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Surgical treatment of isolated tricuspid valve infective endocarditis: 25-year results from a multicenter registry

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ABSTRACT

Background: To assess early and late mortality in patients with isolated acute tricuspid valve infective endocarditis (TVIE) using data from a multicenter registry.
Methods: From 1983 to 2018, isolated acute TVIE was surgically treated in 157 (3.8%) patients [mean age 47 ± 16 years (range 15–86 years), 25% females]. Of these, 142 (90%) had native tricuspid regurgitation, 7 (5%) native tricuspid valve (TV) steno-regurgitation, and 8 (5%) prosthetic TVIE. Intravenous drug use (IVDU) was recorded in 38% of patients, infection involved cardiac implantable electronic device leads in 21%, and vascular catheters for dialysis in 1%; in the remaining cases, the cause was unknown. The primary endpoint was in-hospital outcome, long-term freedom from recurrence and overall survival.

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Intravenous drug use
Cardiac implantable electronic device

Results: Overall, 77 (49%) patients underwent TV repair, 72 (46%) TV replacement, and 8 (5%) prosthetic TV replacement. Early mortality was 11% (n = 17). Expected early mortality according to EndoSCORE was 12%, with age (odds ratio 1.06) and redo (odds ratio 6.64) as risk factors. Late deaths occurred in 31 patients and TVIE recurrences in 4. Survival rates at 10, 20, and 25 years were 66%, 60%, and 44%, respectively. Risk factors were age [hazard ratio (HR) 1.06], mycotic TVIE (HR 4.2), IVDU (HR 4.90), infected prosthesis replacement (HR 4.4), and presence of cardiac implantable electronic device leads (HR 3.0). No significant difference was found in valve repair vs. replacement and in IVDUs vs. non-IVDUs.
Conclusions: Patients with isolated acute TVIE undergoing surgical treatment show acceptable early and late outcomes. TVIE recurrence was low, and repair of the affected valve does not seem to confer any advantage either at early or long term up to 25 years.

1. Introduction

Acute infective endocarditis (IE) is becoming increasingly prevalent among cardiovascular diseases [1,2]. In addition, patient profile and clinical presentation with related impact on outcome are rapidly changing, with more aggressive forms, higher rates of complex valvular involvement and complications, and more frequent need for surgical intervention [1,2]. Among IE, right-sided valvular infection represents a minority, accounting for 5–10% of all cases, but with a clear trend towards a higher incidence in recent years [1–4]. Tricuspid valve IE (TVIE) is therefore a rare entity, mainly observed in peculiar patient subgroups [3,4] and with a high success rate with conservative treatment [5]. Surgical treatment is usually required in <10% of TVIE [3], but only a few reports have specifically addressed this issue, with only few reporting data on long-term outcome [3,4,6]. The National Registry for Surgical Treatment of Native or Prosthetic Valve Infective Endocarditis was created to collect and analyze data from IE patients with the participation of a multicenter working group, and focused on early and long-term patient outcome [7,8]. The aim of this study was to assess data from this registry and provide information about patients affected by isolated acute TVIE, particularly regarding early and late results of surgical treatment during a follow-up reaching 25 years.

2. Materials and methods

2.1. Study population

From February 1979 to January 2018, 4084 patients were included in the Italian Registry for Surgical Treatment of Native or Prosthetic Valve Infective Endocarditis, with the active participation of 21 Centers. From 1983 to 2018, isolated acute TVIE was surgically treated in 157 out of 4069 (3.8%) patients due to native tricuspid regurgitation (TR) in 142 (90%), tricuspid stenosis and regurgitation in 7 (5%), and prosthetic tricuspid valve (TV) endocarditis in 8 (5%).

2.2. Definition of terms and endpoints

All the variables collected in the dataset were defined according to EuroSCORE [8]. The primary endpoint was early mortality, defined as all-cause death within 30 days after surgery, and long-term survival free from TVIE recurrence. Secondary endpoints were long-term survival, 30-day mortality, and major complications [death, acute kidney injury, acute respiratory failure, multiorgan failure, sepsis, major bleeding, stroke, embolic events other than stroke, atrioventricular block requiring pacemaker (PMK) implantation, acute myocardial infarction, malignant ventricular arrhythmias, low output syndrome]. Moreover, the observed/expected mortality ratio was reported using the EndoSCORE [9].

