F-FDG PET/CT in the diagnosis and management of continuous flow left ventricular assist device infections: A Case Series and Review of the Literature

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ABSTRACT

Implantable continuous flow left ventricular assist devices (LVAD’s) are increasingly used in end-stage heart failure treatment as a bridge-to-transplant and destination therapy. However, LVAD’s still have major drawbacks, such as infections that can cause morbidity and mortality. Unfortunately, appropriate diagnosis of LVAD-related and LVAD-specific infections can be very cumbersome. The differentiation between deep and superficial infections, is crucial in clinical decision-making. Despite a decade of experience in using fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) to diagnose various infections, its use in LVAD patients remains scarce. In this case series, we review the current evidence in literature and describe our single center experience using 18F-FDG PET/CT for the diagnosis and management of LVAD infections.

Key words: left ventricular assist devices; infection; 18F-FDG PET/CT.

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INTRODUCTION

Continuous-flow left ventricular assist devices (LVAD’s) are increasingly used as bridge-to-transplantation and/or destination therapy\(^1\). However, driveline and pump infections remain a major point of concern, resulting in significant morbidity and mortality. The consequences of a LVAD infection depend on the location, depth and the severity of the infection. There is currently no gold standard test available for the detection of the exact site of infection or to monitor the response to treatment of LVAD infections\(^2\).

The International Society for Heart and Lung Transplantation (ISHLT) has proposed standard criteria for the clinical, microbiologic, and radiologic diagnosis of infection in LVAD patients\(^2\). These definitions allow for comparative analysis of time course, incidence, outcome, and risk factors for infection in VAD recipients.

However, data regarding the optimal imaging technique to detect infection and monitor the response to treatment in these patients is lacking. In this regard ultrasound imaging and computed tomography angiography can be helpful in detecting fluid collections around drivelines, cannula’s and pump. Historically, nuclear imaging modalities described in case series about LVAD infections, are \(^{99m}\text{Tc}-\text{leucocyte and 67 Gallium scintigraphy}\(^3\)\(^-\)\(^4\). However nowadays \(^{18}\text{F}-\text{Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT)}\) is increasingly used in the diagnostic work-up of infectious endocarditis, especially in the detection of metastatic and primary extra-cardiac infections\(^5\). Despite a decade of experience in using \(^{18}\text{F-FDG PET/CT}\) to diagnose various infections, it’s use in LVAD remains scarce\(^6\)\(^-\)\(^8\).

In this case series, we describe our single center experience using \(^{18}\text{F-FDG PET/CT}\) in the diagnosis and management of LVAD infections. Additionally, we have conducted a literature review on LVAD related and specific infections and the use of diagnostic nuclear imaging with \(^{18}\text{F-FDG PET/CT}\) scans.
METHODS

Patients:
All consecutive HeartMate II (HMII) implantations performed between January 2011 (PET-CT camera installed in the hospital) and May 2016 in our tertiary referral center were reviewed. These data were extracted from the ongoing EuroMacs Registry (European Registry for Patients with Mechanical Circulatory Support) database. Patients have agreed with the registry and signed the informed consent. The patients who had 18F-FDG PET/CT scintigraphy to investigate suspected LVAD related or LVAD specific infections were included in this case series. Their clinical courses were reviewed, including medical history, comorbidities, microbiological and laboratory investigation, and imaging results (Table 1). We categorized these patients into three groups based on their clinical, microbiological and nuclear imaging characteristics: (A) persistent LVAD-specific infection with positive blood cultures, (B) persistent LVAD-specific infection with negative blood cultures and (C) fever of unknown origin with negative blood cultures and swab.

