



## Original research

# The early diagnostic value of C-reactive protein for anastomotic leakage post radical gastrectomy for esophagogastric junction carcinoma: A retrospective study of 97 patients



Litong Ji <sup>a</sup>, Tie Wang <sup>b</sup>, Lining Tian <sup>c</sup>, Meizhuo Gao <sup>a,\*</sup>

<sup>a</sup> The Department of General Surgery, The Forth Affiliated Hospital of Harbin Medical University, Harbin, China

<sup>b</sup> The Department of Gastrointestinal Surgery, Harbin Medical University Cancer Hospital, Harbin, China

<sup>c</sup> The Department of Medical Education, The First Affiliated Hospital of Harbin Medical University, Harbin, China

## HIGHLIGHTS

- Surgical esophagogastric junction carcinoma (EJC) patients have high rates of complications including anastomotic leakage.
- EJC patients with anastomotic leakage showed early elevated serum C-reactive protein (CRP) levels at Day 2 after operations.
- EJC patients with higher levels of serum CRP post-surgery should be examined for the existence of anastomotic leakage.

## ARTICLE INFO

## Article history:

Received 23 December 2015

Accepted 3 February 2016

Available online 6 February 2016

## Keywords:

C-reactive protein

Esophagogastric junction carcinoma

Surgery

Anastomotic leakage

## ABSTRACT

**Background/Aims:** The incidence of esophagogastric junction (EGJ) carcinoma has increased worldwide. The only curable strategy for EGJ carcinoma is surgery, whereas anastomotic leakage is the major complication after operations. We aimed to test whether the serum levels of C-reactive protein have the diagnostic value for anastomotic leakage after surgery for EGJ carcinoma.

**Methods:** In this study, we analyzed the values of CRP before and 5 continuous days after surgery in 97 EGJ carcinoma patients who received surgery as the initial treatment. The levels of CRP in the groups of EGJ patients with or without anastomotic leakage were compared.

**Results:** The CRP levels of patients with anastomotic leakage elevated faster and remained higher compared patients without anastomotic leakage. The CRP value at Day 2 after radical surgery for EGJ carcinoma patients has the early diagnostic value for anastomotic leakage. The cut-off value of CRP for anastomotic leakage at Day 2 is 177 mg/l with the sensitivity of 0.9 and specificity of 0.95 ( $P < 0.0001$ ).

**Conclusion:** Surgical EGJ carcinoma patients with elevated CRP at Day 2 after surgery should be excluded the possibility of anastomotic leakage.

© 2016 IJS Publishing Group Limited. Published by Elsevier Ltd. All rights reserved.

Gastric carcinoma is the fifth most common cancer and one of the leading causes of cancer death worldwide [1]. The only curative therapeutic strategy for gastric cancer is radical gastrectomy combined with lymphadenectomy [2–4]. Although the safety for gastric surgery has been greatly improved, patients still face the postoperative risks.

Esophagogastric junction (EGJ) carcinoma has gained great interest from oncologists and surgeons. Cancer that have its epicenter

in the area extending between 2 cm above and 2 cm below the EGJ is defined as EGJ carcinoma irrespective of histological type [5]. The prognosis of EGJ carcinoma is poor, with an overall 5-year survival rate of 30% even when treated with multiple therapies [6]. The incidence of carcinoma originating from EGJ has been reported to have increased in Western countries [7,8]. A similar trend to higher prevalence of EGJ carcinoma in developing countries has also been observed [9,10]. These epidemiological data suggest that EGJ carcinoma is a worldwide health problem.

The surgical procedures for EGJ carcinoma are major and have a high postoperative complication rate. The anatomic position of EGJ is unique and complex [11], with several adjacent organs including the spleen, pancreas, the diaphragm and thoracic organs. The

\* Corresponding author. The Department of General Surgery, The Forth Affiliated Hospital of Harbin Medical University, No. 37, Yiyuan Street Nangang District, Harbin, Helongjiang Province, 150001, China.

