The Early Diagnostic Value of Procalcitonin in Pneumonia After Off-Pump Coronary Artery Bypass Grafting Surgery

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Background:
The incidence of early postoperative pneumonia (EPOP) after off-pump coronary artery bypass grafting surgery (CABG) is relatively high, but its diagnosis by traditional methods remains difficult, which could be deleterious to the prognosis. Moreover, few data exist regarding procalcitonin (PCT) in early diagnosis of pneumonia after off-pump CABG. Thus, this study was performed to evaluate the value of PCT in diagnosing EPOP after off-pump CABG.

Material/Methods:
A total of 402 consecutive patients undergoing off-pump CABG were retrospectively enrolled. Forty-four patients were diagnosed with EPOP and 112 patients were diagnosed with systemic inflammatory response syndrome (SIRS). Chest roentgenogram, serum PCT, white blood cells, neutral granulocyte ratio, and daily maximum body temperature were recorded. The ability of PCT to diagnose EPOP was evaluated by receiver operating characteristic (ROC) analyses in comparison with traditional methods. Clinical net benefits were estimated via decision curve analysis (DCA).

Results:
PCT presented satisfying accuracy in diagnosing EPOP with a cutoff value of 1.585 ng/mL (area under the curve [AUC] 0.808, 95% confidence interval [CI] 0.724–0.891, sensitivity 73%, specificity 86%). PCT performed better in diagnosing EPOP among SIRS patients (AUC 0.868, 95% CI 0.748–0.988, sensitivity 85%, specificity 89%). DCA showed valuable clinical net benefits of PCT in diagnosing EPOP after off-pump CABG regardless of threshold selected.

Conclusions:
PCT could be a diagnostic marker for EPOP after off-pump CABG. The optimal cutoff value for diagnosing EPOP was 1.585 ng/mL. The application of PCT in diagnosing EPOP in SIRS patients was also satisfying with a cutoff value of 1.775 ng/mL.

MeSH Keywords:
Bacterial • Coronary Artery Bypass • Diagnosis • Off-Pump • Pneumonia

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Background
Postoperative pulmonary infection is a common complication after major cardiac surgery, with high morbidity and mortality [1,2]. About 3–42% patients reported to be diagnosed as pneumonia after cardiac surgery had significant higher fatality rate [1]. Pneumonia after coronary artery bypass grafting (CABG) is associated with 4-fold higher death rate and about 3-fold longer duration of hospitalization compared to patients without it [1]. More than a quarter of patients who need CABG were older than 70 years of age [2]. The rapidly growing proportion of the older patients is often accompanied by the increasing incidence of postoperative pneumonia [3,4].

Current diagnosis and validation of postoperative pneumonia require a combination of many factors, such as chest roentgenogram, white blood cells (WBC), neutral granulocyte ratio, and body temperature, and their measurements often lagged behind the actual occurrence of the condition (not determined in early stage) [5]. The hysteresis of traditional diagnostic methods could delay the treatment, thus hindering postoperative recovery and increasing mortality. Therefore, it is of great significance to develop a more accurate and effective method in diagnosing early postoperative pneumonia (EPOP). Procalcitonin (PCT) is a widely-recognized clinical marker of bacterial infection [3]. We attempted to evaluate the effectiveness and feasibility of PCT in diagnosing EPOP after off-pump CABG in comparison PCT with traditional diagnostic methods.

Material and Methods

Ethics statement
Written inform consents were obtained from all enrolled patients before applying the clinical records. All protocols adopted here were approved by the Ethics Committee at East Hospital (ID: 2017-043) with the clinical trial registration number ChiCTR-RRC-17014055.

Patients
Of the 578 patients undergoing CABG between January 2015 and July 2017 in our department, 402 patients were eventually enrolled in this retrospective observational study. The inclusion criteria were as follows: age >18 years old, first-time isolated off-pump CABG, and normal liver and kidney function before operation. Exclusion criteria were as follows: severe and prolonged cardiogenic shock, preoperative use of glucocorticoids or large-dose antibiotics, preoperative infection disease (including pneumonia), autoimmune disease, carcinoma and malnutrition, death within 3 days after surgery, or incomplete clinical data.

Prior to intubation, all patients routinely took antibiotics every 4 hours during the operation and every 8 hours after the operation until 24 hours later.

After surgical revascularization, patients were routinely transferred to and treated for 1 to 3 days in the intensive care unit (ICU). Following continued mechanical ventilation for 6 to 12 hours and with adequate breathing measurements, all patients were extubated with an uneventful course.

Definition of early postoperative pneumonia (EPOP)
This study focused on patients diagnosed as pneumonia within 3 days after off-pump CABG. EPOP was based on one chest roentgenogram change (new or progressive and persistent infiltration; consolidation; or cavitation) within 72 hours after operation associated with at least one of the following characteristics [6,7]: 1) fever (>38°C) with no other recognized cause; 2) leucopenia (<4000 WBCs/mm³) or leukocytosis (>12 000 WBCs/mm³); 3) purulent secretion; 4) positive bacteriology tests for sputum.

