

УДК 616.126.3-089.819:612.017
 МРНТИ 76.29.30, 76.29.39

PROCALCITONIN AS A PREDICTIVE BIOMARKER AFTER OPEN HEART SURGERY

H. STOEV, Z. VAZHEV, K. DIMITROV

Medical University – Plovdiv, Plovdiv, Bulgaria

Stoev H. – <https://orcid.org/0000-0001-7772-024X>

Dimitrov K. – <https://orcid.org/0000-0002-6406-2687>

Citation/
 библиографиялық сілтеме/
 библиографическая ссылка:

Stoev H, Vazhev Z, Dimitrov K. Procalcitonin as a predictive biomarker after open heart surgery. West Kazakhstan Medical Journal.2020;62(4):244-249

Стоев Х, Важев З, Димитров К. Прокальцитонин жүрекке жасалған операциядан кейінгі болжамды биомаркер ретінде. West Kazakhstan Medical Journal.2020;62(4):244-249

Стоев Х, Важев З, Димитров К. Прокальцитонин как прогностический биомаркер после операции на открытом сердце. West Kazakhstan Medical Journal.2020;62(4):244-249

Procalcitonin as a predictive biomarker after open heart surgery

H. Stoev, Z. Vazhev, K. Dimitrov

Medical University– Plovdiv, Plovdiv, Bulgaria

Posternotomy infections are a serious complication and are directly related to patients' survival in the short and long term. Despite prevention, their expression is still significant - from 0.5% to 6.8%, and the associated hospital mortality rates ranges from 7% to 35%. Procalcitonin (PCT) is a well-known prognostic marker after elective cardiac surgery. However, the impact of elevated PCT in patients with an initially uneventful postoperative course is still unclear.

Purpose: to evaluate procalcitonin levels as a prognostic tool for delayed complications after open cardiac surgery – superficial and deep wound infections, SIRS, sepsis.

Methods. In this prospective study, for the period July 2017 - February 2018, we evaluated 137 elective coronary patients in order to analyze the prognostic value of procalcitonin. Preoperative assessment of left ventricular function (EF) and operative risk (EuroSCORE) was performed. Patients with clinical and laboratory evidence of infection - fever, leukocytosis, toxicoinfectious syndrome and elevated CRP were excluded from the study. PCT was measured 24 hours after the intervention. Patients were followed up within 3 months and postoperative results were evaluated.

Results. Among 137 patients with an initially uneventful postoperative course, 19 patients developed delayed complications. Serum PCT levels on the first postoperative day were significantly higher in these patients compared to the remaining. ROC analyses showed that PCT had a high accuracy to predict delayed complications (AUC of 0.90, sensitivity 83% and specificity 97%). Patients with PCT levels above 2 ng/ml on the first postoperative day had a highly increased risk of superficial and deep wound infections, SIRS and sepsis.

Conclusion. A single measurement of PCT seems to be a useful tool to identify patients at risk of delayed complications despite an initially uneventful postoperative course.

Keywords: cardiac surgery, procalcitonin, risk factor, delayed complications.

Прокальцитонин жүрекке жасалған операциядан кейінгі болжамды биомаркер ретінде

Х. Стоев, З. Важев, К. Димитров

Пловдив медицина университеті, Пловдив, Болгария

Операциядан кейінгі инфекциялар ауыр асқыну және қысқа әрі ұзақ мерзімді перспективада пациенттердің өмір сүруіне тікелей байланысты болып табылады. Профилактикаға қарамастан, олардың айқындылығы әлі де елеулі - 0,5% - дан 6,8% - ға дейін, ал ілеспелі госпитальдық өлім-жітім 7% - дан 35% - ға дейін ауытқиды. Прокальцитонин (ПКТ) жоспарлы кардиохирургиялық операциядан кейін болжамды маркер болып табылады. Алайда, операциядан кейінгі бастапқы рецидивсіз ағымы бар пациенттерге ПКТ деңгейінің жоғарылауының әсері әлі күнге дейін түсініксіз болып қалуда.

