ORIGINAL ARTICLE

Inflammatory markers in the diagnostic workup of pacemaker- and defibrillator-related infections in patients referred for transvenous lead extraction

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C-reactive protein level, infectious complications, permanent cardiac pacing, transvenous lead extraction, white blood cell count

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ABSTRACT

BACKGROUND Infectious complications can be life-threatening in patients with permanent transvenous pacemakers and their diagnosis can be challenging.

AIMS The aim of the study was to assess the diagnostic utility of white blood cell (WBC) count and C-reactive protein (CRP) concentrations in infectious complications in patients with cardiac pacemakers.

METHODS The prospective study included patients who underwent transvenous lead extraction (TLE) due to various indications. The diagnosis of lead-dependent infective endocarditis (LDIE) was based on the modified Duke criteria, and the diagnosis of local infection was based on symptoms related to device pocket. The study population consisted of 640 patients: 63 (9.9%) with LDIE, 61 (9.5%) with local infection, and 516 controls (80.6%) referred for TLE due to noninfectious indications. We evaluated WBC count and CRP concentrations in each group of patients and assessed the predictive value of these tests for the diagnosis of LDIE and local infection.

RESULTS Patients with local infection did not differ in terms of median WBC and CRP values compared with controls (P = 0.99 and P = 0.13, respectively), whereas patients with LDIE had higher median WBC count and CRP level (P <0.001 and P <0.001, respectively). In the LDIE group, WBC diagnostic test showed 46.0% sensitivity, 95.3% specificity, 90.5% accuracy, 51.8% positive predictive value, and 94.2% negative predictive value. The diagnostic test based on CRP levels showed 84.1% sensitivity, 81.8% specificity, 82.0% accuracy, 33.5% positive predictive value, and 97.9% negative predictive value.

CONCLUSIONS In patients undergoing TLE due to infectious indications, inflammatory markers (WBC count, CRP level) were within normal range in the local-infection group and markedly elevated in the LDIE group. Inflammatory markers were useful to determine the extent of the infection in patients with local infection.

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INTRODUCTION Increasing numbers of patients with heart rhythm abnormalities have improved quality of life and life expectancy as a result of cardiac implantable electronic device (CIED) therapy. However, there is also an increasing number of complications related to permanent pacemakers and defibrillators.[1-4] The indications for transvenous lead extraction (TLE) can be divided into 2 categories: infectious and noninfectious.[5,6] The diagnostic workup of cardiac device infections can be challenging because many patients often present

WHAT'S NEW?

White blood cell (WBC) count and C-reactive protein (CRP) concentration are simple, nonspecific markers of inflammatory response. They can be useful in the diagnostic workup of infectious complications in patients with permanent pacemakers and in differentiation between lead-dependent infective endocarditis (LDIE) and local infection. WBC and CRP concentration remain within reference ranges in patients with local infection and are elevated in patients with LDIE, thereby are useful in the assessment of the extent of device-related infection in patients with local infection. Raised inflammatory markers in patients with local infection increase the likelihood of coexisting LDIE, whereas normal values of WBC and CRP support the diagnosis of isolated local infection.

with mild symptoms or remain asymptomatic.[7,8] The management of systemic and local infections is different, particularly with regard to the duration of antimicrobial treatment, therefore it is essential to differentiate between LDIE and local infection not classified as LDIE.[7] In the current 2015 European Society of Cardiology guidelines, inflammatory markers such as WBC count and CRP level were indicated as useful additional diagnostic criteria for LDIE and tests to aid differentiation between isolated local infection and LDIE.[9] There are few reports in the available literature on the utility of WBC count and CRP level in diagnostic workup of infective endocarditis either in the presence of CIED or without it.

Horstkotte et al[10] stated that in infective endocarditis, WBC count and CRP level were regularly elevated, and moreover, a normal CRP level was extremely unlikely. In the study by Le et al,[11] leukocytosis corresponded to a 3.6-fold increased relative risk of LDIE compared with controls with local infection. Lennerz et al[12] showed higher CRP levels in a group of 25 patients with local infection compared with patients without CIED-associated infection. Moreover, WBC count remained normal in both groups.

