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Research Article

Postoperative Serum Procalcitonin Level Can Be a Useful Marker of Bacterial Infection after Cardiac Surgery Utilizing Cardiopulmonary Bypass

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Objectives. Procalcitonin level is generally undetectable from blood sample under normal physiological condition. However, its production can be greatly stimulated by the presence of various inflammatory responses, especially those caused by bacterial infection. We aimed to determine if postoperative procalcitonin level could be used to predict bacterial infection more promptly than bacterial culture results. *Materials and Methods*. We performed a retrospective case-control study by collecting postoperative procalcitonin as well as white blood cell level of patients undergoing cardiac surgery using cardiopulmonary bypass from electronic medical records of Ramathibodi Hospital between 1st January 2019 and 30th June 2023. Patients with pre-existing inflammatory syndromes or proven bacterial infection, who had been receiving preoperative treatment-dose antibiotics or steroids, who underwent non-elective surgery, and whose medical record data were lost or insufficiently recorded were excluded. Demographic data and operative details were also collected and reviewed. *Results*. From a total of 146 patients in our study, 42 patients developed proven postoperative bacterial infection. The level of procalcitonin with greatest association to postoperative bacterial infection from our study was 4.13 ng/dl on postoperative day 7. White blood cell level, however, was less predictive of bacterial infection. *Conclusions*. Procalcitonin level, when utilized alongside clinical presentation, proved to be useful as a predictor of bacterial infection during postoperative day 7. A larger, prospective trial of our continuing series would further strengthen our results.

1. Introduction

Procalcitonin is normally undetectable under normal physiological condition. Its use as a predictor of bacterial infection, especially postoperatively, has always been a subject of debate. To further complicate the matter, patients undergoing cardiac surgery using cardiopulmonary bypass would have postoperative systemic inflammatory response syndrome (SIRS) as a result of both non-cellular and cellular immune system stimulation from blood contact with foreign materials. This could greatly interfere with procalcitonin level as it is one of several inflammatory response proteins. Pediatric patients are exceptionally vulnerable to bacterial infection. Accurate prediction and prompt diagnosis of postoperative bacterial infection are paramount to the improved morbidity and mortality.

Some studies [1–7] found procalcitonin to be a useful predictor of postoperative bacterial infection while others [8, 9] did not. Due to the fact that procalcitonin was, as mentioned earlier, a systemic inflammatory response protein, any cause of inflammation could potentially result in rising of procalcitonin level. Therefore, those who did not find an association emphasized the reason to be the systemic inflammatory responses from cardiopulmonary bypass. From these conflicting results, we intended to find out if postoperative procalcitonin level could be used to accurately predict bacterial infection [10].

2. Materials and Methods

2.1. Data Collection. The study protocol and ethical issues were reviewed and approved by Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (No. MURA2023/776). We collected postoperative procalcitonin and white blood cell level of patients undergoing cardiac surgery using cardiopulmonary bypass from electronic medical records of Ramathibodi Hospital between 1st January 2019 and 30th June 2023. The inclusion criterion was patients undergoing cardiac surgery utilizing cardiopulmonary bypass. The exclusion criteria were patients with pre-existing inflammatory syndromes or proven bacterial infection before surgery, patients who had been receiving preoperative treatment-dose antibiotics due to any cause, patients who had been using steroids preoperatively, those who underwent non-elective surgery, and whose medical record data were lost or insufficiently recorded. The total number of patients undergoing cardiac surgery during the study period was 292. After exclusion, the number came to a total of 146. Demographic data and operative details (including operative time, cardiopulmonary bypass time, aortic cross-clamp time, and circulatory arrest time) were also collected.

