26	24±22	NS
INR	1.3±0.3	1.3±0.2	1.3±0.4	NS
CRP (mg/L)	216±93	198±61	265±138	0.01
Lactate (mmol/L)[a]	2.0±2.1	1.9±2.3	2.4±1.4	NS

Data are n (%) or mean±standard deviation.

Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; IE, infective endocarditis; INR, international normalised ratio; IVDU, intravenous drug use; NS, non-significant; qSOFA, quick Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome.

[a]Lactate value on admission was available for 30 patients only.

with port-a-cath for chemotherapy. All other cases were community-acquired. Intravenous drug users were significantly younger, had higher prevalence of chronic lung disease, hepatitis and psychiatric conditions, and were more likely to be current smokers or unemployed. Non-IVDU patients had higher prevalence of chronic kidney disease (CKD), hypertension, diabetes and immunosuppression, and had higher creatinine and C-reactive protein levels on admission.

Microbiology

Causative organisms isolated from blood culture or surgical specimens are presented in Table 2. The most commonly isolated organism was *Staphylococcus aureus* (n=53, 88.3%), with no methicillin-resistant *S. aureus* (MRSA) identified. There was no culture-negative IE in the studied cohort. *S. aureus* was more commonly associated with IVDUs, but this was not statistically significant (93.0 vs. 76.4%, p=0.09). Neither causative organism nor persistently positive blood culture of >72 hours were predictors of hospital length-of-stay, embolic infections, or hospital mortality. However, patients with *S. aureus* had significantly higher Pitt bacteraemia score on admission (1.8±1.6 vs. 0.4±0.8, p=0.03). Furthermore, patients with polymicrobial infections had significantly longer hospital stays (45±27 vs. 28±17 days, p<0.01).

For patients who survived to discharge from the index admission, the median duration of inpatient treatment was 26 days (interquartile range [IQR]: 15-42 days). Eight (8) (13.3%) patients defaulted prior to completing the prescribed course of treatment (self-discharged against medical advice or recreational drug use in hospital). Most patients were treated with multiple antimicrobial agents, median three (IQR 3-4) agents. The antimicrobials used are presented in Table 3. Rifampicin, flucloxacillin or ciprofloxacin were used in most patients. The total duration of inpatient plus outpatient antimicrobial treatment was median 91 days (IQR 46-182 days). Two (2) patients were prescribed lifelong antibiotics.

Echocardiography

Transoesophageal echocardiography was performed in 20 (33%) patients and was less commonly performed for IVDUs. Findings on echocardiography are presented in Table 4. Fifty-nine (59) (98%) patients had native valve IE, 11 (18%) patients had intracardiac device involvement, and no patient had prosthetic valve IE. The tricuspid valve was most commonly affected (95%), with the anterior and septal leaflets most frequently involved. There were no differences in valvular involvement between IVDU versus non-IVDU patients, but IVDUs had significantly better left ventricular ejection fraction (59±7 vs. 49±19, p<0.01). Paravalvular

Table 2 Microbiology by history of intravenous drug use.

	All Patients (n=60)	IVDU (n=43)	Non-IVDU (n=17)	P-value
Staphylococcus aureus (total)	53 (88.3)	40 (93.0)	13 (76.4)	0.09
MRSA	0 (0.0)	0 (0.0)	0 (0.0)	
MSSA	53 (88.3)	40 (93.0)	13 (76.4)	0.09
Streptococcus species	7 (11.6)	3 (7.0)	4 (23.5)	0.09
Viridans group strep	3 (5.0)	2 (4.7)	1 (5.9)	NS
Group A strep	1 (1.7)	0 (0.0)	1 (5.9)	NS
Group B strep	0 (0.0)	0 (0.0)	0 (0.0)	
Group C strep	2 (3.3)	1 (2.3)	1 (5.9)	NS
Strep. bovis	1 (1.7)	0 (0.0)	1 (5.9)	NS
Enterococcus species	2 (3.3)	2 (4.7)	0 (0.0)	NS
Coagulase-negative *Staphylococcus* species	2 (5.0)	1 (2.3)	1 (5.9)	NS
Fungal	2 (3.3)	2 (4.7)	0 (0.0)	NS
Others[a]	3 (5.0)	1 (2.3)	2 (11.8)	NS
Polymicrobial[b]	10 (16.7)	6 (14.0)	4 (23.5)	NS
Persistent positive blood culture >72 hr	18 (30.0)	14 (32.6)	4 (23.5)	NS

Data are n (%).