2.3. Follow-up

All patients were followed up by phone interview or calling the patient referring physician or cardiologist. Follow-up ended on March 2018; median follow-up was 19.1 (14.3–23.8) years. Seven patients were lost to follow-up (11%).

2.4. Statistics

Normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test. Normally distributed variables are reported as mean ± standard deviation, and non-normally distributed variables as median and interquartile range. Pairwise comparison was performed using *t*-test or Mann-Whitney *U* test for continuous variables and chi-square with Fisher exact test for categorical variables. Variables with a p-value of <0.2 at univariate analysis were entered into the multivariable model. A parsimonious logistic regression model was built to identify the best predictors for early outcome. Results are reported as odds ratio (OR), 95% confidence limits (95CLs) and p-value. The Kaplan-Meier method was used to assess late survival and survival free from TVIE recurrence with log-rank test for univariate comparison. Cox regression was used to identify risk factors for late outcomes. Results are reported as hazard ratio (HR), 95CLs and p-value. SPSS software (version 23, IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. A p-value of <0.05 was considered as threshold for statistical significance.

3. Results

3.1. Clinical profile and operative data

Overall, 157 (3.8%) patients [mean age 47 ± 16 (15–86) years, 25% female] underwent surgical treatment of isolated acute TVIE. *Staphylococcus aureus* was the most common causative agent (45%), followed by streptococci (22%), Staphylococcus other than *S. aureus* (9%), enterococci (3%), mycotic infection (2%), and other pathogens (6%). Blood cultures and specimens were both negative in 13% of patients, whereas data were missing in 8%. Intravenous drug use (IVDU) was recorded in 38% of patients, infection involved cardiac implantable electronic device leads in 21%, and vascular catheters for dialysis in 1%; in the remaining cases, the cause was unknown. TV repair and replacement was performed in 77 (49%) and 72 (46%) patients, respectively, whereas 8 (5%) patients underwent prosthetic TV replacement. Among the 77 patients who underwent TV repair, 22 had vegetectomy, 5 vegetectomy and reconstruction with patch, 34 vegetectomy and annuloplasty, 10 bicuspidalization, 6 unknown.

Differences between intravenous drug users (IVDUs) and non-IVDUs are reported in Table 1.

3.2. Early outcome

Early mortality was 11% (n = 17) (Table 2). Expected mortality according to EndoSCORE was 12% with an observed/expected ratio of 0.9. The 30-day major complication rate was 22% (n = 35). TV repair showed the lowest mortality and major complication rate (6% and 17%, respectively), followed by native TV replacement (11% and 25%,

Table 1
Preoperative and operative data.

