The utility of inflammatory markers in diagnostic work-up of pacemaker and defibrillator infections in patients referred for transvenous lead extraction

Authors: Andrzej Ząbek, Mateusz Ulman, Katarzyna Holcman, Krzysztof Boczar, Maciej Dębski, Magdalena Kostkiewicz, Jacek Lelakowski, Barbara Małecka

Article type: Original article

Received: April 6, 2019.

Accepted: August 19, 2019.

Published online: August 19, 2019.

ISSN: 0022-9032

e-ISSN: 1897-4279

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International License (CC BY-NC-ND 4.0), allowing third parties to download articles and share them with others, provided the original work is properly cited, not changed in any way, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at kardiologiapolska@ptkardio.pl.
The utility of inflammatory markers in diagnostic work-up of pacemaker and defibrillator infections in patients referred for transvenous lead extraction

Andrzej Ząbek¹, Mateusz Ulman¹, Katarzyna Holcman²,³, Krzysztof Boczar¹, Maciej Dębski¹, Magdalena Kostkiewicz²,³, Jacek Lelakowski¹,³, Barbara Małecka¹,³

1. Department of Electrocardiology, The John Paul II Hospital, Krakow, Poland
2. Department of Cardiac and Vascular Diseases, The John Paul II Hospital, Krakow, Poland
3. Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland

Short title: Utility of inflammatory markers in pacemaker and defibrillator infections

Corresponding author:
Andrzej Ząbek, MD, PhD, MSc
Department of Electrocardiology,
The John Paul II Hospital,
Prądnicka street 80, 31-202 Krakow,
Poland
Tel: +48 12 614 22 77, fax: +48 12 633 23 99.
E-mail: andrzej_j_z@poczta.onet.pl

Conflict of interest: none declared.
“What’s New?”

WBC and CRP are simple, non-specific markers of inflammatory response. These markers can be useful in the diagnostic work-up of permanent pacing infectious complications and in differentiation between lead-dependent infective endocarditis (LDIE) and local infection (LI). WBC and CRP remain within norm in patients with LI and are elevated in patients with LDIE, thereby are useful in the assessment of the device-related infection extent in patients with LI. Raised inflammatory markers in patients with LI increase the likelihood of coexisting LDIE, whereas normal values of WBC and CRP support the diagnosis of isolated LI.
Abstract:

Background:
Infectious complications are a life-threatening complications of permanent transvenous pacing. The diagnosis of infectious complications can be challenging.

Aim:
To assess the white blood cell count (WBC) and C-reactive protein (CRP) diagnostic utility in infectious complications of cardiac pacing.

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 diagnosis of local infection (LI) was based on symptoms related to device pocket. The study population consisted of 640 patients: 63 (9.9%) with LDIE, 61 (9.5%) with LI and 516 (80.6%) referred for TLE due to non-infectious indications – control group. We evaluated WBC and CRP in each group of patients and assessed the predictive value of these tests for the diagnosis of LDIE and LI.

Results:
Compared with controls patients with LI not differ in terms of median WBC and CRP, whereas patients with LDIE had statistically significantly higher median WBC and CRP. In LDIE group WBC diagnostic test showed 46.0% sensitivity, 95.3% specificity, 90.5% accuracy, 51.8% positive predictive value (PPV) and 94.2% negative predictive value (NPV). Diagnostic test based on CRP level showed 84.1% sensitivity, 81.8% specificity, 82.0% accuracy, 53.5% PPV and 97.9% NPV.

Conclusions:
In patients undergoing TLE due to infectious indications the inflammatory markers (WBC, CRP) were within normal range in LI group and markedly elevated in LDIE group.

Inflammatory markers were useful in determination of the infection extent in patients with LI.

**Key words:** C-reactive protein; infectious complications; permanent cardiac pacing; transvenous lead extraction; white blood cell count
Introduction:

Increasing numbers of patients with heart rhythm abnormalities have improved quality of life and longevity as a result of cardiac implantable electronic devices (CIEDs) implantation. On the other hand, we have been observing a trend of increasing number of permanent pacemaker and defibrillator complications [1-4]. The indications for transvenous lead extraction (TLE) can be divided into two categories: infectious and non-infectious [5, 6]. Diagnostic process of cardiac device infections (CDI) can be challenging because many patients often present 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 lead-dependent infective endocarditis (LDIE) and local infection (LI) without fulfilled criteria for LDIE [7]. In the current 2015 European Society of Cardiology (ESC) guidelines inflammatory markers such as WBC and CRP were indicated as useful additional diagnostic criteria for LDIE and tests to aid differentiation between isolated LI and LDIE [9]. The available literature comprises few reports on the utility of WBC and CRP in diagnostic work-up of infective endocarditis either in the presence of CIED or without it.

