ORIGINAL ARTICLE



Marseille scoring system for empiric treatment of infective endocarditis

Frédérique Gouriet ^{1,2} • Hervé Tissot-Dupont ^{1,2} • Jean-Paul Casalta ^{1,2} • Sandrine Hubert ³ • Pierre-Edouard Fournier ^{1,2} • Sophie Edouard ^{1,2} • Alexis Theron ⁴ • Hubert Lepidi ¹ • Dominique Grisoli ⁴ • Gilbert Habib ³ • Didier Raoult ^{1,2}

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Abstract

Despite advances in medical, surgical, and critical care, infective endocarditis (IE) remains associated with considerable morbidity and mortality. We evaluated the performance of the Marseille score, including clinical data and biological tests obtained within 2 h, to identify patients at high risk of IE in order to initiate early antimicrobial treatment. This was secondarily confirmed using modified ESC criteria combined with molecular testing and $^{(18)}$ fluorodeoxyglucose-positron emission tomography/computed tomography as diagnostic tools. In a prospective cohort study, we enrolled 484 patients with cardiovascular predisposition and clinical suspicion of IE from 2011 to 2013. The final diagnosis was definite IE in 123 patients and possible IE in 107. Marseille score was calculated adding one point for each present parameter (range 0–9). This score includes clinical, epidemiological (male, fever, splenomegaly, clubbing, vascular disease and stroke) and biological criteria (Leucocytes >10,000/mm3, sedimentation rate (SR) > 50/mm or C reactive protein >10 mg/L and hemoglobin <100 g/l). A score of 2 or more performed best in predicting IE in patients with predisposing heart lesions. Sensitivity was better on left-side heart lesions (94%) than on right-side heart lesions (85%) (p = 0.04) and better for valvulopathy (94%) than intra cardiac devices (84%) (p = 0.02). The predictive positive value of prosthetic valves was greater than that of native valves (p = 0.02). Using our simple Marseille score combined with our standardized diagnostic procedures would help improve IE management by focusing on early empiric treatment within 2 h of admission for patients with cardiac predisposition factors.

Introduction

Despite advances in medicine and surgical care, infectious endocarditis (IE) is still a serious disease with a high morbidity and mortality rate [1, 2]. Successful management of IE depends on maintaining a high index of suspicion for the disease because a patient may present non-specific symptoms. Rapid etiological diagnosis remains a challenge for

- Frédérique Gouriet frederique.gouriet@ap-hm.fr
- ¹ URMITE, Aix Marseille Université, UM63, CNRS 7278, IRD 198, INSERM 1095, AP-HM, URMITE, IHU Méditerranée Infection, 9-21 Boulevard Jean Moulin, 13385 Marseille Cedex 05, France
- ² IHU Méditerranée Infection, 19-21 Boulevard Jean Moulin, 13385 Marseille Cedex 05, France
- Service de Cardiologie, Hôpital de la Timone, 13385 Marseille, France
- Service de Chirurgie Cardiaque, Hôpital de la Timone, 13385 Marseille, France

the medical team. The management strategy needs close cooperation between disciplines including cardiac imaging (echography, (18) fluorodeoxyglucose-positron emission tomography/computed tomography (18 FDG-PET/CT) [3], microbiology [4] (including blood culture, serology and molecular biology), immunology and histological findings [5]. A long delay between diagnosis and treatment is associated with a poor prognosis [6]. Patients with IE should receive adequate antibiotic treatment as soon as possible. Empirical antimicrobial treatment is used for blood culture-negative endocarditis (BCNE) [7, 8] but in most cases the choice of antimicrobial agents is based on pathogen identification and antimicrobial susceptibility. Furthermore, previous studies demonstrated that antimicrobial stewardship improved patient outcomes compared to the reporting of microbiology results alone [9-11]. Standardizing diagnostic procedures for IE meant an etiological diagnosis could be obtained within 5 days for 94% of patients with definite IE [12].