	Overall (n = 157)	IVDUs (n = 60)	Non-IVDUs (n = 97)	p-Value
Age (years)	47 ± 16	36 ± 8	54 ± 17	<0.001
Sex (F/M)	39/118	43/17	75/22	0.426
TV disease				
TR	142 (90%)	57 (95%)	85 (88%)	0.427
TSR	7 (5%)	2 (3%)	5 (5%)	
TP	8 (5%)	1 (2%)	7 (7%)	
Source of infection				
IVDU	60 (33%)	60 (100%)	–	–
PMK/ICD leads	33 (21%)	0	33 (34%)	–
Vascular access for dialysis	2 (1%)	0	2 (2%)	–
Unknown	62 (39%)	0	62 (64%)	–
LVEF (%)	55 ± 9	57 ± 7	54 ± 10	0.086
SB hypertension	41 (26%)	3 (5%)	38 (39%)	<0.001
Diabetes	12 (8%)		12 (12%)	0.004
Obesity	10 (6%)	3 (5%)	7 (7%)	0.581
COPD	15 (10%)	4 (7%)	11 (11%)	0.333
Previous stroke	3 (2%)	1 (2%)	2 (2%)	0.687
Peripheral vasculopathy	4 (3%)	1 (2%)	3 (3%)	0.650
Heart failure	21 (13%)	8 (14%)	13 (13%)	0.847
Shock	10 (6%)	4 (7%)	6 (6%)	0.905
CRF	16 (10%)	2 (3%)	14 (14%)	0.030
Cirrhosis	6 (4%)	4 (7%)	2 (2%)	0.144
Abscess	9 (6%)	1 (2%)	8 (8%)	0.155
Vegetations	83 (53%)	36 (60%)	47 (49%)	0.159
Leaflet perforation	14 (9%)	5 (8%)	9 (9%)	0.840
Prosthesis dehiscence	4 (3%)	1 (2%)	3 (3%)	0.678
Blood/specimen ~~germs~~ (bacterial or fungal causative agents)				0.033
Staphylococcus aureus	75 (48%)	37 (62%)	38 (39%)	
Streptococci	22 (14%)	4 (7%)	18 (18%)	
Staphylococcus other than S. aureus	14 (9%)	1 (2%)	13 (13%)	
Enterococcus	4 (3%)	1 (2%)	3 (3%)	
Mycotic	3 (2%)	1 (2%)	2 (2%)	
Pseudomonas	1 (0.6%)	1 (2%)	0	
Other	5 (3%)	1 (2%)	4 (4%)	
Negative blood culture or specimen	21 (13%)	8 (13%)	13 (13%)	
Missing data	12 (8%)	6 (10%)	6 (6%)	
Surgery				0.055
TV repair	77 (49%)	25 (42%)	52 (54%)	
TV replacement	72 (46%)	34 (57%)	38 (39%)	
With bioprosthesis	46 (64%)	25 (74%)	21 (55%)	0.253
With mechanical prosthesis	13 (18%)	4 (12%)	9 (24%)	
Missing	13 (8%)	5 (15%)	9 (21%)	
Prosthesis replacement	8 (5%)	1 (2%)	7 (7%)	
With bioprosthesis	8 (100%)	1 (100%)	7 (100%)	1.000
CPB time (min)	72 (57–87)	72 (55–83)	72 (60–90)	0.113
Cross-clamping time (min)	46 (38–62)	50 (39–60)	45 (38–64)	0.890

IVDU: intravenous drug user; TR: tricuspid regurgitation; TSR: tricuspid steno-regurgitation; TP: tricuspid prosthesis; PMK: pacemaker; ICD: implantable cardioverter-defibrillator; IE: infective endocarditis; LVEF: left ventricular ejection fraction; SB: systolic blood; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; TV: tricuspid valve; CPB: cardio-pulmonary bypass.

Table 2
Early outcomes.

	Overall (n = 157)	IVDUs (n = 60)	Non-IVDUs (n = 97)	p-Value
Deaths	17 (11%)	4 (7%)	13 (13%)	0.187
Stroke	2 (1%)	0	2 (2%)	0.525
Embolic events other than stroke	4 (3%)	2 (3%)	2 (2%)	0.637
Ventricular arrhythmias	3 (2%)	1 (2%)	2 (2%)	1.000
Postoperative AV block requiring PMK	1 (0.5%)	0	1 (1%)	1.000
Low output syndrome	8 (5%)	0	8 (8%)	0.228
IABP	3 (2%)	0	3 (%)	0.287
ECLS	2 (1%)	0	2 (2%)	0.263
Multi-organ failure	8 (5%)	2 (3%)	5 (5%)	0.734
Respiratory failure	4 (3%)	1 (2%)	3 (3%)	1.000
Acute kidney injury	4 (3%)	0	4 (4%)	0.299
Sepsis	9 (6%)	3 (5%)	6 (6%)	1.000
Major complications	35 (22%)	10 (17%)	25 (26%)	0.183

IVDU: intravenous drug user; AV: atrio-ventricular; PMK: pacemaker; IABP: intra-aortic balloon pump; ECLS: extracorporeal life support.

respectively), and prosthetic TV replacement (50% and 63%, respectively). However, no significant differences were found in TV repair vs. replacement. Regarding perioperative morbidity, one-fifth of the patients experienced major complications, but, interestingly, event rates related to active infection (sepsis), or to acute cardiac as well as renal failure, were low. No significant differences were recorded in mortality and morbidity between IVDUs and non-IVDUs. Multivariable analysis identified age and prosthetic TVIE as risk factors for both higher early mortality (age: OR 1.06, 95CLs 1.03–1.10, p = 0.001; TVIE: OR 6.64, 95CLs 1.52–18.25, p = 0.014) and major complications (age: OR 1.05, 95CLs 1.02–1.07, p = 0.001; prosthetic TVIE: OR 3.98, 95CLs 1.18–22.32, p = 0.044).