Мақсаты. Осы зерттеудің мақсаты-ашық кардиохирургиялық араласулардан кейінгі ұзақ мерзімді асқынулардағы үстірт және терең жара инфекциялары, ЖРВИ, сепсис болжамдық құрал ретінде прокальцитонин деңгейін бағалау.

Әдістер. Бұл проспективті зерттеуде 2017 жылдың шілдесінен 2018 жылдың ақпанына дейін біз прокальцитониннің болжамды құндылығын талдау үшін 137 коронарлық науқасты тексердік. Сол жақ қарыншаның функциясы мен



Hristo Stoev
 e-mail: hristostoev87@gmail.com

Received/
 Келіп түсті/
 Поступила:
 16.11.2020

Accepted/
 Басылымға қабылданды/
 Принята к публикации:
 22.12.2020

ISSN 2707-6180 (Print)
 © 2020 The Authors
 Published by West Kazakhstan Marat Ospanov
 Medical University

операциялық тәуекел (EuroSCORE) операцияға дейінгі бағалау жүргізілді. Зерттеуден қызба, лейкоцитоз, токсоинфекциялық синдром және С реактивті ақуызының деңгейінің жоғарылауы сияқты инфекцияның клиникалық - зертханалық белгілері бар пациенттер шығарылды. ПКТ араласудан кейін 24 сағаттан кейін өлшенді. Науқастар 3 ай бойы бақылауда болды және операциядан кейінгі нәтижелер бағаланды.

Нәтижелер. Операциядан жақсы шыққан 137 пациенттің арасында 19 пациентте ұзақ мерзімді асқынулар дамыды. Операциядан кейінгі алғашқы тәуліктерде қан сарысуындағы ПКТ деңгейі осы пациенттерде басқаларымен салыстырғанда айтарлықтай жоғары болды. ROC талдаулары ПКТ ұзақ мерзімді асқынуларды болжаудың жоғары дәлдігі бар екенін көрсетті (AUC 0,90, сезімталдық 83% және ерекшелігі 97%). ПКТ деңгейі 2 нг/мл-ден жоғары пациенттерде операциядан кейінгі алғашқы тәуліктерде үстірт және терең жара инфекцияларының, ЖРВИ және сепсисінің даму қаупі жоғары болды.

Қорытынды. ПКТ-ны бір реттік өлшеу операциядан кейінгі алғашқы нәтижесіз ағымға қарамастан, кейінге қалдырылған асқынулардың даму қаупі бар пациенттерді анықтау үшін пайдалы құрал болып табылады.

Негізгі сөздер: кардиохирургия, прокальцитонин, қауіп факторы, ұзақ мерзімді асқынулар.

Прокальцитонин как прогностический биомаркер после операции на открытом сердце

Х. Стоев, З. Важев, К. Димитров

Медицинский Университет – Пловдив, Пловдив, Болгария

Послеоперационные инфекции являются серьезным осложнением и напрямую связаны с выживаемостью пациентов в краткосрочной и долгосрочной перспективе. Несмотря на профилактику, их выраженность все еще значительна - от 0,5% до 6,8%, а сопутствующая госпитальная смертность колеблется от 7% до 35%. Прокальцитонин (ПКТ) является хорошо известным прогностическим маркером после плановой кардиохирургической операции. Однако влияние повышенного уровня ПКТ на пациентов с изначально безрецидивным послеоперационным течением до сих пор остается неясным.

Цель. Целью настоящего исследования явилась оценка уровня прокальцитонина как прогностического инструмента при отдаленных осложнениях после открытых кардиохирургических вмешательств – поверхностных и глубоких раневых инфекциях, ОРВИ и сепсисе.