Abbreviations: IVDU, intravenous drug use; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-sensitive *Staphylococcus aureus*; NS, non-significant; *PSSA*, penicillin-sensitive *Staphylococcus aureus*.

[a]Others group included: *Pseudomonas aeruginosa* (n=1), *Propionibacterium acnes* (n=1), *Escherichia coli* (n=1).

[b]Organisms grown in the polymicrobial group include: MSSA and streptococcus (n=2), PSSA and MSSA (n=1), MSSA and coagulase-negative staphylococcus (n=1), MSSA and *Pseudomonas aeruginosa* (n=1), MSSA and *Propionibacterium acnes* (n=1), MSSA and *Enterococcus faecalis* (n=1), MSSA and *Enterococcus faecium* (n=1), MSSA and *Escherichia coli* (n=1), and MSSA and *Candida albicans* (n=1).

Table 3 Antimicrobials used in the treatment of right-sided infective endocarditis.

Antimicrobials	Number of Patients (n=60)
Rifampicin	48 (80%)
Flucloxacillin	41 (68%)
Ciprofloxacin	32 (53%)
Fusidic acid	22 (37%)
Benzylpenicillin	9 (15%)
Dicloxacillin	9 (15%)
Vancomycin	9 (15%)
Ceftriaxone	6 (10%)
Cephazolin	6 (10%)
Amoxicillin±clavulanate	5 (8%)
Gentamicin	5 (8%)
Fluconazole	3 (5%)
Cephalothin	2 (3%)
Caspofungin	1 (2%)
Ceftazidime	1 (2%)
Meropenem	1 (2%)
Moxifloxacin	1 (2%)
Ticarcillin-clavulanate	1 (2%)

abscess was detected in only one patient, who had TTE. Vegetation size was quantified in 57 patients and measured 1.6±0.8 cm. There was no correlation of IVDU status or sepsis severity in terms of the Pitt bacteraemia score with vegetation size. However, among patients with tricuspid valve involvement, vegetation size was significantly larger in those with moderate or severe tricuspid regurgitation (1.8±0.8 vs. 1.3±0.8 cm, p=0.03).

Septic Emboli

Septic emboli were identified in 49 (82%) patients and were more common among IVDUs (Table 5). In particular, pulmonary septic emboli occurred in 68% of patients and were significantly associated with IVDU. Respiratory symptoms on admission (including dyspnoea, cough, chest pain, or haemoptysis) significantly predicted septic pulmonary emboli on imaging (85% [23/27] vs. 55% [18/33], p=0.01). Pleural effusion was present in 52% (31/60) of patients, including 11 who required procedural or surgical drainage. Septic emboli did not predict in-hospital or all-cause mortality. Neither vegetation size nor persistent bacteraemia (>72 hours) predicted septic emboli (Table 6). Patients with intra-abdominal emboli had larger vegetations, but this did not reach statistical significance (2.3±0.2 vs. 1.5±0.8 cm, p=0.07).

Clinical Outcomes

In-hospital mortality was 3.3% (2/60). Vegetation size >2 cm was associated with hospital mortality, but this did not reach statistical significance (12% [2/17] vs. 0% [0/43], p=0.08).

Inpatient cardiothoracic surgery was performed in six (10%) patients, including removal of infected intracardiac device in five patients and tricuspid vegetectomy plus valve repair in one patient who had candidaemia and uncontrolled sepsis. All but one operated patient survived to hospital discharge. Four (4) (7%) patients were deemed too high-risk for surgical intervention and were medically managed, all of whom survived to discharge. Twenty-five (25) (42%) patients required ICU admission for median 3 (IQR 2-9) days, with 8% (2/25) mortality. There were no differences in in-hospital mortality, complications, or disease severity between IVDU versus non-IVDU patients (Table 7).