The Duke Criteria were initially designed in 1994 for diagnosing IE in a clinical and epidemiological study [13]. In 2002, the Duke criteria were modified to improve the diagnosis of IE and enable IE to be classified as *definite*,



possible, or rejected [14], becoming the gold standard. The sensitivity of this classification may be low upon admission as many criteria are missing, but the Duke criteria are mostly used at the end of patient testing to classify uses [15]. In fact, these criteria were not primarily intended to diagnose IE upon admission. The morbidity and mortality of IE could be improved if it was possible to identify patients with a high risk of IE. Therefore, a simple prediction tool to weigh and stratify the risk of endocarditis in a particular patient with predisposing heart lesions would be very helpful in practice and help trigger earlier empiric treatment [16]. Richet et al. proposed the Marseille score to evaluate patients in order to shorten the delay between clinical suspicion and antimicrobial treatment [17], which could be initiated without waiting for blood culture results.

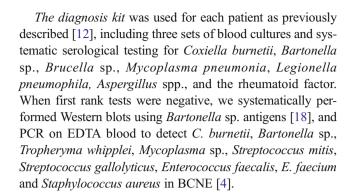
Because IE often occurs in patients with devices and underlying heart disease [1], starting empirical antimicrobial treatment in patients with suspected IE upon admission who have had samples taken for diagnosis is essential. We prospectively include the Marseille score to identify patients with a high probability of IE in a short delay, without replacing the modified ESC criteria used at the end of the investigation.

Patients and methods

Patients

The study design is presented in Fig. 1. From November 2011 to February 2013, we prospectively included all patients with suspected endocarditis consulting at or admitted to Marseille public hospitals (Fig. 1) and who were sampled with the IE diagnosis kit. For each studied patient, a questionnaire was completed by the treating physician. Data were collected upon admission or during patient hospitalization, including: age, sex, signs and symptoms, duration of symptoms, history of antibiotic treatment for any current illness, previous diseases, predisposing factors for IE (prosthetic valve, systemic disease, intravenous drug abuse, dental or surgical procedures), echocardiography (transthoracic or TTE and/or transesophageal TEE) and any treatment received during hospitalization, with its outcome.

Admission score When a predisposing heart lesion was found by interview or TEE, our admission score (Table 1) was performed during the first 24 h of admission. In brief, this score includes clinical and epidemiological criteria (male, fever, splenomegaly, clubbing, vascular disease and stroke) and biological criteria that can be obtained in under 2 h (white blood cells (WB) > 10,000/mm³, sedimentation rate (SR) > 50/mm or C reactive protein >10 mg/L and hemoglobin <100 g/l). We added one point for each predictive factor [17], whereby the score ranged from 0 to 9.



Cardiac valve When cardiac valves were removed, histopathology and PCR were systematically performed as described above [19]. When serology and/or PCRs were positive for *C. burnetii*, *Bartonella* sp. or *T. whipplei*, we performed immunohistochemistry as previously described using specific polyclonal antibodies [5].

¹⁸F-fluorodeoxyglucose PET/CT was performed when possible on samples from patients with suspected IE. The analysis of hypermetabolic intensities in the cardiac area was considered to be abnormal. This uptake had to be confirmed in the uncorrected images. This visual analysis defined whether the PET/CT was positive or negative [20].

Diagnostic criteria

We calculated our Marseille score for all patients based on clinical symptoms and basic blood tests [17] (Table 1). The final diagnosis incorporated the European Society of Cardiology 2015 modified criteria for diagnosing infective endocarditis [21] (microbiological assays, evaluation of auto-antibodies, histology, echocardiogram with added PCR as evidence of bacterial infection [4] and positive PET/CT as major criteria). We classified our patients into three groups: rejected diagnosis, definite endocarditis and possible endocarditis. After hospital discharge, patients with possible and definite IE had a follow-up at 1, 3 and 6 months with biological samples, blood cultures, TTE and/or TEE at our department or by us contacting the patients or their physicians.