E-mail address: [Dr.MZGao@outlook.com](mailto:Dr.MZGao@outlook.com) (M. Gao).

negative upper surgical margin of EGJ carcinoma sometimes is difficult to obtain. The reconstruction procedure is also challenging since the anastomosis is always in the thoracic cavity. All these characteristics of EGJ carcinoma lead to a high postoperative complication rate which includes anastomotic leakage having been reported to be around 8% of the surgical patients with EGJ carcinoma and resulting in an increased postoperative death rate within 90 days [12]. Currently, there is satisfactory treatment for anastomotic leakage of EGJ carcinoma patients. The early detection of anastomotic leakage is very important to improve the general status and the short-term outcome of patients [13,14].

C-reactive protein (CRP) was the first reported acute-phase protein in 1930 [15]. CRP is synthesized by hepatocytes quickly upon the stimulation of interleukin-6 during inflammation [16]. Peak CRP levels have been observed about 48 h after the initiation of an acute inflammatory response [17], and serial CRP tests function as an indicator for postoperative infection [18]. Early diagnosis of anastomotic leakage is important to improve the short-term outcome of patients with EGJ carcinoma undergoing radical gastrectomy. In this study, we aimed to test the hypothesis that postoperative CRP levels can be used as a marker for early detection of anastomotic leakage in EGJ carcinoma patients.

## 1. Patients and methods

### 1.1. Patients

In this retrospective study, we collected patients with EGJ carcinoma who underwent radical gastrectomy in the department of General Surgery of the Fourth Affiliated Hospital of Harbin Medical University between January 1st, 2014 and December 31st, 2014. A total of 97 patients were enrolled into this analysis. All patients received total gastrectomy and Roux-en-Y esophageal-jejunum reconstruction by a circular stapler (Ethicon Inc; NJ, USA) in the thoracic cavity. The anastomosis between proximal and distal jejunum was performed by continuous suture. The clinical features of involved patients were summarized in Table 1. When postoperative anastomotic leakage was suspicious, methylene blue was administered orally. If the fluid from abdominal drain was contaminated with blue dye, diagnosis of anastomotic leakage was then verified.

### 1.2. Ethical considerations

Informed consents were signed and obtained from all patients before being involved in the study. The ethics committee of the Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China approved this study.

### 1.3. Peri-operative management

All patients received a routine pre-operative antibiotic prophylaxis strategy (1.83 g metronidazole and 5.0 g cefazolin, both intravenous) when the anesthesia started to be induced. Another dosage of antibiotic prophylaxis was administered during the surgery if the course of the procedure was longer than 4 h as recommended [19,20].

### 1.4. Serum CRP measurements

The concentration of serum CRP was measured with an automated analytical system (UniCel®DxC 800 Synchron Clinical System; Beckman Coulter, High Wycombe, UK). The analysis procedure followed the manufacture's instruction. The reference range of CRP was less than 8 mg/l, and the detection range of the machine was

3–500 mg/l. The day of surgery was defined as Day 0. Each patient was drawn once per day on Day –1 (the day before the operation), and Day 1–5.

### 1.5. Statistical analysis

Measurement variables were presented mean  $\pm$  SEM (standard error of mean), and analyzed by two-tailed student *t* test. Two-tailed Fisher's exact test was used to analyze category variables (2  $\times$  2 contingency table). Ordinal variables were compared by Mann–Whitney *U* test. Ninety-five percent confidence intervals (95% CI) of proportions were analyzed by the Wilson score procedure with a correction for continuity [21,22]. The cut-off values of CRP were calculated by Youden's *J* statistics. Two-sided *p* values of <0.05 were considered to have statistical significance. Statistical analysis was completed by SPSS Statistics 17.0 for windows (SPSS Inc., Chicago, IL).

## 2. Results

### 2.1. Clinical features of patients

Between January 1st and December 31st of 2014, 97 patients were newly diagnosed histologically with EGJ adenocarcinoma and received open surgical operations as the initial treatment in the department of surgery of the Fourth Affiliated Hospital of Harbin Medical University. All patients had routine CRP tests before and 5 consecutive days after surgery. The median time for operation was 240 min (210 min–330 min). There were no intraoperative complications. No patients in this cohort died within 30 days post operation (95%CI, 0–4.75%). The complication of esophago-jejunum anastomotic leakage occurred in 10 of the patients (10.31%: 95% CI, 5.33%–18.56%). Most of these complications occurred at Day 3 or Day 4. No patients required re-operation for the leakage within 30 days after surgery (95%CI, 0–4.75%). One patient without anastomotic leakage had postoperative pneumonia which was cured by the administration of antibiotics. No other infectious or acute complications were observed after surgery. The clinicopathological features of patients with or without anastomotic leakage were summarized in Table 1. There was no difference between the two groups in terms of clinicopathological characteristics.