Definition of systemic inflammatory response syndrome (SIRS)
SIRS was based on the widely-used definition by Muckart and Bhagwanjee. SIRS was defined as no sign of infection and characterized by the presence of at least 2 of the following 4 criteria: 1) body temperature >38°C (>100.4°F) or <36°C (<96.8°F); 2) heart rate >90 beats/min; 3) respiratory rate >20 breaths/min or partial CO₂ pressure (pCO₂) <32 mmHg (<4.3 KPa), or need for mechanical ventilatory support; 4) WBC >12 000/μL or <4000/μL; or >10% immature forms.

Data collection and biological measurements
Demographic characteristics and clinical data were provided by a computerized database of the hospital. Venous blood was routinely sampled for detection of PCT in the morning of postoperative day (POD1) PCT concentration was detected by electrochemiluminescence assay with a Roche Cobas E602 analyzer in accordance with manufacturer’s instruction in the central laboratory of hospital. The range of the PCT assay was 0–100 ng/mL, and the reference range was 0–0.05 ng/mL (analytic sensitivity=0.001 ng/mL). WBC and neutral granulocyte ratio were measured for at least 3 days after operation. Body temperature was first measured every hour within 8 hours after operation (or every 3 hours until 3 times of temperature measurements were all normal) and then once a day. Chest roentgenogram was usually examined at noon on POD1 and POD2, and then tested again according to patient’s condition. Sputum bacteriology test was implemented at noon on POD1 as an ICU routine. Acute Physiology and Chronic Health
Evaluation II (APACHE II) score was determined within the first 5 hour to the ICU.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, while categorical variables as number and percentage. If the data were normally distributed, Student’s t-test (significance level=0.05) and Leven’s test (significance level=0.2) were applied in statistical analysis; otherwise, between-group comparison was performed by the Mann-Whitney U test, with significant level at P<0.05. The calculations above were conducted on SPSS 22.0 (IBM, Chicago, IL, USA).

Serum PCT, WBC, neutral granulocyte ratio, and body temperature at POD1 were numerical data collected to calculate diagnostic accuracy by receiver operating characteristic (ROC) analyses and clinical practicability by decision curve analysis (DCA). The area under the ROC curve (AUC) was calculated for diagnostic accuracy of each tested variation according to the Delong test. The net benefit of PCT, WBC, neutral granulocyte ratio, and body temperature were analyzed after jointing baseline in the way of DCA weighed by the relative harm of a false-positive and false-negative result. DCA was conducted on R software 3.4.0 (The R Foundation for statistical computing, Jersey, Austria) with package Decision curve.

Results

Demographic data and patient characteristics

The 402 patients were aged 64.71±8.72 years old (37 to 86 years old) (Table 1). Among them, 44 patients (10.95%) were diagnosed as EPOP and 112 (27.86%) patients as SIRS.

The concentration of PCT was 1.50±2.98 ng/mL in total cohort. From the whole view of WBC level fluctuation in blood, the concentration at POD1 was 15.18±3.90×10⁹/uL, culminated at POD2 (17.19±4.67×10⁹/uL) and declined at POD3 (14.52±4.39×10⁹/uL). Neutral granulocyte ratio together with body temperature were analyzed after jointing baseline in the way of DCA weighed by the relative harm of a false-positive and false-negative result. DCA was conducted on R software 3.4.0 (The R Foundation for statistical computing, Jersey, Austria) with package Decision curve.

The perioperative data of EPOP group and non-EPOP group are exhibited in Table 2. PCT serum levels were much higher in the EPOP group than the non-EPOP group (5.21±7.15 versus 1.04±1.39 ng/uL, P<0.001). The hospital mortality in the EPOP group was also significantly higher (9.09% versus 1.96%, P=0.006). Eleven patients (2.7%) including 4 with and 7 without pneumonia died at PODS-17. The 4 EPOP patients died of respiratory failure (3 patients) or malignant arrhythmia (1 patient), while the 7 non-EPOP patients died of heart failure (3 patients), myocardial infarction (2 patients) or malignant arrhythmia (2 patients). However, during the first 3 days after operation, neither WBC level nor body temperature varied largely between the groups. The qualitative results for sputum bacteriology tests shown in Supplementary Table 1 represented different bacteria in the respiratory system, including oral cavity.

Diagnostic value of PCT for EPOP

According to the ROC curves in Figure 1A and calculations in Table 3, the AUC of PCT at POD1 was 0.808 and the cutoff value was about 1.585 ng/mL with sensitivity of 73% and specificity of 86%, indicating the underlying considerable diagnostic value of PCT. The AUCs of WBC, neutral granulocyte ratio, and body temperature from POD1 to POD3 were all worse than PCT along with less optimistic cutoff value and sensitivity. The specificity of WBC at POD1 or POD3 and body temperature at POD2 were relatively high (95%, 92%, and 97%, respectively), but none of the sensitivity was satisfying (14%, 16%, and 5%, respectively).

DCA was conducted to analyze the clinical benefits of different molecules in diagnosing EPOP after off-pump CABG in the validation dataset. The WBC, neutral granulocyte ratio, and body temperature showed very close decision curves, regardless of the threshold selected, and their net benefits were significantly smaller than PCT between 5% and 95% (Figure 2A).