2.2. Diagnosis of Postoperative Bacterial Infection. For diagnosis of bacterial infection, we classified types of infection into 5 broad categories. Urinary tract infection was diagnosed with fever of more than 38°C and positive urine bacterial culture of more than 10^5 colony-forming units (CFUs)/ml. Gastrointestinal tract infection, in our cases bacterial infectious diarrhea, was diagnosed with positive stool bacterial culture and pertinent clinical signs and symptoms of bacterial diarrhea. A diagnosis of respiratory tract infection would be made when sputum bacterial culture was positive combined with clinical signs and symptoms of bacterial pneumonia. Catheter-related blood stream infection (CRBSI) was diagnosed in patients with an indwelling catheter in place for more than 48 hours using simultaneous collection of blood samples from the catheter and 2 peripheral sites. If, combined with fever of more than 38°C, bloodstream bacterial culture from the indwelling catheter was positive within 2 hours of the peripheral sites, or vice versa, and the organisms were genetically identical, CRBSI would be considered the cause of infection. Lastly, septicemia of unknown origin was diagnosed when bloodstream bacterial culture samples from 2 different peripheral sites were positive without any other detectable source of infection.

2.3. Cardiopulmonary Bypass Management Protocol. Principles of cardiopulmonary bypass management were generally the same in all patients. We utilized moderate hypothermia (28°C) bypass and Custodiol® cardioplegic solution was used in all cases with repeated doses as appropriate. For acid-base management protocol in our institution, pH-stat strategy was chosen when patients were less than 10 years old and vice versa for alpha-stat.

2.4. Statistical Analysis. Patient characteristics with continuous variables were compared using Wilcoxon rank-sum (Mann–Whitney U) test while categorical variables were compared with chi-squared test. A p value of less than 0.05 was considered statistically significant. Logistic regression analysis was used to calculate odds of having infection based on procalcitonin and white blood cell levels. We utilized receiver operating characteristic (ROC) curves to determine the best threshold for both procalcitonin and white blood cell levels to predict postoperative bacterial infection. The statistical software used was Stata version 14.1.

3. Results

3.1. Patient Characteristics. A total of 146 patients were enrolled in our study with 42 patients developing proven bacterial infection postoperatively. Patients in the no infection group were significantly older than those in the infection group (41.5 vs 6 months, $p = 0.0003$). They also had significantly higher body weight (12.35 vs 6.03 kg, $p = 0.0014$) and larger body surface area (0.57 vs 0.30 kg/m^2, $p = 0.0004$). Main diagnoses and comorbidities were generally similar. Operative and cardiopulmonary bypass time were also statistically similar. However, aortic cross-clamp time was significantly longer in infection group (78 vs 57.5 minutes, $p = 0.033$) (Table 1).

3.2. Postoperative Results. Procalcitonin level on every postoperative day was higher in infection group compared to no infection group, although without statistical significance (Table 2). White blood cell levels varied widely on most postoperative days. The most common type of infection encountered was respiratory tract infection. We found area under the curve (AUC) to be greatest on postoperative day 7 of both procalcitonin and white blood cell levels. ROC analysis of procalcitonin level on postoperative day 7 demonstrated that procalcitonin level of more than 4.13 ng/dl was predictive of bacterial infection (88.89% specificity and 26.09% sensitivity with AUC of 0.67) (Figure 1). White blood cell level, also on postoperative day 7, of more than 19,870 cells/mm^3 was also predictive of bacterial infection in a similar manner (86.96% specificity and 32.35% sensitivity with AUC of 0.55) (Figure 2). From logistic regression analysis, it was confirmed that procalcitonin level of more than 4.13 ng/dl was a significant risk factor of bacterial infection (OR 3.74 on univariate and 3.41 on multivariate analysis, $p = 0.002$ and 0.004, respectively). However, white blood cell level of more than 19,870 cells/mm^3 has less significant odds of bacterial infection (OR 0.297 and $p = 0.074$ on univariate analysis and OR 1.614 and $p = 0.216$ on multivariate analysis) (Table 3). Temporal distribution of procalcitonin and white blood cell levels on each postoperative day showed that median procalcitonin levels were mostly elevated on postoperative day 2 to 3, although not strongly predictive of infection. White blood cell levels, on the other hand, were randomly scattered (Figure 3).