The median follow-up period for hospital survivors was 6.1 years (IQR 3.0-9.0 years; mean 6.9±4.8 years; range: 1 month–19.1 years). Current IVDU status could be ascertained for 56% (23/41) of IVDUs, of whom 13 continued IVDU. There was no 12-month mortality, whereas late mortality occurred in seven (13%) patients (Table 7). Freedom from late mortality was 100% at 1 year, 96% at 3 years, and 89% at 5 years. Rehospitalisation for recurrent IE occurred in nine (16%) patients at median 12.1 (IQR 5.8–19.6) months after discharge, all of whom were IVDUs. Of these, three (5%) patients had relapse and six (11%) patients had reinfection. Freedom from IE recurrence was 93% at 1 year, 87% at 3 years, and 84% at 5 years.

Predictors of all-cause mortality and recurrent IE are presented in Table 6. Risk of mortality was higher among patients with vegetation size >2 cm (hazard ratio [HR]: 74.95 [3.70-1,518.77], p<0.01, Figure 1), CKD, or the Pitt bacteraemia score on multivariate analysis. Causes of late morality were reliably identified from clinical notes in six cases (86%): myocardial infarction complicating recurrent IE (n=1), acute coronary syndrome (n=1), asthma (n=1), CKD (n=1), acute gastroenteritis (n=1), and malignancy (n=1). Risk of recurrent IE was higher among patients with vegetation size >2.5 cm (HR 14.93 [2.93–76.07], p=0.001, Figure 2), prisoners, or multivalvular IE on multivariate analysis. There were no associations between long-term outcomes and isolated organism, ongoing IVDU, septic embolisation, or default from index admission.

Discussion

Historically, the prognosis of right-sided IE has been relatively favourable compared to left-sided or combined right- and left-sided IE, with overall mortality as low as 6% [4,17]. However, previous reports have primarily focussed on IVDUs [3,4], patients with isolated TV involvement [7,8] or those managed surgically [6,18]. Furthermore, reliable follow-up of patients with IE in the setting of IVDU is notoriously difficult due to patient non-compliance [18]. Recent Australian studies of IE have shed light on the contemporary characteristics of this disease in the local context, but limited data was reported on right-sided IE in particular [19,20]. Our study was one of the largest series in the contemporary era of consecutive patients with

Table 4 Echocardiography by history of intravenous drug use.

	All Patients (n=60)	IVDU (n=43)	Non-IVDU (n=17)	P-value
TOE performed	20 (33.3)	10 (23.3)	10 (58.8)	0.01
Vegetation size (cm)[a]	1.6±0.8	1.6±0.8	1.5±0.8	NS
Vegetation size >2.0 cm	17 (28.3)	13 (30.2)	4 (23.5)	NS
Vegetation size >2.5 cm	7 (11.7)	6 (14.0)	1 (5.9)	NS
LVEF (%)	57±12	59±7	49±19	<0.01
Estimated RVSP (mmHg)[b]	37±10	36±9	42±14	NS
Affected valve/device				
Tricuspid valve	57 (95.0)	41 (95.3)	16 (94.1)	NS
Anterior leaflet only	12 (20.0)	10 (23.3)	2 (11.8)	NS
Septal leaflet only	9 (15.0)	5 (11.6)	4 (23.5)	NS
Posterior leaflet only	3 (5.0)	2 (4.7)	1 (5.9)	NS
Anterior + septal leaflets	14 (23.3)	10 (23.3)	4 (23.5)	NS
Anterior + posterior leaflets	4 (6.7)	4 (9.3)	0 (0.0)	NS
Septal + posterior leaflets	1 (1.7)	1 (2.3)	0 (0.0)	NS
All leaflets	4 (6.7)	4 (9.3)	0 (0.0)	NS
Annulus	3 (5.0)	3 (7.0)	0 (0.0)	NS
Not specified	7 (11.7)	5 (11.6)	2 (11.8)	NS
Pulmonary valve	2 (3.3)	2 (4.7)	0 (0.0)	NS
Intracardiac device[c]	11 (18.3)	0 (0.0)	11 (64.7)	<0.001
Prosthetic valve	0 (0.0)	0 (0.0)	0 (0.0)	
Multivalvular involvement	1 (1.7)	1 (2.3)	0 (0.0)	NS
Complications				
Multiple vegetations	26 (43.3)	16 (37.2)	10 (58.8)	NS
Paravalvular abscess	1 (1.7)	1 (2.3)	0 (0.0)	NS
Leaflet perforation	12 (20.0)	10 (23.3)	2 (11.8)	NS
Tricuspid regurgitation (at least moderate)	32 (53.3)	26 (60.5)	6 (35.3)	0.09
RV systolic dysfunction	8 (13.3)	5 (11.6)	3 (17.6)	NS
RV dilatation	2 (3.3)	1 (2.3)	1 (5.9)	NS
Moderate pulmonary hypertension (RVSP > 40 mmHg)	15/41 (36.6)	9/31 (29.0)	6/10 (60.0)	NS