Statistical methods

An Excel sheet was used to enter clinical and biological data. Sensitivity (Se) (true positive/(true positive + false negative)), Specificity (Sp) (true negatives/(true negative + false positive)), positive predictive values (PPV) (true positive/(true positive + false positive)), negative predictive values (NPV) (true negatives/(true negative + false positive)), and their comparisons were calculated for each score level using the VassarStats Calculator website (www. vassarstats.net). Receiver operating characteristic (ROC) curves were drawn by plotting Se against 1-Sp. Observed



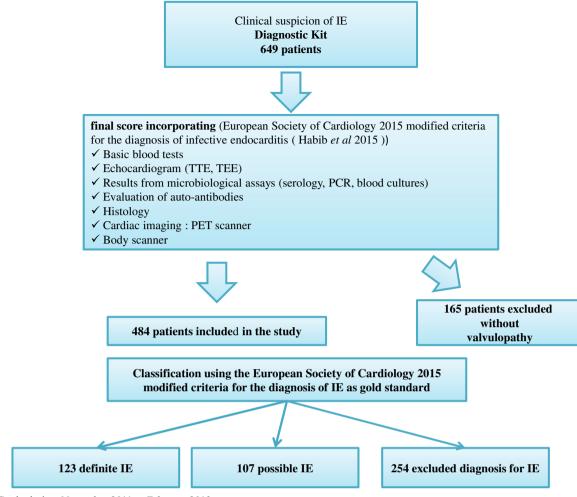


Fig. 1 Study design. November 2011 to February 2013

Table 1 Admission checklist score

Marseille score on the day of admission

Male sex

Fever >38 °C

Peripheral arterial emboli

Stroke

Splenomegaly

Finger clubbing

Leucocytes >10,000/mm³

Hemoglobin level < 100 g/L

Erythrocyte sedimentation rate > 50 mm or C reactive protein >10 mg/L

When a predisposing heart lesion was present the Marseille score was calculated during the first 24 h of patient admission. This score includes clinical and epidemiological criteria (male, fever, splenomegaly, clubbing, vascular disease and stroke) and biological criteria (white blood cells (WB)>10,000/mm³, sedimentation rate (SR)>50/mm or C reactive protein>10 mg/L and hemoglobin<100 g/l). We calculated the score by adding one point for each present parameter (range 0–9)

differences were considered significant when P was <0.05 for two-tailed tests.

Results

Patient characteristics

During the study period, we received 649 endocarditis kits. Patients without a valvular lesion or heart predispositions (*n* = 165) were excluded from the study (Fig. 1). We included 484 patients, with a definite IE diagnosis in 123, possible IE in 107 and rejected IE in 254. The majority was males (318: 65.7%), and the mean age was 66.4 years with a median age at 68.5 years (13–98) (Table 2). Concerning the cardiac predisposing factors: 179 (37%) had a native valve, 114 (23.6%) a bioprosthetic valve, 66 (13.6%) a mechanical valve, 137 (28.3%) an intra-cardiac device, 6 (1.2%) an aortic allograft, 4 (0.8%) a mitral plasty and 4 (0.8%) a Heart Mate. The most frequently damaged valve was the aortic valve with 210 cases (43.4%), followed by the mitral valve with 163 cases (33.7%).