Being aware of the significant challenges in the diagnostic workup of cardiac device infections and difficulties in differentiation between LDIE and local infection, we aimed to perform a single-centre analysis on the utility of WBC count and CRP level in patients referred for TLE.

We aimed to evaluate the utility of inflammatory markers (WBC count, CRP level) in the diagnostic workup of infectious complications of permanent pacemakers and in differentiation between LDIE and local infection in patients referred for TLE.

METHODS The prospective study cohort included patients referred for TLE from October 2011 to December 2018 at a single tertiary reference center. The exclusion criterion was TLE procedure during 12 months after implantation. The institutional ethics committee approved the study protocol, and written informed consent was obtained from all patients for the use of their anonymous data in the present publication. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

The study complied with the principles of the Good Clinical Practice guidelines and was approved by the Jagiellonian University Ethics Committee (no. KBET/259/B/2011).

Clinical, biochemical, and other medical data were recorded. Estimated glomerular filtration rate was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Laboratory investigations CRP levels were determined by the immunoturbidimetric method with the use of Cobas 6000 Analyzer (Roche Diagnostics GmbH, Mannheim, Germany). WBC counts were determined by the flow cytometry method with hydrodynamic focusing with the use of Sysmex Corporation XN 1000 kits (Kobe, Japan).

Echocardiography Transthoracic echocardiography (TTE) was performed in all patients. In addition, patients with suspected LDIE or local infection underwent transesophageal echocardiography (TEE). Scans were performed with Aloka Alpha 10 (Aloka, Osaka, Japan) or Vivid S6 (GE Healthcare, Wauwatosa, Wisconsin, United States) at the time of patient enrolment in compliance with the European Society of Cardiology guidelines.[9,13]

Microbiological diagnostic workup Each patient with device-related infection had serial (at least 3) blood cultures drawn into broth medium enriched with resins for antibiotic neutralization (BACTEC FX Plus Aerobic / F Culture Vialis and BACTEC FX Plus Anaerobic / F Culture Vialis, Wokingham, United Kingdom) for aerobic and anaerobic bacteria. The specimens were analyzed in Bactec Fx system manufactured by Becton Dickinson (BD, Wokingham, United Kingdom). A blood culture result was considered to be positive if isolated microorganisms were different from flora of the skin. Two or more blood cultures positive for specified types of organisms constitute a major Duke criterion. Skin flora growth in a single blood culture was treated as contamination, whereas the growth in more than one blood culture was considered as a minor Duke criterion. At the presence of purulent exudate from the device pocket, the liquid was collected via percutaneous puncture into an aerobic broth medium with antibiotic neutralization. In patients with local infection and pocket fistula, the swabs were rubbed onto the surface of the agar plates and incubated in a hot-air oven for 16 to 18 hours.

Single-photon emission computed tomography with radiolabeled leukocytes From August 2014, patients with intracardiac masses suspected to be vegetations and with negative remaining Duke criteria for LDIE underwent radiolabeled WBC scintigraphy.[14,15] The analysis was performed with Camera Siemens Symbia T16. Acquisition was made 4 and 24 hours after tracer administration. Radionuclide WBC-labeled scintigraphy allowed precise detection of the areas of increased tracer uptake, for instance, in the device pocket, along endocardial leads in blood vessels, and/or septic pulmonary emboli.

Group division criteria The study population was divided into 3 groups according to the main indication for TLE. If a patient presented with more than 1 indication, the assignment to the group was based on the higher priority extraction recommendation class according to the 2009 and 2017 Heart Rhythm Society expert consensus statements.[5,6] For instance, if abandoned lead indication (Class IIb, level of evidence C) co-occurred with LDIE (Class I, level of evidence B) the patient was assigned to the LDIE group.

The first group was the LDIE group (infective endocarditis possible or definite). Possible LDIE diagnosis was established in the presence of only one major Duke criterion: vegetation, positive blood cultures, or septic pulmonary embolism except for pocket infection. Definite diagnosis of LDIE required documentation of at least 2 major Duke criteria or 1 major and 3 minor Duke criteria.[16]

The second group was the local-infection group (local infection which did not fulfil criteria for definite LDIE), and included patients with isolated pocket infection, which was defined as the presence of signs of inflammation including redness, heat, pocket exudate and/or edema, purulent drainage, and skin erosion including fistula. To rule out LDIE, every patient was thoroughly examined and the presence of the following conditions were excluded: vegetations on TTE and TEE; recurrent pulmonary infection, which might be the effect of septic pulmonary embolism; features of chronic pulmonary embolism on TTE along with a positive D-dimer result; positive blood cultures according to the Duke criteria.