Data are n (%) or mean±standard deviation.

Abbreviations: LVEF, left ventricular ejection fraction; NS, non-significant; RV, right ventricular; RVSP, right ventricular systolic pressure; TOE, transoesophageal echocardiography.

[a]Vegetation sizes were quantified in 57 patients.

[b]RVSP was reported for 41 patients only.

[c]Affected intracardiac devices included: permanent pacemaker lead (n=8), automatic implanted cardioverter-defibrillator lead (n=2), central venous cannula (n=1).

right-sided IE, including both IVDU and non-IVDU patients and those managed medically and surgically. Our mean follow-up period of 6.9 years was one of the longest reported for patients with right-sided IE. We demonstrate that vegetation size in right-sided IE carries prognostic significance in predicting late adverse outcomes.

The prognostic importance of vegetation size and its utility as an indication for surgery in right-sided IE remains a topic of contention. Previous studies have associated larger vegetations with adverse outcomes. Hecht et al. [3] studied 121 patients with IVDU-associated right-sided IE and found that vegetations >2 cm were associated with 33% mortality. Similarly, Martín-Dávila et al. [4] studied 220 IVDUs with right-sided IE and reported that vegetation size >2.0 cm was an independent predictor of hospital mortality and potentially warranted early surgery. In contrast, Otome et al. [21] recently reported that right-sided IE patients with large vegetations (>1 cm) could be safely treated with medical therapy alone, provided their Pitt bacteraemia score was <4 and there were no other indications for surgery. Current guidelines do not make firm recommendations on this topic, but suggest that surgical intervention may be reasonable in the presence of persistent TV vegetation >2.0 cm and recurrent pulmonary emboli [22,23]. It has been suggested that the impact of a wider array of cut-off sizes should be investigated [24]. Our study adds weight to the existing

Table 5 Septic emboli by history of intravenous drug use.

	All Patients (n=60)	IVDU (n=43)	Non-IVDU (n=17)	P-value
Septic emboli	49 (81.7)	41 (95.3)	8 (47.1)	<0.001
Pulmonary	41 (68.3)	37 (86.0)	4 (23.5)	<0.001
Intra-abdominal[a]	4 (6.7)	3 (7.0)	1 (5.9)	NS
Intracranial[b]	2 (3.3)	2 (4.7)	0 (0.0)	NS
Musculoskeletal[c]	24 (40.0)	19 (44.2)	5 (29.4)	NS
Vascular aneurysm[d]	2 (3.3)	2 (4.7)	0 (0.0)	NS

Data are n (%).

Abbreviations: IVDU, intravenous drug use; NS, non-significant.

[a]Intra-abdominal septic emboli affected: spleen (n=2), kidney (n=1), spleen and kidney (n=1).

[b]Intracranial septic emboli included: epidural abscess (n=2).

[c]Musculoskeletal septic emboli affected: hip (n=6), vertebrae (n=6), sacroiliac joint (n=5), shoulder (n=5), knee (n=2), wrist (n=2), finger (n=2), ankle (n=1), toe (n=1), osteomyelitis of tibia (n=1), pyomyositis of forearm (n=1), iliacus abscess (n=1), psoas abscess (n=1), gluteal myositis (n=1), and rectus femoris myositis (n=1).

