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A prospective case-control validation of procalcitonin as a biomarker diagnosing pacemaker and implantable cardioverter defibrillator pocket infection

Short title: Procalcitonin as a biomarker for diagnosing cardiac device infection

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WHAT´S NEW?

Accurate diagnosis of cardiac implantable electronic device infections and especially pocket infections is of paramount importance in order to avoid delayed removal of infected systems and unnecessary extraction of non-infected systems. Our study prospectively validates the diagnostic utility of procalcitonin (PCT) with a cut-off value of 0.05 ng/ml for the diagnosis of a pocket infection and supports its value in comparison to classic inflammatory markers. PCT

could also be useful for patients who are difficult to diagnose clinically, such as patients pre-treated with antibiotics or with minimal local inflammatory signs. Low PCT values may assist in ruling out pocket infection and avoidance of unnecessary surgical pocket exploration.

ABSTRACT

Background: The diagnosis of device infections, especially pocket infections, is challenging and relies primarily on the clinical presentation. The prospective DIRT (Device associated infections role of new diagnostic tools) study identified procalcitonin (PCT) among 14 biomarkers as the most promising biomarker to aid the diagnosis of pocket infection and identified an optimized cut-off value of 0.05 ng/ml for a localized generator pocket infection.

Aims: The present study aims to validate the proposed PCT cut-off value of 0.05 ng/ml for the diagnosis of pocket infection in an independent cohort.

Methods: We prospectively enrolled 81 patients with pocket infections and 81 age and renal function matched controls presenting for elective device exchange or lead revision. Patients with concomitant infectious or inflammatory diseases, end-stage renal failure, current active malignancy or receiving immunosuppressive therapy were excluded.

Results: An elevated PCT over 0.05 ng/ml was found in 68% (n = 55) of pocket infections and 24% (n = 19) of controls, corresponding to a sensitivity of 68% and a specificity of 77% for diagnosing a pocket infection. In ROC analysis, PCT showed an area under the curve of 0.75 (95% confidence interval, 0.68–0.83; P <0.001). Sensitivity remained high with antibiotic pretreatment (65% c.f. 69% without pretreatment) and in cases with minimal inflammatory signs (67% c.f. 70% with extensive inflammation).

Conclusion: Our study validates the cut-off value of 0.05 ng/ml PCT for diagnosis of a pocket infection, even in patients pre-treated with antibiotics or with minimal clinical signs of inflammation.

Key words: biomarker, cardiac device infection, pocket infection, procalcitonin

INTRODUCTION

Cardiac implantable electronic devices (CIEDs) such as pacemakers, implantable cardiac defibrillators (ICDs) and cardiac resynchronization therapy (CRT) are essential for the treatment of bradyarrhythmias and important elements of optimal, guideline-directed treatment of heart failure and life-threatening tachyarrhythmias [1]. One of the main complications of

CIEDs are cardiac device infections (CDI), which are associated with increased morbidity and mortality as well as increased health care costs [1, 2].

With the increasing number of CIED implants [1] the incidence of CDI is also rising, but unfortunately at a disproportionate rate [3, 4]. The increase in CDI rates has been attributed to the use of more complex devices in a more comorbid and elderly population in whom the risk of infection is intrinsically higher [1, 3, 4]. Preventive measures include perioperative antibiotic therapy and implantation of local antimicrobial agents or a combination of both strategies [5].

To identify patients at risk for CDI in a clinical setting, several risk scores have been proposed [1, 6]; however over 60 studies and several meta-analyses aimed to identify potential risk factors for CDI have yielded inconsistent results [7]. Recently the PADIT score has been developed from a retrospective analysis of over 19 000 patients (from the PADIT trial) [8]. The PADIT score classifies patients at low, intermediate or high risk of CDI based on 5 independent predictors of device infection: age, renal function, immune deficiency, number and type of prior CEID procedures [2].

An international consensus document on the risk assessment, prevention, diagnosis and treatment of CDI has been published to support the diagnosis and management of CDIs [1]. Depending on the extent and severity of the infection, three categories of CDI are distinguished: 1) pocket infections 2) CIED systemic infections 3) lead related infective endocarditis [1]. While CIED systemic infections and lead related infective endocarditis are associated with bacteremia and systemic inflammatory response, pocket infections are limited to the generator pocket [1, 9]. As such, their diagnosis to date relies on clinical judgement based on local inflammation signs, such as erythema, warmth, swelling, tenderness, or, in severe cases, purulent drainage [1, 9].

Given the heterogeneous presentation of patients with pocket infections, often with few or mild symptoms, the diagnosis is often challenging and can be missed in early stages. However, early diagnosis and aggressive treatment of pocket infections is vital to avoid progression to systemic infection, infective endocarditis and sepsis [1]. A pocket infection is a class I indication for complete device system removal [1] and conservative antimicrobial treatment without immediate device removal was associated with a 7-fold increase in 30-day and 3-fold increase in 1-year mortality in multivariate analysis [10]. On the other hand, non-invasive exclusion of pocket infection avoids unnecessary surgical pocket explorations and complications related to device removal [1, 10].

