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**Comparison between European Society of Cardiology (ESC) and Duke criteria for the diagnosis of Prosthetic Valve Infective Endocarditis.  
The ENDOPET multicenter prospective study**

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Short Title: the ENDOPET study

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## **ABSTRACT**

### **Background:**

<sup>18</sup>F-FDG PET/CT has been added as a major criterion in the ESC 2015 infective endocarditis guidelines, but the benefit of the ESC criteria has not been prospectively compared with the conventional Duke criteria

### **Objectives:**

1. Primary objective: To assess the value of the ESC criteria including <sup>18</sup>F-FDG-PET/CT in prosthetic valve infective endocarditis (PVE).
2. Secondary objectives i: to assess the reproducibility of <sup>18</sup>F-FDG-PET/CT, ii: to compare its diagnostic value with that of echocardiography, and iii: to assess the diagnostic value of the presence of a diffuse splenic uptake

### **Methods :**

Between 2014 and 2017, 175 patients with suspected PVE were prospectively included in 3 French centers. After exclusion of patients with uninterpretable <sup>18</sup>F-FDG PET/CT, 115 patients were evaluated, including 91 definite and 24 rejected IE, as defined by an expert Consensus.

### **Results :**

Cardiac uptake by <sup>18</sup>F-FDG PET/CT was observed in 67/91 patients with definite PVE and 6 with rejected IE (sensitivity 73.6% [95%CI: 63.3 to 82.3%], specificity 75% [53.3% to 90.2%]). The ESC 2015 classification increased the sensitivity of Duke criteria from 57.1% [46.3 to 67.5%] to 83.5% [74.3% to 90.5%], ( $p < 0.001$ ) but decreased its specificity from 95.8% [78.9% to 99.9%] to 70.8% [48.9% to 87.4%].

Intraobserver reproducibility of <sup>18</sup>F-FDG PET/CT was good ( $\kappa = 0.84$ ) but inter observer reproducibility was less satisfactory ( $\kappa = 0.63$ ).

A diffuse splenic uptake was observed in 24 (20.3%) patients, including 23 (25.3%) of definite PVE, and only 1 (4.2%) rejected PVE ( $p = 0.024$ ).

### **Conclusion :**

<sup>18</sup>F-FDG PET/CT is a useful diagnostic tool in suspected PVE, and explains the greater sensitivity of ESC criteria compared to Duke criteria. However, <sup>18</sup>F-FDG PET/CT also presents important limitations concerning its feasibility, specificity and reproducibility. Our study describes for the first time a new endocarditis criterion, i.e. the presence of a diffuse splenic uptake on <sup>18</sup>F-FDG PET/CT.

**Key words:** valve disease, endocarditis, guidelines, nuclear imaging

## CONDENSED ABSTRACT

This study evaluated the value of the ESC criteria including  $^{18}\text{F}$ -FDG PET/CT in diagnosing prosthetic valve infective endocarditis (PVE). Among 115 patients with suspected PVE, 91 had definite and 24 rejected IE. Cardiac uptake by  $^{18}\text{F}$ -FDG PET/CT was observed in 67/91 patients with definite and 6 with rejected PVE (sensitivity=73.6%, specificity=75%). The ESC criteria increased the sensitivity of Duke criteria from 57.1% to 83.5% ( $p < 0.001$ ) but decreased its specificity from 95.8% to 70.8% ( $p=0.031$ ).

The additional value of ESC vs Duke criteria is proven but limitations of  $^{18}\text{F}$ -FDG PET/CT in clinical practice concern both its feasibility, specificity and reproducibility

## ABBREVIATIONS

$^{18}\text{F}$ -FDG PET/CT:  $^{18}\text{F}$ -Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

MSCT: multislice cardiac Tomography

CRP: C-reactive protein

IE: infective endocarditis

IQR: interquartile range

NVE: native valvular endocarditis

PVE: prosthetic valve endocarditis

TEE: transoesophageal echocardiographic

TTE: transthoracic echocardiography

<sup>18</sup>F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (<sup>18</sup>F-FDG PET/CT) has been shown to improve the diagnosis of prosthetic valve endocarditis (PVE) (1 - 4) and to increase the sensitivity of the modified Duke criteria for the diagnosis of PVE (1). A recent meta-analysis confirmed the good diagnostic performance of <sup>18</sup>F-FDG PET/CT in this setting (5). Multi-imaging approach is essential in the diagnostic work out of PVE (6) and has been integrated in the 2015 European Society of Cardiology criteria (7). However, <sup>18</sup>F-FDG PET/CT also suffers several limitations and cannot be performed in all patients and in all centers (8 - 10). To date, the benefit of the ESC criteria including <sup>18</sup>F-FDG PET/CT has not been prospectively compared with the conventional Duke criteria in clinical practice. Therefore, we aimed to demonstrate in a prospective multicenter study the accuracy of <sup>18</sup>F-FDG PET/CT in early diagnosis of PVE, evaluating the benefit and limitations of nuclear imaging implementation on Duke classification. In addition, we compared the value of <sup>18</sup>F-FDG PET/CT to that of echocardiography and tested a new <sup>18</sup>F-FDG PET/CT parameter, i.e. the global splenic uptake (11 – 15).

## **METHODS**

**Population.** From February 2014 to October 2017, all consecutive adults admitted in 3 French centers (La Timone Hospital, Marseille, Georges Pompidou European Hospital, Paris, and Centre Cardiologique du Nord, Paris) for suspected PVE were included. Exclusion criteria included age under eighteen, pregnancy and breastfeeding, cardiac surgery in the previous three months, agitation, inability to lie a long time, antibiotic therapy for more than eight days, loss of blood glucose control (capillary glycemia > 1.8 g/mL), hemodynamic lability, and rhythm trouble preventing CT synchronization. All patients included underwent clinical, biological, microbiological (including blood cultures, serological tests, explanted

tissues cultures in case of surgery, and molecular analysis) and echocardiographic evaluation (TTE and TEE), at admission. Major echocardiographic criteria included vegetation, abscess, pseudoaneurysm, intracardiac fistula, valvular perforation or aneurysm, and new partial dehiscence of prosthetic valve (7). Written informed consent was obtained from all patients using an approved protocol, which was validated by the institutional board of APHM (Assistance Publique des Hôpitaux de Marseille).