18F-FDG PET/CT imaging:
All 18F-FDG PET/CT images were acquired using a Siemens Biograph mCT (Siemens Medical Solutions USA Inc., Malvern, PA). Data were iteratively reconstructed (3 iterations, 21 subsets and 5 mm Gaussian filter) using time-of-flight information and resolution recovery. Low dose CT was used for attenuation correction. The protocol of patient preparation and scanning was according to the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) guidelines. As we were interested in imaging of infection near the myocardium it was important to avoid physiological uptake of glucose by normal myocardium cells. Therefore a low carbohydrate diet for 24h prior to the PET/CT study was recommended to switch the myocardium from using glucose as an energy source to using fatty acids, this is one of the options to reduce physiological myocardial uptake as suggested in the mentioned guidelines. In short: patients had a low carbohydrate diet during one day before the regular fast of 6 hours. 2,3 MBq/kg bodyweight 18F-FDG.
was administered after which patients were resting in a quiet and warm waiting room (to avoid uptake in muscles, brown fat etc.). Imaging started 60 minutes after administration. Low dose CT was directly followed by PET imaging: the latter for 3 min/bed position for patients < 70 kg and for 4 min/bed position for patients > 70 kg. This meant total imaging time of about 30 minutes for scintigraphy from skull to groin. Interpretation of scans was performed on both for attenuation corrected and non-corrected images to avoid false positive judgment caused by artefacts introduced by attenuation correction.

**Literature search:**
Additionally, we performed a PubMed/Medline search by using MeSH terms focusing on articles on LVAD related and LVAD specific infections and on use of diagnostic nuclear imaging with $^{18}$F-FDG PET/CT scans. Basic information collected included journal, author, year published, number of patients, and types of LVAD. Specific data collected included the clinical problem, method(s) of (nuclear) imaging and outcome.

**RESULTS**
Fifty-one HeartMate II implantations were performed in 48 patients between January 2011 and May 2016. In 9 patients (7 males; mean age 54 ± 15 years) with suspected LVAD related infections, a total of 10 $^{18}$F-FDG PET/CT's were performed. The primary indications for LVAD implantation were bridge-to-transplant (8/9) and destination therapy (1/9).

The median duration of LVAD support from implantation or exchange to $^{18}$F-FDG PET/CT was 134 days [range 24-645 days]. The long-term mortality rate was 11%. A (semi-)urgent listing for heart transplantation due to infectious complications was needed in four patients (44%), after a median of 59 days [range 49-200] after the first PET/CT. The detailed clinical characteristics of all patients are summarized in Table 1.

Overall, we describe 9 patients with suspected LVAD infection, either pump and/ or driveline; in 33% blood cultures were positive, in 44% wound cultures were positive. $^{18}$F-FDG PET/CT was performed to establish and determine the extent of LVAD related or specific infections. In 3 patients we performed
the $^{18}$F-FDG PET/CT within 90 days postoperative (= short term) and in 6 patients the $^{18}$F-FDG PET/CT was performed at longer term follow-up. Sixty-seven percent of the patients had unexpected extensive deep infections. In 2/9 patients, $^{18}$F-FDG PET/CT was able to rule out any LVAD related or specific infections, both very early (24 and 29 days respectively) in the postoperative phase. In only one patient there was an isolated pump inflow cannula infection (see Table 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A138).

A. Persistent LVAD-specific infection with positive blood cultures: This type of infection was observed in three patients (see Table 1; case A I, II and III), in which $^{18}$F-FDG PET/CT scans were performed due to recurrent positive blood cultures despite antibiotic therapy for 3 to 6 weeks. In case I (AI in Table 1), the connection between the inflow cannula and the pump body was detected as the source of LVAD infection (Figure 1A). Unfortunately, replacing the LVAD would have been a very high risk operation because of a previous LVAD replacement due to driveline fracture. The patient was placed on the high urgency list for heart transplantation, and was transplanted 49 days later under antibiotic treatment. After explantation of the LVAD, debris was found in the connection between inflow cannula and the pump housing (Figure 1B). Microscopy showed the same monoculture of Staphylococcus epidermidis as in patient's previous cultures. The patient is currently doing well and has not experienced any severe infections 3 years after heart transplantation.