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

Being aware of the significant challenges in the diagnostic work-up of cardiac device infections (CDI) and difficulties in differentiation between LDIE and LI we aimed to perform a single-centre analysis on the utility of WBC and CRP in patients referred for TLE.
Aim:

We aimed to evaluate the utility of inflammatory markers (WBC count, CRP) in the diagnostic work-up of permanent pacing infectious complications and in differentiation between LDIE and LI in patients referred for TLE.

Material and methods:

The prospective study cohort comprised patients referred for TLE from October 2011 to December 2018 in a single tertiary reference centre. The exclusion criterion was TLE procedure before 12 months post 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 (eGFR) was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Biochemical tests:

CRP (immunoturbidimetric method) was performed with the use of Cobas 6000 Analyzer manufactured by Roche Diagnostics GmbH (Mannheim, Germany). WBC (flow cytometry method with hydrodynamic focusing) was performed with the use of Sysmex Corporation XN 1000 (Kobe, Japan) kits.
Echocardiography:

Transthoracic echocardiography (TTE) was performed in all patients. In addition, patients with suspected LDIE or LI underwent transoesophageal echocardiography (TTE). Scans were performed with Aloka Alpha 10 (Aloka, Japan) or Vivid S6 (GE Healthcare, USA) at the time of patient enrolment in compliance with ESC guidelines [9, 13].

Microbiological diagnostic work-up:

Each patient with device infection had serial (at least 3) blood cultures drawn into broth mediums enriched with resins for antibiotic neutralization (BACTEC FX Plus Aerobic/F Culture Vialis and BACTEC FX Plus Anaerobic/F Culture Vialis) for aerobic and anaerobic bacteria. The specimens were analysed in Bactec Fx system manufactured by Becton Dickinson (BD, UK). Blood culture result was considered as positive if microorganisms isolated were different from skin flora. Major Duke criterion for LDIE diagnosis requires two or more positive blood cultures with specified types of organisms. Skin flora growth in single blood culture was treated as contamination, whereas the growth in more than one blood culture was considered as minor Duke criterion. At the presence of purulent exudate from device pocket the liquid was collected via percutaneous puncture into 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 16-18 hours.

SPECT-CT with radiolabelled leucocytes:

In the presence of intracardiac masses suspected to represent vegetations and negative remaining Duke criteria for LDIE, from August 2014 patients underwent radiolabelled white blood cell scintigraphy [14, 15]. The analysis was performed with Camera Siemens Symbia T16. Acquisition was made in 4th and 24th hour after the tracer administration. Radionuclide WBC-labelled scintigraphy allowed to see precisely 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 population was divided into three groups according to the main indication for TLE. If patient presented with more than one indication the assignment to the group was based on the higher priority extraction recommendation class according to 2009 and 2017 Heart Rhythm Society expert consensus statements [5, 6]. For instance, if abandoned lead indication (Class IIb, level of evidence C) co-existed with LDIE (Class I, level of evidence B) the patient was assigned to LDIE group.

**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 two major Duke criteria or one major and 3 minor Duke criteria [16].

**LI group** – local infection which did not fulfil criteria for definite LDIE.

LI group consisted of patients with isolated pocket infection which was defined as the presence of signs of inflammation including redness, heat, pocket exudate and/or oedema, 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 in transthoracic and transoesophageal echocardiography (TTE and TEE),
- recurrent pulmonary infection, which might be the effect of septic pulmonary embolism,
- features of chronic pulmonary embolism in TTE along with positive D-dimer,
- positive blood cultures according to the Duke criteria.

**Control group** – non-infectious indications. This group consisted of the remainder of patients presenting with other than infectious reasons for instance with lead malfunction, device
upgrade in the presence of ipsilateral venous occlusion, etc. Patients from this group composed control group.