Методы. В этом проспективном исследовании за период с июля 2017 года по февраль 2018 года, мы обследовали 137 коронарных больных с целью анализа прогностической ценности прокальцитонина. Проведена предоперационная оценка функции левого желудочка и операционного риска (EuroSCORE). Из исследования были исключены пациенты с клинико - лабораторными признаками инфекции - лихорадкой, лейкоцитозом, токсоинфекционным синдромом и повышенным уровнем С-реактивного белка. ПКТ измеряли через 24 часа после вмешательства. Пациенты находились под наблюдением в течение 3 месяцев и оценивались послеоперационные результаты.

Результаты. Среди 137 пациентов с благоприятным послеоперационным течением, у 19 пациентов развились отдаленные осложнения. Уровень ПКТ в сыворотке крови в первые послеоперационные сутки был достоверно выше у этих пациентов по сравнению с остальными. ROC-анализы показали, что ПКТ обладает высокой точностью прогнозирования отдаленных осложнений (AUC 0,90, чувствительность 83% и специфичность 97%). Пациенты с уровнем ПКТ выше 2 нг/мл в первые послеоперационные сутки имели сильно повышенный риск развития поверхностных и глубоких раневых инфекций, ОРВИ и сепсиса.

Выводы. Однократное измерение ПКТ представляется полезным инструментом для выявления пациентов с риском развития отсроченных осложнений, несмотря на изначально безрезультатное послеоперационное течение.

Ключевые слова: кардиохирургия, прокальцитонин, фактор риска, отдаленные осложнения.

Introduction

Median sternotomy represents a standard surgical access in cardiac surgery, despite the growing popularity of minimally invasive access [1]. Sternal wound infections

represent a serious complication after open heart surgery and are directly related to patient survival in both the short and long term. Moreover, mediastinitis leads to extreme increase in financial costs. Despite prophylaxis, the

incidence remains significant, ranging from 0.5% to 6.8%, and the associated in-hospital mortality ranges from 7% to 35% [2]. Procalcitonin (PCT) is a well-known marker after elective cardiac surgery [3]. It is a 116-amino acid peptide secreted from thyroid parafollicular cells as the precursor of calcitonin [4]. Regarding inflammatory response, PCT is synthesized in nearly all organs like liver, lung, kidney, intestine and almost all other tissues throughout the body [5,6]. The production of PCT can be induced by endotoxins of gram-negative bacteria or by proinflammatory cytokines (IL-1 and IL-6 or TNF- α). High serum PCT has been described in patients with systemic infection [7], strongly correlating with the extent and severity of bacterial infections and in case of systemic inflammatory response (SIRS) [8]. The use of cardiopulmonary bypass leads to various degrees of a systemic inflammatory response syndrome associated with an increase of PCT levels within the first 24h postoperatively [9]. Cardiac patients with increased serum levels of PCT have been found to be related to the development of complications after surgery [8,9]. However, these studies were not focused on patients with an initially uneventful postoperative course. If the initially postoperative course was uneventful, the elevated PCT levels were not included in the decision making process for further therapy concepts.

Methods

This retrospective study is conducted at “St. George” University Hospital - Department of Cardiac Surgery – Plovdiv, Bulgaria. For the period July 2017 - February 2018, we evaluated 137 elective coronary patients in order to analyze the prognostic value of procalcitonin. Written informed consent was obtained from all patients meeting the criteria and being included in this study. Preoperative assessment of left ventricular function (EF) and operative risk (EuroSCORE) was performed. Patients with clinical and laboratory evidence of infection - fever, leukocytosis, toxicoinfectious syndrome and elevated CRP - were excluded from the study. PCT was measured 24 hours after the intervention. Patients were followed up within 3 months and postoperative results were evaluated.

