Preoperative False-Negative Transthoracic Echocardiographic Results in Native Valve Infective Endocarditis Patients: A Retrospective Study from 2001 To 2018

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Research

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Abstract

Background: Infective endocarditis (IE) is a lethal disease that is difficult to diagnose early. Although echocardiography is one of the most widely used diagnostic techniques, it has limited sensitivity. This study surveyed the clinical features of IE patients who underwent surgery and compared transthoracic echocardiography and histological findings to explore the factors related to false-negative echocardiographic results.

Methods: Medical records were extracted from IE patients consecutively hospitalized between June 2001 and June 2018.

Results: A total of 182 patients with native valve IE who underwent surgery were included. Compared to the non-surgery group, the surgery group was more likely to have pre-existing valvular lesions and more serious cardiac conditions and a relative lack of signs of infection and cerebrovascular events, leading to a lower proportion of “definite cases” before surgery. The false-negative rate of echocardiography was 14.5%. Echocardiography has significant disadvantages in diagnosing perivalvular abscesses, valve perforations, and left-sided endocarditis, especially for subjects with both aortic and mitral valve infections. The multivariate analysis identified congenital heart disease and small vegetations (<10 mm) as independent predictors of false-negative echocardiography results. Conversely, fever and heart murmurs on admission served as protective factors.

Conclusions: Under some circumstances, echocardiography provides inconsistent results compared with surgical findings, and negative echocardiography results do not rule out IE. The diagnosis of IE depends on comprehensive evaluations using multiple methods.

Background

Infective endocarditis (IE) is a lethal disease caused by various pathogens such as bacteria, fungi, and rickettsia that directly invade the cardiac valves or mural endocardium. Despite significant technological advances in medical and surgical therapies, IE carries risks of high mortality and poor prognosis. The early identification and diagnosis of this condition remain major challenges.

Echocardiography, either transthoracic echocardiography (TTE) or Transesophageal echocardiography (TOE), is the primary choice for the diagnosis of IE. Valvular vegetations are the diagnostic and pathologic markers of IE and can be preliminarily screened out by echocardiography. In some cases, a clinical diagnosis of IE can be made in the absence of vegetations by using the modified Duke criteria. The sensitivities for the diagnosis of vegetations in native valves are 70% for TTE and 96% for TOE. Their identification may be difficult in IE patients with pre-existing valvular lesions like mitral valve prolapse, degenerative cardiac valve disease, prosthetic valves, small vegetations, recent embolization and in vegetation-negative endocarditis. Therefore echocardiographic results must be interpreted with caution, synthesizing patient’s clinical features and their likelihood of IE.

The role of the pathologist is often decisive. Histological assessment of cardiac valves to demonstrate vegetations and valvular inflammation remains the gold standard for IE diagnosis, especially for complicated cases with atypical clinical manifestations and auxiliary examination results, when bacteriologists fail to isolate a microorganism. Besides, histological analysis can distinguish blood culture-negative endocarditis from
noninfective causes of endocarditis, particularly neoplastic or autoimmune disease\[^4\]. However, due to the high
cost of surgical biopsy and pathological examination, some cases are never histologically diagnosed.

We consecutively collected data from IE patients who underwent surgery at a comprehensive teaching hospital in
southern China to provide better evidence-based medical evidence and identify factors related to false-negative
TTE results.

**Methods**

2.1 Diagnostic criteria

The definition of IE was based on the 2015 European Society of Cardiology algorithm for diagnosis of infective
endocarditis\[^4\], which mainly includes the pathological diagnostic criteria and the modified Duke criteria.

Pathological examination served as the gold standard for IE diagnosis and had to meet at least one of the
following criteria: microorganisms demonstrated by culture or histological examination of a vegetation; a
vegetation that has embolized or an intracardiac abscess specimen; or the presence of pathological lesions,
vegetation, or intracardiac abscesses by histological examination showing active endocarditis. Pathologists were
blinded to clinical parameters and echocardiographic results when diagnosing vegetation samples\[^4\].

The modified Duke criteria (adapted from Li et al.\[^5\]) were used to clinically diagnose cases classified as either
definite or suspected. Three echocardiographic findings are the major criteria in IE diagnosis: vegetation, abscess,
or pseudoaneurysm and new dehiscence of a prosthetic valve\[^7\]. The echocardiographic definitions are listed in the
Appendix.