Table 1: Patient characteristics.

	All ($N = 146$)	Infection ($N = 42$)	No infection ($N = 104$)	p value
Age (months): median (P25, P75 (IQR))	28.5 (7, 84 (77))	6 (1, 42 (41))	41.5 (14.5, 85.5 (71))	0.0003
Gender: N (%)				
Male	84 (57.53)	27 (64.29)	57 (54.81)	0.294
Female	62 (42.47)	15 (35.71)	47 (45.19)	
Weight (kg): median (P25, P75 (IQR))	11.08 (6, 21 (15))	6.03 (3.34, 15.6 (12.26))	12.35 (8.15, 21.4 (13.25))	0.0014
Body surface area (kg/m^2): median (P25, P75 (IQR))	0.52 (0.32, 0.81 (0.49))	0.30 (0.22, 0.61 (0.39))	0.57 (0.42, 0.82 (0.41))	0.0004
Diagnosis: N (%)				
Atrial septal defect	9 (6.16)	0 (0.00)	9 (8.65)	0.049
Ventricular septal defect	21 (14.38)	4 (9.52)	17 (16.35)	0.288
Conotruncal defects	39 (26.71)	8 (19.05)	31 (29.81)	0.183
Endocardial cushion defects	8 (5.48)	2 (4.76)	6 (5.77)	0.809
Aortic defects	8 (5.48)	4 (9.52)	4 (3.85)	0.172
d-Transposition of great arteries	11 (7.53)	6 (14.29)	5 (4.81)	0.050
Valvular heart diseases	14 (9.59)	4 (9.52)	10 (9.62)	0.986
Anomalies of coronary arteries	4 (2.74)	0 (0.00)	4 (3.85)	0.325
Others	32 (21.92)	14 (33.33)	18 (17.31)	0.034
Comorbidities: N (%)				
Down syndrome	3 (2.05)	1 (2.38)	2 (1.92)	0.999
DiGeorge syndrome	1 (0.68)	0 (0.00)	1 (0.96)	0.999
Protein-energy malnutrition	24 (75.00)	4 (80.00)	20 (74.07)	0.999
Operative time (mins): median (P25, P75 (IQR))	225 (165, 290 (125))	240 (165, 360 (195))	210 (162.5, 282 (119.5))	0.100
Cardiopulmonary bypass time (mins): median (P25, P75 (IQR))	116 (78, 160 (82))	124 (83, 204 (121))	113.5 (77.5, 156.5 (79))	0.210
Aortic cross-clamp time (mins): median (P25, P75 (IQR))	63 (23, 115 (92))	78 (39, 123 (84))	57.5 (14.5, 109.5 (95))	0.033
Circulatory arrest time (mins): (minimal, maximal)	(0, 55)	(0, 37)	(0, 55)	0.167

Table 2: Postoperative details.