**<sup>18</sup>F-FDG PET/CT.** Patients fasted for 12 hours before <sup>18</sup>F-FDG PET/CT to limit physiological myocardial <sup>18</sup>F-FDG uptake. PET Computed Tomography was performed on the latest generation equipment (General Electric) taking cardiac movements into account (ECG synchronization) and providing a 2 millimeters spatial resolution. After eating a meal rich in fat and very low in carbohydrates to reduce the physiological uptake of FDG in the myocardium, promoting ketogenesis, the patients fasted for at least 12 hours prior to PET/CT (limiting physiological myocardial uptake). Imaging began 60 minutes after <sup>18</sup>F-FDG injection, in patients lying and resting, by a low dose CT in order to correct attenuation (120 kV, 80 mA), with no administration of iodinated contrast agents. Body PET acquisition was then performed, from cranial vertex to mid-thigh, in a 3D-mode, for a period of 2 minutes by bed position. Interpretation of the nuclear data was done in the major investigator center (Timone Hospital, Marseille), by two nuclear medicine physicians (LT and SC) blinded to clinical, biological and imaging data. PET/CT positivity was defined as a valvular prosthesis uptake, homogeneous or heterogeneous, free of all myocardial uptake. The prosthesis uptake corresponds to a major criterion. The assessment of the uptake intensity is only visual in our study. In addition, whole-body acquisition was performed to detect silent embolic events and septic metastases defined as extracardiac abnormal uptakes (minor criterion).

**Definition of primary and secondary objectives and endpoints.**

The primary objective was the value of  $^{18}\text{F}$ -FDG PET/CT in the diagnosis of PVE, with sensitivity and specificity of PET-CT as primary endpoints. The additional value of the new ESC criteria (7) including  $^{18}\text{F}$ -FDG PET/CT in PVE as compared with Duke criteria was assessed. The gold standard for the diagnosis of definite IE was an expert consensus of the Endocarditis Team, established three months after admission, and based data obtained during follow-up, including results of clinical, microbiological, and repeat imaging new information, visual and pathologic evaluation of explanted prostheses, and molecular biology techniques (2).

The secondary objectives were i: to assess the inter observer and intra observer variability of  $^{18}\text{F}$ -FDG PET/CT, ii: to compare the diagnostic values of echocardiography and  $^{18}\text{F}$ -FDG PET/CT, iii: to assess the diagnostic value of the presence of a diffuse splenic uptake, iiiii: to assess the influence of potential confounding factors (high level of CRP or white blood cells, delay between initiation of antibiotic therapy and  $^{18}\text{F}$ -FDG PET/CT study) on diagnostic value of  $^{18}\text{F}$ -FDG PET/CT

**Statistical analysis.** To describe the population, we used mean or median [range] for continuous variables and counts (%) for categorical ones. In the initial protocol the sample size was 139 patients with definite IE to: 1) estimate precisely ( $\pm 5\%$ ) a sensitivity expected 90% or higher and 2) detect with a power higher than 90% a 25% increase in sensitivity from 65% with “TEE” to 90% with  $^{18}\text{F}$ -FDG PET/CT (paired two-sided test with type I error of 5%). As “TEE” is included in Duke criteria, we reframed our main objective to compare the sensitivity of Duke and ESC 2015 criteria. With 91 patients with definite IE, we were able to evaluate the sensitivity of ESC 2015 criteria with a precision of  $\pm 8\%$  (83.5% 95%CI [74.3% to 90.5%]) and we still had a power higher than 90% (97% power) to detect the 26% increase

in sensitivity observed (from 57.1% to 83.5%) in this case. Intra observer and inter observer reproducibility for binary outcomes and ordinal outcomes was estimated using Cohen's kappa and weighted kappa respectively. Mc Nemar tests was used to compare sensitivity and specificity of different tests. For all analyses, a  $p < 0.05$  was considered statistically significant. A binary logistic regression model was used to study the association between  $^{18}\text{F}$ -FDG PET/CT criteria and the diagnosis of IE after adjustment for clinical criteria. Only factors associated with PET/CT criteria or IE with  $p < 0.20$  in univariate analysis were entered in the model. A penalized logistic regression model was used (using the `logistf` package for R 3.6) as vascular criteria was only present when patient had an IE. All tests were two-sided. Statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Inc., New York, USA) except 95% confidence intervals and weighted kappas computed using the packages `epiR psy` and `boot` for R 3.6.0 software (The R Foundation for Statistical Computing Platform, Vienna, Austria).

## RESULTS

**Baseline characteristics.** Among 175 patients with suspected PVE, 115 were finally included in the study, including 91 definite IE and 24 rejected IE, as defined by an expert Consensus of Endocarditis Team after 3-month follow-up as Gold Standard. We excluded 60 patients for reasons explained in the flowchart of the study shown in **Figure 1**.

The baseline characteristics are summarized in **Table 1**. The median age of the patients was 71 (range: 22 to 89) years, and 65.2% were male. Echocardiography at admission was positive in 71 patients (61.7%), blood cultures in 77 (67.0%). The most frequent identified pathogens were *Enterococcus* species (14.8%), *oral streptococci* and *Streptococcus gallolyticus*, (13.9%) and *Staphylococcus aureus* (11.3%).

The mean hospitalization duration was 23 days (0-79), and delay to surgery 14 days (0-46).

**Incidence of primary endpoint.** Significant cardiac uptake by  $^{18}\text{F}$ -FDG PET/CT (major criterion) was observed in 67 among 91 patients with definite PVE and 6 among 24 patients with rejected IE (sensitivity 73.6% [95% CI: 63.3% to 82.3%], specificity 75% [53.3% to 90.2%], positive predictive value 91.8% [83.0% to 96.9%], negative predictive value 42.9% [27.7% to 59.0%]). **Table 2** represents  $^{18}\text{F}$ -FDG PET/CT major and minor criteria according to the presence of major or minor Duke criteria. Of interest is the presence of a major  $^{18}\text{F}$ -FDG PET/CT criterion in 40.9% of patients without major echo criteria. Considering cardiac uptake as a major criterion, the ESC 2015 classification increased the sensitivity of Duke criteria from 57.1% [46.3% to 67.5%], to 83.5% [74.3% to 90.5%], ( $p < 0.001$ ) but decreased its specificity from 95.8% [78.9% to 99.9%] to 70.8% [48.9% to 87.4%], ( $p = 0.031$ ). (**figure 2, and Central Illustration**).

Accuracy was higher for ESC criteria than for Duke criteria (80.9% vs 65.2%,  $p = 0.002$ ).