Ten patients suffered esophago-jejunal anastomotic leakage, mainly occurring at 3 or 4 days post-operatively. No leakages of jejuno-jejunal anastomosis occurred. Nine of the 10 (90%) patients with anastomotic leakage were treated conservatively. The therapeutic strategies for these patients included antibiotics, enteric nutrition via a naso-jejunal tube whose end was placed in the distal jejunum, parental nutrition, and effective drainage. One patient needed ultrasonic-guided subphrenic space puncture for additional drainage. None of the 10 patients underwent re-operation. The median length of hospital stay of patients with leakage was 22.5 (21–35) days after surgery, which was longer than that of patients without leakage (median 7 (6–9) days, *p* < 0.001).

### 2.2. CRP levels

CRP levels before and after surgery are routinely measured in the department of surgery of the Fourth Affiliated Hospital of Harbin Medical University. There was no difference of CRP levels before surgery between the two groups (without leakage v.s. with leakage: 6.86  $\pm$  0.77 mg/l v.s. 7.00  $\pm$  0.15 mg/l, *p* = 0.20). CRP levels have been observed to increase in all post-surgery patients. The patients with anastomotic leakage had higher concentration of serum CRP compared to those without this complication starting at

**Table 1**  
Clinicopathological features of involved patients.

	Patients without anastomosis leakage (n = 87)	Patients with anastomosis leakage (n = 10)	P Value
Sex			1.00
Female	35	4	
Male	52	6	
Age			1.00
<=65	55	7	
>65	32	3	
Siewert type			0.736
I	10	1	
II	53	7	
III	24	2	
Tumor size			0.682
<= 3 cm	17	1	
> 3 cm	60	9	
Borrmann type			1.00
0,1,2	11	1	
3,4	76	9	
Differentiation			0.837
Well	15	2	
Moderately	35	4	
Poorly	37	4	
Lauren type			0.588
Intestinal	22	3	
Diffuse	50	6	
Mixed	15	1	
Depth of tumor invasion			0.7145
T0, T1, T2	22	3	
T3-4	65	7	
Lymph node metastasis			0.515
N0	5	1	
N1	6	1	
N2-3	76	8	
Distant metastasis			0.591
M0	78	10	
M1	9	0	
Peritoneal metastasis			1.00
P0	87	10	
P1	0	0	
Hepatic metastasis			1.00
H0	87	10	
H1	0	0	
TNM stage			0.804
I	5	1	
II	6	1	
III	71	7	
IV	5	1	
Residual tumor			1.00
R0	80	9	
R1-2	7	1	
Surgical approach			0.182
Transthoracic	3	0	
Abdominal-transhiatal	82	9	
Abdominothoracic	2	1	

Day 2 after surgery (Fig. 1), which was earlier than the onset of anastomotic leakage occurring at Day 3 or 4. Peak mean levels of serum CRP were observed at Day 2 after surgery for patients with and without anastomotic leakage. However, for patients with leakage, the levels of CRP remained higher than those without leakage through Day 2 to Day 5 after operation and slowly decreased.

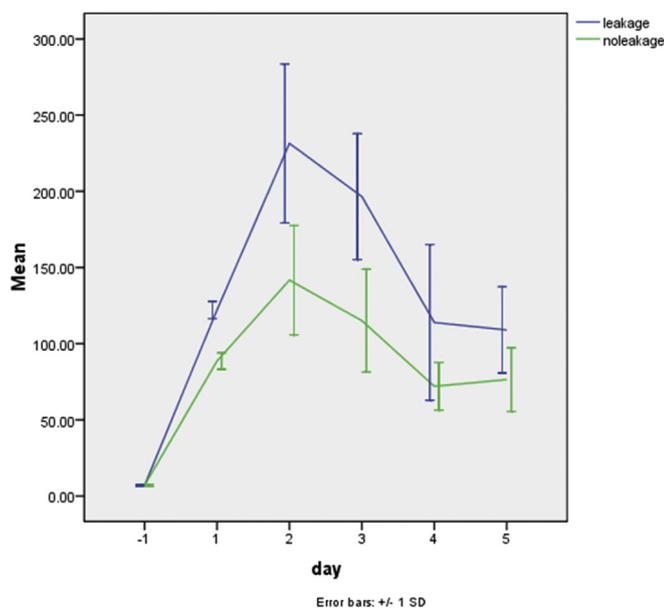
### 2.3. Diagnostic value of CRP for anastomotic leakage after EGJ cancer surgery.