The third group was the control group (noninfectious indications), which included the remainder of patients presenting with reasons other than infection, for instance, with lead malfunction, device upgrade in the presence of ipsilateral venous occlusion.

The study group consisted of 640 patients who underwent TLE between October 2011 and December 2018. There were 63 patients (9.9%) with LDIE (the LDIE group), 61 patients (9.5%) with local infection (the local-infection group), and 516 patients (80.6%) with noninfectious indications (the control group). Concomitant LDIE and local infection was diagnosed in 16 patients from the LDIE group. In patients with CIED-related infection who were receiving antimicrobial therapy and were transferred from other centers (20 patients with LDIE and 19 patients with local infection), we analyzed CRP levels and WBC counts obtained before the commencement of treatment.

Statistical analysis The analysis was performed using the StatSoft Statistica version 13.1 (StatSoft, Tulsa, Oklahoma, United States). Continuous variables were expressed as mean (SD) and additionally as median and interquartile range (IQR). The Shapiro–Wilk test was used to assess the normality of continuous variables. The categorical variables were presented as the number of observations in each category and the percentage of observations in this category out of all observations. For comparisons of 3 independent groups of continuous variables, we used 1-way analysis of variance (ANOVA), and for variables with nonnormal distribution, we used the nonparametric Kruskal–Wallis test. Groups were compared using the χ^2 test for discrete variables. For 2×2 tables we used either the χ^2 test, Yates correction, or Fisher exact test. For multiple comparisons between groups, the Bonferroni correction was applied. To compare the predictive value of WBC count and CRP level we constructed receiver operating characteristic (ROC) curves and determined the area under the curve (AUC) with 95% confidence intervals (CI). The operative characteristics of WBC counts and CRP levels were assessed by calculating sensitivity, specificity, accuracy (ACC), positive and negative predictive values (PPV, NPV), and the positive and negative likelihood ratios (LR+, LR–). The interpretation of likelihood ratios (LRs) was preformed according to a report by Jaeschke et al.[17] The test has a real diagnostic utility if LR is 10 or higher or 0.1 or lower. The values between 5 and 10 or between 0.1 and 0.2 show that the test is moderately useful. The LR between 0.5 and 2 indicates that the test has no diagnostic value. Finally, the optimal cut-off value of WBC and CRP biomarkers (ie, the maximized sum of sensitivity and specificity; Youden index) was derived. All statistical tests were 2-tailed and a P value of less than 0.05 was considered significant.

RESULTS In the analyzed group, 396 patients (61.9%) had a permanent pacemaker, 167 (26.1%) had an implantable cardioverter–defibrillator (ICD), 9 (1.4%) were implanted with a cardiac resynchronization therapy pacemaker, and 68 (10.6%) with a cardiac resynchronization therapy