[d]Vascular aneurysms affected: pulmonary artery (n=1), brachial artery (n=1).

evidence in highlighting the negative prognostic significance of larger vegetations. We found no correlation between vegetation size and hospital mortality, likely due to the low hospital mortality in our cohort, However, vegetation size was significantly associated with moderate or severe tricuspid regurgitation. Furthermore, vegetation >2 cm was an independent predictor of all-cause late mortality, even after adjusting for sepsis severity on admission. Our findings

Table 6 Predictors of all-cause mortality, septic embolisation and IE recurrence.

All-cause mortality	Univariate Predictor		Multivariate Predictor	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Vegetation size >2cm	5.37 (1.34–21.50)	<0.02	74.95 (3.70–1,518.77)	<0.01
CKD	5.93 (1.18–29.80)	0.03	76.98 (1.86–3,187.18)	0.02
Pitt bacteraemia score	1.40 (0.99–1.98)	0.056	1.93 (1.05–3.57)	0.04
IVDU	0.30 (0.08–1.13)	0.08		
Paravalvular abscess	27.76 (2.51–306.49)	<0.01		
Older age (yr)	1.03 (1.00–1.07)	0.08		
Diabetes	8.32 (2.07–33.54)	<0.01		
LVEF <40%	3.3 (0.8–13.4)	0.09		
Fungal infection		NS		
Septic embolisation		NS		
Septic embolisation	**OR (95% CI)**		**P-value**	
IVDU	23.06 (4.17–127.41)		<0.001	
Staph aureus	4.22 (0.79–22.53)		0.092	
Vegetation size			NS	
Positive blood cultures >72 hr			NS	
Rehospitalisation for recurrent IE[a]	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Vegetation >2.5cm	7.58 (1.88–30.61)	<0.01	14.93 (2.93–76.07)	0.001
Prisoner	5.2 (1.2–21.0)	0.02	10.39 (2.06–52.32)	<0.01
Multivalvular IE	10.0 (1.2–85.5)	0.04	30.02 (2.74–328.33)	<0.01
Ongoing IVDU[b]		NS		
Default from index admission		NS		

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IE, infective endocarditis; IVDU, intravenous drug use; LVEF, left ventricular ejection fraction; OR, odds ratio; NS, non-significant.

[a]All patients with recurrent IE had history of IVDU.

[b]Current IVDU status was known for 23 patients, of whom 13 were ongoing IVDUs.

Table 7 Clinical outcomes by history of intravenous drug use.

	All Patients (n=60)	IVDU (n=43)	Non-IVDU (n=17)	P-value
Hospital stay[a] (d)	31±20	32±20	27±21	NS
Follow-up from discharge[b] (yr)	6.9±4.8	7.1±5.3	6.4±3.4	NS
All-cause mortality				
In-hospital mortality	2 (3.3)	1 (2.3)	1 (5.9)	NS
Late mortality	7 (12.0)	3 (7.1)	4 (25.0)	0.08
Overall mortality[c]	9 (16.1)	4 (9.8)	5 (33.3)	NS
Rehospitalisation for IE[c]				
Relapse	3 (5.4)	3 (7.3)	0 (0.0)	NS
Reinfection	6 (10.7)	6 (14.6)	0 (0.0)	NS
Interval since discharge (mo)	20±21	20±21	-	
Overall recurrence	9 (16.1)	9 (22.0)	0 (0.0)	0.05
In-hospital complications				
Underwent cardiac surgery[d]	6 (10.0)	1 (2.3)	5 (19.4)	<0.01
Anaemia requiring blood transfusion	14 (23.3)	11 (25.6)	3 (17.6)	NS
Acute kidney injury	21 (35.0)	13 (30.2)	8 (47.1)	NS
Arrythmia	5 (8.3)	2 (4.7)	3 (17.6)	NS
Cardiac arrest	2 (3.3)	1 (2.3)	1 (5.9)	NS
Coagulopathy	12 (20.0)	10 (23.2)	2 (11.8)	NS
CVA	1 (1.7)	0 (0.0)	1 (5.9)	NS
Delirium	8 (13.3)	5 (11.6)	3 (17.6)	NS
DIC	3 (5.0)	3 (7.0)	0 (0.0)	NS
Mechanical ventilation[e]	12 (20.0)	8 (18.6)	4 (23.5)	NS
Multiorgan failure	5 (8.3)	4 (9.3)	1 (5.9)	NS
New need for renal replacement therapy	7 (11.7)	5 (11.6)	2 (11.8)	NS
VTE	9 (15.0)	7 (16.3)	2 (11.8)	NS
Need for ICU admission[f]	25 (41.7)	19 (44.2)	6 (35.3)	NS
ICU stay (d)	6±7	6±6	7±9	NS
SOFA score	9±4	9±4	9±4	NS
APACHE II score	20±9	19±7	24±14	NS