Identification of relevant biomarkers to aid diagnosis of such pocket infection is thus of vital importance. Conventional systemic inflammation parameters, such as leukocytosis, elevated

C-reactive protein (CRP) levels or erythrocyte sedimentation rate, can be indicative of systemic CDIs, but are non-specific and often within normal range in pocket infection [11, 12]. An exploratory biomarker study in confirmed pocket infection cases identified procalcitonin (PCT) as a marker of pocket infection out of 14 different biomarkers including white blood cell count (WBC) and CRP. With ROC analysis and Youden´s statistic an optimized cut-off value of 0,05 ng/mL PCT was identified, 10-fold lower than the established cut-off value of 0.5 ng/mL used clinically for diagnosing sepsis. Using this optimized cut-off value of 0,05 ng/mL, PCT could predict the presence of pocket infection with a sensitivity of 60% and specificity of 82% [12]. The aim of this study is to prospectively validate the PCT cut-off value of 0,05 ng/mL as a biomarker of pocket infection and to assess its sensitivity and specificity in distinguishing pocket infections from infection-free controls. In a secondary analysis, we compare inflammatory markers including PCT between patients with pocket infection and systemic CDI.

METHODS

The trial is designed as a case-control validation study based on a prospective single-center register of a cohort of CIED recipients with and without CIED infection. The study was approved by the local ethic committee and conducted according to the principles of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov with the identifier NCT05007158.

Study population

All patients with confirmed isolated pocket infection, CIED systemic infection or lead related infective endocarditis treated at the German Heart Centre Munich between December 2011 and May 2021 were included. Patients presenting for elective device exchange or planned lead revision without local or systemic infections were selected as controls. Patients with concomitant infectious or inflammatory diseases, recent trauma, surgery, or burns, as well as patients with current active malignancy or receiving immunosuppressive therapy were excluded. Patients with end-stage renal failure (defined as glomerular filtration rate <= 25 ml/min or on renal dialysis) were also excluded. Study group and control group were matched for age and renal function.

All patients were evaluated for the presence of isolated pocket infection, CIED systemic infections and lead related infective endocarditis. Lead-associated infective endocarditis was diagnosed according to modified Duke criteria [13]. CIED systemic infections were diagnosed

as the presence of pocket infection accompanied by bacteremia or echocardiographic finding suggestive of infective endocarditis, but not fulfilling the Duke criteria. Isolated pocket infection was diagnosed in the presence of local signs of inflammation (one or more of erythema, pain, warmth, swelling, induration, tenderness, or fluctuation), wound dehiscence, hardware protrusion or pus discharge at the pocket in the absence of systemic findings. The diagnosis was confirmed by surgical exploration of the generator pocket site.

All patients were treated according to clinical guidelines with a transvenous removal of all hardware material. All patients underwent laboratory workup including PCT, CRP, WBC and peripheral blood cultures at admission before surgery. Microbiological cultures of intraoperative smears, biopsies of pocket tissue, extracted lead tips were obtained for patients with local pocket infection, systemic CIED infection and lead-associated infective endocarditis.

Outcomes

For our primary analysis, we assessed the diagnostic value of PCT in differentiating local pocket infection from infection-free controls and calculated the sensitivity and specificity of the pre-established cut-off value of 0.05 ng/ml. As pre-specified subgroup analyses, we calculated sensitivity and specificity of PCT with a cut-off value of 0.05 ng/ml in patients with and without antibiotic pre-treatment as well as in patients with minimal or extensive local inflammation. Any antibiotic administration before admission was considered antibiotic pre-treatment, irrespective of type or duration of therapy. For the subgroup analysis of minimal or extensive local inflammation, all patients with signs of wound dehiscence or hardware protrusion were excluded, as skin perforation itself is diagnostic for pocket infection [1]. The remaining patients were classified according to the number of local inflammatory signs having a “minimal local inflammation” with up to two local inflammation signs, or having “extensive local inflammation” with more than two signs out of the following: erythema, pain, warmth, swelling, induration, tenderness or fluctuation.

We assessed sensitivity and specificity of the conventional inflammatory markers CRP and WBC with the respective, clinically established, cut-off values of 5 mg/dl and 10^9/L. Finally, we compared the values of all inflammatory markers between local pocket infections and systemic CIED infections and lead-associated infective endocarditis.

Statistical analysis

All statistical analyses were performed using SPSS V22 (IBM Corporation, Armonk, NY, US). Categorical data are presented as absolute and relative frequencies, continuous data as median with interquartile range (IQR). The diagnostic accuracy of PCT with the pre-established cut-off value of 0.05 ng/ml was described by values of sensitivity and specificity. Receiver operating characteristic (ROC) curves were drawn and the area under the ROC curve (AUC) with 95% confidence intervals (95%CI) was calculated. Comparisons were performed using either Pearson's χ^2 or Fisher's exact tests for categorical variables as appropriate. Continuous variables were analyzed using the Mann Whitney U test or the Kruskal-Wallis test as appropriate. We considered a *P*-value <0.05 to result in statistically significant differences.

RESULTS

Baseline characteristics

Between 2011 and April 2021, 81 patients with pocket infection, 23 patients with CIED systemic infection and 34 with lead related infective endocarditis were identified. Another 81 age and renal function matched patients presenting for device exchange or lead revision unrelated to infection were included as controls.

Baseline characteristics are shown in Table 1 and Table 2. There was no significant difference in age, sex, presence of diabetes, kidney failure or device type between the pocket infection group and the control group. The median interval from the previous CIED procedure was shorter in the pocket infection group (0.7 [IQR, 0.1–2.3] years vs. 7.8 [IQR, 3.9–9.6] years; *P* <0.001) as well as the median implant duration (7.4 [IQR, 2.2–13.1] years vs. 9.6 [IQR, 7.2–12.5] years; *P* = 0.03).