Diagnostic value of PCT in SIRS patients

The 402 patients were divided into a SIRS group and a non-SIRS group (Supplementary Table 2), which involved 13 and 31 EPOP patients, respectively. Figure 1B and 1C present AUCs of PCT, WBC, neutral granulocyte ratio, and body temperature, and Table 4 summaries the calculations according to the AUC and validation dataset. In the SIRS group, PCT performed better with AUC of 0.868 (95% CI 0.748–0.988), cutoff value of 1.775 ng/mL, sensitivity of 85% and specificity of 89%. In the non-SIRS group, PCT performed better with AUC of 0.784 (95% CI 0.680–0.889), cutoff value of 1.580 ng/mL, sensitivity of 68% and specificity of 86%.

In the SIRS group, the decision curves of WBC, neutral granulocyte ratio, and body temperature also remained close regardless of the threshold selected, but their net benefits were significantly fewer than PCT between 5% and 100% (Figure 2B). In the non-SIRS group, PCT was not superior over the other 3 methods, and the 4 decision curves remained close regardless of the threshold selected (Figure 2C).

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PCT is widely acknowledged as a valuable marker of inflammatory response after cardiac surgery [8]. The serum PCT concentration is very low among non-infected healthy people (<0.05 ng/mL), but could be remarkably increased by about 10-fold by bacterial infection instead of other organism infection [9]. After injection of bacterial endotoxin, the serum PCT level in healthy people could increase within 3 to 4 hours and exceed the maximum by about 1700-fold within 24 hours [10]. PCT level reflects the response activity of systemic inflammation and is affected by the size and types of infected organs, bacterial species, degree of inflammation and immune response [11]. However, the PCT levels in these

Table 1. Clinical characteristics of 402 consecutive off-pump CABG patients.

|                                | Total (N=402) |
|--------------------------------|---------------|
| Age (y)                        | 64.71±8.72 (37–86) |
| <70 (n, %)                     | 276 (68.7) |
| ≥70 (n, %)                     | 126 (31.3) |
| Female (n, %)                  | 88 (21.89) |
| Weight (kg)                    | 69.50±10.78 (45–125) |
| Height (cm)                    | 166.72±7.33 (142–185) |
| BMI (kg/m²)                    | 24.96±3.19 (16.98–38.58) |
| Morbid obesity (n, %)          | 244 (60.70) |
| Body surface area (m²)         | 1.75±0.17 (1.30–2.55) |
| Diabetes (n, %)                | 114 (28.36) |
| Hypertension (n, %)            | 240 (59.70) |
| Renal failure (n, %)           | 2 (0.50) |
| Serum creatinine (µmol/L)      | 77.20±29.32 (29.20–413.70) |
| Endogenous creatinine clearance rate (mL/min) | 83.54±29.52 (6.42–246.55) |
| Cerebrovascular accident (n, %)| 34 (8.46) |
| COPD (n, %)                    | 20 (4.98) |
| Peripheral vascular disease (n, %) | 7 (1.74) |
| Previous PCI (n, %)            | 31 (7.71) |
| Atrial flutter and fibrillation (n, %) | 8 (1.99) |
| Accompanied by pulmonary hypertension (n, %) | 99 (24.63) |
| Myocardial infarction (n, %)   | 36 (8.96) |
| Unstable angina pectoris (n, %) | 186 (46.27) |
| Number of diseased coronary vessels (n) | 2.84±0.49 (1–3) |
| Three-vessel coronary disease (n, %) | 358 (89.05) |
| NYHA IV (n, %)                 | 10 (2.49) |
| LVEF (%)                       | 59.79±8.91 (20.90–73.10) |
| Preoperative IABP (n, %)       | 4 (1.00) |
| Status of surgery              |               |
| Elective (n, %)                | 372 (92.54) |
| Urgent (n, %)                  | 30 (7.46) |
| Number of grafts (n)           | 3.61±1.01 (1–6) |
| PCT (ng/mL)                    | 1.50±2.98 (0.04–40.88) |
| POD1 WBC (×10⁶/µL)            | 15.18±3.90 (7.01–36.12) |
| POD2 WBC (×10⁶/µL)            | 17.19±4.67 (4.14–33.86) |
| POD3 WBC (×10⁶/µL)            | 14.52±4.39 (4.53–32.76) |
| POD1 neutrophil ratio (%)      | 89.66±3.13 (76.67–97.04) |
| POD2 neutrophil ratio (%)      | 88.10±3.37 (72.22–97.32) |
| POD3 neutrophil ratio (%)      | 87.54±4.50 (70.01–99.27) |
| PO temperature (C)             | 37.05±0.58 (35.30–38.70) |
| POD1 temperature (C)           | 37.59±0.51 (35.90–40.10) |
| POD2 temperature (C)           | 37.49±0.58 (36.20–39.50) |
| POD3 temperature (C)           | 37.20±0.51 (36.20–39.30) |
| APACHE II score                | 19.36±2.00 (14.00–25.00) |
| SIRS (n, %)                    | 112 (27.86) |
| SIRS (n, %)                    |               |
| EPOP (n, %)                    | 44 (10.95) |
| ICU LOS (d)                    | 2.52±2.50 (1–16) |
| Readmission ICU (n, %)         | 20 (4.98) |
| Hospital mortality (n, %)      | 11 (2.74) |