Data are n (%) or mean±standard deviation.

Abbreviations: APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; ICU, intensive care unit; IE, infective endocarditis; SOFA, Sequential Organ Failure Assessment; NS, non-significant; VTE, venous thromboembolism.

[a]Excludes patients who had in-hospital mortality.

[b]n=56, excluding 2 patients lost to follow-up on discharge.

[c]Percentage out of n=56 (excludes 2 patients who died during admission and 2 patients lost to follow-up on discharge).

[d]Cardiac surgery included: device lead removal (n=5), tricuspid vegetectomy and valve repair (n=1).

[e]Excludes intubation for surgery without other indication.

[f]Excludes routine ICU admissions post cardiac surgery.

suggest that large vegetations have a substantial impact on treatment outcomes, which may persist beyond hospital discharge. It is possible that patients with large vegetations were at the worse end of the spectrum of right-sided IE, which predisposed them to poorer functional recovery and lower health status in the long-term. Alternatively, larger vegetations might have been a reflection of these patients' poorer premorbid health status, which predisposed them to more virulent infections and larger vegetations. Interestingly, we found no correlation between vegetation size and sepsis severity on admission, which suggests that such impact may not be apparent on initial clinical findings. Furthermore, we found no correlation of septic embolic events with vegetation size in right-sided IE, in contrast to the conventional understanding with left-sided IE that the risk of embolisation increases with increasing vegetation size [25]. Septic emboli were found in as much as 82% of our cohort, with the majority found in the lungs. It is possible that right-sided vegetations have a higher propensity to embolise at smaller size thresholds as compared to left-sided vegetations, such that most affected patients would have had an embolic event by the time of diagnosis. Fortunately, pulmonary septic emboli seem to be well tolerated and do not predict adverse clinical outcomes, as is evident in our cohort and others [3]. Nevertheless, the increased risk of late mortality among patients with vegetation >2.0 cm suggests that perhaps we should

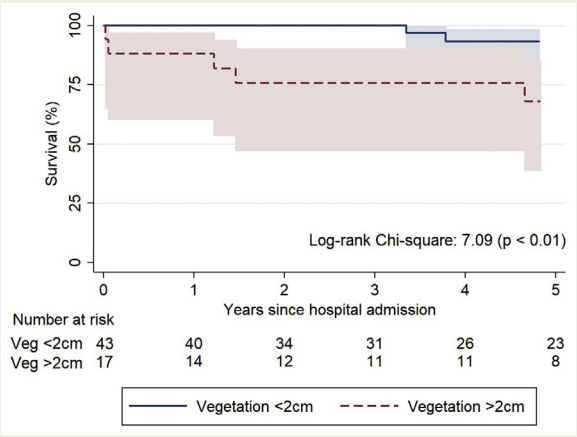

Figure 1 Kaplan-Meier survival curve for patients with right-sided infective endocarditis, stratified by vegetation size >2 cm. Shaded area is 95% confidence interval.

follow them more closely after discharge, particularly with a focus on right heart function.