The study group consisted of 640 patients who underwent TLE between October 2011 and December 2018. There were 63 (9.9%) patients with LDIE (LDIE group), 61 (9.5%) patients with LI (LI group) and 516 (80.6%) patients with non-infectious indications (control group). Concomitant LDIE and LI was diagnosed in 16 patients from LDIE group. In patients transferred from other centres with CIED infection (20 pts with LDIE and 19 pts with LI) with ongoing antimicrobial therapy we analysed CRP and WBC results obtained before commencement of treatment.

**Statistical analysis:**

The analysis was performed using StatSoft Statistica version 13.1 (StatSoft, Tulsa, Oklahoma, United States).

Continuous variables were expressed as mean and standard deviation (SD) and additionally as median (Me) and interquartile range (IQR). Shapiro–Wilk W test was used to assess the continuous variables normality. 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 three independent groups of continuous variables we used one-way analysis of variance (ANOVA), and for variables with non-normal distribution we used a nonparametric Kruskal–Wallis test. Groups were compared using the chi-square test for discrete variables. For 2x2 tables we used either chi-square test or 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 we constructed receiver operating characteristic (ROC) curves and determined the area under the curve (AUC) with 95% confidence intervals (95% CI). The operative characteristics of WBC and CRP were assessed calculating sensitivity, specificity, accuracy (ACC), positive and negative predictive
values (PPV, NPV) and the positive and negative likelihood ratio (LR+, LR-). The
terpretation of likelihood (LR) ratios was performed according to the report of Jaeschke
[17]. The test has a real diagnostic utility if LR ≥ 10 or ≤ 0.1. 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 (i.e., the maximized sum of sensitivity and specificity; Youden’s index) was
derived. All statistical tests were 2-tailed and a P-value < 0.05 was considered statistically
significant.

**Results:**
In the analysed group 396 (61.9%) patients had a permanent pacemaker (PPM), 167 (26.1%)
had an implantable cardioverter-defibrillator (ICD), 9 (1.4%) patients were implanted with
cardiac resynchronisation therapy pacemaker (CRT-P) and 68 (10.6%) with cardiac
resynchronisation therapy defibrillator (CRT-D). High voltage therapies prior to admission
were found in 28 patients (2 pts with LDIE, 26 pts with non-infectious indications for TLE).
The mean (SD) age of patients at the time of TLE was 67.0 (13.6), range 18.9-93.0 years,
there were 232 (36.3%) females. The clinical characteristics of patients and the types of
devices in each group were presented in Table 1. Mean age of patients in LI group was
significantly higher than in other groups. Patients from LDIE group had markedly lower left
ventricular ejection fraction than the rest of patients. Female gender was the most prevalent in
the control group and coronary artery disease in the LDIE group. The analysed groups did not
differ statistically significantly in terms of CIED type or prevalence of diabetes (Table 1). The
inflammatory markers (WBC and CRP) were significantly increased in LDIE group compared
to LI group and control group (P < 0.001). In 2 patients with LDIE who had experienced ICD
shocks CRP 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
CRP level was 4.6 (6.3) mg/L and 2.0 (3.0) mg/L. In 5 (19.2%) pts from that group CRP was higher than established cut-off value on 5 mg/L (range 1.0-27.0 mg/L).

Mean (SD) WBC count was similar in LI group and control group, 6.9 (1.8) *10^3/uL vs 6.9 (3.5) *10^3/uL respectively (P = 0.79). Mean (SD) CRP level was slightly higher in LI group compared to 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 WBC and CRP comparison between control group versus LDIE and LI groups were shown in Table 2 and Figure 1. WBC and CRP did not differ between LI group and control group (WBC: 6.7*10^3/uL vs 6.6*10^3/uL, AUC = 0.487, 95% CI 0.413-0.561, P = 0.73; CRP: 3.0 mg/L vs 2.0mg/L, AUC = 0.569, 95% CI 0.495-0.642, P = 0.07). On the other hand, compared to controls the patients with LDIE had statistically significantly higher WBC (9.3*10^3/uL vs 6.6*10^3/uL, AUC = 0.774, 95% CI 0.701-0.846, P < 0.001) and CRP (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 and CRP the optimized cut-off values (9.14*10^3/uL and 11.0 mg/L, respectively) resulted in moderate diagnostic power to discriminate between patients with LDIE and healthy controls. CRP exhibited better sensitivity and specificity than WBC (Table 3). The worst combination of sensitivity and specificity exhibited established WBC count. Better were optimized WBC count and established CRP biomarker. The best combination of sensitivity and specificity showed optimized CRP biomarker, Table 3.