TABLE 1 Clinical characteristics, types of devices and leads

Variable		LDIE group (n = 63)	Local-infection group (n = 61)	Control group (n = 516)	*P* value
Age, y, mean (SD); median (IQR)		67.5 (14.5); 70.5 (20.1)	72.6 (11.8); 75.7 (15.7)	66.2 (13.5); 67.6 (17.1)	0.03 1.00[a] 0.01[b] 0.10[c]
Women, n (%)		15 (23.8)	18 (29.5)	199 (38.6)	0.04
LVEF, %, mean (SD); median (IQR)		37.2 (16.2); 35.0 (25.0)	45.2 (15.8); 50.0 (28.0)	44.5 (16.0); 47.0 (30.0)	0.02 0.002[a] 1.00[b] 0.02[c]
Implanted device, n (%)	Pacemaker	32 (50.8)	39 (63.9)	325 (63.0)	0.16
	ICD	19 (30.1)	14 (23.0)	134 (26.0)	0.65
	CRT-P	1 (1.6)	1 (1.6)	7 (1.3)	0.98
	CRT-D	11 (17.5)	7 (11.5)	50 (9.7)	0.17
Diabetes mellitus, n (%)		25 (39.7)	24 (39.4)	166 (32.2)	0.30
Coronary artery disease, n (%)		44 (69.8)	39 (63.9)	272 (52.7)	0.01
Creatinine, µmol/l, mean (SD); median (IQR)		117.2 (56.4); 101.0 (53.0)	100.4 (32.2); 91.0 (38.0)	98.0 (53.0); 89.0 (30.0)	0.04 0.02[a] 1.00[b] 0.21[c]
eGFR, ml/min/1.73 m^2, mean (SD); median (IQR)		62.1 (26.4); 59.0 (37.0)	64.4 (19.9); 66.0 (29.0)	69.6 (21.8); 70.2 (32.0)	0.09
WBC, × 10^3/µl, mean (SD); median (IQR)		10.6 (4.4); 9.3 (6.9)	6.9 (1.8); 6.7 (2.6)	6.9 (3.5); 6.6 (2.3)	<0.001 <0.001[a] 1.00[b] <0.001[c]
CRP, mg/l, mean (SD); median (IQR)		80.6 (84.5); 66.0 (97.0)	11.6 (34.5); 3.0 (5.6)	3.7 (5.7); 2.0 (3.0)	<0.001 <0.001[a] 0.13[b] <0.001[c]

a Bonferroni correction in comparisons between LDIE and control groups **b** Bonferroni correction in comparisons between LI and control groups **c** Bonferroni correction in comparisons between LDIE and LI groups

SI conversion factors: to convert CRP to nmol/l, multiply by 9.524.

Abbreviations: CRP, C-reactive protein; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LDIE, lead-dependent infective endocarditis; LI, local infection; LVEF, left ventricular ejection fraction; WBC, white blood cell count

defibrillator. High-voltage therapies prior to admission were administered in 28 patients (2 patients with LDIE, 26 patients with non-infectious indications for TLE). The mean (SD) age of patients at the time of TLE was 67.0 (13.6) years (range, 18.9–93.0 years). There were 232 women (36.3%). Patient clinical characteristics and the types of devices in each group are presented in TABLE 1. Mean age of patients in the local-infection group was higher than in other groups. Patients from the LDIE group had markedly lower left ventricular ejection fraction than the rest of patients. Female sex was prevalent in the control group. Coronary artery disease was prevalent in the LDIE group. The analyzed groups did not differ in terms of CIED type or prevalence of diabetes (TABLE 1). The inflammatory markers (WBC count and CRP level) were significantly increased in the LDIE group compared with local-infection group and control group (P <0.001). In 2 patients with LDIE who had experienced ICD shocks, CRP level was 127.0 mg/l and 214.0 mg/l. On the other hand, in 26 patients with a recent history of high voltage ICD therapies due to dysfunctional ICD lead, mean (SD) and median (IQR) CRP level was 4.6 (6.3) mg/l and 2.0 (3.0) mg/l, respectively. In 5 patients (19.2%) from that group, CRP level was higher than established cut-off value on 5 mg/l (range, 1.0–27.0 mg/l).

TABLE 2 Comparison of white blood cell counts and C-reactive protein levels in the lead-dependent infective endocarditis group, local-infection group, and control group using absolute concentration

Type of infection	Biomarker	Concentration, median (IQR)		AUC (SE)	*P* value
		Infection	Controls		
LDIE	WBC, × 10³/µl	9.3 (6.9)	6.6 (2.3)	0.774 (0.037)	<0.001
	CRP, mg/l	66.0 (97.0)	2.0 (3.0)	0.904 (0.026)	<0.001
LI	WBC, × 10³/µl	6.7 (2.6)	6.6 (2.3)	0.487 (0.038)	0.73
	CRP, mg/l	3.0 (5.6)	2.0 (3.0)	0.569 (0.037)	0.07

Abbreviations: AUC, area under curve; SE, standard error; others, see TABLE 1

Mean (SD) WBC count was similar in the local-infection group and the control group and was 6.9 (1.8) × 10³/µl vs 6.9 (3.5) × 10³/µl, respectively (P = 0.79). Mean (SD) CRP level was slightly higher in the local-infection group compared with the control group: 11.6 (34.5) mg/l vs 3.7 (5.7) mg/l (P = 0.01) (TABLE 1).