In our center, all elective patients with initially uneventful postoperative course were admitted to our intensive care unit for extubation. If the patients could be extubated within 9 h of surgery and showed an apparently uneventful postoperative course, the patients were discharged from our intensive care unit at latest the morning after surgery. The initially uneventful postoperative course is defined as: less than 24 h within an intensive care unit (ICU), the patients were in a clinically stable hemodynamic and respiratory condition, they did

not show signs of stroke or bleeding necessitating wound reexploration and were without acute renal failure after the first night of surgery (defined by AKIN criteria) [10]. Delayed complications were defined as: complications occurring after initially uneventful postoperative course resulting in superficial and deep wound infections, SIRS, sepsis. All 137 open heart operations are performed in 3 operating rooms (OR), equipped with a standard ventilation and air conditioning system. The air exchange is 25 times/hour. The temperature in the OR is kept constant - 18-20°C. The operative team consists of 8 \pm 1 people - an operator, one or two assistant-surgeons, an anesthesiologist and a nurse anesthetist, two scrub nurses, a perfusionist (cardiovascular technician). Reagents and a multiparametric immunoassayer Mini VIDAS® (bioMérieux, France) were used to study the proposed predictive biomarker - PCT. Blood was sampled for inflammatory markers (leukocytes and C-reactive protein) the day before surgery from a peripheral vein and on the first postoperative morning from a central venous catheter - PCT (24h postoperatively). Based on the main purpose and objectives of the study, as well as the volume, type and distribution of the data in the study, the following statistical methods were used - ROC-curve for analysis and evaluation of the predictive value of the analyzed biomarker; the significance level of the null hypothesis was $P < 0.05$. Statistical data processing was performed using the software product SPSS v.17, MicroSoft Excel 2010 was used for visual graphical presentation of the results.

The ratio between the two sexes was 3.3:1 in favor of males. The mean age was 67 years.

The risk of cardiac surgery was assessed with an average EuroScore of 8.35 (0.85 to 52.25).

Results

The average stay of the patients in the intensive care unit was 5 days (from 0 to 46 days), and the average total hospital stay was 15.6 days (from 5 to 55 days).

During the study period, 137 patients underwent cardiac surgery with cardiopulmonary bypass (CPB). Of these, 19 patients developed delayed complications after discharge from the intensive care unit. Patients developing delayed complications were generally older, had poorer preoperative renal function, a higher EuroScore and lower left-ventricular ejection fraction. Operation time and CBP time were longer in this group. The complications that occurred in the postoperative period are summarized in Diagram 3.

Looking in detail at the statistical analysis of data, PCT is a major predictive marker for the development of

Table 1. In-hospital stay and ICU stay of the studied group of patients (n = 137)

	Mean \pm SE	Median	Min	Max	95% CI
ICU	4,98 \pm 0,74	3,00	0	46,00	[3,51; 6,45]
Total in-hospital stay	15,62 \pm 0,71	13,00	5,00	55,00	[14,21; 17,02]

