Received: 2018.10.19
Accepted: 2019.01.07
Published: 2019.04.26

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

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Source of support:

This work was supported by the Six Major Talent Summit of Jiangsu Province (2015-WSW-019) and the Practice Innovation Training Program projects for Jiangsu students in college (201710312063X)

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, neutrophil 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

Full-text PDF:

<https://www.medscimonit.com/abstract/index/idArt/913704>

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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 ($>38^{\circ}\text{C}$) with no other recognized cause; 2) leucopenia (<4000 WBCs/ mm^3) or leukocytosis ($>12\,000$ WBCs/ mm^3); 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 $>38^{\circ}\text{C}$ ($>100.4^{\circ}\text{F}$) or $<36^{\circ}\text{C}$ ($<96.8^{\circ}\text{F}$); 2) heart rate >90 beats/min; 3) respiratory rate >20 breaths/min or partial CO_2 pressure (pCO_2) <32 mmHg (<4.3 kPa), or need for mechanical ventilatory support; 4) WBC $>12\,000/\mu\text{L}$ or $<4000/\mu\text{L}$; 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 manufacture'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 $\pm$ 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 $15.18\pm 3.90\times 10^3/\mu\text{L}$, culminated at POD2 ($17.19\pm 4.67\times 10^3/\mu\text{L}$) and declined at POD3 ($14.52\pm 4.39\times 10^3/\mu\text{L}$). Neutral granulocyte ratio together with body temperature within 3 days after operation are showed in Table 1.

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 POD5-17. 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 summarizes 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)

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

Total (N=402)			Total (N=402)		
Age (y)	64.71±8.72	(37–86)	Three-vessel coronary disease (n, %)	358	(89.05)
<70 (n, %)	276	(68.7)	NYHA IV (n, %)	10	(2.49)
≥70 (n, %)	126	(31.3)	LVEF (%)	59.79±8.91	(20.90–73.10)
Female (n, %)	88	(21.89)	Preoperative IABP (n, %)	4	(1.00)
Weight (kg)	69.50±10.78	(45–125)	Status of surgery		
Height (cm)	166.72±7.33	(142–185)	Elective (n, %)	372	(92.54)
BMI (kg/m ²)	24.96±3.19	(16.98–38.58)	Urgent (n, %)	30	(7.46)
Morbid obesity (n, %)	244	(60.70)	Number of grafts (n)	3.61±1.01	(1–6)
Body surface area (m ²)	1.75±0.17	(1.30–2.55)	PCT (ng/mL)	1.50±2.98	(0.04–40.88)
Diabetes (n, %)	114	(28.36)	POD1 WBC (×10 ³ /uL)	15.18±3.90	(7.01–36.12)
Hypertension (n, %)	240	(59.70)	POD2 WBC (×10 ³ /uL)	17.19±4.67	(4.14–33.86)
Renal failure (n, %)	2	(0.50)	POD3 WBC (×10 ³ /uL)	14.52±4.39	(4.53–32.76)
Serum creatinine (μmol/L)	77.20±29.32	(29.20–413.70)	POD1 neutrophil ratio (%)	89.66±3.13	(76.67–97.04)
Endogenous creatinine clearance rate (mL/min)	83.54±29.52	(6.42–246.55)	POD2 neutrophil ratio (%)	88.10±3.37	(72.22–97.32)
Cerebrovascular accident (n, %)	34	(8.46)	POD3 neutrophil ratio (%)	87.54±4.50	(70.01–99.27)
COPD (n, %)	20	(4.98)	PO temperature (C)	37.05±0.58	(35.30–38.70)
Peripheral vascular disease (n, %)	7	(1.74)	POD1 temperature (C)	37.59±0.51	(35.90–40.10)
Previous PCI (n, %)	31	(7.71)	POD2 temperature (C)	37.49±0.58	(36.20–39.50)
Atrial flutter and fibrillation (n, %)	8	(1.99)	POD3 temperature (C)	37.20±0.51	(36.20–39.30)
Accompanied by pulmonary hypertension (n, %)	99	(24.63)	APACHE II score	19.36±2.00	(14.00–25.00)
Myocardial infarction (n, %)	36	(8.96)	SIRS (n, %)	112	(27.86)
Unstable angina pectoris (n, %)	186	(46.27)	EPOP (n, %)	44	(10.95)
Number of diseased coronary vessels (n)	2.84±0.49	(1–3)	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 N=44		Non EPOP group N=358		P
Age (y)	66.61±7.64	(48–81)	64.47±8.82	(37–86)	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	(45–97)	69.94±10.70	(47–125)	0.019
Height (cm)	165.80±7.60	(144–182)	166.84±7.30	(142–185)	0.375
BMI (kg/m ²)	23.96±3.45	(16.98–33.56)	25.08±3.14	(17.72–38.58)	0.028
Morbid obesity (n, %)	26	(59.09)	219	(61.17)	0.644
Body surface area (m ²)	1.70±0.17	(1.30–2.13)	1.76±0.17	(1.35–2.55)	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)	0.077
Serum creatinine (μmol/L)	83.74±55.91	(29.20–413.70)	76.39±24.14	(36.40–269.00)	0.394
Endogenous creatinine clearance rate (mL/min)	75.59±34.11	(6.42–231.86)	84.52±28.81	(8.51–246.55)	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)	0.006
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)	
Number of diseased coronary vessels (n)	2.95±0.21	(2–3)	2.82±0.51	(1–3)	0.136
Three-vessel coronary disease (n, %)	42	(95.45)	316	(88.27)	
NYHA IV (n, %)	1	(2.27)	9	(2.51)	0.882
LVEF (%)	60.16±8.95	(33.70–72.80)	59.75±8.92	(20.90–73.10)	0.775
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)	23	(6.42)	
Number of grafts (n)	3.75±0.87	(2–5)	3.59±1.02	(1–6)	0.374
PCT (ng/mL)	5.21±7.15	(0.11–40.88)	1.04±1.39	(0.04–13.07)	0.000
POD1 WBC (×10 ³ /uL)	15.50±4.20	(8.42–26.88)	15.14±3.87	(7.01–36.12)	0.566
POD2 WBC (×10 ³ /uL)	17.40±4.94	(9.61–30.13)	17.17±4.64	(4.14–33.86)	0.760
POD3 WBC (×10 ³ /uL)	14.85±5.95	(5.67–32.76)	14.48±4.16	(4.53–28.91)	0.684