Diagnostic test using established WBC 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). Diagnostic test using established CRP level 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 two-fold for WBC and increased more than two-fold for CRP biomarker (Table 3). Diagnostic test using optimal cut-off CRP can be useful to diagnose LDIE (real diagnostic utility, LR+ = 10.199).

Discussion:
The available literature lacks information on the utility of inflammatory biomarkers in diagnosis of infectious complications of pacing/defibrillator therapy. According to our analysis, in LI the inflammatory markers such as WBC and CRP are predominantly within normal limits and therefore provide minimal diagnostic value. Our observation regarding WBC is supported by Lennerz et al. who showed that the values of WBC in patients with LI compared to control group (i.e. patients without evidence of CIED-associated infection) were similar and never exceeded established cut-off value [12]. On the other hand, Lennerz et al. showed that CRP levels were more often elevated in LI group versus the controls and that maker was considered as useful to differentiate pocket infections and controls. Our opinion is consistent with the views of Lennerz et al. that the diagnosis of isolated pocket infection will continue to require a critical clinical awareness, careful patient history assessment, thorough physical examination, and a basic work-up (i.e. blood cultures, transthoracic and transoesophageal echocardiography).

Present study demonstrates that the WBC and CRP might be valuable tools in LDIE diagnostic work-up. Both laboratory tests were useful in differentiation between LDIE and control group. We proved that, compared to WBC, CRP marker test has a higher diagnostic value, whereas WBC test may be applicable in diagnosis of LDIE.
Golzio et al. performed a similar analysis in which inflammatory markers (WBC and CRP) were significantly elevated in LDIE group compared to other type of device-related infections, however authors did not provide cut-off values [18].

Ipek et al. in the group of 34 patients with infectious complications (24 pts with LI, 5 pts with LDIE and 5 pts with local and systemic infection) observed elevated mean CRP results and normal WBC [19]. As opposed to our results, authors did not show significant difference between inflammatory markers in reference to the type of infection, which might have been caused by a small number of patients in these groups. Importantly, CRP is usually moderately elevated following high voltage ICD therapies and therefore its usefulness in discrimination of the source of device infection might be reduced [20, 21]. However, we think that in the setting of ICD shocks high CRP level may indicate LDIE, whereas moderately increased CRP levels are likely the sequelae of high voltage therapy and LI may be considered. In the latter, the diagnosis should be based on the local symptoms such as presence of signs of inflammation including redness, heat, pocket exudate and/or oedema, 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 taking into consideration WBC and CRP level is useful in LDIE diagnostic work-up. In patients who have not been recently treated with antimicrobial agents the normal result of both inflammatory markers helps to rule out infective endocarditis with confidence. Negative inflammatory markers are particularly helpful for confirmation of the isolated LI diagnosis. On the other hand, elevated inflammatory markers in patients with LI significantly raise the likelihood of infective endocarditis, hence should prompt physicians to perform meticulous diagnostic work-up. Importantly, inflammatory markers are non-specific and become elevated in other infectious and non-infectious conditions and after recent invasive procedures [22].
Conclusions:

1. WBC and CRP are simple, non-specific markers of inflammatory response.
2. These markers remain within norm in patients with LI and are elevated in patients with LDIE, thereby are useful in the assessment of the device-related infection extent in patients with LI.
3. Raised inflammatory markers in patients with LI increases the likelihood of coexisting LDIE, whereas normal values of WBC and CRP support the diagnosis of isolated LI.

Study limitations:

The major study limitation is a relatively small sample size and the analysis of only two types of inflammatory markers (WBC and CRP). An additional limitation is a large disproportion in the number of pts between LDIE / LI groups and control group.

Contribution statement:

AZ: the conception and design of the study, acquisition of data, statistical analysis, interpretation of data, writing the manuscript.

MU, KH, KB, MD, MK, JL: revising article critically for important intellectual content.

BM: data interpretation and revising article critically for important intellectual content.

All authors edited and approved the final version of the manuscript.