Given the high prevalence of EI (79.1%) in our sample, the absolute increase in the occurrence of true positive (+20.9%) was higher than the absolute decrease in the occurrence of false positive (-5.2%) using ESC instead of Duke criteria. The number of patients to scan with ESC to add a true positive (NNS=5) is four-time lower than the number of patients to scan with ESC to add a false positive (NNS=20).

When comparing patients in whom the addition of  $^{18}\text{F}$ -FDG PET/CT was useful (decreased false negative rate,  $n = 24$ ) to patients where the addition of  $^{18}\text{F}$ -FDG PET/CT had no or even deleterious effect (increased false positive rate),  $n = 91$ , adding  $^{18}\text{F}$ -FDG PET/CT seemed to be most useful in female patients with negative blood cultures and no clinical embolic events.

Other clinical or biological factors had no influence on the additional value of PET (supplementary table 1).

By multivariable analysis, only valvular uptake on PET/CT, positive blood cultures, and vascular phenomena were significantly associated with the diagnosis of IE. (**Table 3**).

### Variability of $^{18}\text{F}$ -FDG PET/CT measurements

Intraobserver reproducibility of valvular uptake evaluation (major criterion) was good ( $\kappa = 0.84$ ) but inter observer reproducibility was less satisfactory ( $\kappa = 0.63$ ). Intraobserver and interobserver reproducibility of minor PET criterion was poor (respectively  $\kappa = -0.11$  and  $0.54$ ). Results of reproducibility measurements are reported in **table 4**.

### Diagnostic values of echocardiography and $^{18}\text{F}$ -FDG PET/CT

Echocardiography found a major criterion in 62 (68.1%) of patients with a final diagnosis of definite PVE and 9 (37.5%) in patients with a final diagnosis of rejected PVE, giving a sensitivity of 68.1% [57.5% to 77.5%] and a specificity of 62.5% [40.6% to 81.2%]. Sensitivity of  $^{18}\text{F}$ -FDG PET/CT was 73.6% [63.3% to 82.3%] and its specificity was 75.0% [53.3% to 90.2%]. **Figure 3** shows that  $^{18}\text{F}$ -FDG PET/CT presents with a better sensitivity than echocardiography for the diagnosis of PVE.

### Diagnostic value of the presence of a diffuse splenic uptake

A diffuse splenic uptake was observed in 24 (20.3%) patients, including 23 (25.3%) of definite PVE, and only 1 (4.2%) rejected PVE ( $p=0.024$ ). The specificity of this new criterion was 96.0%. Implementing diffuse splenic uptake as a minor criterion over Duke criteria increased its sensitivity to 60.4% by reclassifying 3 possible IE as definite and changed their specificity from 95.8% to 91.7%. Implementing diffuse splenic uptake as a minor criterion over ESC criteria increased their sensitivity to 85.7% by reclassifying 1 *possible* and 1 *rejected* IE as *definite* IE without change in specificity (**figure 2**).

### Influence of potential confounding factors

Considering the whole population of 115 patients, CRP values (74.9 +/- 69.9 vs 75.5 +/- 69.6 mg/l), white blood cells (19.0 +/- 23.1 vs 19.1 +/- 23.2 n/ mm<sup>3</sup>), and time elapsed between

initiation of antibiotic therapy (3.7 +/- 3.3 vs 3.8 +/- 3.2 days) were similar between patients with positive and negative <sup>18</sup>F-FDG PET/CT study. However, among the 91 patients with definite IE, those with a true positive PET study presented with more frequent positive echocardiography, while patients with a false negative PET study had a significant lower CRP value (p= 0.034, table 5). Finally, among the 26 cases of rejected endocarditis, no significant difference was observed between the 6 patients with a false positive PET/CT study and the 18 other patients, except an older age (supplementary table 2),

## DISCUSSION

The main results of our study are the following:

- <sup>18</sup>F-FDG PET/CT is a useful diagnostic tool in suspected PVE, and explains a greater sensitivity of ESC criteria than Duke criteria
- However, <sup>18</sup>F-FDG PET/CT also presents with important limitations concerning its feasibility, specificity and reproducibility
- Our study describes for the first time a new potential endocarditis criterion, i.e. the presence of a diffuse splenic uptake on <sup>18</sup>F-FDG PET/CT.

### 1 – Value of <sup>18</sup>F-FDG PET/CT for the diagnosis of PVE.

Early and accurate diagnostic assessment is a key issue in suspected PVE. However, both TTE and TOE are of limited value in this setting, with reported sensitivity and specificity of 50% and 92%, respectively (7). Similar results were found in our study. <sup>18</sup>F-FDG PET/CT associates morphological and functional assessment of patients with PVE and has been shown to improve the value of diagnostic criteria (1), without significant decrease in specificity. Studies performed after 2015 ESC Guidelines (2), reported even better results (Se 87.2%, Sp 92%). Our study not only confirmed the good diagnostic value of <sup>18</sup>F-FDG PET/CT but also

highlight the superiority of ESC over Duke criteria for the diagnosis of PVE. Considering cardiac uptake as a major criterion, the ESC 2015 classification increased the sensitivity of Duke criteria from 57 to 84%, by reclassifying several *possible* IE into *definite* IE.

## **2 - Limitations of <sup>18</sup>F-FDG PET/CT for the diagnosis of PVE**

<sup>18</sup>F-FDG PET/CT presents with several well-known limitations concerning its availability and specificity. For instance, false positive studies have been related to postoperative inflammation period (7), to the physiologic uptake of aortic root graft associated to prosthetic valve replacement or to surgical adhesives used during cardiac surgery (16, 17). More important, some degree of prosthetic uptake has been described in several normal non-infected prostheses, making the differentiation between normal and pathologic uptake sometimes difficult (18). Interpretation of <sup>18</sup>F-FDG PET/CT studies thus needs specific expertise and knowledge of the confounding normal and pathological conditions which may resemble IE uptake (16, 17). Combination of <sup>18</sup>F-FDG PET/CT with CT angiography may improve the interpretation of prosthetic uptake (2).