CABG – coronary artery bypass grafting surgery; BMI – body mass index; COPD – chronic obstructive pulmonary disease; PCI – percutaneous coronary intervention; NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; PCT – procalcitonin; POD – postoperative day; WBC – white blood cell; PO – postoperative; APACHE – Acute Physiology and Chronic Health Evaluation; SIRS – systemic inflammatory response syndrome; EPOP – early postoperative pneumonia; ICU – intensive care unit; LOS – length of stay.

Discussion

PCT is widely acknowledged as a valuable marker of inflammatory response after cardiac surgery [8]. The serum PCT concentration is very low among non-infected healthy people (<0.05 ng/mL), but could be remarkably increased by about 10-fold by bacterial infection instead of other organism infection [9]. After injection of bacterial endotoxin, the serum PCT level in healthy people could increase within 3 to 4 hours and exceed the maximum by about 1700-fold within 24 hours [10]. PCT level reflects the response activity of systemic inflammation and is affected by the size and types of infected organs, bacterial species, degree of inflammation and immune response [11]. However, the PCT levels in these
Table 2. Comparison of patients in EPOP and non EPOP groups.

|                               | EPOP group  | Non EPOP group | P     |
|--------------------------------|-------------|----------------|-------|
| Age (y)                       | 66.61±7.64  | 64.47±8.82     | 0.124 |
| ≥70 (n, %)                    | 19 (43.18)  | 107 (29.89)    | 0.073 |
| Female (n, %)                 | 12 (27.27)  | 76 (21.23)     | 0.361 |
| Weight (kg)                   | 65.92±10.85 | 69.94±10.70    | 0.019 |
| Height (cm)                   | 165.80±7.60 | 166.84±7.30    | 0.375 |
| BMI (kg/m²)                   | 23.96±3.45  | 25.08±3.11     | 0.028 |
| Morbid obesity (n, %)         | 26 (59.09)  | 219 (61.17)    | 0.644 |
| Body surface area (m²)        | 1.70±0.17   | 1.76±0.17      | 0.029 |
| Diabetes (n, %)               | 16 (36.36)  | 98 (27.37)     | 0.212 |
| Hypertension (n, %)           | 28 (63.64)  | 212 (59.22)    | 0.573 |
| Renal failure (n, %)          | 1 (2.27)    | 1 (0.28)       | 0.361 |
| Serum creatinine (µmol/L)     | 83.74±55.91 | 76.39±24.14    | 0.394 |
| Endogenous creatinine clearance rate (mL/min) | 75.59±34.11 | 84.52±28.81    | 0.058 |
| Cerebrovascular accident (n, %)| 5 (11.36)   | 29 (8.10)      | 0.509 |
| COPD (n, %)                   | 4 (9.09)    | 16 (4.47)      | 0.184 |
| Peripheral vascular disease (n, %) | 1 (2.27)  | 6 (1.68)       | 0.775 |
| Previous PCI (n, %)           | 8 (18.18)   | 23 (6.42)      | 0.066 |
| Atrial flutter and fibrillation (n, %) | 0 (0.00)   | 8 (2.23)       | 0.317 |
| Pulmonary hypertension (n, %)  | 13 (29.55)  | 86 (24.02)     | 0.423 |
| Myocardial infarction (n, %)   | 3 (6.82)    | 33 (9.22)      | 0.752 |
| Unstable angina pectoris (n, %)| 23 (52.27)  | 163 (45.53)    | 0.752 |
| Number of diseased coronary vessels (n) | 2.95±0.21  | 2.82±0.51      | 0.136 |
| Three-vessel coronary disease (n, %) | 42 (95.45) | 316 (88.27)    | 0.082 |
| NYHA IV (n, %)                | 1 (2.27)    | 9 (2.51)       | 0.775 |
| LVEF (%)                      | 60.16±8.95  | 59.75±8.92     | 0.098 |
| Preoperative IABP (n, %)       | 1 (2.27)    | 3 (0.84)       | 0.998 |
| Status of surgery             |             |                |       |
| Elective (n, %)               | 40 (90.91)  | 332 (92.74)    | 0.677 |
| Urgent (n, %)                 | 4 (9.09)    | 22 (6.42)      |       |
| Number of grafts (n)          | 3.75±0.87   | 3.59±1.02      | 0.374 |
| PCT (ng/mL)                   | 5.21±7.15   | 1.04±1.39      | 0.000 |
| POD1 WBC (×10⁹/µL)           | 15.50±4.20  | 15.14±3.87     | 0.566 |
| POD2 WBC (×10⁹/µL)           | 17.40±4.94  | 17.17±4.64     | 0.760 |
| POD3 WBC (×10⁹/µL)           | 14.85±5.95  | 14.48±4.16     | 0.684 |
cases probably induced by the release of cytokines or bacterial shifting from the gut are significantly lower than those with bacterial infection [12].