Surgery was performed during the course of the appropriate antimicrobial therapy and was indicated for at least
one of the following conditions, which were in accordance with the current guidelines\[^4, 10\]: severe valvular
dysfunction in the presence of heart failure, abscess or perivalvular extension, large vegetations at high risk of
embolization (or recurrent embolization during antibiotic treatment), and failure of conservative medical treatment.

2.2 Study sample

We consecutively collected data from 313 consecutive IE cases through the electronic medical records system of
Nanfang Hospital, a comprehensive teaching hospital, between June 2001 and June 2018. The partial results of
this study were published in 2019\[^11\]. We excluded 11 cases of prosthetic valve IE and 2 cases with a history of
pacemaker transplantation.

Data included demographic information, predisposing factors, clinical manifestations, echocardiography results,
pathologic findings, and in-hospital mortality.

This clinical study was a retrospective and descriptive study performed in accordance with the principles of the
Helsinki declaration.

2.3 Statistical analyses

All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables with
normal distributions are expressed as mean ± standard deviation; categorical variables are expressed as frequency
and percentage. Paired $\chi^2$ tests (McNemar tests) were used to assess differences between echocardiogram and surgical histopathology results. Univariate comparisons were evaluated with $\chi^2$ tests or Fisher's exact test for categorical variables, as appropriate. Variables with theoretical clinical importance and those that achieved a $P<0.10$ in the univariate analysis were included in the binary logistic regression analysis. A forward conditional method was used to select the most useful predictors for inconsistency between echocardiographic and surgical findings. Results were considered statistically significant at the 0.05 level.

**Results**

3.1 **Difference between the surgery and non-surgery groups**

A total of 300 patients were consecutively diagnosed with native valvular endocarditis, and 182 underwent surgery. Table 1 details the basic information, clinical features, echocardiographic findings, diagnostic basis, and in-hospital mortality of the surgery and non-surgery groups.
| Variable                                      | Total N = 300 | Surgery N = 182 | None surgery N = 118 | P  |
|----------------------------------------------|--------------|----------------|---------------------|----|
| Basic heart disease                          | 126 (42.0)   | 85 (46.7)      | 41 (34.5)           | 0.003 |
| Degenerative calcific valvular disease       | 27 (9.0)     | 18 (9.9)       | 9 (7.6)             | 0.606 |
| Rheumatic heart disease                      | 59 (19.7)    | 41 (22.5)      | 18 (15.1)           | 0.122 |
| Congenital heart disease                     | 58 (19.3)    | 42 (23.1)      | 16 (13.4)           | 0.053 |
| Clinical features                            |              |                |                     |     |
| Fever                                        | 251 (83.7)   | 141 (77.5)     | 110 (92.4)          | 0.000 |
| Heart murmurs                                | 253 (84.3)   | 162 (89.0)     | 91 (76.5)           | 0.006 |
| Ischemic stroke                              | 65 (21.7)    | 31 (17.0)      | 34 (28.6)           | 0.016 |
| Hemorrhagic stroke                           | 26 (8.7)     | 10 (5.5)       | 16 (13.4)           | 0.015 |
| Heart insufficiency                          | 175 (58.3)   | 124 (68.1)     | 51 (42.9)           | 0.000 |
| Acute heart failure                          | 64 (21.3)    | 41 (22.5)      | 23 (19.3)           | 0.531 |
| Positive blood culture                       | 172 (57.3)   | 93 (51.1)      | 79 (66.4)           | 0.007 |
| *Staphylococcus aureus*                      | 43 (14.3)    | 14 (7.7)       | 29 (24.4)           | 0.000 |
| Positive echocardiographic results           |              |                |                     |     |
| Vegetation                                   | 266 (88.7)   | 157 (86.3)     | 109 (91.6)          | 0.103 |
| Left heart                                   | 193 (64.3)   | 117 (64.3)     | 76 (63.9)           | 0.983 |
| Only on aortic valve                         | 70 (23.3)    | 42 (23.1)      | 28 (23.5)           | 0.896 |
| Only on mitral valve                         | 101 (33.7)   | 57 (31.3)      | 44 (37.0)           | 0.285 |
| Aortic valve and mitral valve                | 22 (7.3)     | 18 (9.9)       | 4 (3.4)             | 0.035 |
| Right heart                                  | 58 (19.3)    | 32 (17.6)      | 26 (21.8)           | 0.340 |
| Only on tricuspid valve                      | 54 (18.0)    | 29 (15.9)      | 25 (21.0)           | 0.247 |
| Variable                        | Total N = 300 | Surgery N = 182 | None surgery N = 118 | P     |
|--------------------------------|---------------|-----------------|----------------------|-------|
| Only on pulmonic valve         | 4 (1.3)       | 3 (1.6)         | 1 (0.8)              | 0.940 |
| Left heart and right heart     | 9 (3.0)       | 2 (1.1)         | 7 (5.9)              | 0.040 |
| Perivalvular abscess           | 4 (1.3)       | 3 (1.6)         | 1 (0.8)              | 0.940 |
| Aortic sinus aneurysm          | 6 (2.0)       | 4 (2.2)         | 2 (1.7)              | 1.000 |
| Perforation                    | 20 (6.7)      | 11 (6.0)        | 9 (7.6)              | 0.591 |
| Severe valve insufficiency     | 176 (58.7)    | 122 (67.0)      | 54 (45.4)            | 0.000 |
| Size of vegetations            |               |                 |                      |       |
| >1 cm                          | 236 (78.7)    | 144 (79.1)      | 92 (77.3)            | 0.811 |
| Modified Duke's criteria       |               |                 |                      |       |
| Definite IE                    | 166 (55.3)    | 81 (44.5)       | 85 (71.4)            | 0.000 |
| Suspected IE                   | 113 (37.7)    | 80 (44.0)       | 33 (27.7)            | 0.005 |
| Excluded                       |               | *21 (11.5)      |                      |       |
| Pathological criteria          |               |                 |                      |       |
| Pathological confirmed         |               | *173 (95.1)     |                      |       |
| Pathological excluded          |               | *9 (4.9)        |                      |       |
| In-hospital death              | 32 (10.7)     | 8 (4.4)         | 24 (20.2)            | 0.000 |