	All ($N = 146$)	Infection ($N = 42$)	No infection ($N = 104$)	p value
PCT level (ng/dl): median (P25, P75 (IQR))				
POD 0	0.48 (0.1, 3.19 (3.10))	0.52 (0.10, 3.20 (3.1))	0.48 (0.11, 3.19 (3.08))	0.667
POD 1	13.75 (4.11, 37.9 (33.80))	14.8 (6.95, 45.3 (28.35))	13.2 (3.67, 32.5 (28.83))	0.308
POD 2	15.7 (3.99, 43.5 (39.51))	18.1 (4.64, 90.4 (85.76))	15.7 (3.33, 39.3 (35.97))	0.405
POD 3	11.45 (2.36, 37.55 (35.20))	16.4 (3.18, 66.1 (62.92))	11.2 (2.1, 18.1 (16.0))	0.227
POD 4	5.36 (1.82, 14.4 (12.58))	7.46 (2.22, 21.2 (18.98))	4.93 (1.52, 9.84 (8.32))	0.139
POD 5	3.15 (1.2, 10.1 (8.9))	3.53 (1.33, 15.4 (14.07))	3.09 (1.2, 5.71 (4.51))	0.563
POD 6	1.54 (0.8, 4.9 (4.1))	2.25 (0.99, 9.55 (8.56))	1.36 (0.71, 2.29 (1.58))	0.057
POD 7	1.15 (0.54, 3.36 (2.82))	1.85 (0.86, 4.13 (3.27))	0.77 (0.38, 3.25 (2.87))	0.072
WBC level (cells/mm^3): median (P25, P75 (IQR))				
POD 0	11950 (9060, 16900 (7840))	9345 (7000, 12500 (5500))	13040 (10030, 17780 (7750))	0.0005
POD 1	13265 (10605, 18360 (7755))	11460 (8340, 13000 (4660))	14540 (11110, 19000 (7890))	0.0009
POD 2	14545 (10660, 19030 (8370))	12635 (9580, 15400 (5820))	15520 (11695, 20000 (8305))	0.0018
POD 3	13690 (10445, 16865 (6420))	12060 (7930, 15600 (7670))	13965 (11400, 17500 (6100))	0.067
POD 4	12895 (10280, 16300 (6020))	12905 (10250, 16395 (6145))	12895 (10280, 16190 (5910))	0.981
POD 5	13100 (10400, 17385 (6985))	13740 (10400, 17810 (7410))	12980 (10400, 17100 (6700))	0.651
POD 6	14400 (10900, 18200 (7300))	13900 (10950, 18200 (7250))	15340 (10630, 17920 (7290))	0.747
POD 7	13465 (10435, 18570 (8135))	13810 (11000, 20220 (9220))	13415 (10280, 16950 (6670))	0.417
Types of infection: N (%)				
Urinary tract infection	12 (8.22)	12 (28.57)	—	—
Gastrointestinal tract infection	4 (2.74)	4 (9.52)	—	—
Respiratory tract infection	18 (12.33)	18 (42.86)	—	—
Catheter-related bloodstream infection	2 (1.37)	2 (4.76)	—	—
Septicemia (unknown source)	6 (4.11)	6 (14.29)	—	—
Reoperation within 30 days: N (%)				
Yes	4 (2.74)	1 (2.38)	3 (2.88)	0.999
No	142 (97.26)	41 (97.62)	101 (97.12)	

Note. PCT, procalcitonin; POD, postoperative day; WBC, white blood cell.

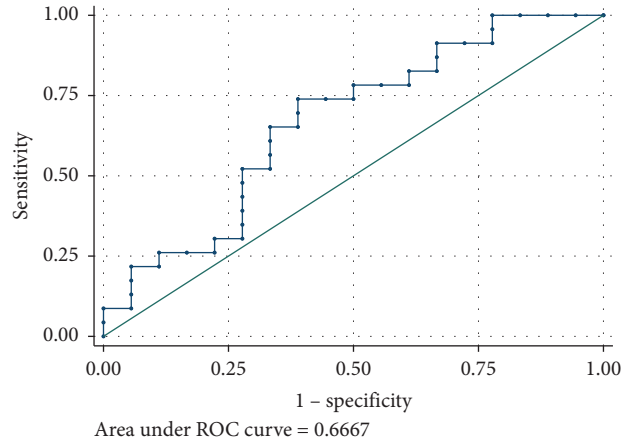

Figure 1: Receiver operating characteristic (ROC) curve showing the relation between sensitivity (true positive) and 1-specificity (true negative) in determining the predictive value of procalcitonin level on postoperative day 7.