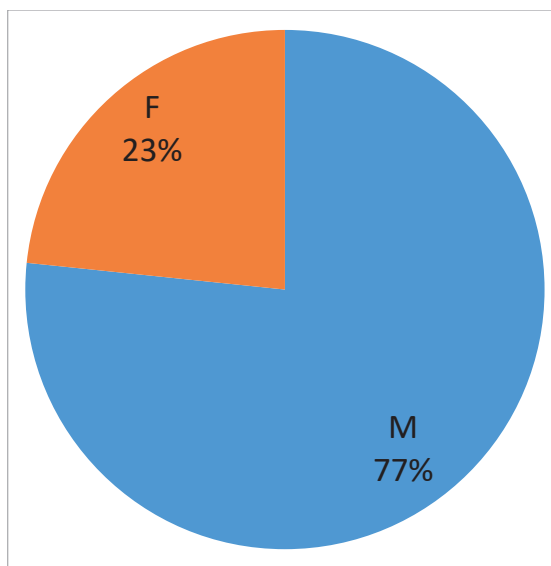


Diagram 1. Sex distribution in the studied group

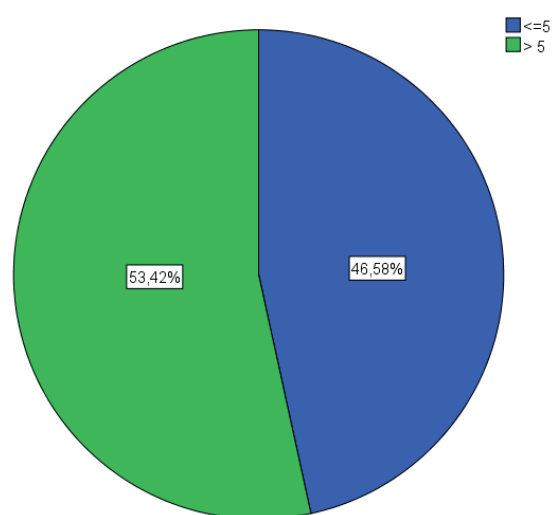


Diagram 2. Distribution of patients with deep wound infections according to EuroScore

SIRS, sepsis, superficial and deep wound infections. It is more specific and more sensitive than CRP. PCT values above 2 ng/ml were associated with an extremely high risk of developing wound infections.

ROC analyses of postoperative PCT serum levels and the occurrence of any delayed complication revealed an AUC of 0.90.

Discussion

After decades of numerous studies and various attempts to analyze inflammatory markers after cardiac

surgery, it is probably time to standardize the assessment of inflammatory status before and after cardiac surgery. Procalcitonin may play such a role. PCT is a 116-amino acid peptide secreted by parafollicular thyroid cells as a precursor to calcitonin. In terms of the inflammatory response, PCT is synthesized in almost all organs such as the liver, lungs, kidneys, intestines and almost all other tissues in the body [5]. PCT production can be induced by gram-negative bacteria endotoxins or by inflammatory cytokines (e.g., IL-1 and IL-6 or TNF- α). High levels of serum PCT strongly correlate with the degree and

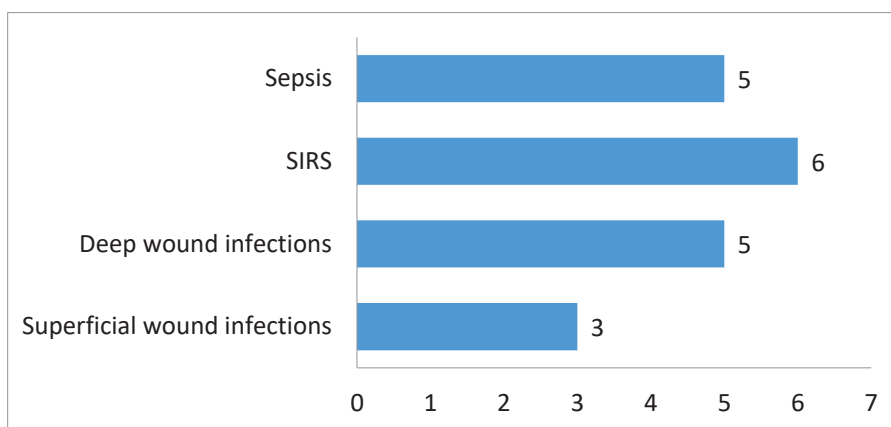
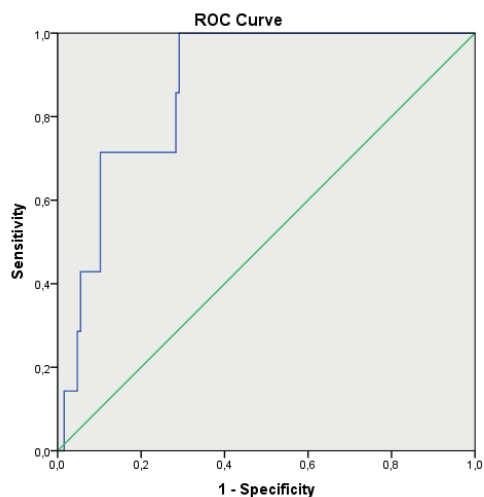