The diagnostic value of CRP levels is summarized in Table 2. The cut-off values of each day after surgery were calculated by Youden's J statistics. Since the patients with anastomotic leakage showed significantly higher levels of CRP starting at Day 2 and the increase occurred earlier than the clinical manifestation, the cut-off value at

Day 2 is more important in terms of the prediction of anastomotic leakage.

### 3. Discussion

Anastomotic leakage is not a rare complication after a gastrointestinal surgery. The cause for anastomotic leakage is still unknown which may include ischemia, lack of surgical skills [23], staple dehiscence or inappropriate post-surgery management. Although anastomotic leakage is not related to the long-term outcome after surgery for EGJ cancer [24–26], it is the major cause of perioperative death and 21% of anastomotic leakage patients died during surgical hospitalization [24]. Early diagnosis for this surgical complication helps to prevent subsequent sepsis and improve the mortality and morbidity related to surgical procedures. The manifestations of anastomotic leakage are usually



**Fig. 1.** The dynamic of CRP levels in surgical EGJ patients with anastomotic leakage (the blue curve) and without this complication (the green curve). Serum CRP levels were measured at Day -1 (the day before surgery) and five consequent days after surgery (Day 1–5). All patients had normal CRP levels before operations. Patients with leakage showed higher levels of CRP as early as Day 2 and had increased levels for the entire observation period.

**Table 2**  
Diagnostic value of CRP for anastomotic leakage after surgery for EGJ cancer.

	CRP cut-off (mg/l)	Sensitivity	Specificity	AUC	$P_{AUC}$
Day 1	117	0.9	0.89	0.994	<0.0001
Day 2	177	0.9	0.95	0.908	<0.0001
Day 3	153	0.9	0.89	0.936	<0.0001
Day 4	89	0.9	0.95	0.917	<0.0001
Day 5	92	0.9	0.95	0.881	<0.0001

CRP cut-off values were optimized by Youden's J statistics. AUC, area under the receiver operating characteristic (ROC) curve which was calculated by the SPSS software.  $P_{AUC}$ ,  $P$  value for distinguishing cases with or without anastomotic leakage after EGJ cancer operations.

fever, tachycardia, abdominal pain, subdiaphragmatic sepsis, and intestinal contents seen in the surgical drains. However, these signs often happen late and some patients with anastomotic leakage even do not show any abnormal signs. In our cohort, 3 of 10 patients with anastomotic leakage showed normal postoperative courses. One patient was diagnosed when purulent exudate was observed three weeks after discharge. Given by these facts, early detection of the leakage is important to improve the surgical outcomes.

CRP is a reliable marker for early detection of anastomotic leakage. A prospective study involving 177 patients [27] proved that CRP as a detection method had a sensitivity and specificity of 100% at Day 3 for leakage or sepsis after laparoscopic sleeve gastrectomy which was higher than the corresponding leukocyte and neutrophil count. CRP, which was discovered in the 1930s, is one member of a family of acute phase proteins. This family of proteins is involved in the pathophysiological process of acute inflammation. CRP is mainly synthesized in the liver in response to the presence of endotoxins or other cytokines including interleukin (IL)-6, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$ . CRP levels could increase very quickly which usually occurs within 6 h after the acute stimuli. The half time of serum CRP is about 20 h. CRP is a good marker for

acute inflammation with high sensitivity but low specificity for the site of sepsis or acute inflammation [28,29]. In practice, high levels of CRP are a sign for acute inflammation rather than infection especially in critical and emergency cases. In this cohort, we detected early increased serum levels of CRP at Day 2 in patients with anastomotic leakage which occurred before the manifestation of this complication. Since the increased level of CRP is not specific to anastomotic leakage, other infectious and inflammatory conditions should be excluded when a high level of CRP is detected. In our observation, one patient suffering postoperative pneumonia also showed high levels of CRP compared to the calculated cutoffs in our cohort.