References:


2. Poole JE, Gleva MJ, Mela T, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures:


Table 1. Clinical characteristics of patients and the types of devices and leads in study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>LDIE group (n=63)</th>
<th>LI group (n=61)</th>
<th>Control group (n=516)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of pts (years) [mean (SD); Me (IQR)]</td>
<td>67.5 (14.5); 70.5 (20.1)</td>
<td>72.6 (11.8); 75.7 (15.7)</td>
<td>66.2 (13.5); 67.6 (17.1)</td>
<td>P=0.03 P=1.000# P=0.01## P=0.10###</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>15 (23.8)</td>
<td>18 (29.5)</td>
<td>199 (38.6)</td>
<td>P=0.04</td>
</tr>
<tr>
<td>LVEF (%) [mean (SD); Me (IQR)]</td>
<td>37.2 (16.2); 35.0 (25.0)</td>
<td>45.2 (15.8); 50.0 (28.0)</td>
<td>44.5 (16.0); 47.0 (30.0)</td>
<td>P=0.02 P=0.002# P=1.000## P=0.02###</td>
</tr>
<tr>
<td>Implanted device</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker, n (%)</td>
<td>32 (50.8)</td>
<td>39 (63.9)</td>
<td>325 (63.0)</td>
<td>P=0.16</td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>19 (30.1)</td>
<td>14 (23.0)</td>
<td>134 (26.0)</td>
<td>P=0.65</td>
</tr>
<tr>
<td>CRT-P, n (%)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>7 (1.3)</td>
<td>P=0.98</td>
</tr>
<tr>
<td>CRT-D, n (%)</td>
<td>11 (17.5)</td>
<td>7 (11.5)</td>
<td>50 (9.7)</td>
<td>P=0.17</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>25 (39.7)</td>
<td>24 (39.4)</td>
<td>166 (32.2)</td>
<td>P=0.30</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>44 (69.8)</td>
<td>39 (63.9)</td>
<td>272 (52.7)</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Creatinine (umol/l) [mean (SD); Me (IQR)]</td>
<td>117.2 (56.4); 101.0 (53.0)</td>
<td>100.4 (32.2); 91.0 (38.0)</td>
<td>98.0 (53.0); 89.0 (30.0)</td>
<td>P=0.04 P=0.02# P=1.000##</td>
</tr>
<tr>
<td></td>
<td>LDIE Group (Mean ± SD)</td>
<td>Control Group (Mean ± SD)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²) [mean (SD); Me (IQR)]</td>
<td>62.1 (26.4); 59.0 (37.0)</td>
<td>64.4 (19.9); 66.0 (29.0)</td>
<td>0.21**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>69.6 (21.8); 70.2 (32.0)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>WBC (*10³/uL) [mean (SD); Me (IQR)]</td>
<td>10.6 (4.4); 9.3 (6.9)</td>
<td>6.9 (1.8); 6.7 (2.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.9 (3.5); 6.6 (2.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L) [mean (SD); Me (IQR)]</td>
<td>80.6 (84.5); 66.0 (97.0)</td>
<td>11.6 (34.5); 3.0 (5.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.7 (5.7); 2.0 (3.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:

CRP, C-reactive protein; CRT-D, cardiac resynchronisation therapy with defibrillator; CRT-P, cardiac resynchronisation therapy with pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; Me, median; WBC, white blood cell count.

# - Bonferroni correction between LDIE and control groups.

## - Bonferroni correction between LI and control groups.

### - Bonferroni correction between LDIE and LI groups.
Table 2. Comparison of WBC and CRP levels in LDIE group, LI group and Control group using absolute concentration.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Median</th>
<th>IQR</th>
<th>Median</th>
<th>IQR</th>
<th>AUC</th>
<th>Standard Error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDIE group</td>
<td>Control Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (*10^3/uL)</td>
<td>9.3</td>
<td>6.9</td>
<td>6.6</td>
<td>2.3</td>
<td>0.774</td>
<td>0.037</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>66.0</td>
<td>97.0</td>
<td>2.0</td>
<td>3.0</td>
<td>0.904</td>
<td>0.026</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>LI group</td>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (*10^3/uL)</td>
<td>6.7</td>
<td>2.6</td>
<td>6.6</td>
<td>2.3</td>
<td>0.487</td>
<td>0.038</td>
<td>P=0.73</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.0</td>
<td>5.6</td>
<td>2.0</td>
<td>3.0</td>
<td>0.569</td>
<td>0.037</td>
<td>P=0.07</td>
</tr>
</tbody>
</table>