CABG is the most common cardiac surgery and the largest number of operations performed in cardiac surgery. Contact of the blood with the surface of artificial extracorporeal circulation pipeline in on-pump CABG can induce systemic inflammatory response in the blood mediated by abundant secretion of inflammatory factors. The infectious markers are sensitive to inflammation after cardiac surgery, which needs extracorporeal circulation. Off-pump CABG has become a commonly used bypass method because it is more beneficial for patients as it avoids additional myocardial injury, inflammatory reaction and influence on blood flow dynamics [13]. The off-pump pattern is more commonly used in China [14]. Moreover, the aging problem of coronary artery disease patients is a concern in developing countries (e.g., China) in addition to developed countries. In this study, 31.3% of the patients were older than 70 years old. Therefore, pneumonia still frequently occurred after off-pump CABG, accompanied by the increasing proportion of older patients [15]. Patients with pneumonia were likely to have a prolonged postoperative hospital stay and higher risk of mortality [1]. In our study, the incidence of EPOP was 10.95% and the mortality of EPOP patients was significantly higher than the non-EPOP patients.

Diagnosis of EPOP could benefit the prognosis by shortening the ICU stay time and eventually guide early risk stratification and antibiotic application [16]. However, early diagnosis of infectious complications is still difficult for patients assigned to ICU after cardiac surgery [17]. Chest roentgenogram examination is necessary for diagnosis of postoperative pneumonia, but is not sufficient and should be supplemented by other indicators. Traditional infectious markers including leukocytes, neutral granulocyte ratio, and body temperature are valuable indicators. Traditional infectious markers including leukocytes, neutral granulocyte ratio, and body temperature are valuable indicators. However, early diagnosis of infectious complications is still difficult for patients assigned to ICU after cardiac surgery [17]. Chest roentgenogram examination is necessary for diagnosis of postoperative pneumonia, but is not sufficient and should be supplemented by other indicators. Traditional infectious markers including leukocytes, neutral granulocyte ratio, and body temperature are valuable indicators. Traditional infectious markers including leukocytes, neutral granulocyte ratio, and body temperature are valuable indicators.

In the past decade, PCT has been studied during ICU stays after cardiac surgery as a diagnostic monitoring of bacterial infection, and could be used as an early marker to differentiate inflammation with or without bacterial infection and to evaluate clinical course or prognosis of inflammatory disease [16]. However, early diagnosis of infectious complications is still difficult for patients assigned to ICU after cardiac surgery [17]. Chest roentgenogram examination is necessary for diagnosis of postoperative pneumonia, but is not sufficient and should be supplemented by other indicators. Traditional infectious markers including leukocytes, neutral granulocyte ratio, and body temperature are valuable indicators. Traditional infectious markers including leukocytes, neutral granulocyte ratio, and body temperature are valuable indicators.

### Table 2 continued. Comparison of patients in EPOP and non EPOP groups.

|                           | EPOP group          | Non EPOP group        | P     |
|---------------------------|---------------------|-----------------------|-------|
| POD1 neutrophil ratio (%) | 89.68±3.77 (81.32–97.04) | 89.65±3.04 (76.67–95.95) | 0.965 |
| POD2 neutrophil ratio (%) | 89.01±3.47 (78.16–97.32) | 87.98±3.34 (72.22–96.91) | 0.056 |
| POD3 neutrophil ratio (%) | 88.94±3.81 (79.83–95.31) | 87.36±4.55 (70.01–99.27) | 0.027 |
| PO temperature (C)        | 37.12±0.66 (36.20–38.70) | 37.04±0.57 (35.30–38.70) | 0.480 |
| POD1 temperature (C)      | 37.66±0.55 (36.40–39.00) | 37.58±0.50 (35.90–40.10) | 0.323 |
| POD2 Temperature (C)      | 37.40±0.62 (36.30–39.30) | 37.50±0.58 (36.20–39.50) | 0.262 |
| POD3 temperature (C)      | 37.28±0.56 (36.30–39.10) | 37.19±0.50 (36.20–39.30) | 0.316 |
| APACHE II score           | 19.80±2.24 (15.00–25.00) | 19.30±1.96 (14.00–24.00) | 0.168 |
| SIRS (n, %)               | 13 (29.55)          | 99 (27.65)            | 0.792 |
| ICU LOS (d)               | 2.45±2.24 (1–10)    | 2.53±2.53 (1–16)      | 0.860 |
| Readmission ICU (n, %)    | 3 (6.82)            | 17 (4.75)             | 0.552 |
| Hospital mortality (n, %) | 4 (9.09)            | 7 (1.96)              | 0.006 |

**EPOP** – early postoperative pneumonia; **BMI** – body mass index; **COPD** – chronic obstructive pulmonary disease; **PCI** – percutaneous coronary intervention; **NYHA** – New York Heart Association; **LVEF** – left ventricular ejection fraction; **PCT** – procalcitonin; **POD** – postoperative day; **WBC** – white blood cell; **PO** – postoperative; **APACHE** – Acute Physiology and Chronic Health Evaluation; **SIRS** – systemic inflammatory response syndrome; **ICU** – intensive care unit; **LOS** – length of stay.
a half-life of 18 hours to 24 hours. Therefore, we tested serum PCT at POD1 to investigate its correlation with EPOP.