There are also some potential pitfalls in this study. Firstly, this is a retrospective observation. It is important to test whether CRP levels can be used as a predictive factor for anastomotic leakage in surgical EGJ cancer patients in a future prospective study. Secondly, our cohort is relatively small. Since EGJ cancer is not a common disease, it is hard to recruit a large population for the observation. Again, a prospective multicenter study is needed for a more accurate value of CRP in detecting this complication in the future. Last, postoperative CRP levels have been reported to be related to long-term outcomes in cardiologic patients [30], it is valuable to check the association between CRP levels of outcomes in EGJ patients. In this cohort, all patients are being followed up, and we will publish the results of long-term follow up for these patients.

In conclusion, early elevated CRP levels have diagnostic value for anastomotic leakage in EGJ patients undergoing radical surgery. When an EGJ patient shows high levels of CRP post-operatively, a careful physical examination and other image scans are needed to determine the presence of anastomotic leakage.

## Ethical approval

Please state whether Ethical Approval was given, by whom and the relevant Judgment's reference number.

The ethics committee of the Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China approved this study.

## Funding

This study was supported by Heilongjiang Province Natural Science Funding for Young Investigator (QC2011C066).

## Author contribution

Dr. L. Ji designed the study and collected the data. Dr. T. Wang wrote the first manuscript. Dr. T. Wang and Dr. L. Tian performed the statistics analysis. Dr. M. Gao designed the study as well and supervised the process.

## Conflicts of interest

No conflicts of interest.

## Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Dr. Meizhuo Gao is responsible for the entire process of the study.

## Research registration Unique Identifying Number (UIN)

Researchregistry750

## Acknowledgment

We thank Elaine de Heuvel at the University of Calgary read the manuscript and helped to improve it.

This study was supported by Heilongjiang Province Natural Science Funding for Young Investigator (QC2011C066).