In case AII this 67-years-old male LVAD patient was admitted 175 days after LVAD exchange by sternal infection with CNS bacteremia. Ongoing deep infection despite AB therapy proved by $^{18}$F-FDG PET/CT led to semi-urgent heart transplantation. The interval after LVAD removal and heart transplantation was complicated by infection, and bacteremia with Enterobacter aerogenes detected in fluid aspirated from the substernal region and in the explanted drive line. A reoperation to address a possible mediastinitis was considered and planned. At day seventeen post-heart transplantation, a newly performed $^{18}$F-FDG PET/CT showed a hot spot just caudal to the sternum, which was a non-encapsulated fluid collection from which the same Enterobacter species was cultured after an
ultrasound-guided puncture. The former drive line route was no longer considered as infected and the planned operation for a mediastinitis was cancelled. The patient has had no infectious problems at 31 months of FUP post HTx.

In one patient (case AIII; Figure 2) osteomyelitis was detected at the level of the 5th lumbar vertebra (L5), in addition to a LVAD and drive line infection. Unfortunately, due to severe infection, he became a destination therapy patient and died after acute LVAD failure 1219 days after implantation. Large bacterial growths were found at the insertion opening of the drive line, and around the LVAD on autopsy. The treatment of the rest of this group of patients varied according to the findings from 18F-FDG PET/CT placement on urgent transplantation list, to continued antibiotic therapy with or without vacuum-assisted-closure (VAC) therapy.

B. Persistent LVAD-specific infection with negative blood cultures: As shown in Figure 3 the 3 patients found in this group (cases B-I to BIII; Table 1). In this group of 3 patients clinical symptoms of infection that progressed during antibiotics (AB) therapy, despite negative blood cultures, the clinical signs and symptoms of infection were progressive during AB. Figure 3 is an example from this group of patients. These patients (Table 1) were all admitted or unable to be discharged after LVAD implantation due to fever with negative blood cultures. The time between implantation of LVAD and 18F-FDG PET/CT varied from 37 days to 371 days. 18F-FDG PET/CT showed infection of different parts of the LVAD and/or deep drive line infection despite negative blood cultures while patients had persistent fever.

Ongoing AB therapy was accepted in case BI due to extended LVAD specific infection 37 days after HM II concomitant with aortic valve replacement (AVR). This patient had no deterioration of chronic infection at follow-up of 831 days on continuing LVAD support.

In case BII there was persisting driveline infection with Staphylococcus aureus 40 days after implantation until heart transplantation and despite several antibiotic regimens and surgical interventions. The abscess around the driveline exit was drained and treatment with intravenous
flucloxacillin was started. However, she developed recurring cellulitis and the cultures taken from the driveline entrance remained positive despite antibiotic treatment. A 18F-FDG PET/CT showed high intensity in the abdominal segment due to FDG accumulation along the driveline route. Two hundred days after LVAD implantation she underwent heart transplantation and is still doing well.

In case BIII (Figure 3A) a 61-year-old male with LVAD was admitted with a suspected driveline infection due to cellulites of the abdominal skin at the driveline exit. The cultures showed Staphylococcus aureus in the driveline exit, but blood cultures were negative. An abdominal ultrasound was performed which showed an infiltrated aspect of the skin. After 16 days of antibiotic therapy the fluid collection around the driveline decreased. The 18F-FDG PET/CT showed subcutaneous fat infiltration along the driveline with abnormal FDG accumulation. There was no other suspicion of infection beside this deep driveline infection on 18F-FDG PET/CT. The patient was listed for urgent heart transplantation. Despite antibiotic therapy a control 18F-FDG PET/CT showed extension of increased uptake in the infected region; from the driveline exit to the outflow cannula (Figure 3B). He was transplanted 5 days after the 18F-FDG PET/CT scan. Postoperative cultures of the LVAD showed Staphylococcus aureus and Candida species.

C. LVAD patients with fever of unknown origin and negative cultures: in these three patients 18F-FDG PET/CT was used following negative blood and swab cultures to either detect or excluded LVAD specific or related infection and detect other causes for fever. The first patient (CI in Table 1) is a 75-year-old female who received a LVAD as destination therapy (DT). She was previously admitted with superficial sternum infection and was treated with empirical AB therapy, however she was re-admitted with fever and progression of the sternal wound infection. The 18F-FDG PET/CT showed an infected system and mediastinitis due to migration of the infection. She was treated with VAC therapy and AB because of a diffuse infected pump, driveline and mediastinum. There was no other infection unrelated to LVAD, particularly not around the implantable cardioverter defibrillator (ICD). At an optimal moment after VAC therapy an rectus abdominis muscle flap reconstruction was performed 82 days after initiation.
of AB and VAC therapy to reconstruct the sternal wound. Figure 4 shows this case as an example of the worst case scenario for persisting progressive sternum infections with negative cultures during antibiotic therapy.