In the present study, the serum PCT level at POD1 and neutral granulocyte ratios at POD2 and POD3 in the EPOP group were all significantly higher than in the non-EPOP group. However, the cutoff value of PCT in diagnosing EPOP exceeds 1.585 ng/mL with sensitivity of 73% and specificity of 86%, and its diagnostic value is reliable and superior over body temperature, WBC, and neutral granulocyte ratio. The diagnosis of EPOP based on serum PCT is earlier and more accurate than other traditional markers according to ROC analysis. Overall, the composite

Figure 1. (A) ROC show the value of PCT (value on POD1), WBC (value on POD1), neutrophil ratio (value on POD1), and body temperature (value on POD1) for the diagnosis of EPOP in total patient cohort. (B) ROC curves show the value of PCT, WBC, neutrophil ratio, and body temperature for the diagnosis of EPOP in SIRS group. (C) ROC curves show the value of PCT, WBC, neutrophil ratio, and body temperature for the diagnosis of EPOP in non-SIRS group. ROC – receiver operating characteristic; POD – postoperative day; PCT – procalcitonin; EPOP – early postoperative pneumonia; WBC – white blood cell; SIRS – systemic inflammatory response syndrome.
Table 3. ROC analysis to diagnosis EPOP in the whole cohort.

|               | AUC   | 95%CI          | P value | Cutoff | Sensitivity (%) | Specificity (%) |
|---------------|-------|----------------|---------|--------|-----------------|-----------------|
| PCT (ng/mL)   | 0.808 | 0.724–0.891    | 0.000   | >1.585 | 73              | 86              |
| POD1 WBC      | 0.519 | 0.425–0.613    | 0.682   | >21.425| 14              | 95              |
| POD2 WBC      | 0.500 | 0.403–0.597    | 0.999   | >20.30 | 34              | 79              |
| POD3 WBC      | 0.482 | 0.385–0.580    | 0.703   | >21.005| 16              | 92              |
| POD1 neutrophil% | 0.500 | 0.400–0.599    | 0.996   | >92.111| 30              | 79              |
| POD2 neutrophil% | 0.601 | 0.513–0.689    | 0.029   | >88.820| 66              | 59              |
| POD3 neutrophil% | 0.596 | 0.508–0.683    | 0.038   | >92.148| 30              | 88              |
| POD1 temperature | 0.557 | 0.460–0.654    | 0.217   | >37.75 | 57              | 65              |
| POD2 temperature | 0.448 | 0.356–0.540    | 0.261   | >38.75 | 5               | 97              |
| POD3 temperature | 0.545 | 0.454–0.635    | 0.334   | >37.15 | 59              | 52              |

ROC – receiver operating characteristic; EPOP – early postoperative pneumonia; AUC – area under the curve; CI – confidence intervals; PCT – procalcitonin; POD – postoperative day; WBC – white blood cell.

Figure 2. (A) Decision curves show the clinical usefulness of PCT, WBC, neutrophil ratio, and body temperature in diagnosis of EPOP in total patient. (B) Decision curves show the clinical usefulness of PCT, WBC, neutrophil ratio, and body temperature in diagnosis of EPOP in SIRS group. (C) Decision curves show the clinical usefulness of PCT, WBC, neutrophil ratio, and body temperature in diagnosis of EPOP in non-SIRS group. PCT – procalcitonin; WBC – white blood cell; EPOP – early postoperative pneumonia; SIRS – systemic inflammatory response syndrome.
expression for PCT in diagnosing EPOP and in clinical use is relatively superior over the 3 traditional diagnostic markers.

Serum PCT is an important index of bacterial infection with great guiding effects on antibiotics choice in the early stage for infection [16] and smart reflection of the severity and long-term prognosis [19], and thus is useful in diagnosis of postoperative SIRS after CABG. As has been reported, the PCT levels were different between the severe SIRS group and the control group, but not between the SIRS patients and the non-SIRS patients [20]. The incidence of SIRS in our study was 27.86%. Our analysis suggests PCT has no value in diagnosing SIRS, which is in accordance with the literatures aforementioned. Our patients did not have severe SIRS. The degree of systemic inflammatory response without cardiopulmonary bypass was also reduced compared with on-pump cardiac surgery [21]. Therefore, PCT was not different between SIRS and non-SIRS groups. However, the diagnosis of EPOP after off-pump CABG was extremely accurate especially in SIRS patients. The cutoff value of PCT in predicting EPOP in the SIRS group was 1.775 ng/mL with sensitivity of 85% and specificity of 89%, indicating PCT is valuable for infection diagnosis in more complex complications.