Patients with pocket infections had significantly higher PADIT scores than infection-free controls, despite similar age, renal function and CIED device type at presentation (median, 8.5 [IQR, 4.0–9.0] vs. 4.0 [IQR, 2.0–9.0]; *P* = 0.004). This difference was also noted when analyzing the CDI group as a whole, including pocket infections, CIED systemic infections and lead-associated infective endocarditis (6.0 [IQR, 4.9–9.0] for CDI vs. 4.0 [IQR, 2.0–9.0] for controls; *P* = 0.014). Overall, 36% (48/134) of patients with CDI were at low, 19% (26/134) at intermediate and 45% (60/134) at high risk for infection, whereas in the infection-free control group 52% (42/81), 12% (10/81), 36% (29/81) of patients were at low, intermediate and high risk for infection, respectively (Figure 1).

Microbiological results

A pathogen was identified in 82% (66/81) of the pocket infection group. Of patients with a pocket infection 76% (60/79) had a positive culture from an intraoperative smear, 63% (50/79) from extracted lead tips and 60% (4/67) from a tissue biopsy of the infected pocket. Patients with lead-associated infective endocarditis had positive blood cultures in 88% (30/34) of cases, positive lead tip cultures in 42% (14/33), positive intraoperative smears in 19% (6/31) and positive tissue biopsy culture in only 7% (1/14). Patients with CIED systemic infections had high rates of positive cultures from intraoperative smears (86%, 18/21) and tissue biopsies (85%, 17/20) similar to pocket infections, but had higher rates of positive blood cultures (52%, 12/23) and culture-positive lead tips (77%, 17/22).

The results of the microbiological cultures are shown in supplemental Table 1. The most commonly identified bacteria in pocket infection were coagulase-negative staphylococci. Most systemic CIED infections had a similar bacterial spectrum as pocket infections, whereas staphylococcus aureus was the predominant pathogen in lead-associated infective endocarditis and some systemic CIED infections.

Antibiotic pretreatment was frequent in patients with lead-associated infective endocarditis (91%, 31/34), but also present in about one third of patients with systemic CIED infections (39%, 9/23) and with isolated pocket infection (32%, 26/81). Patients with pocket infections pre-treated with antibiotics received antibiotics for a median of 3 (IQR, 2.0–6.3) days. Cefuroxime was most commonly prescribed (31%, 8/26), followed by Ampicillin/Sulbactam (14%, 4/26) and Ceftriaxone (8%, 3/26) or Piperacillin/Tazobactam (8%, 3/26).

Biomarkers for diagnosing a pocket infection

Median values of the biomarkers PCT, CRP and leukocytes are shown in table 3. The PCT level was significantly elevated in all 3 sub-types of CIED infection compared to the control group (Figure 2).

Prognostic value of PCT cut-off value 0.05 ng/ml

An elevated PCT over 0.05 ng/ml was found in 68% (55/81) of pocket infections, 78% (18/23) of CIED systemic infections, 88% (30/34) of lead-associated infective endocarditis and 24% (19/81) of controls. Using the pre-defined cut-off value of 0.05 ng/ml PCT had a sensitivity of 75% and a specificity of 77% for diagnosing any CDI (pocket infections, CIED systemic infections and lead-associated infective endocarditis, positive predictive value (PPV) 84%, negative predictive value (NPV) 64%; P <0.001). In ROC analysis PCT showed an AUC of 0.81 (95% CI, 0.76–0.87; P <0.001) for differentiating CDI from controls (Figure 3A).

The sensitivity and specificity for PCT dichotomized at 0.05 ng/ml PCT for discrimination of isolated pocket infections from controls was 68% and 77%, respectively (P <0.001, Table 4). The ROC analyses revealed an AUC of 0.75 (95% CI, 0.68–0.83; P <0.001, Figure 3B and Table 4). Thus, the results are in line with those of the former DIRT study (Figure 4).

To further assess the diagnostic value of PCT with a cut-off of 0.05 ng/ml for identifying local pocket infections, a subgroup analysis of patients pre-treated with antibiotics and patients with minimal local signs of inflammation was performed. The results are summarized in Table 4 and Figure 3C–F. Analyzing only treatment-naïve patients PCT with a cut-off value of 0.05 ng/ml had a sensitivity of 69% for detecting local pocket infections, whereas it fell to 65% in patients with antibiotic pre-treatment. Comparing patients with extensive and minimal signs of inflammation the cut-off value of 0.05 ng/ml PCT yielded a specificity of 70% and 67%, respectively. Similarly, the ROC analyses for PCT showed an AUC of 0.78 (95% CI, 0.69–0.86; P <0.001) and 0.70 (95% CI, 0.57–0.84; P = 0.002) for patients with without and with antibiotic pre-treatment as well as 0.77 (95% CI, 0.68–0.86; P <0.001) and 0.75 (95% CI, 0.54–0.96; P =0.014) for patients with pronounced or discrete local inflammation signs, respectively.

Conventional biomarkers (leukocytosis and CRP)

Leukocytosis, defined as leukocyte levels above 10^9/L according to routine clinical cut off values, had a similar incidence in pocket infection and controls (12% vs. 4% respectively; P = 0.079). Leukocytosis was more common in patients suffering from CIED systemic infections and from lead-associated infective endocarditis, affecting 22% (5/23) and 35% (12/34) respectively. The sensitivity of leukocytosis for diagnosing a local pocket infection was 12%, the specificity 96% (PPV, 77%; NPV, 52%; P = 0.079).