The median concentrations, IQR, and the AUC for ROC of the WBC count and CRP level comparison between the control group versus LDIE and local-infection groups are shown in TABLE 2 and FIGURE 1. WBC counts and CRP levels did not differ between the local-infection group and control group (WBC, 6.7 × 10³/µl vs 6.6 × 10³/

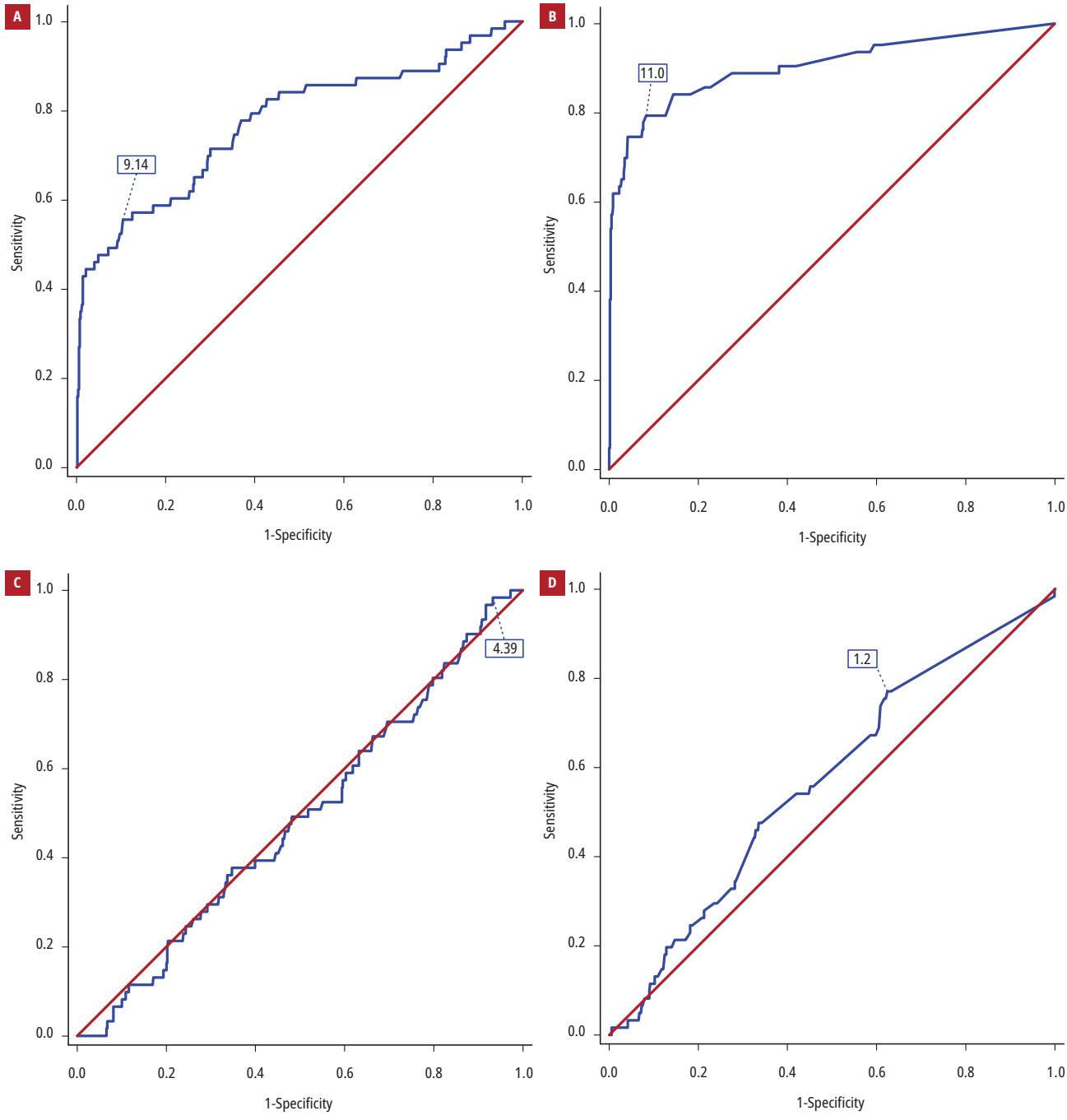

FIGURE 1 Receiver operator characteristic curve (ROC) analysis of white blood cell (WBC) and C-reactive protein (CRP) biomarkers in lead-dependent infective endocarditis and local-infection groups. ROC for WBC and CRP in LDIE and control groups (**A**, **B**), and local infection and control groups (**C**, **D**). Suggested cut-off values presented in boxes.

TABLE 3 Comparison of diagnostic parameters for white blood cell counts and C-reactive protein levels using established or suggested cut-off values in the lead-dependent infective endocarditis group

Parameter	WBC count		CRP level	
	Established cut-off value, 10.00×10^3/µl	Suggested cut-off value, 9.14×10^3/µl	Established cut-off value, 5.0 mg/l	Suggested cut-off value, 11.0 mg/l
Sensitivity	46.0 (35.4–56.0)	54.0 (42.3–65.1)	84.1 (73.1–91.6)	77.8 (66.8–86.3)
Specificity	95.3 (94.2–96.4)	89.8 (88.5–91.0)	81.8 (80.6–82.6)	92.4 (91.2–93.3)
Youden index	0.414 (0.296–0.524)	0.437 (0.308–0.561)	0.659 (0.537–0.742)	0.702 (0.580–0.796)
PPV	51.8 (39.9–63.0)	36.6 (28.7–44.1)	33.5 (29.1–36.5)	52.7 (45.2–58.5)
NPV	94.2 (93.0–95.3)	94.7 (93.4–96.0)	97.9 (96.5–98.9)	97.4 (96.2–98.4)