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

	EPOP group N=44		Non EPOP group N=358		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.

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 by-pass 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 in diagnosis of delayed complications, but are hindered in diagnosing EPOP for their prolonged accumulation to peak level [5].

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]. As reported, the increased serum PCT levels after CABG are correlated with infectious complications [18]. The PCT level elevation induced by endotoxin after bacterial infection can be summarized in 2 phases [10]: first, the PCT level elevates quickly mainly due to endotoxin stimulation within 2 to 4 hours after infection; second, serum PCT increases more rapidly and maximizes in the next 6 to 8 hours mainly due to synthesis and release of inflammatory factors from multiple tissues out of thyroid, which sustains for 24 hours in the body and has

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.

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

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.

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

	AUC	95%CI	P value	Cutoff	Sensitivity (%)	Specificity (%)
SIRS group						
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						
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.

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%

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.

Acknowledgements

We wish to thank Yanyan Qi, Siyu Hua, Shipeng Lan, Dengyuan Feng for their help.

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%)
<i>Klebsiella pneumoniae</i>	7	(15.91%)	12	(3.35%)
<i>Baumannii</i>	9	(20.45%)	6	(1.68%)
<i>Candida albicans</i>	1	(2.27%)	1	(0.28%)
Fungal spore	2	(4.55%)	3	(0.84%)
<i>Pseudomonas aeruginosa</i>	5	(11.36%)	7	(1.96%)
<i>Streptococcus pneumoniae</i>	0	(0.00%)	2	(0.56%)
<i>Haemophilus influenzae</i>	0	(0.00%)	2	(0.56%)
<i>Hemophilus parainfluenzae</i>	0	(0.00%)	2	(0.56%)
<i>Candida glabrata</i>	0	(0.00%)	1	(0.28%)
<i>Aerobacter cloacae</i>	2	(4.55%)	2	(0.56%)
<i>Bacillus prodigiosus</i>	1	(2.27%)	2	(0.56%)
<i>Enterobacteriaceae</i> Ludwig	0	(0.00%)	1	(0.28%)
<i>Morganella morganii</i>	0	(0.00%)	1	(0.28%)
<i>Raoultella ornithinolytica</i>	0	(0.00%)	1	(0.28%)
<i>Streptococcus agalactiae</i>	0	(0.00%)	1	(0.28%)
<i>Staphylococcus human</i> subspecies	0	(0.00%)	1	(0.28%)
<i>Enterobacter aerogenes</i>	1	(2.27%)	0	(0.00%)