An elevated CRP over 5 mg/dl was found in 14% of controls, 49% of pocket infections, 61% of CIED systemic infections and 100% of lead-associated infective endocarditis, P <0.001. The sensitivity of CRP with a cut-off of 5 mg/dl for diagnosing a local pocket infection was 49%, the specificity 86% (PPV, 78%; NPV, 63%; P <0.001).

DISCUSSION

In the present study, we aimed to prospectively validate the diagnostic value of PCT with an optimized cut-off of 0.05 ng/ml for diagnosing CIED pocket infections in a real-world setting. This optimized cut-off value is 10-fold lower than the established cut-off used for diagnosing sepsis. We found that PCT with the cut-off of 0.05 ng/ml had a sensitivity of 68%, a specificity of 77%, PPV of 74% and a NPV of 71% for detecting a local pocket infection. These results

are in line with the exploratory study that identified PCT as a promising biomarker to diagnose local pocket infection, which found a sensitivity of 60% and a specificity of 82% for PCT with a cut-off of 0.05 ng/ml (Figure 4) [12].

Age and renal impairment can influence inflammation and therefore PCT levels, this potential bias was minimized by matching the control group for these two variables. Renal impairment affect PCT levels only mildly [14] and PCT has been proven to accurately diagnose infections in patients with kidney disease [15].

To further analyze the diagnostic value of PCT for diagnosing local pocket infection in a real-world setting we analyzed the influence of antibiotic pre-treatment on its sensitivity and specificity. PCT levels respond rapidly to antibiotic treatment [16] and a lack of decrease during antibiotic treatment is associated with an increase in in-hospital mortality in sepsis patients [17]. Consistently, in our study, the sensitivity of a positive PCT result increased to 69% if only patients without antibiotic pre-treatment were analyzed, whilst it fell to 65% in patients pre-treated with antibiotics. The relatively small change in sensitivity despite antibiotic pre-treatment with a mean duration of 3 days suggests PCT values above 0.05 ng/ml remains a robust marker for pocket infections even in patients already treated with antibiotics.

Besides pre-treatment, a subtle or atypical clinical presentation makes diagnosing pocket infections even more difficult. Diagnosing a pocket infection is straightforward where extensive local inflammatory, wound dehiscence, hardware protrusion or pus discharge at the pocket are present [1, 9]. In more subtle cases with minimal local inflammation signs, the diagnosis can be easily missed [9]. A clinically unremarkable pocket infection with few or no inflammation signs is challenging to diagnose even for an experienced clinician, demanding auxiliary diagnostic tools, such as biomarkers [9]. However, the extent of local inflammation might also have an influence on PCT values [18] and as such the sensitivity of a positive PCT value would be expected to be lower. Though we did see a lower sensitivity of PCT in patients with minimal inflammatory signs (67% vs. 70%) the difference was relatively small and unlikely to be of clinical relevance. Furthermore, the sensitivity of PCT remained significantly higher than that of CRP or leukocytosis (49% and 12% respectively). Importantly, the high NPV of 95% for PCT even in patients with minimal local inflammatory signs might help to identify patients without pocket infections and thus prevent unnecessary pocket explorations or device extractions.

Although CRP was better than leukocytosis, both have limited use in diagnosing pocket infections, especially considering the already pre-selected patient cohort. Patients with isolated pocket infections do not present with leukocytosis; median leukocytes were not elevated with

7.1 (IQR, 6.2–8.9) 10^9/l. Thus, white blood count yields only little diagnostic value and the absences of leukocytosis does not exclude a local pocket infection, as previously shown [12, 19–21]. CRP is synthesized in response to infections, both bacterial and viral, but also to other causes of systemic inflammation, such as trauma or autoimmune diseases [22]. As our study excluded patients with conditions that might influence inflammation parameters, such as active malignancies, recent operations or burns the specificity of CRP might be even lower in a real-life clinical setting. On the contrary, PCT seems to be a more accurate biomarker for identifying infections and is known to differentiate bacterial from viral causes [16, 22]. Thus, PCT seems more helpful than conventional biomarkers for diagnosing pocket infection even in challenging clinical situations, such as antibiotic pre-treatment or subtle clinical presentation.

In our study, PCT levels were significantly higher in patients with systemic CIED infections and lead-associated infective endocarditis compared to pocket infections (Table 3). As PCT levels indicate the extent of systemic manifestation and disease severity [18, 23], exceptionally high PCT levels may help to identify patients suffering from systemic CIED infection or even lead related infective endocarditis and have subsequent influences on antibiotic treatment duration.

Besides validating PCT as a diagnostic biomarker for pocket infections, our study also supports the moderate predictive power of the PADIT score [2] for predicting CIED infections. In our cohort, patients suffering from pocket infection or any CIED infections had significantly higher PADIT scores than infection-free controls, despite similar age, renal function and CIED devices at presentation lending credence to the predictive nature of the number of prior CIED interventions which explains the difference in the PADIT scores in our cohorts. Although there were no differences between the pocket infection and control group regarding the type of device those with pocket infections had a greater number of leads consistent with the PADIT study findings that CRT pertains a higher infection risk than non-CRT devices. Nevertheless, 36% of the infection-free control group were considered at high risk for infection by the PADIT score. Thus, the control group appears adequately balanced in regards to risk of CDI.

The microbiological spectrum with a predominance of staphylococcus species detected in our study is consistent with previous reports [24, 25]. The microbiological spectrum differed between the subgroups of CDIs, with coagulase-negative staphylococci being the main pathogen in the local pocket infections as well as systemic CDIs and staphylococcus aureus in lead-associated infective endocarditis, as previously shown [25]. This finding supports a different pathogenesis behind pocket infections, primarily transdermal infections, and lead-

associated infective endocarditis, hematological seeding due to bloodstream infection, as well as migration from an infected pocket to the leads.