 Table 2
 Patient's characteristics

Characteristic	Total		Excluded		Possible		Definite		Possible + Definite		<i>p</i> -value
	number nb	%	number nb	%	number nb	%	number nb	%	number nb	%	
Number of patients	484		254		107		123		230		
Men	318	65.7%	157	61.8%	73	68.2%	88	71.5%	161	70.0%	0.07
Mean age \pm SD	66.4 ± 15.5		66.6 ± 15.5		68.3 ± 14.3		64.4 ± 15.8		66.2 ± 15.5		
Median [min-max]	68.5	[13-98]	69	[14-98]	71	[30-97]	66	[13-95]	68	[13-97]	
Cardiac predisposition											
Valve native	179	37.0%	85	33.5%	32	29.9%	62	50.4%	94	40.9%	
Bioprosthesis	114	23.6%	59	23.2%	30	28.0%	25	20.3%	55	23.9%	
Mechanical prosthesis	66	13.6%	49	19.3%	14	13.1%	3	2.4%	17	7.4%	0.0002
Intra-cardiac device	137	28.3%	67	26.4%	35	32.7%	35	28.5%	70	30.4%	
Mitral repair	4	0.8%	4	1.6%	_	-	-	-	-	_	
Heart Mate	4	0.8%	3	1.2%	1	0.9%	-	-	1	0.4%	
Aortic homograft	6	1.2%	3	1.2%	2	1.9%	1	0.8%	3	1.3%	
Aortic disease	210	43.4%	111	43.7%	41	38.3%	58	47.2%	99	43.0%	
Mitral disease	163	33.7%	86	33.9%	36	33.6%	41	33.3%	77	33.5%	
Tricuspid	14	2.9%	8	3.1%	5	4.7%	1	0.8%	6	2.6%	
Left heart	347	71.7%	187	73.6%	71	66.4%	89	72.4%	160	69.6%	
Right heart	151	31.2%	75	29.5%	40	37.4%	36	29.3%	76	33.0%	
Post-surgery	16	3.3%	10	3.9%	5	4.7%	1	0.8%	6	2.6%	
Micro-organisms											
Negative	249	51.4%	249	98.0%	0	0.0%	0	0.0%	0	0.0%	< 0.0001
Blood culture negative IE	79	16.3%	1	0.4%	64	59.8%	14	11.4%	78	33.9%	< 0.0001
Enterococcus faecalis	30	6.2%		0.0%	6	5.6%	24	19.5%	30	13.0%	< 0.0001
Staphylococcus aureus	37	7.6%		0.0%	9	8.4%	28	22.8%	37	16.1%	< 0.0001
Coagulase negative Staphylococcus	18	3.7%	1	0.4%	4	3.7%	13	10.6%	17	7.4%	< 0.0001
Streptococcus sp.	48	9.9%		0.0%	14	13.1%	34	27.6%	48	20.9%	< 0.0001
Others micro-organism	23	4.8%	3	1.2%	10	9.3%	10	8.1%	20	8.7%	< 0.0001

From November 2011 to February 2013, we compared the clinical and demographic characteristic of the 484 patients with valvular or heart predispositions with definite IE, possible IE, and excluded patients according to the ESC criteria. Infective endocarditis (definite and possible) was significantly associated with men, mechanical prosthesis and blood culture (negative or positive)

Among the 230 possible and definite IE patients, 52 (22.6%) underwent surgery, with 24 (46%) revealing IE upon histological examination of the cardiac valve. Blood cultures for IE were positive in 152 patients (66%). BCNEs were diagnosed in 78 patients (34%). *Staphylococcus aureus*, blood culture negative IE, *Streptococus sp.* IE, and *Staphylococcus* coagulase negative were the most common final diagnoses.

Test performance characteristics of Marseille score

In Table 3, we show the sensitivity, specificity, and predictive values for different cut-off points of the Marseille score. The goal of the score is to begin empiric antibiotic treatment as soon as possible while awaiting confirmation of the diagnosis, thus favoring the sensitivity and the negative predictive value (Fig. 2a). The choice of a cut-off score of 2 for screening would have resulted in only 19 false negatives and 109 true negative patients (score 0 and 1), and 211 true positives (120 definite IE; possible 91 IE) (PPV = 59%) but 145 false positives. If we use a higher cut-off

score of 3, false positives would be reduced to 81 but false negatives increased to 63.

For the false negative IE found with a score <2, the distribution was as follows: score 0: 3 cases (2 possible, 1 definite); score 1: 16 cases (14 possible; 2 definite). BCNE

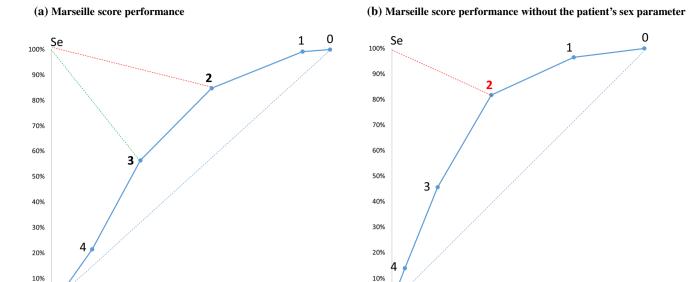
Table 3 Marseille score performance

Marseille score	≥ 1	≥ 2	≥ 3	≥ 4	≥ 5	6
Sensitivity (%)	99%	92%	73%	37%	9%	1%
Specificity (%)	10%	43%	68%	85%	97%	100%
Positive predictive value (%)	50%	59%	67%	69%	71%	100%
Negative predictive value (%)	89%	85%	73%	60%	54%	53%