3.3. Late outcome

Late mortality was 19.8% (n = 31), and survival rates were 66 ± 5%, 60 ± 6%, and 44 ± 9% at 10, 20, and 25 years, respectively. Patients still alive were 40, 15, and 7 at 10, 20, and 25 years, respectively. No significant differences were found in TV repair vs. replacement among patients with isolated native TVIE.

Five patients showed IE recurrence on the native or prosthetic TV, with 4 deaths. Survival free from TVIE recurrence was 65 ± 5%, 59 ± 6%, and 43 ± 9% at 10, 20 and 25 years, respectively (Fig. 1).

No significant differences were found in IVDUs vs. non-IVDUs (48 ± 12% vs. 41 ± 11%, p = 0.234). However, after adjustment for age, presence of *S. aureus*, hypertension and chronic renal failure, IVDUs showed worse survival free from TVIE recurrence (18 ± 12% vs. 58 ± 10%, p = 0.009).

Among non-IVDUs, survival free from TVIE recurrence was 100% in patients on dialysis and 52 ± 21% in patients with unknown cause of TVIE. Patients with infected PMK/implantable cardioverter-defibrillator (ICD) leads showed the worst survival free from TVIE recurrence (20 ± 12%; p = 0.001).

Among patients with isolated native TVIE, TV repair and replacement were associated with similar survival rates (44 ± 13% and 44 ± 13%, respectively). Patients undergoing surgery for prosthetic TVIE showed significantly lower survival free from TVIE recurrence (25 ± 20%, p = 0.008). Among patients with native TVIE undergoing TV replacement, those receiving a bioprosthesis showed a survival free from TVIE recurrence of 69 ± 8%, whereas those receiving a mechanical prosthesis had a survival free from TVIE recurrence of 28 ± 16% (p = 0.408).

At multivariable analysis, age, prosthetic TV replacement, IVDU, and the presence of PMK/ICD leads were risk factors for both unfavorable late survival and lower survival free from TVIE recurrence (Table 3).

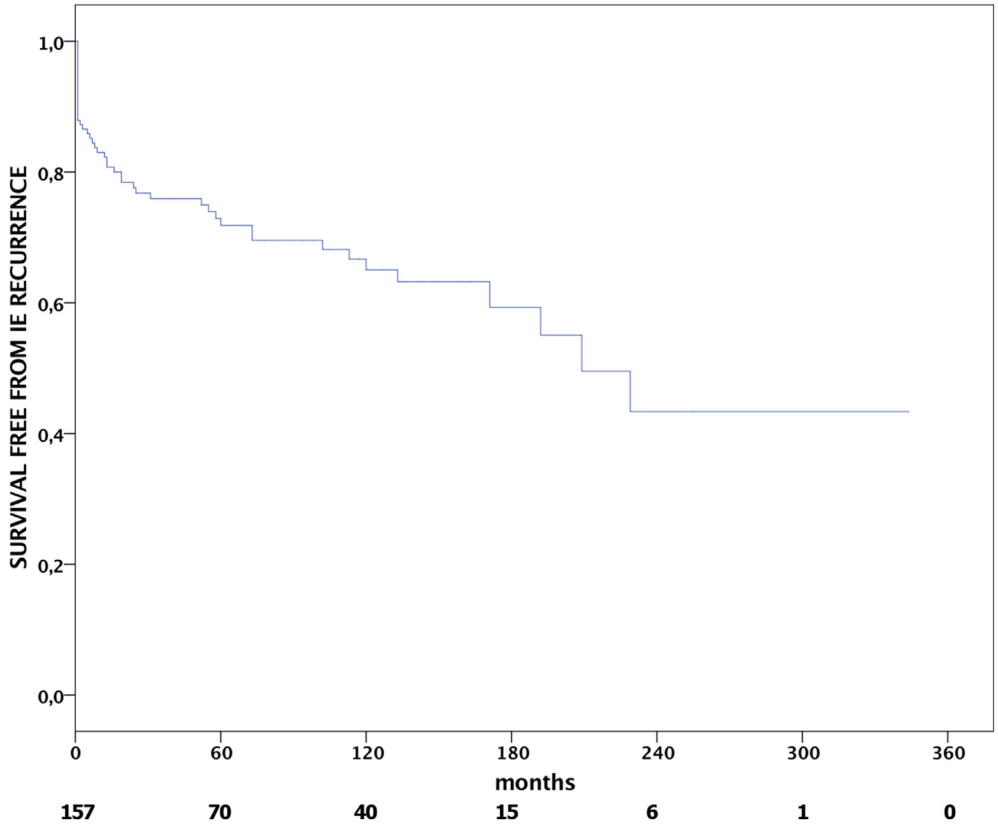

Fig. 1. Survival free from tricuspid valve infective endocarditis recurrence.