Strengths and limitations

The main strength of our study is the prospective design in a real-world clinical setting and the large cohort. Given the high rates of positive microbiological cultures our patients with pocket infections, our cohort has high internal validity.

A possible limitation of our study is that patient numbers in the sub-group analyses are relatively small and so these results should be interpreted with caution. Given sub-groups such as antibiotic pre-treated patients are a rare entity this study represents the largest cohort in the literature on the subject. We also excluded patients with active malignancies or burns, with recent operations or traumata, on immunosuppression and end-stage renal failure. Therefore, the diagnostic relevance of PCT in these special patient populations would require further research.

CONCLUSION

Our study validates the diagnostic utility of a cut-off value of 0.05 ng/ml PCT for the diagnosis of a pocket infection. The diagnostic value of 0.05 ng/ml PCT may be clinically useful for patients who are difficult to diagnose clinically, such as patients pre-treated with antibiotics or with minimal local inflammatory signs. Furthermore, PCT levels were significantly higher in patients with systemic CIED infections and lead-associated infective endocarditis, differentiating them from local pocket infections.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

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Table 1. Baseline characteristics of pocket infection and control group

Characteristic	**Pocket infection (n = 81)**	**Control group (n = 81)**	***P*-value**
Age, years	77.0 (67.8–82.5)	73.2 (63.9–80.1)	0.074
Sex, male (n, %)	60 (74)	64 (79)	0.458
Diabetes mellitus (n, %)	21 (26)	27 (33)	0.302
Device at presentation (n, %)			0.882
Device, DDD-PM	40 (49)	39 (48)	
Device, VVVI-PM	2 (3)	3 (4)	
Device, DDD-ICD	8 (10)	7 (9)	
Device, VVVI-ICD	10 (12)	15 (19)	
Device, CRT-D	18 (22)	15 (19)	
Device, CRT-P	3 (4)	2 (3)	
Number of leads, n	2.0 (2.0–3.0)	2.0 (2.0–2.0)	0.004
Years since first CIED implantation	7.4 (2.2–13.1)	9.6 (7.2–12.5)	0.030
Years since last CIED procedure	0.7 (0.1–2.3)	7.8 (3.9–9.6)	<0.001
PADIT score	8.5 (4.0–9.0)	4.0 (2.0–9.0)	0.004
Creatinine, mg/dl	1.07 (0.94–1.35)	1.07 (0.92–1.35)	0.856
GFR, ml/min	65 (50–83)	70 (53–84)	0.351

The data for the variables age, number of leads, years since first and last CIED procedure, PADIT score, creatinine and GFR are presented as median (interquartile range [IQR]). The data for the variables sex, diabetes mellitus and device at presentation are shown as number (n) and percentage (%). *P*-values from Pearson-χ^2-test or Mann-Whitney-U-test between pocket infection and controls

Abbreviations: CIED, cardiovascular implantable electronic device; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy without defibrillator; DDD, dual chamber; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; PM, pacemaker; VVI, single chamber

Table 2. Baseline characteristics of different subgroups of cardiac device infections

Characteristic	**Pocket infection**	**CIED systemic infection**	**Lead-related Infective Endocarditis**	***P*-value**
Number, n	81	23	34	
Age, in years	77.0 (67.8–82.5)	72.0 (62.7–80.8)	73.4 (66.2–78.5)	0.187
Sex, male (n,%)	60 (74)	19 (83)	26 (77)	0.697
Diabetes mellitus (n,%)	21 (26)	6 (26)	14 (41)	0.242
Device at presentation (n,%)				0.232
Device, DDD-PM	40 (49)	9 (39)	8 (24)	
Device, VVVI-PM	2 (3)	0 (0)	0 (0)	
Device, DDD-ICD	8 (10)	3 (13)	3 (9)	
Device, VVVI-ICD	10 (12)	4 (17)	7 (20)	
Device, CRT-D	18 (22)	7 (30)	12 (35)	
Device, CRT-P	3 (4)	0 (0)	4 (12)	
Number of leads, n	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.835
Years since first CIED implantation	7.4 (2.2–13.1)	6.3 (1.2–15.9)	4.0 (1.9–7.9)	0.094
Years since last CIED procedure	0.7 (0.1–2.3)	0.8 (0.2–3.1)	2.3 (0.6–4.2)	0.133
PADIT score	8.5 (4.0–9.0)	5.0 (4.0–9.0)	5.0 (3.0–9.0)	0.152
Creatinine, mg/dl	1.07 (0.94–1.35)	1.08 (0.93–1.65)	1.29 (0.94–1.78)	0.109
GFR, ml/min	65 (50–83)	52 (41–73)	44 (34–76)	0.021

The data for the variables age, number of leads, years since first and last CIED procedure, PADIT score, creatinine and GFR are presented as median (interquartile range [IQR]). The data for the variables sex, diabetes mellitus and device at presentation are shown as number (n) and percentage (%). *P*-values from Pearson-χ^2-test or Kruskal-Wallis-test between groups
Abbreviations: see Table 1

Table 3. Median values and interquartile ranges (IQR) for the biomarkers procalcitonin (PCT), C-reaktive protein (CRP) and leukocytes. *P*-values from Kruskal-Wallis-test for independent samples