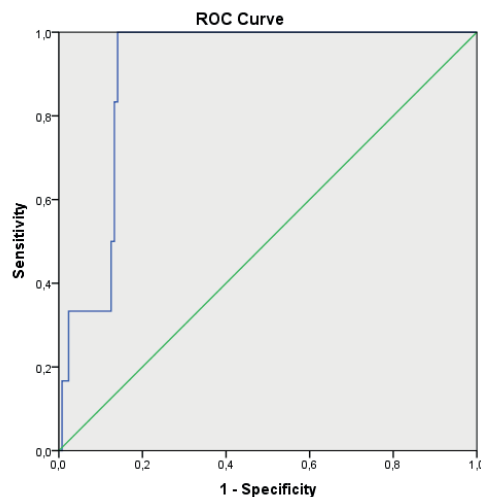
Diagram 3. Frequency of major complications

Table 2. Analysis of the predictive value of procalcitonin with respect to the studied complications

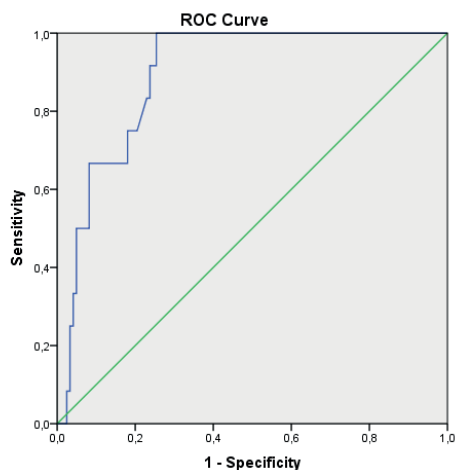
Complication	AUC	SE	95% CI	P value
Superficial wound infections	0.872	0.045	[0.783; 0.961]	0.001
Deep wound infections	0.906	0.032	[0.844; 0.968]	0.001
SIRS	0.893	0.032	[0.830; 0.956]	0.0001
Sepsis	0.847	0.041	[0.767; 0.927]	0.001



A

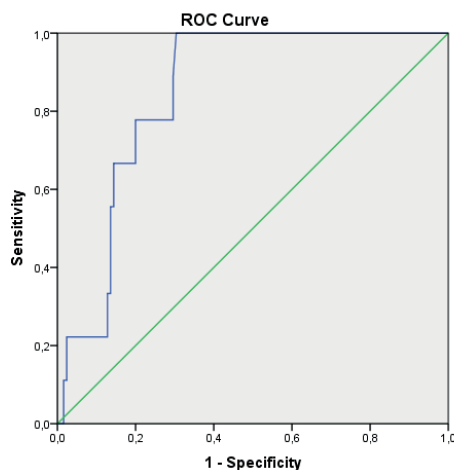


B



C

Diagonal segments are produced by ties.



D

Diagonal segments are produced by ties.

Diagram 4. A: ROC curve of sensitivity and specificity of procalcitonin with respect to superficial wound infections; B – deep wound infections; C – SIRS; D – Sepsis

severity of bacterial infections and in cases of SIRS. The use of cardiopulmonary bypass in cardiac surgery leads to varying degrees of SIRS, which is associated with an increase in PCT levels within the first 24 hours postoperatively; although a report by Boeken suggests that CPB have no effect on PCT [8,11]. PCT has been found to be elevated in infectious complications following open heart surgery, including wound infections, and plays an important role in their diagnosis and decision-making for further therapeutic concepts [9,12]. However, these studies did not focus on patients with an initially uneventful postoperative course. The predictive value of elevated first postoperative day PCT levels in patients with initially uneventful postoperative course is still unknown. In our prospective study, the predictive value was analyzed in a single measurement of serum PCT to identify the risk of infectious complications, in particular wound infections, in patients after open heart surgery. Despite the opinion that the single measurement of PCT has no particularly

prognostic significance [13], the present study manages to prove the opposite.