We evaluate the sensitivity, specificity and predictive values for different cut-off points of the Marseille score. Score ≥ 2 and ≥ 3 was chosen as cut point from receiver-operating characteristic curve analysis that jointly optimizes sensitivity and specificity



1-Sp



1-Sp

Fig. 2 Receiver operating characteristic analysis for the prediction of infective endocarditis

was the most common diagnosis with 18 (2 definite, 16 possible) versus 1 caused by *Propionibacterium acnes* IE. In 11 cases (57, 9%), IE was on the right side. The point attributed to the Marseille score was elevated erythrocyte sedimentation or protein C reactive (9/16), male gender (5/16) and fever (2/16).

Concerning the 145 false positives in this group, the gender ratio was 111 men to 35 females. The most common factors for Marseille scoring were attributed to elevated erythrocyte sedimentation or C reactive protein (120/145), male gender (111/145), fever (73/145), leucocytosis (65/145), anemia (35/145), stroke (5/145) and peripheral arterial emboli (3/145); none had finger clubbing. In most patients no microorganism was found in the blood culture (141/145). In three cases, Gram-negative bacteria were isolated from blood cultures from two patients with lymphangitis, one with prostatitis and one with sigmoid abscess. In most cases, cardiac predispositions and abnormalities were situated on the left side of the heart (113/145, 77.9%) with aortic abnormalities (42/113, 42%) and mitral abnormalities (47/113, 32.4%). Right-side heart predispositions (34/145, 3.4%) were intra cardiac devices (31/34) and tricuspid lesions (5/34). In 10 out of 145 cases, patients had had recent cardiac surgery.

A score of two or more was studied according to the different cardiac predispositions (Table 4). The score performed better on left-side than on right-side heart lesions (p = 0.04) and better for valvulopathy than intra cardiac devices (p = 0.02). Sensitivity was 94% versus 85% and 94% versus 84%, respectively. The PPV performed better on prosthetic valves than on native valves (p = 0.02).

Test performance characteristics of Marseille score without the patient's sex

In this study, the majority of patients were male (318, 65.7%). In Table 5, we evaluated the performance of the score without the sex, and calculated the sensitivity, specificity, and predictive values for various cut-off points of the Marseille score. The ROC curve is shown in Fig. 2b. In order to favor the sensitivity and the negative predictive value, we chose a cut-off score ≥ 2 for screening IE. A score ≥ 2 (without sex) increased the false negatives to 42 and reduced the false positives to 100.

The distribution of the false negatives (score < 2) was as follows: 31 possible IE and 11 definite IE, with score of 0 in 8 cases (8 possible IE, 2 definite IE) and a score of 1 in 34 cases (25 possible IE, 9 definite IE). In most cases, cardiac predispositions or abnormalities were more often related to the left side of the heart (13 bioprosthesis, 4 mechanical prosthesis and 8 native valves) than to the right side (19 cardiac devices). BCNE was the most commonly encountered diagnosis (34/42, 80.9%), followed by coagulase-negative Staphylococcus (3/42), Staphylococcus aureus (2/42), Enteroccocus faecalis (1/42) and P. acnes (1/42). The most commonly encountered factors for Marseille scoring were elevated erythrocyte sedimentation or C reactive protein (24/42), fever (7/42), leucocytosis (1/42) and anemia (2/42).

Concerning the 100 false positives in this group, the median age was: 66.5 ± 16 . The most frequently encountered factors for Marseille scoring were attributed to



Table 4 Marseille score and cardiac predisposition

Cardiac predisposition	Sensitivity	<i>p</i> -value	Specificity	<i>p</i> -value	PPV	<i>p</i> -value	NPV	<i>p</i> -value
All patients	92%		43%		59%		85%	
Right heart Left heart	85% 94%	0.04	51% 39%	_	63% 57%	0.34	78% 88%	0.14
Catheter or pace maker	84%	0.02	52%	-	64%	0.32	76%	0.08
Valvulopathy	94%		40%		57%		88%	
Prosthetic valve Native valve	97% 90%	0.10	40% 39%	0.01	64% 50%	0.02	92% 86%	0.5