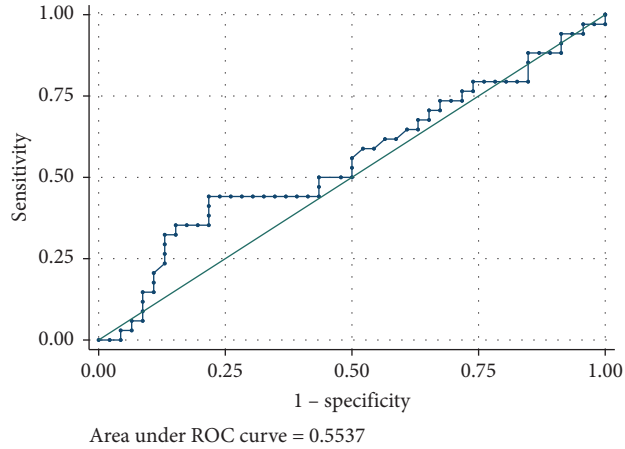

Figure 2: Receiver operating characteristic (ROC) curve showing the relation between sensitivity (true positive) and 1-specificity (true negative) in determining the predictive value of white blood cell level on postoperative day 7.

Table 3: Logistic regression analyses demonstrating procalcitonin and white blood cell levels as risk factors of bacterial infection.

Variables	All ($N = 146$) N (%)	Infection ($N = 42$) N (%)	p value	Univariate analysis		95% CI	Multivariate analysis		95% CI
				OR	p value		OR	p value	
PCT level at POD 7 (ng/dl)									
≥4.13	113 (77.40)	25 (59.52)	0.001	3.74	0.002	1.66–8.45	3.410	0.004	1.49–7.81
<4.13	33 (22.60)	17 (40.48)							
WBC level at POD 7 (cells/mm^3)									
≥19,870	83 (56.85)	19 (45.24)	0.096	0.297	0.074	0.94–4.00	1.614	0.216	0.76–3.44
<19,870	63 (43.15)	23 (54.76)							

Note. PCT, procalcitonin; POD, postoperative day; WBC, white blood cell; CI, confidence interval.

4. Discussion

Under normal physiological condition, procalcitonin, a polypeptide consisting of 116 amino acids, is normally produced and secreted from parafollicular cells (or C-cells) of the thyroid gland. Due to its very low circulating concentration, it is almost undetectable from blood examination. However, procalcitonin production could also be stimulated by various inflammatory processes in the body such as non-infectious causes of SIRS. Under these circumstances, various organs such as lungs, liver, or intestines serve as new sources of procalcitonin production. This causes its level to rise enough to be detectable. It is believed that inflammatory responses caused by bacterial infections would greatly stimulate the production of procalcitonin far more than inflammatory responses from other causes such as viral or noninfectious ones [11].

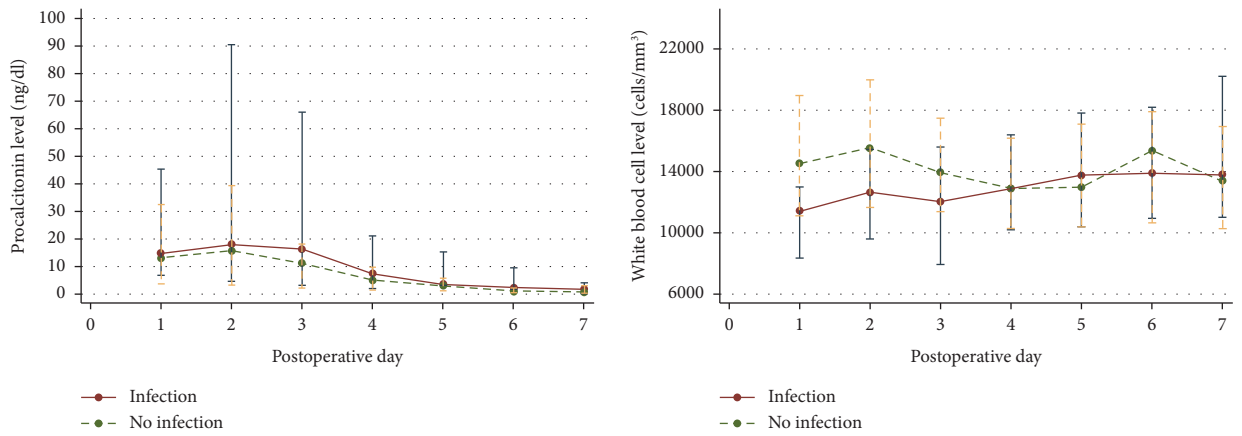

Figure 3: Median procalcitonin and white blood cell levels on postoperative days 0 to 7.