	Pocket infection	**CIED syst. Inf.**	**Lead-rel. IE**	**Control group**	***P*-value**
PCT, ng/ml	0.06 (0.05–0.09)	0.08 (0.55–0.43)	0.28 (0.12–1.39)	0.04 (0.03–0.05)	<0.001
CRP, mg/dl	5.1 (1.7–12.0)	14.0 (4.2–55.4)	68.1 (31.8–124.0)	1.4 (0.7–2.6)	<0.001
Leukocytes, 10^9/l	7.1 (6.2–8.9)	8.3 (7.2–9.7)	8.6 (6.3–11.4)	6.7 (5.5–8.0)	<0.001

Table 4. Sensitivity, specificity, positive predictive value (PPV) negative predictive value (NPV) and *P*-value from χ^2-test for procalcitonin (PCT) with a cut-off of 0.05 ng/ml. Area under the curve (AUC) and p-value from receiver operating characteristics (ROC) analysis for procalcitonin (PCT) differentiating pocket infections from controls

PCT, 0.05 ng/ml	**N**	**Sensitivity, %**	**Specificity, %**	**PPV, %**	**NPV, %**	***P*-value χ^2-test**	**AUC (95% CI)**	***P*-value ROC**
All pocket infections	81	68	77	74	71	<0.001	0.75 (0.676–0.829)	*P* <0.001
Subgroup analyses								
Pocket infections **with** Antibiotic-pretreatment	26	65	77	47	87	<0.001	0.70 (0.57–0.84)	*P* = 0.002
Pocket infections **without** Antibiotic-pretreatment	55	69	77	67	79	<0.001	0.78 (0.69–0.86)	*P* <0.001
Pocket infections **with extensive** Local findings	40	70	77	60	84	<0.001	0.77 (0.68–0.86)	*P* <0.001
Pocket infections **with minimal** Local findings	9	67	77	24	95	0.012	0.75 (0.54–0.96)	*P* = 0.014

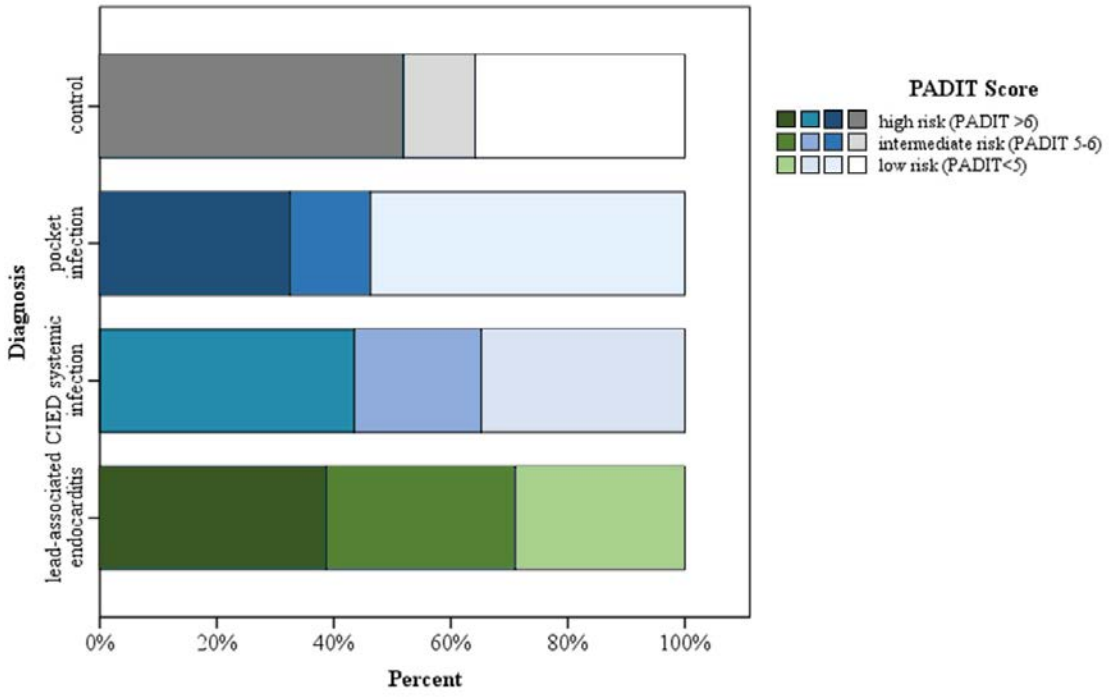


Figure 1. Percentage (%) of patients with low, intermediate or high PADIT score within the control, pocket infection, cardiac implantable electronic device systemic infection and lead-associated endocarditis group