Although PCT is valuable in diagnosing infection after cardiac surgery, the cutoff value is not consistent, as it is affected by the types of surgical procedures used among different medical centers. As previously reported, PCT had a cutoff value of 4 ng/mL, sensitivity of 86% and specificity of 98% in predicting infection among 59 CPB-treated patients [22]. The level of PCT (>2 ng/mL) had a sensitivity of 83% and a specificity of 75%

Table 4. ROC analysis to diagnosis EPOP in SIRS and non SIRS groups.

| SIRS group | AUC   | 95% CI | P value | Cutoff | Sensitivity (%) | Specificity (%) |
|------------|-------|--------|---------|--------|----------------|----------------|
| PCT (ng/mL)| 0.868 | 0.748–0.988 | 0.000 | >1.775 | 85 | 89 |
| POD1 WBC  | 0.596 | 0.406–0.787 | 0.260 | >17.49 | 46 | 80 |
| POD2 WBC  | 0.447 | 0.260–0.634 | 0.534 | >20.645 | 31 | 80 |
| POD3 WBC  | 0.426 | 0.249–0.602 | 0.386 | >21.745 | 15 | 95 |
| POD1 N%   | 0.347 | 0.176–0.519 | 0.074 | >95.395 | 8 | 100 |
| POD2 N%   | 0.577 | 0.425–0.730 | 0.366 | >85.96 | 92 | 31 |
| POD3 N%   | 0.490 | 0.318–0.661 | 0.902 | >92.117 | 23 | 89 |
| POD1 temp | 0.542 | 0.384–0.700 | 0.627 | >37.75 | 92 | 28 |
| POD2 temp | 0.406 | 0.244–0.568 | 0.272 | >36.85 | 100 | 6 |
| POD3 temp | 0.448 | 0.268–0.628 | 0.546 | >38.65 | 15 | 97 |

| Non SIRS group | AUC   | 95% CI | P value | Cutoff | Sensitivity (%) | Specificity (%) |
|----------------|-------|--------|---------|--------|----------------|----------------|
| PCT (ng/mL)    | 0.784 | 0.680–0.889 | 0.000 | >1.580 | 68 | 86 |
| POD1 WBC       | 0.487 | 0.382–0.593 | 0.820 | >13.35 | 68 | 38 |
| POD2 WBC       | 0.522 | 0.409–0.635 | 0.690 | >20.3 | 35 | 79 |
| POD3 WBC       | 0.504 | 0.387–0.621 | 0.942 | >21.005 | 16 | 93 |
| POD1 N%        | 0.567 | 0.454–0.679 | 0.225 | >92.111 | 36 | 79 |
| POD2 N%        | 0.613 | 0.505–0.720 | 0.040 | >88.812 | 71 | 57 |
| POD3 N%        | 0.637 | 0.538–0.735 | 0.013 | >87.392 | 77 | 48 |
| POD1 temp      | 0.559 | 0.435–0.682 | 0.287 | >37.75 | 42 | 79 |
| POD2 temp      | 0.433 | 0.319–0.548 | 0.224 | >37.95 | 7 | 95 |
| POD3 temp      | 0.591 | 0.479–0.703 | 0.099 | >37.15 | 58 | 61 |

ROC – receiver operating characteristic; EPOP – early postoperative pneumonia; SIRS – systemic inflammatory response syndrome; AUC – area under the curve; CI – confidence intervals; PCT – procalcitonin; POD – postoperative day; WBC – white blood cell; N – neutrophil; temp – temperature.
in infection discrimination [23]. In the present study, the cut-off point of PCT in predicting EPOP was 1.585 ng/mL, but rose to 1.775 ng/mL in the SIRS group. Although the cutoff values were different, the increasing PCT levels were consistent with the postoperative infection.

DCA is a predictive model widely used in clinical decision-making to evaluate the accuracy of diagnostic methods [24]. Unlike ROC analysis which only concerns the accuracy from the perspectives of specificity and sensitivity, DCA developed by Vickers et al. concerns the net benefits and has greater clinical value [25]. In our study, DCA was proved a convincing clinical method for PCT in diagnosing EPOP both in total cohort and in SIRS group regardless of the threshold selected.

Limitations

Firstly, this retrospective monocentric survey had no long-term follow-up for these patients. Secondly, the sample size was small, which should be supplemented by larger sample of patients. Thirdly, this study was focused only on EPOP patients who had undergone off-pump CABG. Fourthly, this study was limited by the discrepancy between the EPOP and non EPOP cohorts.

Conclusions

PCT is an available and valuable marker in distinguishing early pneumonia for off-pump CABG. The diagnosing accuracy of PCT is higher than traditional methods. PCT also show satisfactory performance on diagnosing EPOP in SIRS patients.