## References

- [1] J. Ferlay, I. Soerjomataram, R. Dikshit, et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, *Int. J. Cancer J. Int. du Cancer* 136 (2015) E359–E386.
- [2] M. Sasako, T. Sano, S. Yamamoto, et al., D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer, *N. Engl. J. Med.* 359 (2008) 453–462.
- [3] H.H. Hartgrink, E.P. Jansen, N.C. van Grieken, C.J. van de Velde, Gastric cancer, *Lancet* 374 (2009) 477–490.
- [4] R. Wadhwa, S. Song, J.S. Lee, Y. Yao, Q. Wei, J.A. Ajani, Gastric cancer-molecular and clinical dimensions, *Nat. Rev. Clin. Oncol.* 10 (2013) 643–655.
- [5] Japanese Gastric Cancer A, Japanese classification of gastric carcinoma: 3rd english edition, *Gastric Cancer off. J. Int. Gastric Cancer Assoc. Jpn. Gastric Cancer Assoc.* 14 (2011) 101–112.
- [6] B.A. Whitson, S.S. Groth, Z. Li, R.A. Kratzke, M.A. Maddaus, Survival of patients with distal esophageal and gastric cardia tumors: a population-based analysis of gastroesophageal junction carcinomas, *J. Thorac. Cardiovasc. Surg.* 139 (2010) 43–48.
- [7] F. Cellini, A.G. Morganti, F.M. Di Matteo, G.C. Mattiucci, V. Valentini, Clinical management of gastroesophageal junction tumors: past and recent evidences for the role of radiotherapy in the multidisciplinary approach, *Radiat. Oncol.* 9 (2014) 45.
- [8] W.J. Blot, S.S. Devesa, R.W. Kneller, J.F. Fraumeni Jr., Rising incidence of adenocarcinoma of the esophagus and gastric cardia, *JAMA J. Am. Med. Assoc.* 265 (1991) 1287–1289.
- [9] J. Powell, C.C. McConkey, E.W. Gillison, R.T. Spychal, Continuing rising trend in oesophageal adenocarcinoma, *Int. J. Cancer J. Int. du Cancer* 102 (2002) 422–427.
- [10] K.D. Crew, A.I. Neugut, Epidemiology of upper gastrointestinal malignancies, *Semin. Oncol.* 31 (2004) 450–464.
- [11] J.F. Delattre, C. Avisse, C. Marcus, J.B. Flament, Functional anatomy of the gastroesophageal junction, *Surg. Clin. N. Am.* 80 (2000) 241–260.
- [12] M. Rutegard, P. Lagergren, I. Rouvelas, J. Lagergren, Intrathoracic anastomotic leakage and mortality after esophageal cancer resection: a population-based study, *Ann. Surg. Oncol.* 19 (2012) 99–103.
- [13] K. Alanezi, J.D. Urschel, Mortality secondary to esophageal anastomotic leak, *Ann. Thorac. Cardiovasc. Surg. Off. J. Assoc. Thorac. Cardiovasc. Surg. Asia* 10 (2004) 71–75.
- [14] H. Lang, P. Piso, C. Stukenborg, R. Raab, J. Jahne, Management and results of proximal anastomotic leaks in a series of 1114 total gastrectomies for gastric carcinoma, *Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol.* 26 (2000) 168–171.
- [15] W.S. Tillett, T. Francis, Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus, *J. Exp. Med.* 52 (1930) 561–571.
- [16] J.S. Yudkin, C.D. Stehouwer, J.J. Emeis, S.W. Coppack, C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler. Thromb. Vasc. Biol.* 19 (1999) 972–978.
- [17] R. Mofidi, M.D. Duff, S.J. Wigmore, K.K. Madhavan, O.J. Garden, R.W. Parks, Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis, *Br. J. Surg.* 93 (2006) 738–744.
- [18] M. Adamina, T. Steffen, I. Tarantino, U. Beutner, B.M. Schmied, R. Warschkow, Meta-analysis of the predictive value of C-reactive protein for infectious complications in abdominal surgery, *Br. J. Surg.* 102 (2015) 590–598.
- [19] G. Zanetti, R. Giardina, R. Platt, Intraoperative redosing of cefazolin and risk for surgical site infection in cardiac surgery, *Emerg. Infect. Dis.* 7 (2001) 828–831.
- [20] K.S. Scher, Studies on the duration of antibiotic administration for surgical prophylaxis, *Am. Surg.* 63 (1997) 59–62.
- [21] E.B. Wilson, Probable inference, the law of succession, and statistical inference, *J. Am. Stat. Assoc.* 22 (1927) 209–212.
- [22] R.G. Newcombe, Two-sided confidence intervals for the single proportion: comparison of seven methods, *Stat. Med.* 17 (1998) 857–872.
- [23] P. Viklund, M. Lindblad, M. Lu, W. Ye, J. Johansson, J. Lagergren, Risk factors for complications after esophageal cancer resection: a prospective population-based study in Sweden, *Ann. Surg.* 243 (2006) 204–211.
- [24] A. Sauvanet, C. Mariette, P. Thomas, et al., Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors, *J. Am. Coll. Surg.* 201 (2005) 253–262.
- [25] E. Ancona, M. Cagol, M. Epifani, et al., Surgical complications do not affect longterm survival after esophagectomy for carcinoma of the thoracic esophagus and cardia, *J. Am. Coll. Surg.* 203 (2006) 661–669.
- [26] B.Z. Atkins, A.S. Shah, K.A. Hutcheson, et al., Reducing hospital morbidity and mortality following esophagectomy, *Ann. Thorac. Surg.* 78 (2004) 1170–1176 discussion -6.
- [27] K. Albanopoulos, L. Alevizos, M. Natoudi, et al., C-reactive protein, white blood cells, and neutrophils as early predictors of postoperative complications in patients undergoing laparoscopic sleeve gastrectomy, *Surg. Endosc.* 27 (2013) 864–871.
- [28] C. Lichtenstern, T. Brenner, H.J. Bardenheuer, M.A. Weigand, Predictors of survival in sepsis: what is the best inflammatory marker to measure? *Curr. Opin. Infect. Dis.* 25 (2012) 328–336.
- [29] C. Pierrakos, J.L. Vincent, Sepsis biomarkers: a review, *Crit. Care* 14 (2010) R15.
- [30] J.J. Min, K. Nam, T.K. Kim, et al., Relationship between early postoperative C-reactive protein elevation and long-term postoperative major adverse cardiovascular and cerebral events in patients undergoing off-pump coronary artery bypass graft surgery: a retrospective study, *Br. J. Anaesth.* 113 (2014) 391–401.