The second patient (C II in Table 1) is a 54-year-old man (Figure 5) with LVAD and concomitant aortic valve replacement (AVR) who was admitted to cardiac ICU due to driveline fracture with recurrent LVAD alarms more than two years post LVAD implantation. Due to driveline dysfunction the LVAD device was exchanged. Three days after surgery due to fever and increased infection parameters, diagnostic CT thorax was performed which showed signs of empyema of the left pleural space. It was treated by thoracic drainage and 

vancomycin, cefuroxim, clindamycin and rifampicin for two weeks (blood cultures showed growth of Micrococcus luteus and Staphylococcus aureus). After discontinuation of intra-venous (i.v.) AB, oral clindamycin was continued for one month. A \(^{18}\)F-FDG PET/CT was performed 24 days after LVAD exchange to monitor the infection and the effect of treatment. There were no signs of an infected LVAD or active infections elsewhere. He is currently alive on LVAD support for more than 3 years.

The last patient (C-III; 40-years-old male) with LVAD and AVR was admitted for recurrent cardiac tamponade. Due to persisting fever on day 19 post LVAD implantation a thoracic CT scan was done, showing air bubbles in the pericardium which was concluded to be a normal postoperative effect. Ten days later, after initiation of broad spectrum AB for two weeks, a \(^{18}\)F-FDG PET/CT was performed which ruled out LVAD infections and/or prosthetic valve endocarditis. After 410 days on LVAD support, he has no signs of infection at the outpatient clinic.

DISCUSSION

In this paper, we present nine different LVAD patients who suffered from clinically suspected or proven infections in which \(^{18}\)F-FDG PET/CT imaging supported clinical decision making in LVAD specific and related infection. To our best knowledge, our case series contains yet the largest population of HMII patients ever managed by \(^{18}\)F-FDG PET/CT. However, limited data exists regarding the
management and outcomes of LVAD infections. In the current literature, we found only four studies with case reports and series with a total of 47 cases: two case reports and two case series with $^{18}$F-FDG PET/CT were published between 2013 and 2016. The findings of these four studies are summarized in Table 2.

One of the major drawbacks for long-term LVAD support are LVAD specific and LVAD related infections resulting in high risk of morbidity and mortality. Prompt diagnosis of LVAD related infections can be particularly challenging in cases involving pump of cannula infections, pocket infections and/or deep sternal wound or mediastinal infections. Innovations in cardiovascular imaging strategies have emerged to resolve these issues such as: multi-slice CT, 3D echocardiography, $^{18}$F-FDG PET scan, molecular imaging, and cardiac magnetic resonance.

$^{18}$F-FDG PET/CT appeared to be a useful nuclear imaging diagnostic tool to assess LVAD infections. In a clinical study of 31 LVAD patients, $^{18}$F-FDG PET/CT had a sensitivity of 100% and a specificity of 80% of $^{18}$F-FDG PET/CT in detecting infections of LVAD components, both in patients with and without obvious infection. In our current case series we found a sensitivity and specificity of 100% in 9 HMII patients including early and very early performed $^{18}$F-FDG PET/CT in contrast to previous studies and recommendations. Additionally, the timing when to perform a $^{18}$F-FDG PET/CT varies greatly in the current literature (Table 2). Even though our sample size is small, $^{18}$F-FDG PET/CT was able to evaluate and rule out LVAD infections as early as three weeks post-implantation, in contrast to the current paradigm of waiting three to six months after LVAD implantation. This was in line with the first paper on nuclear imaging in 8 HM II patients with suspected infection (mean durations after implantation 54 days) without any false positive result. In our case series $^{18}$F-FDG PET/CT was used to detect the site and extent of infection and to guide duration of antibiotic treatment in 7 of 9 patients, (Table 1). The study accurately ruled out infection in 2/9 patients. Therefore, given the clinical experience in the current literature and our paper, we believe that $^{18}$F-FDG PET/CT is a crucial imaging
tool in the diagnosis and management in infection specific and related to LVAD patients. However, some issues remain unresolved and require further investigation.