The most impressive conclusion from this study is that a single postoperative measurement of PCT levels predicts late complications in patients after cardiac surgery. Analysis of the data showed that 24 hours after the intervention, PCT levels were significantly increased in patients who developed infectious complications. Regarding postoperative CRP levels and white blood cell counts, they proved to be insufficiently accurate indicators to distinguish those patients who would develop delayed complications from the rest. ROC analysis reveals that postoperative serum PCT levels have the strongest prognostic value for the development of infectious complications. It can be concluded that PCT is a major predictive marker for the development of SIRS, sepsis, superficial and deep wound infections. It is more specific and more sensitive than CRP. PCT values above 2 ng/ml are associated with an extremely high risk of developing

wound infections.

Regarding our results, monitoring postoperative PCT levels could be a helpful tool to predict likelihood of delayed complications independently of the patient's clinical appearance the first postoperative day. That can be easily integrated into clinical practice and help decision-making processes for planning postoperative monitoring. We assume that the focus to see every patient and therapy more individually could be helpful to improve patient outcome.

Conclusions

In this single-center, observational cohort study, a single measurement of serum PCT level the morning after elective cardiac surgery seems to be an independent predictor for delayed complications in patients with an apparently uneventful postoperative course. PCT is in certain circumstances an interesting concept in which the true clinical value of this idea should be evaluated in a large prospective study.

Список литературы:

1. Dalton ML, Connally SR. Median sternotomy. *Surgery, gynecology & obstetrics*. 1993;176(6):615–24
2. Ridderstolpe L, Gill H, Granfeldt H, Ahlfeldt H, Rutberg H. Superficial and deep sternal wound complications: incidence, risk factors and mortality. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2001;20(6):1168–75
3. Meisner M, Rauschmayer C, Schmidt J, Feyrer R, Cesnjevar R, Bredle D, Tschaikowsky K. Early increase of procalcitonin after cardiovascular surgery in patients with postoperative complications. *Intensive Care Med*. 2002;28(8):1094–102
4. Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. *Physiol Res*. 2000;49(Suppl 1):S57–61
5. Bunchorntavakul C, Chamroonkul N, Chavalitdhamrong D. Bacterial infections in cirrhosis: a critical review and practical guidance. *World J Hepatol*. 2016;8(6):307–21
6. Muller B, White JC, Nylén ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-*r* gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab*. 2001;86(1):396–404
7. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341(8844):515–8
8. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care*. 2004;10(3):208–12
9. Macrina F, Tritapepe L, Pompei F, Sciangula A, Evangelista E, Toscano F, Criniti A, Brancaccio G, Puddu PE. Procalcitonin is useful whereas C-reactive protein is not, to predict complications following coronary artery bypass surgery. *Perfusion*. 2005;20(3):169–75
10. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury N. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31
11. Boeken U, Feindt P, Micek M, Petzold T, Schulte HD, Gams E. Procalcitonin (PCT) in cardiac surgery: diagnostic value in systemic inflammatory response syndrome (SIRS), sepsis and after heart transplantation (HTX). *Cardiovasc Surg*. 2000;8(7):550–554
12. Loebe M, Locziewski S, Brunkhorst FM, Harke C, Hetzer R. Procalcitonin in patients undergoing cardiopulmonary bypass in open heart surgery—first results of the Procalcitonin in Heart Surgery study (ProHearts). *Intensive Care Med*. 2000;26(Suppl 2):S193–8
13. Lipinska-Gediga M, Mierzchala-Pasierb M, Durek G. Procalcitonin kinetics—prognostic and diagnostic significance in septic patients. *Arch Med Sci*. 2016;12(1):112–9