Among bacterial and fungal pathogens, mycotic TVIE was associated with worse late outcome, though without reaching statistical significance ($p = 0.052$) (Table 3).

4. Discussion

This retrospective multicenter study provides evidence that early and long-term outcomes of patients undergoing surgery for acute TVIE, despite the high-risk profile, are satisfactory. A younger patient age, valve repair rather than replacement, IVDU, and *S. aureus* as the most common pathogen, were the most relevant patient-related factors affecting outcomes. In-hospital mortality was ~10%, and a complicated perioperative course occurred in one-fifth of the patients. Post-discharge findings showed that IE recurrence rates were low, with acceptable survival rates achieved up to 25 years. Predictors of unfavorable early outcome in terms of both perioperative complications and in-hospital mortality, were age and redo operation, whereas age, fungal TVIE, IVDU, redo operation, and presence of cardiac implantable electrical device leads, were negative determinants of late outcome.

Table 3
Multivariate analysis for late mortality and infective endocarditis recurrence.

Risk factor	HR	95% lower limit	95% upper limit	p-Value
Late death				
Age (years)	1.06	1.04	1.09	<0.001
Mycotic TVIE	2.50	0.98	10.2	0.056
IVDU	4.43	1.64	12.1	0.003
PMK/ICD lead	2.34	1.06	5.16	0.014
Prosthetic TVIE	3.65	1.29	10.2	0.014
Late death and IE recurrence				
Age (years)	1.06	1.03	1.09	<0.001
Mycotic TVIE	4.24	0.98	18.3	0.052
IVDU	4.89	1.74	13.7	0.002
PMK/ICD lead	3.02	1.32	6.89	0.008
Prosthetic TVIE	4.37	1.82	10.4	0.001

TVIE: tricuspid valve infective endocarditis; IVDU: intravenous drug use; PMK: pacemaker; ICD: implantable cardioverter-defibrillator; IE: infective endocarditis.

The prevalence of TVIE is constantly increasing, though still representing a minority of cardiac valve-related endocarditis, accounting for 5% to 10% of all cases of valve IE [1–5]. Our findings are consistent with these figures, with TVIE accounting for nearly 4% of all IE recorded in the registry [7].

A substantial change in the "typical" patient profile in valve-related IE has been observed in recent years, shifting from IE affecting mainly rheumatic or congenital valves in the past, to IE affecting mostly patients with prosthetic valves, undergoing catheter-based treatments, on immunosuppression, or making use of intravenous drugs [1,2]. The patient profile of our study population was similar, showing a younger patient age on admission, with almost 40% of the cases diagnosed in IVDUs, and more than 20% of TVIE associated with cardiac electrical devices implanted. Notwithstanding this, native TVIE occurred in 90% of patients, but this finding accounts for the only few prosthetic valves in the TV position. The prevalence of TVIE due to IVDU in our series is in line with that reported by others (30–40%) [10]. Device- or lead-related infection is also a well-established risk factor for IE, with a ~100% increased incidence from mid-2000 s [11]. Cardiac implantable electrical device-related IE usually affects one-fifth of TVIE patients [12,13], and, in our population, it was found to be also a negative predictor of late survival.

Regarding the causative agent, our study confirmed the high prevalence of *S. aureus*-related infections, with a prevalence ranging between 40% and 90% in TVIE patients [3,5,12–14] and a substantial increase in methicillin resistance [1,5]. In particular, the prevalence of *S. aureus* is significantly higher in IVDUs than in non-IVDUs.