Swart et al (4), in the largest reported series on the use of <sup>18</sup>F-FDG PET/CT in 160 patients with a prosthetic valve, also observed false positive and false negative in their patients, but found that both qualitative and quantitative assessment accuracy improved after exclusion of confounders, such as low inflammatory activity (suggesting a confounding role of previous antibiotic therapy) and presence of surgical adhesives. However, their study was retrospective, finally included only 80 definite cases of PVIE, and needed to exclude 69 (43%) patients with CRP of <40 mg/l in order to improve the accuracy of <sup>18</sup>F-FDG PET/CT (4). In addition, the influence of antibiotic therapy on the diagnostic accuracy of <sup>18</sup>F-FDG PET/CT is debated and was not observed in a recent study (19). In our study however,

significant lower CRP values were observed between patients with true positive and false negative  $^{18}\text{F}$ -FDG PET/CT

Our study presents the advantage of being prospective, without excluding patients with potential confounders, and thus representing a “real-life” study on the use of  $^{18}\text{F}$ -FDG PET/CT in suspected PVE. Our study confirms that, even in experienced hands, the risk of false positive  $^{18}\text{F}$ -FDG PET/CT studies exists, resulting in a lower specificity than expected from previously reported studies (1,2), including one study from one of the centers involved in the current study (1). The consequence is that, although ESC criteria including  $^{18}\text{F}$ -FDG PET/CT are clearly better than the Duke criteria in terms of sensitivity, they also provoke some decrease in specificity, as compared with Duke criteria. The consequence might be an increased incidence of deleterious effects of high-dose antibiotic therapy, i.e. renal failure or allergic reaction.

However, the prognosis of prosthetic valve IE is so bad that any effort should be made to increase sensitivity, even if some patients are treated by excess. Consequently, the primary objective was to increase the sensitivity of the diagnostic classification, and to avoid false negatives, with the help of PET/CT, i.e. to promote sensitivity over specificity.

Another limitation of  $^{18}\text{F}$ -FDG PET/CT is its relatively low reproducibility. Our study reveals a relatively low reproducibility of  $^{18}\text{F}$ -FDG PET/CT in patients with suspected PVE, both in terms of interobserver and intraobserver variabilities. This result is probably the consequence of the subjectivity and the lack of real gold standard in the interpretation of  $^{18}\text{F}$ -FDG PET/CT studies. It also might be related to the analysis method, limited to visual interpretation, since our study started in 2014, where quantitative analysis (Standardized Uptake Value) was not performed routinely in our center (4). Our results also underline the need to perform  $^{18}\text{F}$ -FDG PET/CT in highly trained centers with high expertise in the field of both endocarditis management and nuclear medicine performance and interpretation. (7).

Finally, in this “real-life” study, a large number of patients (60/175) were excluded from analysis, mainly due to myocardial uptake related to a non-respected ketogenic diet, but also because  $^{18}\text{F}$ -FDG PET/CT could not be performed in some frail patients, admitted in intensive care unit with hemodynamically unstable conditions, not allowing an adequate preparation of their PET/CT study.

### **3 – global splenic uptake**

Diffuse splenic uptake is a visual observation on PET/CT corresponding to a global capture of  $^{18}\text{F}$ FDG by the organ, relative to liver uptake. This phenomenon, described and used as a potential severity criterion in oncology (**11-14**), hardly referred in pyogenic infections (**15**), has never been reported in IE. In this prospective study, this phenomenon was observed in 24 patients, among them 23 IE (resulting in a specificity of 96%). However, our patients were selected because of suspected IE, possibly representing a recruitment bias. Further studies including a sample of patients without IE are warranted. Moreover, including diffuse splenic uptake did not improve ESC criteria, because of its low sensitivity and thus low diagnostic accuracy. Conversely, its very high specificity means that a pattern of diffuse splenic uptake might be a strong argument for the diagnosis of IE.

### **Study limitations**

The major criticism of the present study lies in the choice of the gold standard, defined as the expert consensus at three months after hospitalization. It can be argued that the gold standard basically includes all clinical data which form the basis of both criteria systems and that expert reviewers were not blinded to the PET/CT. However, such a gold standard has already been used in previous studies (2) and was obtained in the current study by several specialists (cardiologists, infectious diseases physicians, microbiologists, pathology physicians,

radiologists, nuclear physicians) with a large experience in the disease. No better alternative was available, since Duke criteria themselves suffer from relatively low sensitivity in prosthetic valve IE.

Another limitation of the study is the use of an only qualitative analysis of cardiac uptake, mainly based on visual interpretation defining a positive or negative PET/CT study. Semi-quantitative assessment of FDG uptake, expressed as SUVmax or SUVratio, may add support to the visual information (2, 4, 5), and was not used in our study. However, the additional diagnostic value of semiquantitative over qualitative assessment has not been proved, many factors that may affect measurements, and different threshold values have been reported by different teams (2, 4) thus limiting its clinical application.

## CONCLUSION

Our study confirms the diagnostic value of  $^{18}\text{F}$ -FDG PET/CT in PVIE. The additional value of ESC vs Duke criteria is proven but limitations of  $^{18}\text{F}$ -FDG PET/CT in clinical practice concern both its feasibility, specificity and reproducibility. A special effort should be made to improve reproducibility of  $^{18}\text{F}$ -FDG PET/CT measurements and to allow the generalization of its use in all hospitals. Finally, the value of a new diagnostic parameter, the diffuse splenic uptake, should be prospectively assessed in future studies.

**CLINICAL PERSPECTIVES:****COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS.**

<sup>18</sup>F-Fluorodeoxyglucose Positron Emission Tomography /Computed Tomography (<sup>18</sup>F-FDG PET/CT) has a key role to diagnose prosthetic valve infective endocarditis (IE), but also suffers from some limitations. Knowing advantages and limitations of the technique, the clinicians should learn when to use it and how to utilize its results in the management of their patients with IE

**TRANSLATIONAL OUTLOOK:**

Future studies will focus on how to include <sup>18</sup>F-FDG PET/CT in the arsenal of imaging techniques of endocarditis and how to include its results within an individualized management strategy of patients with IE.