Bold values were considered significant. A score ≥ 2 was chosen as cut-off; we evaluated its performance for infective endocarditis prediction according to the different cardiac predisposition. The performance was significantly better in left heart compared to right heart lesion as well as for vavulopathy compared to intra-cardiac device

elevated erythrocyte sedimentation or C reactive protein (93/100), fever (65/100), leucocytosis (59/100), anemia (35/100), stroke (5/145) and peripheral arterial emboli (3/100); no patients had finger clubbing. In most cases, the cardiac predispositions were related to the left side of the heart (80/100, 80%) with aortic abnormalities (51/100, 51%) and mitral abnormalities (34/100, 34%). Predispositions on the right side of the heart (23/100, 23%) were intra cardiac devices (19/23) and tricuspid lesions (4/19).

The performance of the score ≥ 2 was studied according to the different cardiac predispositions (Table 6). The score showed better performance on left-side heart lesions than on right-side heart lesions (p = 0.049), as well as better performance for valvulopathy over intra cardiac devices (p = 0.024). The specificity was better for valvulopathy located on the left side of the heart versus intra-cardiac devices (p = 0.06) with 54% versus 40%, respectively. The NPV is better on valvulopathy than on intra-cardiac devices (p = 0.08). The PPV was better on prosthesis valves than native valves (p = 0.029).

Table 5 Marseille score without sex parameter

Marseille score	≥ 0	≥ 1	≥2	≥ 3	≥4	≥ 5
Sensitivity (%) Specificity (%)	100% 0%	97% 28%	82% 61%	46% 82%	14% 95%	2% 100%
Positive predictive value (%)	48%	55%	65%	70%	71%	80%
Negative predictive value (%)	52%	90%	79%	62%	55%	53%

Bold values were considered significant. In the study most of the patients were male, we calculated the Marseille score without the sex parameter and evaluated the sensitivity, specificity, and predictive values for different cut-off points of the Marseille score



Discussion

In this study we evaluated the Marseille score performed on 484 patients, including 107 possible IE and 123 definite IE cases, between 2011 and 2013. The score ≥2 offered the best performance for predicting IE in patients with predisposing heart diseases. It performed better on left-side heart lesions (Se 94%) than on right-side heart lesions (p = 0.04) as well as for valvulopathy over intra cardiac devices (p = 0.02). PPV was better on prosthetic valves compared to native valves (p = 0.02), enabling rapid antibiotic treatment within a few hours for those patients. Since the majority of patients were males (65.7%), we evaluated the Marseille score without the sex parameter. Again, the score ≥ 2 offered better performance in identifying high IE risk in patients with the same predisposing conditions but misdiagnosis (false negatives) increased to 42 versus 19 when considering the sex in the score. The interest of using such a score is to begin antibiotic treatment urgently while awaiting confirmation of the IE diagnosis. Reducing false negatives (which require treatment but are not detected by the score) is the main goal. Of the 42 false negative patients, 8 (6 possible IE and 2 definite IE) had a score equal to 0; and 34 patients had a score of 1 (25 possible IE and 9 definite). In 45% of cases, the patients had an intracardiac device. However, a short antibiotic treatment urgently for the 100 false positives may not be harmful as most (90%) of these patients presented an infection (although not an IE) and would not generate false negative microbiological tests as the sampling kit is performed within 2 h of treatment.

If we used a high cut-off to target high-risk patients, we would improve specificity but reduce sensitivity. The Marseille score, which includes non-specific biologic tests and clinical symptoms, coupled with our IE diagnostic strategy, allowed us to treat patients (Fig. 3) as soon as possible and

Table 6 Marseille score without sex parameter and cardiac predisposition

Cardiac predisposition	Sensitivity	<i>p</i> -value	Specificity	<i>p</i> -value	PPV	<i>p</i> -value	NPV	<i>p</i> -value
All patients	82%		61%		65%		79%	
Right heart Left heart	86% 94%	0.049	52% 40%	0.07	64% 57%	0.23	78% 88%	0.14
Catheter or pace maker	84%	0.024	54%	0.06	66%	0.17	77%	0.08
Valvulopathy	94%		40%		57%		89%	
Prosthetic valve Native valve	97% 90%	0.10	40% 40%	1.00	63% 50%	0.029	92% 86%	0.5