The unique characteristic of procalcitonin is its delayed peak concentration and early reduction of concentration. It takes no less than 24 hours to reach its peak level and no more than a total of 72 hours to return to baseline. In contrast, C-reactive protein (CRP) level rises more rapidly and stays at high level for a longer period of time. This characteristic suggests that if procalcitonin level is to rise more rapidly or to be persistently elevated for an extended period, there could be another cause of its rising other than normal physiological condition, for instance, bacterial infection. This fact has been demonstrated by our study in which procalcitonin level on as late as postoperative day 7 would be most predictive of bacterial infection, significantly longer than the usual physiological procalcitonin level not caused by bacterial infection.

There have been many works [1–7] on using procalcitonin as a predictor of postoperative bacterial infection. They have found that the higher the procalcitonin level, the greater the chance of having bacterial infection. These studies, therefore, suggested that using procalcitonin level to predict the probability of bacterial infection seemed to be justified as waiting for the bacterial cultures results would have taken a considerably longer time. Even though we did not include cost-effectiveness analysis in our study, we could still confidently state that the total cost of a few procalcitonin laboratory studies (around 19.58 USD each) would be significantly less than the cost of treatment in case there was proven bacterial infection with its possible complications. From this perspective, we could also say that by utilizing procalcitonin as a marker of early bacterial infection, we could greatly reduce the use of empirical antibiotic treatment which we were all aware that this came at a high cost. All in all, we were determined to include cost-effectiveness analysis in our further study. Some studies [8, 9] did not find procalcitonin to be a useful predictor of postoperative bacterial infection. They found no association between procalcitonin level and the incidence of proven bacterial infection by cultures. The reason, presumably, was the fact that all their patients underwent surgery using cardiopulmonary bypass (CPB). As we are all aware, CPB causes activation of both non-cellular and cellular immune responses via contact of blood to non-biological surfaces. This results in the body responding with high grade of systemic inflammation. As a consequence, procalcitonin production will be greatly stimulated despite without any source of infection. Therefore, they have concluded that this was the one important limitation of using procalcitonin as a predictor of postoperative infection, including bacterial. We included only patients undergoing cardiac surgery using cardiopulmonary bypass in our study. Our results demonstrated that procalcitonin levels in the infection group were higher than those in the no infection group on all postoperative days. However, the differences were not statistically significant. We believed that the limited number of patients in our study was the main contributing factor and that our ongoing prospective trial on this matter might show more promising results.

Although an association between level of procalcitonin and bacterial infection had been found, the exact level of greatest association still could not be agreed between studies. One study suggested a cutoff level of as low as 2 ng/dl [12] to be a reliable predictor of postoperative bacterial infection while others found the level to be significantly higher. Other than the ability to predict a broad spectrum of bacterial infection, a few studies found an association between procalcitonin level and a specific disease or factor such as higher incidence of ventilator-associated pneumonia (VAP) [13], increased patient's early morbidity and mortality [14], and also septicemia [15]. Therefore, utilizing procalcitonin level as a predictor of the aforementioned events might theoretically improve patient's outcomes. Probably due to the limited number of our patients, AUCs of ROC curves of both procalcitonin and white blood cell levels were less than 0.7. Despite that, we could still obtain acceptable specificity of predictive values of both procalcitonin and white blood cell levels at 88.89 and 86.96%, respectively. Moreover, we confirmed from logistic regression analysis that procalcitonin level at 4.13 ng/dl was in fact a significant risk factor of bacterial infection. From this fact, we strongly believed that procalcitonin level, if utilized alongside clinical presentation or more specifically, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score [16], could be a useful predictor of postoperative bacterial infection and patients' morbidity and mortality.