Abbreviations:
AUC, area under curve; CRP, C-reactive protein; IQR, interquartile range; WBC, white blood cell count.
Table 3. Comparison of diagnostic parameters for WBC and CRP using established or suggested cut-off values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WBC</th>
<th></th>
<th>CRP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Established cut-off value</td>
<td>Suggested cut-off value</td>
<td>Established cut-off value</td>
<td>Suggested cut-off value</td>
</tr>
<tr>
<td>WBC</td>
<td>10.00*10^3/uL</td>
<td>9.14*10^3/uL</td>
<td>5.0 mg/L</td>
<td>11.0 mg/L</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>46.0</td>
<td>54.0</td>
<td>84.1</td>
<td>77.8</td>
</tr>
<tr>
<td>(95% CI) [%]</td>
<td>(35.4-56.0)</td>
<td>(42.3-65.1)</td>
<td>(73.1-91.6)</td>
<td>(66.8-86.3)</td>
</tr>
<tr>
<td>Specificity</td>
<td>95.3</td>
<td>89.8</td>
<td>81.8</td>
<td>92.4</td>
</tr>
<tr>
<td>(95% CI) [%]</td>
<td>(94.2-96.4)</td>
<td>(88.5-91.0)</td>
<td>(80.6-82.6)</td>
<td>(91.2-93.3)</td>
</tr>
<tr>
<td>Youden’s index</td>
<td>0.414</td>
<td>0.437</td>
<td>0.659</td>
<td>0.702</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.296-0.524)</td>
<td>(0.308-0.561)</td>
<td>(0.537-0.742)</td>
<td>(0.580-0.796)</td>
</tr>
<tr>
<td>PPV</td>
<td>51.8</td>
<td>36.6</td>
<td>33.5</td>
<td>52.7</td>
</tr>
<tr>
<td>(95% CI) [%]</td>
<td>(39.9-63.0)</td>
<td>(28.7-44.1)</td>
<td>(29.1-36.5)</td>
<td>(45.2-58.5)</td>
</tr>
<tr>
<td>NPV</td>
<td>94.2</td>
<td>94.7</td>
<td>97.9</td>
<td>97.4</td>
</tr>
<tr>
<td>(95% CI) [%]</td>
<td>(93.0-95.3)</td>
<td>(93.4-96.0)</td>
<td>(96.5-98.9)</td>
<td>(96.2-98.4)</td>
</tr>
<tr>
<td>ACC</td>
<td>90.5</td>
<td>86.3</td>
<td>82.0</td>
<td>90.9</td>
</tr>
<tr>
<td>(95% CI) [%]</td>
<td>(88.4-92.4)</td>
<td>(84.0-88.4)</td>
<td>(79.9-83.5)</td>
<td>(88.8-92.6)</td>
</tr>
<tr>
<td>LR+</td>
<td>9.837</td>
<td>5.278</td>
<td>4.623</td>
<td>10.199</td>
</tr>
<tr>
<td>(95% CI) [%]</td>
<td>(6.074-15.609)</td>
<td>(3.680-7.221)</td>
<td>(3.765-5.268)</td>
<td>(7.568-12.890)</td>
</tr>
<tr>
<td>LR-</td>
<td>0.566</td>
<td>0.513</td>
<td>0.194</td>
<td>0.241</td>
</tr>
<tr>
<td>(95% CI) [%]</td>
<td>(0.456-0.686)</td>
<td>(0.484-0.652)</td>
<td>(0.102-0.334)</td>
<td>(0.147-0.364)</td>
</tr>
</tbody>
</table>

Abbreviations:

ACC, accuracy; CRP, C-reactive protein; CI, confidence interval; LR+, likelihood ratio positive; LR-, likelihood ratio negative; NPV, negative predictive value; PPV, positive
predictive value; WBC, white blood cell count.
Figure 1. Receiver operator characteristic curve (ROC). Analysis of WBC and CRP biomarkers in LDIE and LI groups. ROC for WBC and CRP in LDIE and Control groups (A, B), and LI and control groups (C, D).