ACC	90.5 (88.4–92.4)	86.3 (84.0–88.4)	82.0 (79.9–83.5)	90.9 (88.8–92.6)
LR+	9.837 (6.074–15.609)	5.278 (3.680–7.221)	4.623 (3.765–5.268)	10.199 (7.568–12.890)
LR–	0.566 (0.456–0.686)	0.513 (0.484–0.652)	0.194 (0.102–0.334)	0.241 (0.147–0.364)

Data are presented as % (95% CI).

Abbreviations: ACC, accuracy; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; others, see TABLE 1

µl; AUC, 0.487; 95% CI, 0.413–0.561; $P = 0.73$; CRP, 3.0 mg/l vs 2.0 mg/l; AUC, 0.569; 95% CI, 0.495–0.642; $P = 0.07$). On the other hand, compared with controls, patients with LDIE had higher WBC counts (9.3×10^3/µl vs 6.6×10^3/µl; AUC, 0.774; 95% CI, 0.701–0.846; $P < 0.001$) and CRP levels (66.0 mg/l vs 2.0 mg/l; AUC, 0.904; 95% CI, 0.853–0.954; $P < 0.001$).

Additionally, optimized cut-off values with maximized sensitivity and specificity were obtained from ROC analysis applying the Youden index. For WBC counts and CRP levels, the optimized cut-off values (9.14×10^3/µl and 11.0 mg/l, respectively) resulted in moderate diagnostic power to discriminate between patients with LDIE and healthy controls. CRP levels exhibited better sensitivity and specificity than WBC counts (TABLE 3). The established cut-off WBC count had the worst combination of sensitivity and specificity. The optimized WBC count and established cut-off CRP value had better sensitivity and specificity. Optimized CRP had the best combination of sensitivity and specificity (TABLE 3).