Procalcitonin level alone might prove to be inadequate to be an accurate predictor of postoperative bacterial infection as proposed by some studies [17–20]. They suggested using other factors alongside procalcitonin to increase the accuracy, such as white blood cell count or interleukin-6 cytokine level. They found that their levels would increase in conjunction with procalcitonin level if bacterial infection were to be present. In our study, we also collected and analyzed postoperative white blood cell level to compare with procalcitonin level as predictors of bacterial infection. However, we found minimal if not no association between procalcitonin and white blood cell levels in both infection and no infection groups. The reason behind this might be the fact that we had a heterogeneous cohort and white blood cell level could have been interfered by different factors such as patient's comorbidities and other postoperative care measures.

As stated earlier, timing of procalcitonin level measurement is crucial. Because procalcitonin level rises slowly and decreases rapidly, it is important to determine the most appropriate time for measurement for greatest accuracy of predicting bacterial infection. One study [21] suggested that a one-time postoperative measurement was adequate while another study [22] encouraged using trends of rising and falling of procalcitonin level for greater accuracy. We supported the idea of a one cut-point measurement of greater ease of utility.

Due to the fact that procalcitonin level is unaffected by renal function [23], its use has become more popular among patients undergoing surgery involving CPB. As CPB proves to cause damaging effects on renal function, likely contributing to non-pulsatile blood flow and high embolic load, some patients may develop transient kidney injury postoperatively. Unaffected by renal function, procalcitonin theoretically proves to be a reliable predictor of postoperative bacterial infection after surgery utilizing CPB. There have also been studies focusing only on patients without postoperative bacterial infection [24] and their corresponding postoperative procalcitonin level, patients undergoing non-CPB surgery [25], and also the use of intravenous immunoglobulin (IVIG) in patients with high postoperative procalcitonin level to reduce the incidence of bacterial infection [26]. These topics are of our interest and are being currently explored in our ongoing prospective study. Because many unfavorable events could potentially occur during cardiac surgery utilizing cardiopulmonary bypass [27, 28], resulting in increased incidence of postoperative bacterial infection, thorough studies involving using procalcitonin level as a prompt predictor of infection might prove to further reduce patients' morbidity and mortality.

4.1. Limitations. As this was a retrospective case-control study, bias could not be fully eliminated. The number of patients enrolled was limited and some of the data on postoperative procalcitonin level were either not recorded or missing. Furthermore, there were no standardized protocols in our institution on regular postoperative blood sampling for procalcitonin level.

5. Conclusions

When appropriately used alongside clinical examination, procalcitonin would be a useful predictor of postoperative bacterial infection. Earlier detection of bacterial infection associated with high APACHE-II score would greatly contribute to morbidity and mortality after cardiac surgery. Procalcitonin level at 4.13 ng/dl on postoperative day 7 was greatly associated with postoperative bacterial infection in which prompt treatment with antibiotics should be strongly considered. A prospective study of our series is ongoing and would further validate our current results.

Data Availability

The data that support the findings of this study are available from Division of Cardiothoracic Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Usage of these data was approved by the ethics committee and restrictions apply to the availability of these data. Data are available from the authors with the permission of Division of Cardiothoracic Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

Ethical Approval

The study protocol and ethical issues were reviewed and approved by Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (No. MURA2023/776).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Niramol Tongboon was responsible for concept and design, data correction, data review, analysis and interpretation of data, original draft preparation, article revision, and final approval. Khunthorn Kadeetham and Piya Samankatiwat were responsible for data correction, data review, article revision, and final approval. Niramol Tongboon and Khunthorn Kadeetham contributed equally to this work.

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