Organism	EPOP group N=44		Non EPOP group N=358	
<i>Escherichia coli</i>	2	(4.55%)	0	(0.00%)
<i>Staphylococcus aureus</i>	2	(4.55%)	0	(0.00%)
Coagulase negative staphylococcus	1	(2.27%)	0	(0.00%)
<i>Moraxella catarrhalis</i>	0	(0.00%)	1	(0.28%)

EPOP – early postoperative pneumonia.

Supplementary Table 2. Comparison of patients in SIRS and non SIRS groups.

	SIRS group N=112		Non SIRS group N=290		P
Age (y)	63.77±8.89	(42–84)	65.07±8.64	(37–86)	0.180
≥70 (n, %)	33	(29.46)	93	(32.07)	0.614
Female (n, %)	30	(26.79)	58	(20.00)	0.141
Weight (kg)	70.13±9.64	(48–100)	69.26±11.20	(45–125)	0.470
Height (cm)	166.24±7.81	(146–185)	166.91±7.14	(142–182)	0.415
BMI (kg/m ²)	25.33±2.76	(19.59–33.56)	24.81±3.33	(16.98–38.58)	0.144
Morbid obesity (n, %)	112	(100.00)	132	(45.52)	0.000
Body surface area (m ²)	1.76±0.16	(1.35–2.19)	1.75±0.17	(1.30–2.55)	0.657
Diabetes (n, %)	34	(30.36)	80	(27.59)	0.581
Hypertension (n, %)	59	(52.68)	181	(62.41)	0.075
Renal failure (n, %)	1	(0.89)	1	(0.34)	0.484
Serum creatinine (μmol/L)	77.46±40.71	(29.20–413.70)	77.10±23.58	(36.40–233.60)	0.912
Ccr (mL/min)	86.35±29.06	(17.45–231.86)	82.46±29.67	(6.42–246.55)	0.237
Cerebrovascular accident (n, %)	12	(10.71)	22	(7.59)	0.313
COPD (n, %)	3	(2.68)	17	(5.86)	0.189
Peripheral vascular disease (n, %)	3	(2.68)	4	(1.38)	0.373
Previous cardiac surgery (n, %)	10	(8.93)	21	(7.24)	0.570
Atrial flutter and fibrillation (n, %)	3	(2.68)	5	(1.72)	0.540
Pulmonary hypertension (n, %)	30	(26.79)	69	(23.79)	0.533
Myocardial infarction (n, %)	11	(9.82)	25	(8.62)	0.525
Unstable angina pectoris (n, %)	47	(41.96)	139	(47.93)	
Number of diseased coronary vessels (n)	2.82±0.49	(1–3)	2.84±0.49	(1–3)	0.373
Three-vessel coronary disease (n, %)	97	(86.61)	261	(90.00)	
NYHA IV (n, %)	4	(3.57)	6	(2.07)	0.347
LVEF (%)	60.24±9.03	(34.10–71.90)	59.62±8.88	(20.90–73.10)	0.535
Preoperative IABP (n, %)	1	(0.89)	3	(1.03)	0.713

	SIRS group N=112		Non SIRS group N=290		P
Status of surgery					
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 (×10 ³ /uL)	15.35±3.65	(8.18–26.88)	15.12±4.00	(7.01–36.12)	0.591
POD2 WBC (×10 ³ /uL)	17.06±4.64	(4.14–27.72)	17.24±4.69	(7.36–33.86)	0.727
POD3 WBC (×10 ³ /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
POD2N ratio (%)	87.53±3.66	(72.22–94.84)	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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