The optimal conditions for $^{18}$F-FDG PET/CT acquisition that allows us to improve the image contrast and to better discriminate between positive and negative scans, have to be further determined. $^{18}$F-FDG PET/CT could have a widespread use based on practical reasons, however it is limited by meticulous test preparation with low-carbohydrate diet. In the latter circumstance, physiological myocardial uptake can be seen, reducing the specificity of scan findings. It is therefore unfortunate that among all of the studies reported so far, only two included a high fat, low-carbohydrate diet in addition to the fasting period in the patients’ preparation. Furthermore, image analysis should be standardized regarding both the pattern and the quantification of the uptake. Additionally, the impact of factors such as antibiotic treatment and the type of infective agent needs to be evaluated more precisely. The initiation of antibiotic therapy and, if present, its duration prior to imaging is likely to alter the inflammatory response of the host and thus FDG uptake\textsuperscript{5}. Also, it is acknowledged that some bacteria strains may escape immune response either by producing a biofilm on prosthetic material, or by using an intracellular cycle, allowing them to be hardly detectable by immune cells\textsuperscript{7}.

The timing of $^{18}$F-FDG PET/CT remains controversial due to recent surgery\textsuperscript{13}. Nevertheless, in our small cohort there is a promising use of this imaging technique to rule out function even in an early postoperative period (3 to 6 weeks). Larger studies and comparisons are needed to optimize timing of $^{18}$F-FDG PET/CT when there is an ongoing suspicion of LVAD specific infections without source control in both in the outpatient and inpatient setting. In particular, it is important to define who are the patients that would benefit the most from this test according to their probability of infection based on clinical evaluation, echo(cardio)graphy results and risk factors for development of infection during LVAD support.
CONCLUSION

In this case series of nine patients with continuous flow-LVAD type HeartMate II, $^{18}$F-FDG PET/CT imaging provided accurate information on the localization and extent for LVAD specific and/or related infections as early as 3 weeks post-implantation. Review of the current literature with two case reports and two case series with a total of 47 cases, confirms the promising role of this novel imaging modality.

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REFERENCES


Table and figure legends

Table 1. Overview of all patients with a left ventricular assist device needing $^{18}$F-FDG PET/CT’s in the correct localization of infections. Clinical, microbiologic and nuclear imaging characteristics.

Table 2. Overview of all published studies on left ventricular assist device related infections and $^{18}$F-FDG PET/CT.

Figure 1A. Case AI: $^{18}$F-FDG PET/CT images of a high FDG ring around the inflow cannula of the LVAD. Banded ring with high degree of accumulation in the connection part of the inflow cannula with the housing.

Figure 1B. Case AI: Picture of the debris we found in the connection between inflow cannula and pump housing (hands of APWMM).

Figure 2. Case AIII; 59-years-old man with inflammation of driveline, subcutaneous part as well as intra-abdominal portion close to pump housing. Beside this there is a strongly suspected osteomyelitis of Lumbar vertebra L5.

Figure 3A. Case BIII, 61-years-old male with example of a deep driveline infection; Driveline in situ with subcutaneous fat infiltration visible around the course of the line in the abdominal wall (dotted green arrows).

Figure 3B. In case B III, the second $^{18}$F-FDG PET/CT showed 54 days later persisting and increased metabolic activity around the subcutaneous driveline in abdominal wall. Furthermore appearance of increased metabolic activity around the outflow cannula of the LVAD near to ascending aortae (green arrows).