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Supplementary Tables

Supplementary Table 1. Comparison of bacterium detected in EPOP and non EPOP groups.

| Organism                        | EPOP group N=44 | Non EPOP group N=358 |
|---------------------------------|-----------------|----------------------|
| Gram positive coccus           | 1 (2.27%)       | 15 (4.19%)           |
| Gram negative bacilli          | 16 (36.36%)     | 134 (37.43%)         |
| Klebsiella pneumoniae          | 7 (15.91%)      | 12 (3.35%)           |
| Baumanii                       | 9 (20.45%)      | 6 (1.68%)            |
| Candida albicans               | 1 (2.27%)       | 1 (0.28%)            |
| Fungal spore                   | 2 (4.55%)       | 3 (0.84%)            |
| Pseudomonas aeruginosa         | 5 (11.36%)      | 7 (1.96%)            |
| Streptococcus pneumoniae       | 2 (0.00%)       | 3 (0.84%)            |
| Haemophilus influenzae         | 2 (0.00%)       | 2 (0.56%)            |
| Haemophilus parainfluenzae     | 0 (0.00%)       | 2 (0.56%)            |
| Candida glabrata               | 2 (0.00%)       | 2 (0.56%)            |
| Bacillus prodigiosus           | 1 (2.27%)       | 2 (0.56%)            |
| Enterobacteriaceae Ludwig      | 0 (0.00%)       | 1 (0.28%)            |
| Morganella morganii            | 0 (0.00%)       | 1 (0.28%)            |
| Raoultella ornithinolytica     | 0 (0.00%)       | 1 (0.28%)            |
| Streptococcus agalactiae       | 0 (0.00%)       | 1 (0.28%)            |
| Staphylococcus human subspecies| 0 (0.00%)       | 1 (0.28%)            |
| Enterobacter aerogenes         | 1 (2.27%)       | 0 (0.00%)            |
### Supplementary Table 2. Comparison of patients in SIRS and non SIRS groups.

| Organism                        | EPOP group N=44 | Non EPOP group N=358 |
|---------------------------------|------------------|----------------------|
| Escherichia coli                | 2 (4.55%)        | 0 (0.00%)            |
| Staphylococcus aureus           | 2 (4.55%)        | 0 (0.00%)            |
| Coagulase negative staphylococci| 1 (2.27%)        | 0 (0.00%)            |
| Moraxelle catarrhalis           | 0 (0.00%)        | 1 (0.28%)            |

EPOP – early postoperative pneumonia.
| Status of surgery               | SIRS group N=112 | Non SIRS group N=290 | P  |
|--------------------------------|------------------|----------------------|----|
| Elective (n, %)                | 99 (88.39)       | 273 (94.14)          | 0.055 |
| Urgent (n, %)                  | 13 (11.61)       | 14 (4.83)            |    |
| Number of grafts (n)           | 3.58±1.05 (1–6)  | 3.62±0.99 (1–6)      | 0.742 |
| PCT (ng/ml)                    | 1.52±2.25 (0.13–13.07) | 1.49±3.22 (0.04–40.88) | 0.918 |
| POD1 WBC (+10³/ul)             | 15.35±3.65 (8.18–26.88) | 15.12±4.00 (7.01–36.12) | 0.591 |
| POD2 WBC (+10³/ul)             | 17.06±4.64 (14.4–27.7) | 17.24±4.69 (7.36–33.86) | 0.727 |
| POD3 WBC (+10³/ul)             | 14.69±4.17 (5.34–27.52) | 14.45±4.47 (4.53–32.76) | 0.626 |
| POD1 N ratio (%)               | 89.19±3.24 (79.48–96.17) | 89.84±3.07 (76.67–97.04) | 0.064 |
| POD2 N ratio (%)               | 87.53±3.66 (72.2–94.84) | 88.32±3.23 (78.06–97.32) | 0.036 |
| POD3 N ratio (%)               | 87.66±4.54 (71.86–95.38) | 87.49±4.49 (70.01–99.27) | 0.724 |
| PO Temp (°C)                   | 37.21±0.63 (35.50–38.70) | 36.99±0.54 (35.30–38.70) | 0.001 |
| POD1 Temp (°C)                 | 38.02±0.49 (36.90–40.10) | 37.42±0.40 (35.90–38.70) | 0.000 |
| POD2 Temp (°C)                 | 37.98±0.63 (36.50–39.50) | 37.30±0.44 (36.20–38.50) | 0.000 |
| POD3 Temp (°C)                 | 37.52±0.61 (36.50–39.30) | 37.08±0.40 (36.20–38.20) | 0.000 |
| APACHE II score               | 19.06±2.14 (14–24) | 19.47±1.93 (15–25)   | 0.067 |
| EPOP (n, %)                    | 13 (11.61)       | 31 (10.69)           | 0.792 |
| ICU LOS (d)                    | 2.97±2.60 (1–11) | 2.34±2.44 (1–16)     | 0.023 |
| Readmission ICU (n, %)         | 6 (5.36)         | 14 (4.83)            | 0.827 |
| Hospital mortality (n, %)      | 4 (3.57)         | 7 (2.41)             | 0.524 |

SIRS – systemic inflammatory response syndrome; BMI – body mass index; Scr – serum creatinine; Ccr – endogenous creatinine clearance rate; COPD – chronic obstructive pulmonary disease; PCI – percutaneous coronary intervention; NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; PCT – procalcitonin; POD – postoperative day; WBC – white blood cell; N – neutrophil; PO – postoperative; Temp – temperature; APACHE – Acute Physiology and Chronic Health Evaluation; EPOP – early postoperative pneumonia; ICU – intensive care unit; LOS – length of stay.

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