*These data were only available to surgery group

The surgery group was more likely to suffer from basic heart diseases (85% vs. 41%, odds ratio [OR] = 0.488, 95% confidence interval [CI]: 0.301–0.786) and had more heart murmurs (89.0% vs. 76.5%, OR = 2.403, CI: 1.277–4.525) and heart insufficiency (68.1% vs. 42.9%, OR = 2.809, CI: 1.739–4.536) at admission. Conversely, evidence of infections like fever (77.5 vs. 92.4%, OR = 0.250, CI: 0.113–0.555) and positive blood culture results (51.1% vs. 66.4%, OR = 0.516, CI: 0.319–0.835), as well as cerebrovascular events like hemorrhagic stroke (5.5% vs. 13.4%, OR = 0.371, CI: 0.162–0.848) and ischemic stroke (17.0% vs. 28.6%, OR = 0.507, CI: 0.291–0.884), were significantly less common in the surgery group.

Patients in the surgery group were more likely to have both aortic and mitral valve infections (9.9% vs. 3.4%, OR = 3.128, CI: 1.031–9.486) and suffer from severe valve insufficiency (67.0% vs. 45.4%, OR = 2.410, CI: 1.497–3.879).
However, the left and right heart valves were less likely to be simultaneously infected (1.1% vs. 5.9%, OR = 0.176, CI: 0.036–0.863).

In the surgery group, there were clinically fewer definite IE cases (44.5% vs. 71.4%, OR = 0.311, CI: 0.189–0.512), but more suspected IE cases (44.0% vs. 27.7%, OR = 2.020, CI: 1.229–3.322) before surgery. Nine cases did not meet the histological diagnostic criteria but had a high level of clinical evidence to support the diagnosis of IE. In-hospital mortality was significantly lower in the surgery group (4.4% vs. 20.2%, OR = 0.180, CI: 0.079–0.417).

3.2 Pathological and echocardiographic results in the surgery group

The pathological and echocardiographic results of 182 surgery patients are shown in Table 2. The preoperative echocardiographic findings mainly included vegetations (86.3%), perivalvular abscess (1.6%), perforation (6.0%), and aortic sinus aneurysm (2.2%). Echocardiography has significant disadvantages in identifying perivalvular abscess (1.6% vs. 7.1%, \( P = 0.013 \)) and valve perforation (6.0% vs. 13.7%, \( P = 0.013 \)) compared to actual operative findings. Based on a comparative analysis, the location of vegetations was significantly different between echocardiography and surgical findings (86.3% vs. 95.1%, \( P = 0.007 \)). Left-sided endocarditis was more likely to be missed by echocardiography (64.3% vs. 70.9%, \( P = 0.050 \)), especially in patients with both aortic and mitral valve infections (9.9% vs. 14.3%, \( P = 0.039 \)).