A diagnostic test using the established cut-off WBC count showed high ACC and NPV (90.5% and 94.2%, respectively) and can be useful to diagnose LDIE (LR+, 9.837). After setting the optimal cut-off value for the test using WBC, PPV and ACC decreased from 51.8% to 36.6% and from 90.5% to 86.3%, respectively (TABLE 3). A diagnostic test using established cut-off CRP value showed high ACC and NPV (82.0% and 97.9%, respectively) and can be useful to diagnose LDIE (LR–, 0.194). After setting the optimal cut-off value for the test using CRP, PPV and ACC increased from 33.5% to 52.7% and from 82.0% to 90.9%, respectively (TABLE 3). For the optimal cut-off value, LR+ decreased almost 2-fold for WBC and increased more than 2-fold for CRP (TABLE 3). A diagnostic test using optimal cut-off CRP can be useful to diagnose LDIE (real diagnostic utility; LR+, 10.199).

DISCUSSION There is no information in the available literature on the utility of inflammatory biomarkers in the diagnostic workup of infectious complications of pacemaker or defibrillator therapy. According to our analysis, the inflammatory markers such as WBC count and CRP level are predominantly within normal limits in local infection and therefore provide minimal diagnostic value. Our observation regarding WBC count is supported by Lennerz et al,[12] who showed that WBC counts in patients with local infection compared with control group (ie, patients without evidence of CIED-associated infection) were similar and never exceeded the established cut-off value. On the other hand, Lennerz et al[12] showed that CRP levels were more often elevated in the local-infection group as compared with the controls and that marker was considered as useful to differentiate between pocket infections and controls.

Our opinion is consistent with the views of Lennerz et al[12] that the diagnosis of isolated pocket infection will continue to require critical clinical awareness, careful patient history assessment, thorough physical examination, and a basic workup (ie, blood cultures, TTE, and TEE).

The present study demonstrates that WBC count and CRP level might be valuable tools in the diagnostic workup of LDIE. Both laboratory tests were useful in differentiation between the LDIE and control groups. We proved that, compared with WBC count, CRP marker test has

a higher diagnostic value, whereas WBC test may be applicable in the diagnosis of LDIE.

Golzio et al[18] performed a similar analysis in which inflammatory markers (WBC count and CRP level) were elevated in the LDIE group as compared with patients with other type of device-related infections; however, the authors did not provide cut-off values.[18]

Ipek et al[19] observed elevated mean CRP levels and normal WBC counts in a group of 34 patients with infectious complications (24 patients with local infection, 5 patients with LDIE, and 5 patients with local and systemic infections). As opposed to our results, data from Ipek et al[19] did not show differences between inflammatory markers in reference to the type of infection, which might have been caused by a small number of patients in the study groups. Importantly, CRP level is usually moderately elevated following high-voltage ICD therapies and therefore its diagnostic accuracy for detection of device infection may be reduced in that setting.[20,21] However, we think that in the setting of ICD shocks, elevated CRP levels may indicate LDIE, whereas moderately increased CRP levels are likely the sequelae of high voltage therapy, and local infection may be considered. In the latter, the diagnosis should be based on local symptoms, such as presence of signs of inflammation, including redness, heat, pocket exudate and/or edema, purulent drainage, and skin erosion including fistula.

To date, the inflammatory markers have not been considered as diagnostic criteria for LDIE.[9] Present analysis proves that WBC counts and CRP levels are useful in the diagnostic workup of LDIE. In patients who have not been recently treated with antimicrobial agents, normal results of both inflammatory markers help to definitely rule out infective endocarditis. Negative inflammatory markers are particularly helpful to confirm the diagnosis of isolated local infection. On the other hand, elevated inflammatory markers in patients with local infection significantly raise the likelihood of infective endocarditis, hence should prompt physicians to perform a meticulous diagnostic workup. Importantly, inflammatory markers are nonspecific and are elevated in other infectious and noninfectious conditions as well as after recent invasive procedures.[22]

Study limitations The major study limitation is the relatively small sample size and the analysis of only 2 types of inflammatory markers (WBC count and CRP level). An additional limitation is the large disproportion in the number of patients between the LDIE and local-infection groups as compared with the control group.

Conclusions WBC counts and CRP levels are simple, nonspecific markers of inflammatory response. They remain within the reference range in patients with local infection and are elevated in patients with LDIE, and thus are useful in the assessment of the device-related infection extent in patients with local infection. Raised inflammatory markers in patients with local infection increase the likelihood of coexisting LDIE, whereas normal values of WBC and CRP support the diagnosis of isolated local infection.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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