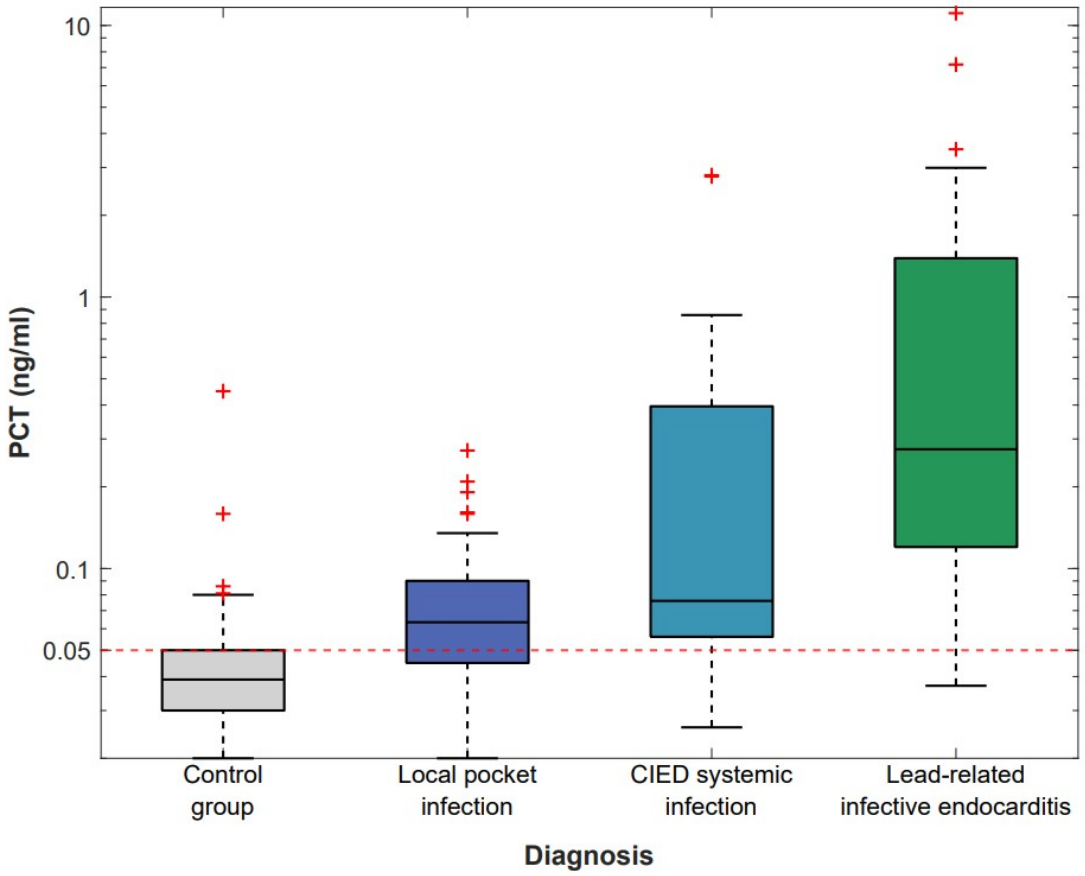
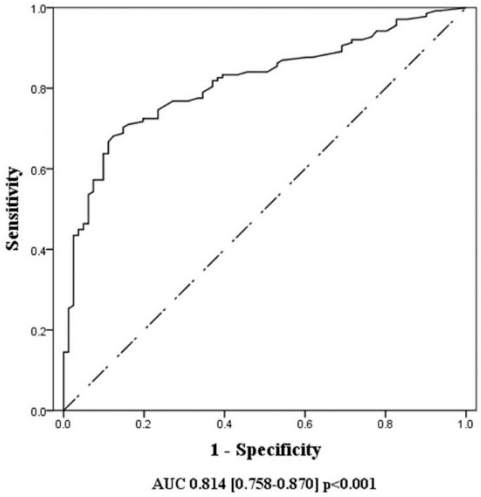


Figure 2. Boxplot comparison of PCT level between the three infection groups and the non-infective control cohort

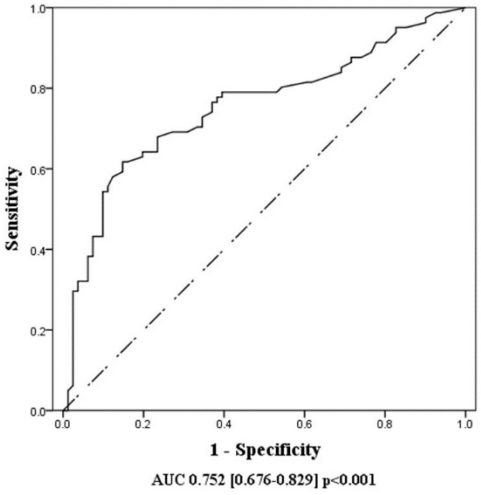
Abbreviation: PCT, procalcitonin, of note: y-axis displays logarithmically the PCT level