| Pathology                      | Pathology | Echocardiography | McNemar test |
|-------------------------------|-----------|------------------|--------------|
| Perivalvular abscess          | 13 (7.1)  | 3 (1.6)          | 0.013        |
| Perforation                   | 25 (13.7)| 11 (6.0)         | 0.013        |
| Aortic sinus aneurysm         | 4 (2.2)   | 4 (2.2)          | 1.000        |
| Vegetation                    | 173 (95.1)| 157 (86.3)      | 0.007        |
| Left heart                    | 129 (70.9)| 117 (64.3)      | 0.050        |
| Aortic valve                  | 40 (22.0)| 42 (23.1)        | 0.832        |
| Mitral valve                  | 63 (34.6)| 57 (31.3)        | 0.180        |
| Aortic valve and mitral valve | 26 (14.3)| 18 (9.9)         | 0.039        |
| Right heart                   | 33 (18.1)| 32 (17.6)        | 1.000        |
| Tricuspid valve               | 27 (14.8)| 29 (15.9)        | 0.687        |
| Pulmonic valve                | 6 (3.3)   | 3 (1.6)          | 0.250        |
| Left heart and right heart    | 6 (3.3)   | 2 (1.1)          | 0.219        |
| *Abnormal cardiac structure   | 12 (6.6)  | 8 (4.4)          | 0.388        |

*Including vegetations found on atrial septum, ventricular septum, ductus arteriosus, etc.
The majority (70.9%) of echocardiographic and surgical results were completely consistent. Negative echocardiographic results were observed in 25 (13.7%) cases. The remaining 28 cases (15.4%) showed misdiagnosis based on echocardiography (wrong distribution and quantity of valvular lesions) before surgery. The false-negative rate was 14.5% (25/173).

3.3 Factors related to the false-negative TTE results

To investigate the specific factors that caused the false-negative results of echocardiographic findings compared to histological results, we performed univariate and multivariate analyses (Table 3). The multivariate analysis revealed that congenital heart disease (26.2% vs. 10.0%, OR = 2.907, 1.062–7.956) and small-size vegetations (< 10 mm; 37.5% vs. 8.7%, OR = 4.329, CI: 1.733–10.753) were independent predictors of false-negative results on echocardiography. Fever (10.6% vs. 24.4%, OR = 0.309, 0.108–0.882) and heart murmurs (11.1% vs. 35.0%, OR = 0.165, CI: 0.050–0.546) at admission served as protective factors.

3.4 Discussion

IE is a fatal disease with high mortality despite novel diagnostic and therapeutic strategies. Timely and early diagnosis of IE remains a challenge. Our study was aimed to clarify the characteristics of IE patients who underwent a surgery over an 18-year period in our hospital and to identify factors related to the false-negative echocardiography results. To our knowledge, this is the largest, long-term study on IE performed in our region.

4.1 Features of patients in the surgery group

For non-surgery patients, we adopted the modified Duke criteria for diagnosis, but only those who met the criteria of “definite IE” or “suspected IE” could be enrolled to ensure the reliability of the collected data. For patients in the surgery group, beyond the clinical diagnostic criteria, pathological results played a more critical role as the gold standard for diagnosis. A subset of patients had been never considered to have IE until intraoperative findings of vegetations or intracardiac abscesses. In our study, patients who underwent surgery were more likely to have pre-
existing valvular lesions (basic heart disease), more heart murmurs and heart deficiency, and a relative lack of
signs of infection (fever and positive blood culture results) and cerebrovascular events. Therefore, patients in the
surgery group were less frequently classified as “definite cases,” and were more likely to be “suspected cases”
before surgery.

By comparing differences between echocardiographic and surgical findings within the surgery group, we found
that missed diagnosis by echocardiography was more likely when perivalvular abscesses and valve perforation
developed or when vegetations affected both the mitral and aortic valves. This is a novel finding; one possible
explanation is that the pre-existing valvular disease with structural abnormalities and calcification are more likely
to affect both the mitral and aortic valves, which may affect echocardiographic observations.

The International Collaboration on Endocarditis-Prospective Cohort Study reported that the average in-hospital
mortality of IE was 18% worldwide[12]. In contrast, the in-hospital mortality of our study was 10.7%. The mortality
of patients who underwent surgery was almost one-sixth of that of patients who did not undergo surgery in our
study. Several previous studies pointed out that surgery was independently associated with a lower risk of in-
hospital mortality[13][14, 15]. We previously performed a multivariate analysis in 313 cases of IE (including prosthetic
valve endocarditis)[11] and identified intravenous drug addiction, prosthetic valve endocarditis, hemorrhagic stroke,
acute congestive heart failure, renal insufficiency, left-sided endocarditis, and early surgery as independent
predictors of in-hospital mortality. According to this data, we concluded that the surgery and less frequent
occurrence of hemorrhagic stroke were protective factors for good prognosis of IE in the surgery group. This
finding highlights that surgery is a crucial treatment for improving prognosis.