**REFERENCES**

1. Saby L, Laas O, Habib G, et al. Positron Emission Tomography / Computed Tomography for diagnosis of prosthetic valve endocarditis. *J. Am. Coll. Cardiol.* 2013;61:2374–2382
2. Pizzi MN, Roque A, Fernandez-Hidalgo N, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with 18F-FDG positron emission tomography / computed tomography. *Circulation* 2015;132:1113–1126
3. Granados U, Fuster D, Pericas JM, et al. Diagnostic Accuracy of 18F-FDG PET/CT in Infective Endocarditis and Implantable Cardiac Electronic Device Infection: A Cross-Sectional Study. *J. Nucl. Med.* 2016;57:1726–1732
4. Swart LE, Gomes A, Scholtens AM, et al. Improving the Diagnostic Performance of <sup>18</sup>F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography in Prosthetic Heart Valve Endocarditis. *Circulation* 2018;138:1412–1427
5. Mahmood M, Ayse TK, Ajmal S, et al. Meta-Analysis of 18F-FDG PET/CT in the Diagnosis of Infective Endocarditis. *J. Nucl. Cardiol.* 2019;26:958–970
6. Thuny F, Gaubert JY, Jacquier A, et al. Imaging investigations in infective endocarditis: Current approach and perspectives. *Arch. Cardiovas. Dis.* 2013;106:52–62
7. Habib G, Lancellotti P, Antunes MJ, et al. ESC Guidelines for the management of infective endocarditis. *Eur. Heart. J.* 2015;36:3075–3128
8. Kouijzer IJE, Vos FJ, Janssen MJR et al. The value of 18F- FDG PET/CT in diagnosing infectious endocarditis. *Eur. J. Nucl. Med. Mol. Imaging.* 2013;40:1102–1107
9. Tattevin P, Mainardi JL. Analysis of the 2015 American and European guidelines for the management of infective endocarditis. *Méd. Maladies. Infect.* 2016;46:406–410
10. Chen W, Kim J, Molchanova-Cook O, et al. The potential of FDG PET/CT for early diagnosis of cardiac device and prosthetic valve infection before morphologic damages ensue. *Curr. Cardiol. Rep.* 2014;16:459

11. Kim SY, Moon CM, Yoon HJ, et al. Diffuse Splenic FDG Uptake Is Predictive of Clinical Outcomes in Patients with Rectal Cancer. *PLOS One* 2018;13:e0196110
12. Ege Aktas G, Sarikaya A, Demir SS. Diffusely Increased Splenic Fluorodeoxyglucose Uptake in Lung Cancer Patients. *Turk. Thorac. J.* 2017;18:6–10
13. Kim K, Kim SJ, Kim IJ, et al. Factors Associated with Diffusely Increased Splenic F-18 FDG Uptake in Patients with Cholangiocarcinoma. *Nucl. Med. Mol. Imaging.* 2014;32:1155–1161
14. Yoon HJ, Bom SK, Chang MM, et al. Prognostic Value of Diffuse Splenic FDG Uptake on PET/CT in Patients with Gastric Cancer. *PLOS One* 2018;13:e0196110
15. Kim K, Kim SJ, Kim IJ, et al. Diffuse Increased Splenic F-18 Fluorodeoxyglucose Uptake May Be an Indirect Sign of Acute Pyogenic Cause Rather than Tuberculous in Patients with Infectious Spondylitis. *Nucl. Med. Commun.* 2011;32:1155–1161
- 16 - Swart LE, Scholtens AM, Tanis W, et al. <sup>18</sup>F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography and computed tomography angiography in Prosthetic Heart Valve Endocarditis: from guidelines to clinical practice. *Eur Heart J.* 2018; 39:3739-49
- 17 - Scholtens AM, Swart LE, Verberne HJ, Tanis W, Lam MG, Budde RP. Confounders in FDG-PET/CT Imaging of Suspected Prosthetic Valve Endocarditis. *JACC Cardiovasc Imaging.* 2016; 9: 1462-5.
- 18 - Mathieu C, Mikail N, Benali K, et al. Characterization of <sup>18</sup>F-Fluorodeoxyglucose Uptake Pattern in Noninfected Prosthetic Heart Valves. *Circ Cardiovasc Imaging.* 2017 ;10: e005585.
- 19 - Kagna, O, Kurash M, Ghanem-Zoubi N, Keidar Z, Israel O. “Does Antibiotic Treatment Affect the Diagnostic Accuracy of <sup>18</sup>F-FDG PET/CT Studies in Patients with Suspected Infectious Processes?” *J. Nucl. Med.* 2016. 58: 1827–30.

## **FIGURE LEGENDS**

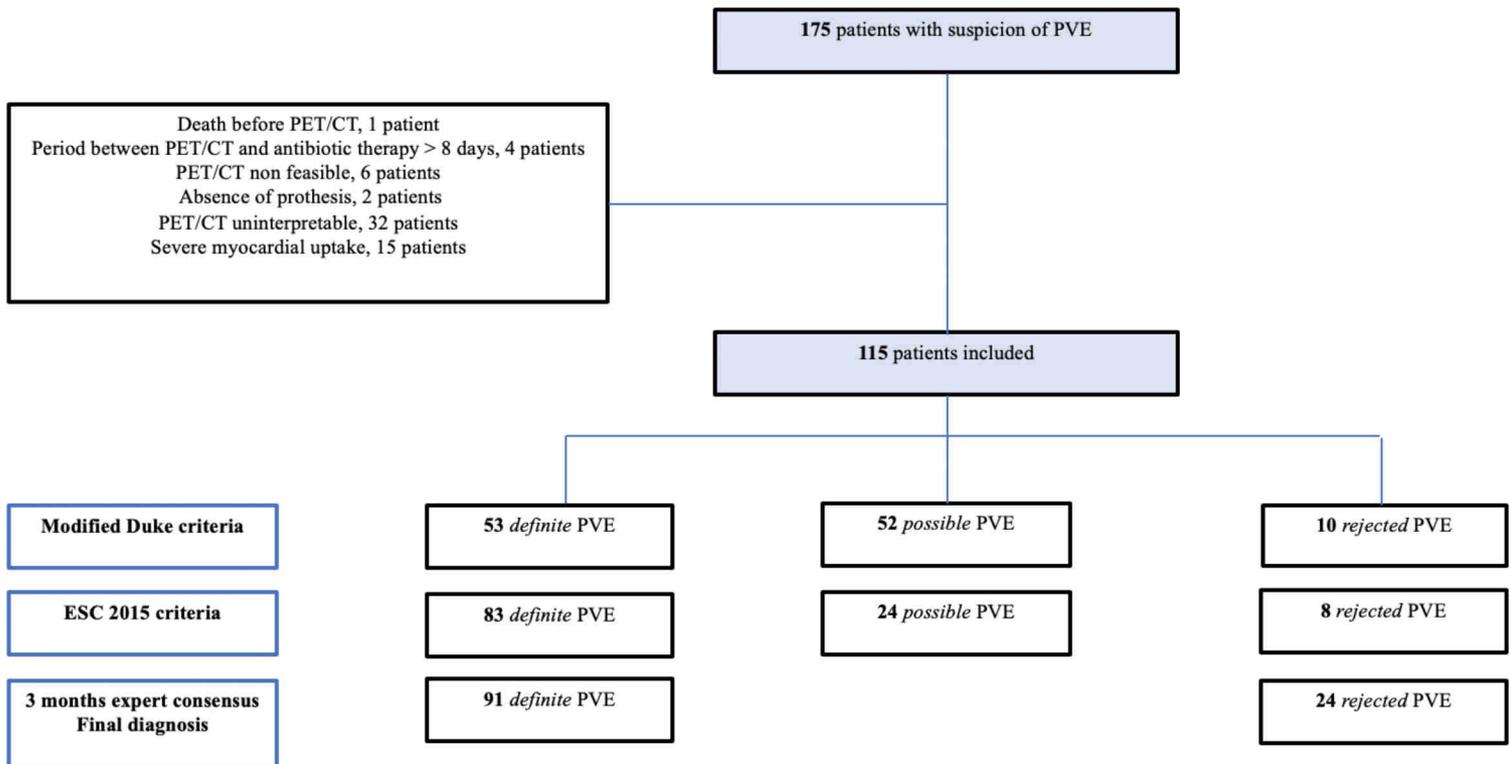
**FIGURE 1: Flowchart of the study.** On the 175 patients with suspicion of PVE, 115 were included and classified according the modified Duke classification, the ESC 2015 classification, and the final diagnosis by expert consensus after three-month follow-up. PVE = Prosthetic valve endocarditis, PET/CT = Positron emission tomography/ computed tomography