A **All CIED infections**



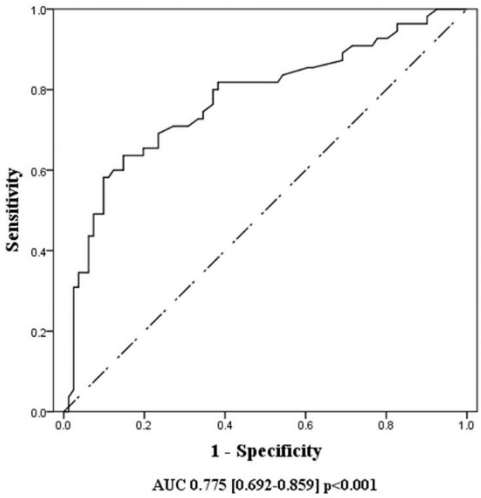
AUC 0.814 [0.758-0.870] p<0.001

B **Pocket infections**



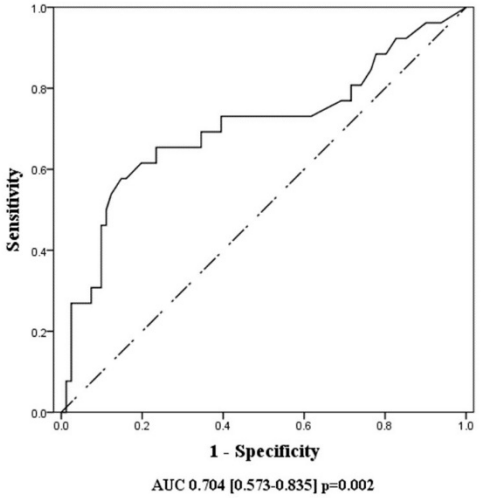
AUC 0.752 [0.676-0.829] p<0.001

C **Pocket infections without antibiotic-pretreatment**



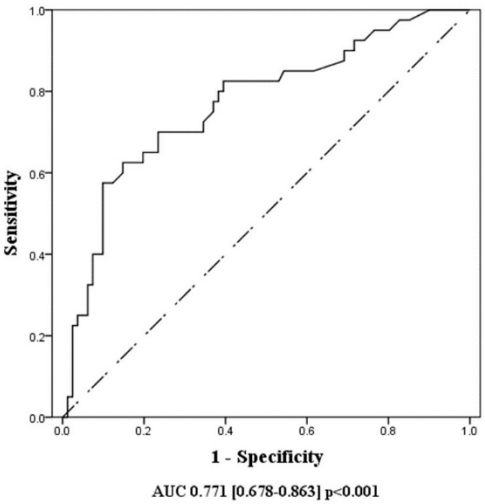
AUC 0.775 [0.692-0.859] p<0.001

D **pocket infections with antibiotic-pretreatment**



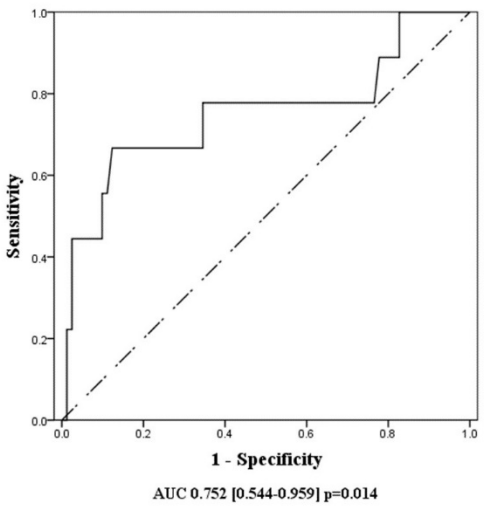
AUC 0.704 [0.573-0.835] p=0.002

E **Pocket infections with pronounced local inflammation excluding perforation**



AUC 0.771 [0.678-0.863] p<0.001

F **Pocket infections with discrete or no local inflammation excluding perforation**



AUC 0.752 [0.544-0.959] p=0.014

Figure 3. A, B. ROC analysis for (**A**) all CDIs vs. controls (**B**) pocket infections vs. controls. **C, D.** ROC analysis for pocket infections vs. controls in subgroups (**C**) without antibiotic pre-treatment and (**D**) with antibiotic pretreatment. **E, F.** ROC analysis for pocket infections vs. controls in subgroups (**E**) with pronounced local inflammation signs and (**F**) with discrete or no inflammation signs, excluding patients with wound dehiscence or hardware protrusion
Abbreviations: CDI, cardiac device infections; ROC, receiver operating characteristic

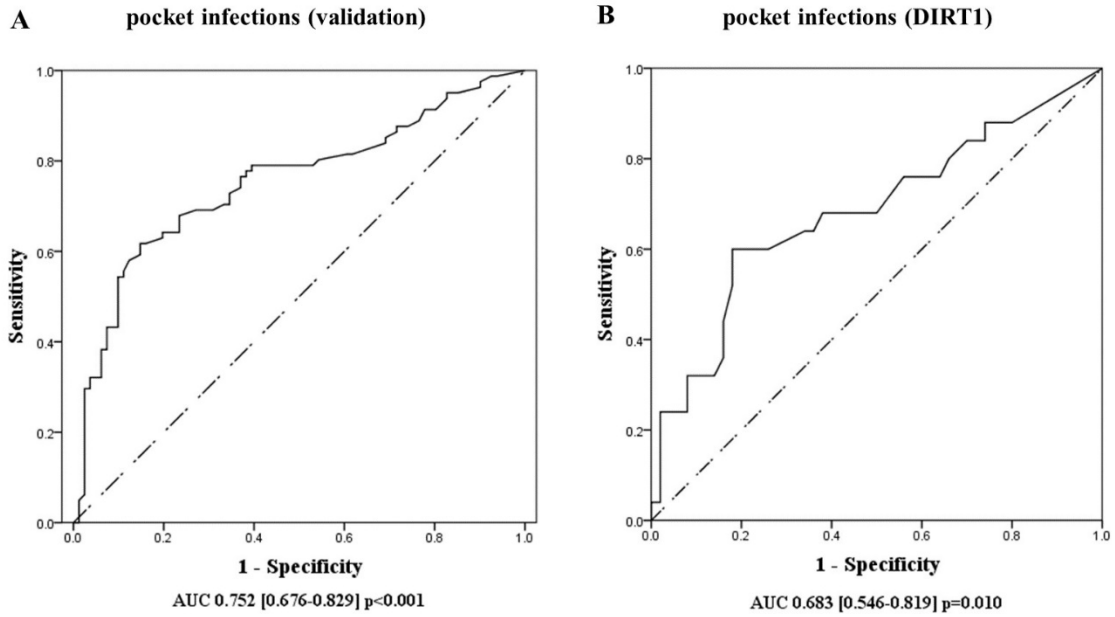


Figure 4. A, B. Receiver operating characteristic analysis for (**A**) pocket infections vs. controls in our validation study and (**B**) pocket infections s controls as reported in DIRT1 [12]