4.2 Factors related to the false-negative results of echocardiography

Our false-negative TTE rate was 14.5%, similar to other studies[7, 16]. Previous reports indicated that an
echocardiographic diagnosis of endocarditis may be correct but sometimes incomplete[16, 17]. Regardless of the
possible error in subjective assessments and operation caused by ultrasound technicians, the most common
explanations for false-negative or erroneous echocardiographic results are atypical position of the vegetation,
relatively fixed vegetation without swinging, and small vegetation[18]. One study also proposed that motion
artefacts could influence the results[19]. Our findings were in line with the previous conclusions. The multivariate
analytic results showed that congenital heart disease and vegetation size <10 mm were risk factors for false-
negative echocardiographic results, while fever and heart murmurs were protective factors. The latter two factors
are typical manifestations of infective endocarditis and might cause alarm among clinicians, thus affecting the
echocardiographic diagnosis.

Clinicians must be aware that echocardiography sensitivity is not 100%, and negative echocardiography results do
not rule out IE. Sometimes echocardiography should be repeated several times[2], and real-time 3-dimensional TOE
is recommended as it allows better characterization of IE vegetation[20].

Some studies have pointed out that the diagnostic sensitivity of TTE in S. aureus-related IE is significantly lower,
while TEE significantly improves the diagnostic sensitivity [21]. However, another publication expressed
reservations[22]. Our study also attempted to explore the effect of blood culture results on the accuracy of
echocardiographic diagnosis of IE, but the results were not satisfactory. In our previous study[11], we mentioned
that the blood culture positive rate of IE in our hospital was only 58.2% due to antibiotic abuse and other reasons,
which was roughly consistent with the results of the present study. We speculated that this might affect the univariate analysis results.

Pathological examination of cardiac valves remains the gold standard for IE diagnosis. However, 9 cases of definite IE in our study did not meet the pathological diagnosis criteria. Detachment or disintegration of small vegetations after antibiotic therapy probably responsible for the false negative results of pathological results. In the absence of pathological evidence, the sensitivity of clinical diagnosis of IE using the modified Duke's standard alone is ~80%[23]. Still, Duke's standard is also an important reference when we fail to obtain ideal pathological results.

Whether in the surgery or non-surgery group, the sensitivity of TTE remains a question. Factors related to false-negative echocardiographic results were also observed in the non-surgical group. In other words, if patients who did not undergo surgery were admitted to a surgery, it is possible that there were similar inconsistencies between echocardiographic and surgical findings.

This was a single-center study performed in a general teaching hospital, so the findings may not be applicable to all populations and areas. Besides, referral bias should be taken into consideration when describing the echocardiographic and surgical outcomes of IE, as patients with more complicated and serious illness were more likely to be treated at a tertiary hospital[24]. Finally, the echocardiographic and pathological results are somewhat subjective, making detailed comparisons difficult.

**Conclusion**

Compared to the non-surgery group, the surgery group was more likely to have pre-existing valvular lesions and more serious cardiac conditions and fewer signs of infection and cerebrovascular events, leading to a lower proportion of “definite cases.” Missed diagnosis by echocardiography was more likely to occur when perivalvular abscess and valve perforation developed, and when vegetations affected the mitral and aortic valves. Congenital heart disease, fever, heart murmurs manifested at admission, and vegetations with small size (< 10 mm) were independent predictors of false-negative echocardiography results. The diagnosis of IE depends on comprehensive evaluations using multiple methods.

**Abbreviations**

IE: Infective endocarditis  
TTE: transthoracic echocardiography  
TOE: Transesophageal echocardiography  
OR: Odd ratio  
CI: Confidence interval

**Declarations**

Ethics approval and consent to participate
The study was approved by the clinical research ethics committee of Nanfang Hospital of Southern Medical University. This was a retrospective study that did not need informed consent.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests

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**Authors’ contributions**

Study conception and design: JP and SHC. Acquisition, analysis and/or interpretation of data: ZNR and JZ. Drafting/revision of the work for intellectual content and context: JP and SHC. Final approval and overall responsibility for the published work: JP. All of the authors read and approved the final manuscript.

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**Author's information**

Not applicable

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