Bold values were considered significant. In the study most of the patients were male; Marseille score was calculated without the sex parameter we chose the cut-off ≥2, and evaluated its performance for infective endocarditis prediction according to the cardiac predisposition. The performance was significantly better in left heart compared to right heart lesion as well for vavulopathy compared to intra-cardiac device

just after using the sampling diagnostic kit. The management of patients with susptected IE or bacteremia with microorganisms belonging to major ESC modified criteria [21] is a significant challenge in clinical practice. For example, in the case of *S. aureus* and *Enterococcus* sp. bacteremia, the predictive tool is useful in ruling out the diagnosis of IE. Recently, a simple scoring system was proposed to simplify the use of echocardiography in the case of *S. aureus* bacteremia in order

to evaluate the risk of IE [22]. Bouza et al. used a simple clinical score to rule out endocarditis among patients with enterococcal bacteremia [23]. A predictive model that identifies patients at very low risk for endocarditis in febrile injection drug users was also developed [24].

Our study is subject to limitations. The reliable detection of IE is of critical importance. Our study was performed in our center which is a tertiary care unit, where a major interest in

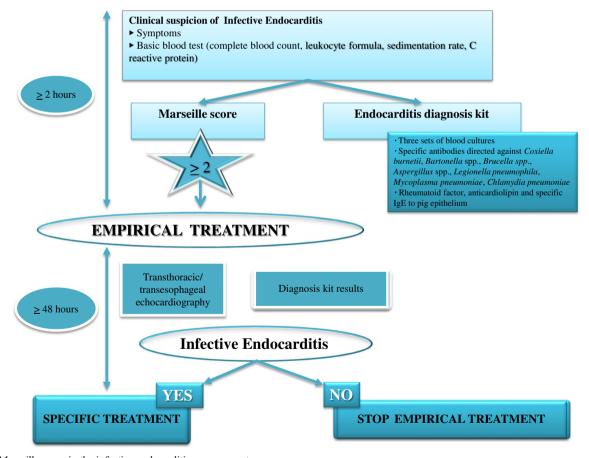


Fig. 3 Marseille score in the infective endocarditis management

the field of IE has developed. To investigate IE, systematic TEE and/or TTE was performed on our patients; all were admitted to Cardiology, Cardiac Surgery, Infectious Diseases or Internal Medicine departments. A multidisciplinary team took care of patients with suspected IE [9, 25]. This could be a bias and has to be taken into account. It has been shown that having an infectious disease consultation service improves detection of IE [26]. For example, cases of S. aureus bacteremia IE and metastatic infection were detected more frequently [27] in routine consultation with an infectious diseases specialist. The population of our cohort was heterogeneous; we had patients with biological and mechanical prosthesis, pacemakers and intracardiac catheters. This heterogeneity may have had an impact on the ability of the scoring system to identify patients with a high probability of endocarditis. We had 19 patients with Marseille score < 2, with three definite and 16 possible IE cases. A strict application of the scoring system would have resulted in not treating these patients; therefore, clinicians should follow their strong clinical suspicion even if it does not meet the scoring criteria. As we are a reference center for IE, some patients would have been categorized by modified Duke Criteria as definite IE before our center performed the diagnostic kit, TEE or TTE. The Marseille score would have been influenced by this kind of patient. An evaluation of Marseille score performance should be done in a larger cohort, in a secondary care unit or another tertiary care unit. This could be interesting to evaluate the ability of our score to improve treatment decision in cases of suspected IE in patients with high-risk cardiac conditions, or intravenous drug abuse. Failure of early diagnosis of IE in patients with cardiac predispositions could impact on IE prognosis. Using our simple Marseille score combined with our standardized diagnostic procedures would help improve IE management by focusing on early empiric treatment within 2 h of admission in patients with cardiac predisposition factors.

We propose applying our score when patients are admitted in order to save time in IE management, in addition to the ESC modified criteria performed during patient hospitalization.

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Compliance with ethical standards

Conflict of interest None.

Ethical approval Ethics registration: 2012–39.

Informed consent
Informed consent was obtained from all patients.

Data access and authors role All authors had access to the data and a role in writing the manuscript.



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