**CENTRAL ILLUSTRATION: Additional diagnostic value of ESC 2015 criteria including PET valvular uptake over Duke criteria**

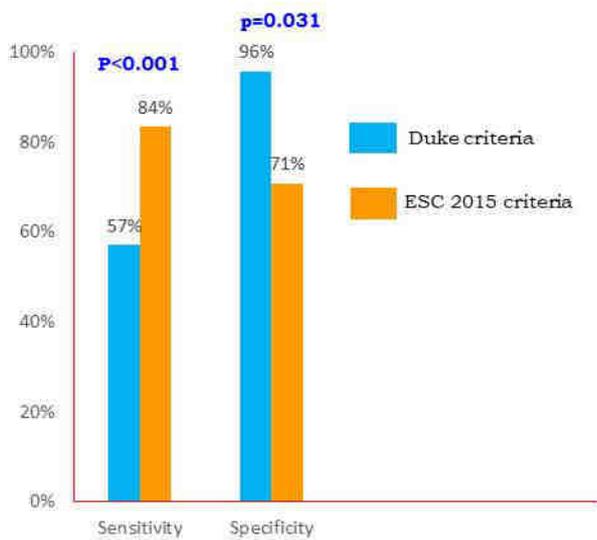
**FIGURE 2:  $^{18}\text{F}$ -FDG PET/CT versus echocardiography in PVE diagnosis.** PET/CT = positron emission tomography / computed tomography

**FIGURE 3: Additional diagnostic value of ESC 2015 criteria including PET valvular uptake and of diffuse splenic uptake vs Duke criteria**