Recurrent infections impose a significant burden on endocarditis survivors. In a large cohort of 328 patients who survived an initial episode of predominantly left-sided IE, Thuny and colleagues [26] reported recurrence rates of 7% at 1 year and 13% at 5 years, which was also an independent predictor of excess mortality. The rising incidence of IVDU in developed countries globally over recent years has been followed by a significant increase in admissions for IVDU-associated IE [2]. Recidivism is common among patients with IVDU-associated IE and has been associated with high rates of IE recurrence [19,27]. In our cohort, freedom from IE recurrence was 84% at 5 years, consistent with previous studies [6]. However, although all patients with recurrent IE were IVDUs, IVDU *per se* was not a significant predictor of recurrence, likely because almost three-quarters of our hospital survivors were IVDUs. Importantly, vegetations >2.5 cm was an independent predictor of IE recurrence in the medium-term. As most of our patients were medically managed, including those with large vegetations, it is possible that vegetations of substantial sizes persist in these patients despite clinical improvement on discharge. Such niduses of infection may precipitate relapses in case of non-compliance with ongoing treatment, which is common among patients with IVDU-associated IE. Furthermore, large vegetations may be a marker of virulent organisms or patient susceptibility to reinfections due to comorbidities. Our findings suggest that patients with vegetations >2.5 cm may warrant more aggressive treatment and intense follow-up to prevent disease recurrence.

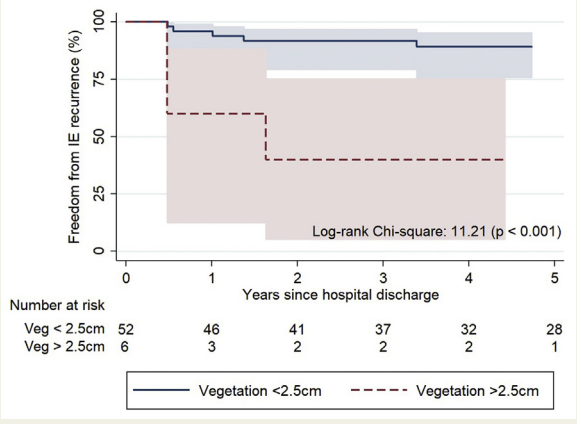

Figure 2 Kaplan-Meier freedom from IE recurrence after discharge for right-sided IE, stratified by vegetation size >2.5 cm. Shaded area is 95% confidence interval. Abbreviation: IE, infective endocarditis.

Limitations

Our retrospective study was constrained by several important limitations. Firstly, our cohort was relatively small and based at a single centre, which might have limited the statistical robustness of our findings. Furthermore, echocardiography was performed based on clinical need and not all patients underwent TOE, thus concurrent left-sided IE or paravalvular abscess might have been present in our cohort but not detected. Finally, identification of hospital readmissions or recurrent IE relied on correspondence with patients' last known points of clinical contact, thus readmissions elsewhere might have been missed. The determination of current IVDU status and late mortality was likewise limited. Data matching with the national death index may provide a more accurate picture of late mortality.

Conclusions

Patients with right-sided IE and small vegetations generally do well with medical management and this should continue to be the preferred strategy. However, those with large vegetations have poorer outcomes in terms of higher risks of late mortality and disease recurrence. These findings highlight the importance of aggressive treatment and close follow-up of patients with large vegetations.

Conflicts of Interest

There are no conflicts of interest to disclose.

Financial Support

None.

Author statement

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original draft. Edward Buratto: Conceptualisation, Formal Analysis, Investigation, Methodology, Writing – review & editing. Jim Dimitriou: Conceptualisation, Supervision, Writing – review & editing. Nima Yaftian: Writing – review & editing. Andrew Wilson: Writing – review & editing. Jonathan Darby: Writing – review & editing. Andrew Newcomb: Conceptualisation, Supervision, Writing – review & editing.

References

[1] Chahoud J, Sharif Yakan A, Saad H, Kanj SS. Right-sided infective endocarditis and pulmonary infiltrates: an update. Cardiol Rev. 2016;24(5):230–7.

[2] Wright A, Otome O, Harvey C, Bowe S, Athan E. The current epidemiology of injecting drug use-associated infective endocarditis in Victoria, Australia in the midst of increasing crystal methamphetamine use. Heart Lung Circ. 2018;27(4):484–8.