Figure 4. Case CI: 74-years-old female with mediastinitis in diffuse LVAD infection after re-admission due to progressive clinical signs of sternal wound infection during antibiotic treatment.
Figure 5. Case CII; 54-years-old male 24 days after LVAD exchange (678 days on support) PET/CT guided exclusion of active infection. Mild increased activity around the pleural fluid in the right lung, as well as slightly increased activity in multiple mediastinal and hilar lymph nodes bilaterally as well as in pleural nodular; all possible still reactive. There is no focus of infection. Other finding is subcutaneous emphysema with pneumothorax right sided.
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<td>Fever of unknown origin. CRP: 27; Leuco’s: 8; LDH: 497</td>
<td>Driveline: negative Blood: Staph. epidermidis (CNS)</td>
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<td>Clinical: Fever of unknown origin Culture: CNS bacteremia PET/CT: Inflow cannula infection</td>
<td>Prolonged AB; High Urgent HTx due to persisting positive blood cultures (49 days after PET-CT)</td>
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<td>Superficial sternal infection CRP 26; Leuco’s 3; LDH 225</td>
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<td>AIII</td>
<td>59/Male/ICM</td>
<td>645 days</td>
<td>Fever and hemolysis complicated by CVA CRP 86; Leuco’s 12; LDH 1817</td>
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<td>Sternal wound infection CRP 12; Leuco’s 7; LDH 251</td>
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<td>Clinical: Sternal wound infection Culture: Candida parapsilosis, CNS and Propionibacterium acnes PET/CT: pump connection to the heart, sternum and driveline infection</td>
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<td>BI1</td>
<td>26/Female/DCM</td>
<td>182 days</td>
<td>Recurrent driveline exit infection CRP 33; Leuco’s 10; LDH 267</td>
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<td>Driveline infection</td>
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<td>Negative</td>
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**AB, antibiotics; CNS, coagulase negative *Staphylococcus epidermidis*; CRP, C-reactive protein in mg/L (N<1); d, days; CVA, cerebrovascular accident, DCM, dilated cardiomyopathy; HTx, heart transplantation; ICM, ischemic cardiomyopathy; Leuco’s, Leucocytes in 10^9/L (N=3.5-10); LDH, Lactate dehydrogenase (N<247); LVAD, left ventricular assist device; VAC, vacuum-assisted-closure therapy.**
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<td>Case report</td>
<td>2015</td>
<td>Eur Heart J Cardiovasc Imaging.</td>
<td>Takeo Fujino et al.</td>
<td>DuraHeart (1)</td>
<td>1</td>
<td>240 and 30 days after AB</td>
<td>2 18F-FDG PET/CT • 1 TP • 1 TN</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Case series</td>
<td>2016</td>
<td>Ann Thorac Surg.</td>
<td>Angelo Maria Dell’Aquila et al.</td>
<td>HeartMate II (4) HeartWare (28) Incor (6) Ventracor (2)</td>
<td>31</td>
<td>384 ± 348 days</td>
<td>40 18F-FDG PET/CT • 30 TP • 8 TN • 2 FP</td>
<td>(Semi-urgent) HTx (16) Surgical revision (2) Antibiotics (9) Others (3)</td>
</tr>
<tr>
<td>Case series</td>
<td>2016</td>
<td>Current report</td>
<td>HeartMate II (9)</td>
<td></td>
<td></td>
<td>Median 134 days [range 24-645]</td>
<td>10 18F-FDG PET/CT: • 8 TP • 2 TN</td>
<td>(Semi-urgent) HTx (4) Surgical revision / VAC therapy (2) Prolonged antibiotics (7), antifungal (2)</td>
</tr>
<tr>
<td>Summary</td>
<td>2013-2016</td>
<td></td>
<td></td>
<td>HeartMate II (18) HeartWare (29) Rest (9)</td>
<td>47</td>
<td></td>
<td>58 18F-FDG PET/CT • 44 TP • 12 TN • 2 FP</td>
<td>(Semi-urgent) HTx (23; 41%) Surgical revision (7; 13%) Antibiotics (19; 34%) Others (7; 13%)</td>
</tr>
</tbody>
</table>

HTx denotes Heart transplantation; FP, false positive; TN, true negative; TP, true positive.


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Figure 1(A).

Figure 1A
Figure 1(B).
Figure 2.
Figure 3.
Figure 4.
Figure 5.