PET/CT = positron emission tomography / computed tomography



# Suspected Prosthetic Valve Endocarditis

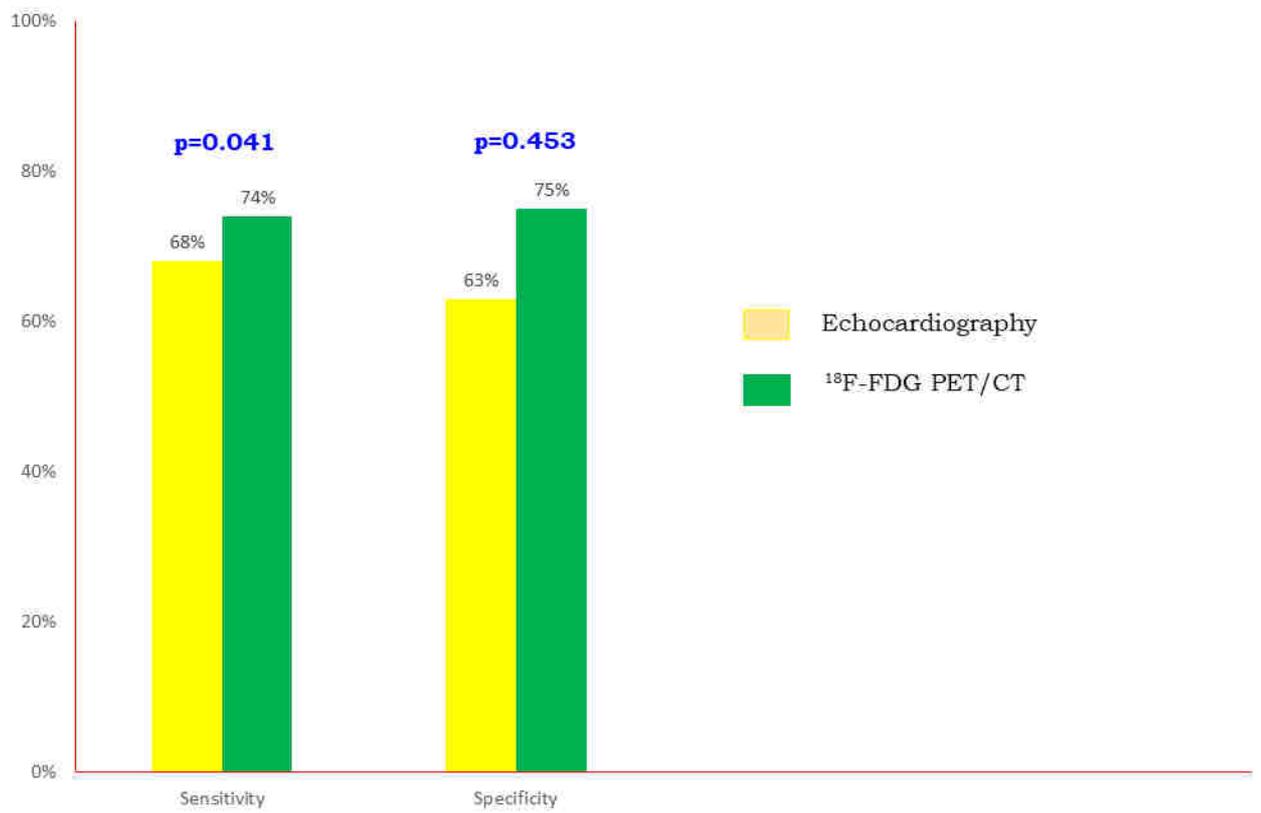


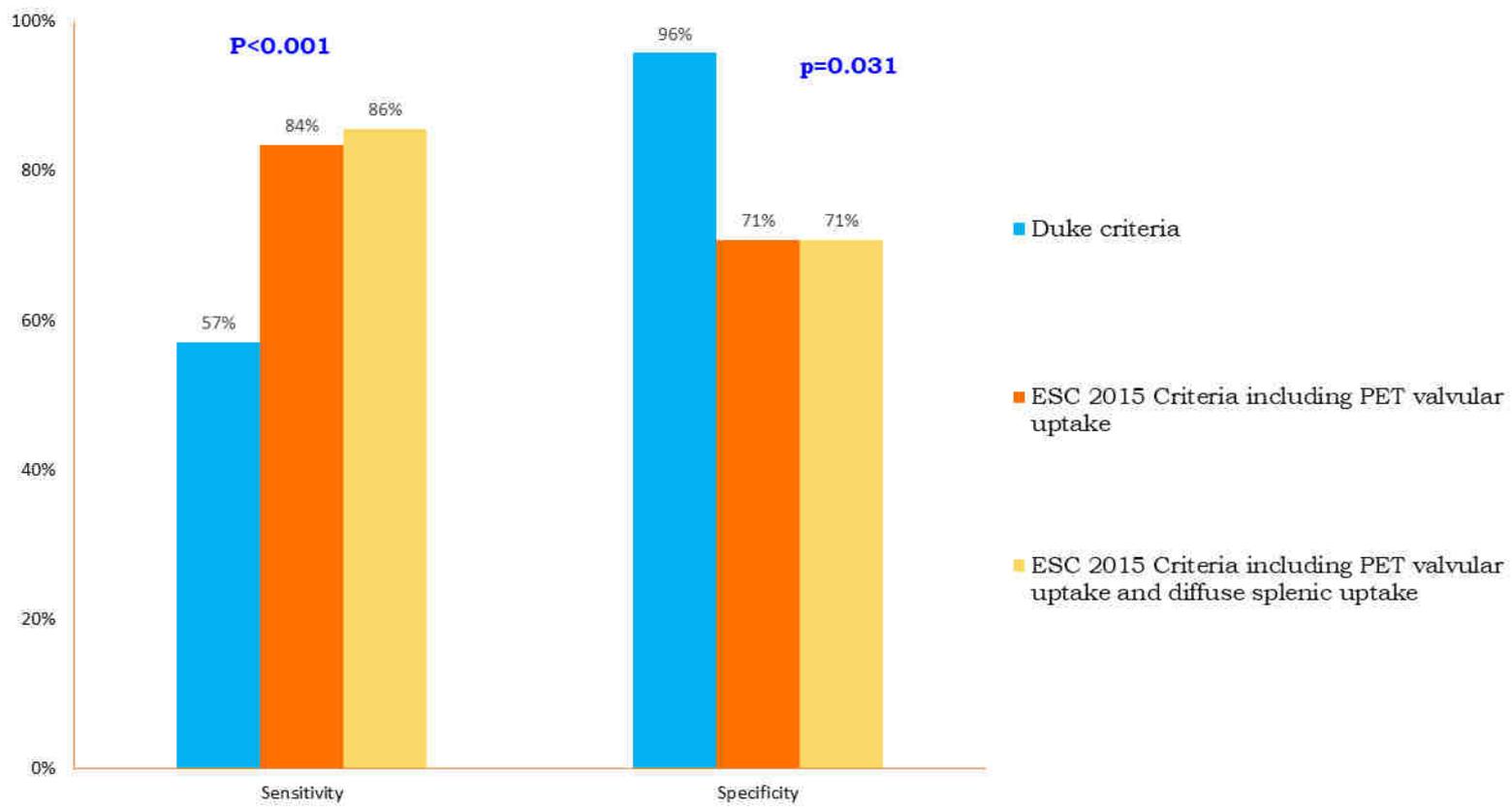
DUKE CRITERIA	FINAL DIAGNOSIS	
	<i>Definite PVE</i>	<i>Rejected PVE</i>
<i>Definite PVE</i>	52 (57.1%)	1 (4.2%)
<i>Possible or rejected PVE</i>	39 (42.9%)	23 (95.8%)
ESC 2015 CRITERIA		
	Definite PVE	Rejected PVE
<i>Definite PVE</i>	76 (83.5%)	7 (29.2%)
<i>Possible or rejected PVE</i>	15 (16.5%)	17 (70.8%)