As for the treatment strategy, a slight larger number of valve repair, as compared to valve replacement, was observed with no significant differences in outcome. Likewise, the application of reparative techniques in other experiences did not apparently confer any benefit or advantage over replacement, either at early or long term [15,16]. Other series have

shown a protective role of reparative procedures in relation to 30-day mortality [14,17]. Also the type of prosthesis seemed not to provide any difference in outcome in TVIE [18,19]. Such controversial findings may suggest that, in right-sided IE, other factors than the surgical technique and the material or procedure used, play a crucial role in short-term morbidity and mortality. In our series, tricuspid valvectomy [20] found no application, indicating that such a technique is rarely considered by the vast majority of the surgical community, although it represented a surgical option in more than 7% of the TVIE operated in North America [15].

The improved diagnostic modalities, the use of multidisciplinary teams, and better therapeutic strategies, including a more aggressive and early surgical management during the last years, led to a significant reduction of early and mid-term mortality in right-sided IE [21,22]. Despite these undisputable advances, in-hospital mortality of acute TVIE remains significant, although lower than that observed for left-sided IE [1], with an in-hospital mortality, as in our series, ranging from 7% to 12.5% [4,13–15,23]. The lower in-hospital mortality observed in right-sided IE, particularly in TVIE, as compared to left-sided IE, may be related to the low invasiveness shown by this type of IE [24]. However, full understanding of the mechanisms and causes underlying these reduced adverse event rates is still lacking [25].

As opposed to medically managed cases, early outcome of patients undergoing surgery for TVIE did not change significantly over the last years [23]. Age and a complicated postoperative course with the occurrence of major adverse events were stronger predictors of unfavorable early outcome. Interestingly, in this multicenter experience, the incidence of septic or low cardiac output events after surgical correction remained low, suggesting that severe infection and right ventricular dysfunction, well known factors associated with poor prognosis in TVIE, were most likely not prevented or adequately controlled by concurrent medical management. Immunosuppression status as well as renal and right ventricular failure have been shown to identify patients at high risk for in-hospital mortality in TVIE [26,27], and these factors should be closely considered in the decision making in order to guide surgical timing.

In our series, also long-term outcome was satisfactory, with 10, 20 and 25-year survival rates being consistent with previous data. Recurrence episodes were few, but with an extremely ominous prognosis, underlining the relevance and complexity of the disease in such circumstances. The type of surgical procedure did not seem to affect postoperative results in this setting [4,5,12–15,17,18], suggesting that patient condition and predisposing factors may play a major role. In our analysis, age, mycotic TVIE, IVDU, redo operation for an infected prosthetic valve, and the presence of PMK leads, were all predictors of unfavorable outcome. The presence of a prosthetic valve and the impact of mycotic infection in cardiac valve endocarditis in terms of IE recurrence and risk factors for outcome have been well underscored in recent guidelines as well as in other series [1,18,28]. The outcome related to IVDUs undergoing surgery as far as TVIE is concerned, remains a controversial issue. The high chance of early recurrent IE episodes after surgical treatment in active IVDUs has previously been reported [29]. Mid-term survival in this setting, however, does not appear prohibitive, and, therefore, the presence of active IVDU does not represent a contraindication for surgical treatment of TVIE, as repetitively reported [1–5,12–15], but it is definitely associated with high chance of post-discharge IE recurrence, including reoperation.

4.1. Study limitations

Several limitations should be acknowledged. The retrospective nature of the study significantly impacts data interpretation. Furthermore, this is a 25-year follow-up study, with obvious influence on surgical and medical expertise and quality in patient care. Indications and patient clinical conditions varied greatly during the study period, including guidelines and recommendations for IE and, specifically, for TVIE. The clinical scenarios and management strategies showed remarkable variability. However, the National Registry for Surgical Treatment of Native and Prosthetic Valve Infective Endocarditis allowed early and long-term assessment of patients undergoing surgery for TVIE, with relevant information about actual results in this setting. Nonetheless, the obvious variability across centers in surgical indications, techniques, and perioperative management, and the impact of the different approaches used may have also influenced patient outcome.

In conclusion, although TVIE represents a well-known challenging setting, surgical treatment provides satisfactory results in terms of early and late outcomes. Preoperative patient profile and disease features may identify patients at higher risk for less favorable prognosis. Our overall results, however, suggest that surgically treated TVIE is associated with low recurrence rates and excellent survival, regardless of the surgical approach used.

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Declaration of Competing Interest

None of the Authors has any conflict of interest to disclose.

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