[3] Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic features in 102 episodes. Ann Intern Med. 1992;117(7):560–6.

[4] Martin-Davila P, Navas E, Fortun J, Moya JL, Cobo J, Pintado V, et al. Analysis of mortality and risk factors associated with native valve endocarditis in drug users: the importance of vegetation size. Am Heart J. 2005;150(5):1099–106.

[5] Musci M, Siniawski H, Pasic M, Grauhan O, Weng Y, Meyer R, et al. Surgical treatment of right-sided active infective endocarditis with or without involvement of the left heart: 20-year single center experience. Eur J Cardiothorac Surg. 2007;32(1):118–25.

[6] Witten JC, Hussain ST, Shrestha NK, Gordon SM, Houghtaling PL, Bakaeen FG, et al. Surgical treatment of right-sided infective endocarditis. J Thorac Cardiovasc Surg. 2019;157(4):1418–1427.e14.

[7] Hussain ST, Witten J, Shrestha NK, Blackstone EH, Pettersson GB. Tricuspid valve endocarditis. Ann Cardiothorac Surg. 2017;6(3):255–61.

[8] Shetty N, Nagpal D, Koivu S, Mrkobrada M. Surgical and medical management of isolated tricuspid valve infective endocarditis in intravenous drug users. J Card Surg. 2016;31(2):83–8.

[9] Horyniak D, Higgs P, Jenkinson R, Degenhardt L, Stoove M, Kerr T, et al. Establishing the Melbourne injecting drug user cohort study (MIX): rationale, methods, and baseline and twelve-month follow-up results. Harm Reduct J. 2013;10:11.

[10] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633–8.

[11] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.

[12] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med. 2003;31(4):1250–6.

[13] Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med. 1989;87(5):540–6.

[14] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.

[15] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.

[16] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685–713. quiz 86-8.

[17] Kamaledeen A, Young C, Attia RQ. What are the differences in outcomes between right-sided active infective endocarditis with and without left-sided infection? Interact Cardiovasc Thorac Surg. 2012;14(2):205–8.

[18] Kim JB, Ejiofor JI, Yammine M, Ando M, Camuso JM, Youngster I, et al. Surgical outcomes of infective endocarditis among intravenous drug users. J Thorac Cardiovasc Surg. 2016;152(3):832–841.e1.

[19] Holland DJ, Simos PA, Yoon J, Sivabalan P, Ramnarain J, Runnegar NJ. Infective endocarditis: a contemporary study of microbiology, echocardiography and associated clinical outcomes at a major tertiary referral centre. Heart Lung Circ. 2020;29(6):840–50.

[20] Sy RW, Chawantanpipat C, Richmond DR, Kritharides L. Development and validation of a time-dependent risk model for predicting mortality in infective endocarditis. Eur Heart J. 2011;32(16):2016–26.

[21] Otome O, Guy S, Tramontana A, Lane G, Karunajeewa H. A retrospective review: significance of vegetation size in injection drug users with right-sided infective endocarditis. Heart Lung Circ. 2016;25(5):466–70.

[22] Baddour LM, Wilson WR, Bayer AS, Fowler Jr VG, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. Circulation. 2015;132(15):1435–86.

[23] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075–128.

[24] Brink J, d'Udekem Y. So, vegetation size in right-sided endocarditis does not matter, or does it? Heart Lung Circ. 2016;25(5):419–20.

[25] Vilacosta I, Graupner C, San Román JA, Sarriá C, Ronderos R, Fernández C, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol. 2002;39(9):1489–95.

[26] Thuny F, Giorgi R, Habachi R, Ansaldi S, Le Dolley Y, Casalta JP, et al. Excess mortality and morbidity in patients surviving infective endocarditis. Am Heart J. 2012;164(1):94–101.

[27] Rosenthal ES, Karchmer AW, Theisen-Toupal J, Castillo RA, Rowley CF. Suboptimal addiction interventions for patients hospitalized with injection drug use-associated infective endocarditis. Am J Med. 2016;129(5):481–5.