**Sensitivity 57.1% Specificity 95.8%**

**Sensitivity 83.5% Specificity 70.8%**

**Adding <sup>18</sup>F-FDG PET/CT increases the sensitivity of Duke criteria but decreases their specificity**





**Table 1. Baseline characteristics of the 115 patients with PVE suspicion.**

<b>TABLE1. Patients characteristics</b>	<b>All (n=115)</b>	<b>Definite PVE (n=91)</b>	<b>Rejected PVE (n=24)</b>	<b>p-value</b>
<b>Demographic and clinical data</b>				
Age, (years, range)	70 [22-89]	69 [22-89]	75 [53- 89]	0.069
Male sex, n (%)	75 (65.2)	58 (63.7)	17 (70.8)	0.516
Charlson comorbidity index (n, range)	4 [0-19]	4 [0-19]	4 [0-8]	0.694
Aortic prosthesis, n (%)	81 (70.4)	64 (70.3)	17 (70.8)	0.962
Mitral prosthesis, n (%)	48 (41.7)	37 (40.7)	11 (45.8)	0.647
Pacemaker (ICD), n (%)	28 (24.3)	21 (23.1)	7 (29.2)	0.536
Defibrillator (ICD), n (%)	2 (1.7)	1 (1.1)	1 (4.2)	0.375
Diabetes mellitus, n (%)	28 (24.3)	22 (24.2)	6 (25.0)	0.933
History of atrial fibrillation, n (%)	52 (45.2)	44 (48.4)	8 (33.3)	0.189
History of stroke, n (%)	7 (6.1)	7 (7.7)	0 (0.0)	0.342
History of IE, n (%)	25 (21.7)	17 (18.7)	8 (33.3)	0.122
HIV, n (%)	2 (1.7)	1 (1.1)	1 (4.2)	0.375
Renal insufficiency, n (%)	17 (14.8)	13 (14.3)	4 (16.7)	0.752
Cancer, n (%)	16 (13.9)	14 (15.4)	2 (8.3)	0.517
Heart failure, n (%)	16 (13.9)	12 (13.2)	4 (16.7)	0.741
<b>Biological data, mean(range)</b>				
Creatinine, micromol/L	61 [46-93]	51 [38-71]	90 [60-120]	0.040*
Leukocytes count, G/L	14.5 [2.2-86]	14.0 [2.6-86.0]	16.4 [2.2-86.0]	0.529
CRP, mg/L	79.3 [1-321]	81.7 [1-321]	70.3 [1-235]	0.515
<b>Microbiological data</b>				
Positive blood cultures, n (%)	77 (67.0)	69 (75.8)	8 (33.3)	<0.001*
- <i>Enterococcus species</i> , n (%)	17 (14.8)	17 (18.7)	0 (0)	0.021*
- <i>Staphylococcus aureus</i> , n (%)	13 (11.3)	13 (14.3)	0 (0.0)	0.067*
- Coagulase negative staphylococci, n (%)	7 (6.1)	7 (7.7)	0 (0.0)	0.343
- <i>Oral streptococci ans and Streptococcus gallolyticus</i> , n (%)	16 (13.9)	14 (15.4)	2 (8.3)	0.517
- Other bacteria, n (%)	24 (20.9)	18 (19.8)	6 (25.0)	0.655
Negative blood cultures	38 (33.0)	22 (24.2)	16 (66.7)	<0.001*
<b>Echocardiographic data</b>				
LVEF (%), mean (range)	56 [25-73]	56 [25-70]	56 [25-73]	0.761
Positive echocardiography, n (%)	71 (61.7)	62 (68.1)	9 (37.5)	0.006*
Vegetation, n (%)	37 (32.2)	35 (38.5)	2 (8.3)	0.005*
Abscess, n (%)	9 (7.8)	9 (9.9)	0(0)	0.200
Other perivalvular complications, n (%)	12 (10.4)	10 (11.0)	2 (8.3)	1.000
<b>Surgery, n (%)</b>	31 (27.0)	28 (30.8)	3 (12,5)	0.073
<b>Embolism (clinical / TDM / MRI), n (%)</b>	31 (27.0)	31 (34.1))	0 (0)	<0.001*
Relevant population characteristics data. Abbreviations : PVE: Prosthetic valve endocarditis, ICD: Intracardiac device, HIV: Human Immunodeficiency Virus. CRP: C-reactive protein. LVEF: left ventricular ejection fraction				

**TABLE 2: Interobserver and intraobserver reproducibility**

	<b>Intraobserver reproducibility</b> <b>Kappa coefficient</b> <b>(95% confidence interval)</b>	<b>Interobserver reproducibility</b> <b>Kappa coefficient</b> <b>(95% confidence interval)</b>
PET interpretability	K = 0.61 (0.18 to 1)	K = 0.67 (0.52 to 0.82)
Major PET criteria (valvular uptake)	K = 0.84 (0.32 to 1)	K = 0.63 (0.45 to 0.81)
Minor PET criteria	K = -0.11 (-0.59 to 0.38)	K = 0.54 (0.37 to 0.71)
Diffuse splenic uptake	K = 0.63 (0.14 to 1)	K = 0.22 (0.05 to 0.40)

\*Weighted kappa for ordinal variables

**Table 3:** Comparison between patients with **Positive versus Negative PET** among the 91 cases of definite PVE

	<b>PET + (n=67)</b>	<b>PET - (n=24)</b>	<b>p value</b>
<b>Demographic and clinical data</b>			
Age, (years, range)	68 [22-88]	74 [58- 89]	0.026
Male sex, n (%)	40 (59.7)	18 (75.0)	0.181
Charlson comorbidity index (n, range)	4 [0-8]	5 [2-19]	0.156
Aortic prosthesis, n (%)	47 (70.1)	17 (70.8)	0.950
Mitral prosthesis, n (%)	30 (44.8)	7 (29.2)	0.182
Pacemaker (ICD), n (%)	14 (20.9)	7 (29.2)	0.409
Defibrillator (ICD), n (%)	1 (0.0)	0 (0.0)	1.000
Diabetes mellitus, n (%)	14 (20.9)	8 (33.3)	0.222
History of atrial fibrillation, n (%)	35 (52.2)	9 (37.5)	0.215
History of stroke, n (%)	5 (7.5)	2 (8.3)	1.000
History of IE, n (%)	12 (17.9)	5 (20.8)	0.766
HIV, n (%)	1 (1.5)	0 (0.0)	1.000
Renal insufficiency, n (%)	9 (13.4)	4 (16.7)	0.738
Cancer, n (%)	9 (13.4)	5 (20.8)	0.510
Heart failure, n (%)	11 (16.4)	1 (4.2)	0.172
<b>Biological data, mean(range)</b>			
Creatinine, micromol/L	123 [36-409]	99 [61-120]	0.043
Leukocytes count, G/L	18 [2.6-86.0]	21 [2.2-86.0]	0.698
CRP, mg/L	81.7 [1-321]	70.3 [1-235]	0.034
<b>Microbiological data</b>			
Positive blood cultures, n (%)	50 (74.6)	19 (79.2)	0.656
- <i>Enterococcus species</i> , n (%)	13 (19.4)	4 (16.7)	1.000
- <i>Staphylococcus aureus</i> , n (%)	10 (14.9)	3 (12.5)	1.000
- Coagulase negative <i>Staphylococcus</i> , n (%)	5 (7.5)	2 (8.3)	1.000
- <i>Streptoc. species (viridans and gallolyticus)</i> , n (%)	10 (14.9)	4 (16.7)	1.000
- Other bacteria, n (%)	12 (17.9)	6 (25.0)	0.552
Negative blood cultures	17 (25.4)	5 (20.8)	0.656
<b>Echocardiographic data</b>			
LVEF (%), mean (range)	56 [25-70]	59 [40-69]	0.131
Positive echocardiography, n (%)	51 (76.1)	11 (45.8)	0.006
Vegetation, n (%)	28 (41.8)	7 (29.2)	0.275
Abscess, n (%)	8 (11.9)	1 (4.2)	0.436
Other perivalvular complications, n (%)	8 (11.9)	2 (8.3)	1.000
<b>Surgery, n (%)</b>	<b>23 (34.3)</b>	<b>5 (20.8)</b>	<b>0.304</b>
<b>Embolism (clinical / TDM / MRI), n (%)</b>	<b>25 (37.3)</b>	<b>6 (25.0)</b>	<b>0.324</b>
Abbreviations : PVE: Prosthetic valve endocarditis, ICD: Intracardiac device, HIV: Human Immunodeficiency Virus. CRP: C-reactive protein. LVEF: left ventricular ejection fraction			