J Med Biochem 2018; 37 (2) DOI: 10.1515/jomb-2017-0046

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 37: 110–120, 2018

Original paper
Originalni naučni rad

CLINICAL UTILITY OF SURVIVIN (BIRC5), NOVEL CARDIAC BIOMARKER, AS A PROGNOSTIC TOOL COMPARED TO HIGH-SENSITIVITY C-REACTIVE PROTEIN, HEART-TYPE FATTY ACID BINDING PROTEIN AND REVISED LEE SCORE IN ELDERLY PATIENTS SCHEDULED FOR MAJOR NON-CARDIAC SURGERY: A PROSPECTIVE PILOT STUDY

KLINIČKA ZNAČAJNOST SURVIVINA (BIRC5), NOVOG SRČANOG BIOMARKERA, KAO PROGNOSTIČKOG SREDSTVA U POREĐENJU SA VISOKO SEZITIVNIM C-REAKTIVNIM PROTEINOM, SRČANIM PROTEINOM KOJI VEZUJE MASNE KISELINE I REVIDIRANIM LEE SKOROM KOD STARIJIH PACIJENATA KOJI SE PRIPREMAJU ZA OPSEŽNE NEKARDIOHIRURŠKE OPERACIJE: PROSPEKTIVNA PILOT STUDIJA

Danica Marković[1], Tatjana Jevtović-Stoimenov[2], Vladan Ćosić[3], Biljana Stošić[4], Vesna Dinić[1], Bojana Marković-Živković[5], Radmilo J. Janković[4]

[1]Center for Anesthesiology and Reanimatology, Clinical Center in Niš, Niš, Serbia
[2]Department for Biochemistry, Medical School, University in Niš, Niš, Serbia
[3]Center for Medical Biochemistry, Clinical Center in Niš, Niš, Serbia
[4]Department for Emergency Medicine, Medical School, University in Niš, Niš, Serbia
[5]Medical High School »dr Milenko Hadžić«, Niš, Serbia

Summary

Background: Recent studies indicate that survivin (BIRC5) is sensitive to the existence of previous ischemic heart disease, since it is activated in the process of tissue repair and angiogenesis. The aim of this study was to determine the potential of survivin (BIRC5) as a new cardiac biomarker in the preoperative assessment of cardiovascular risk in comparison with clinically accepted cardiac biomarkers and one of the relevant clinical risk scores.
Methods: We included 79 patients, female (41) and male (38), with the mean age of 71.35±6.89. Inclusion criteria: extensive non-cardiac surgery, general anesthesia, age >55 and at least one of the selected cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking and positive family history). Exclusion criteria: emergency surgical procedures and inability to understand and sign an informed consent. Blood sampling was performed 7 days prior surgery and levels of survivin (BIRC5), hsCRP and H-FABP were measured.

Kratak sadržaj

Uvod: Novije studije ukazuju da je survivin (BIRC5) osetljiv na prisustvo prethodnih ishemijskih srčanih oboljenja s obzirom na činjenicu da se aktivira u procesu obnove tkiva i angiogeneze. Cilj ove studije je bio da se odredi potencijal survivina (BIRC5) kao novog srčanog biomarkera u preoperativnoj proceni kardiovaskularnog rizika u poređenju sa klinički prihvaćenim srčanim biomarkerima i relevantnim kliničkim rizik indeksom.
Metode: Uključeno je 79 pacijenata, žena (41) i muškaraca (38) prosečne starosti 71,35±6,89 godina. Kriterijumi uključivanja u studiju su bili: opsežne ne-kardiohirurške operacije, operacija sprovedena pod opštom anestezijom, više od 55 godina i barem jedan od izabranih kardiovaskularnih faktora rizika (hipertenzija, diabetes mellitus, hiperlipidemija, pušenje i pozitivna porodična istorija). Kriterijumi za isključivanje iz studije su bili: hitna hirurška procedura i nesposobnost pacijenta da razume i potpiše informisani pristanak. Uzorkovanje krvi je obavljeno 7 dana pre operacije i određivani su

Address for correspondence:
Dr Danica Markovic
Josifa Pančića 6/50, 18000 Niš, Niš, Serbia
danica.markovic.1983@gmail.com

List of abbreviations: CVS-cardiovascular; ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; hsCRP, high sensitivity C-reactive protein; H-FABP, heart-type fatty acid binding protein; ELISA, enzyme-linked immunosorbent assay; ROC, receiver operating characteristic; AUC, area under the curve.

Results: Revised Lee score was assessed based on data found in patients' history. Levels of survivin (BIRC5) were higher in deceased patients (P<0.05). It showed AUC=0.807 (95% CI, P<0.0005, 0.698–0.917), greater than both H-FABP and revised Lee index, and it increases the mortality prediction when used together with both biomarkers and revised Lee score. The determined cut-off value was 4 pg/mL and 92.86% of deceased patients had an increased level of survivin (BIRC5), (P=0.005).
Conclusions: Survivin (BIRC5) is a potential cardiac biomarker even in elderly patients without tumor, but it cannot be used independently. Further studies with a greater number of patients are needed.

Keywords: survivin, cardiac morbidity: pre-operative factors, sensitivity, specificity, peri-operative risk of MI

nivoi survivina (BIRC5), hsCRP-a and H-FABP-a. Revidirani Lee indeks je određivan pomoću prethodno uzetih podataka o pacijentu.
Rezultati: Nivoi survivina (BIRC5) u serumu su bili viši kod preminulih pacijenata (P<0,05). Survivin (BIRC5) je pokazao AUC=0,807 (95% CI, P<0,0005, 0,698–0,917), veći u poređenju sa H-FABP i revidiranim Lee indeksom. Takođe je povećavao predikciju mortaliteta kada se koristio u kombinaciji sa oba biomarkera i revidiranim Lee indeksom. Određena je cut-off vrednost od 4 pg/mL. Ukupno 92,86% preminulih pacijenata je imalo povišene nivoe survivina (BIRC5) (P=0,005) u serumu.
Zaključak: Survivin (BIRC5) je potencijalni srčani biomarker čak i kod starijih pacijenata bez prisustva tumora, međutim ne može se koristiti nezavisno. Potrebne su dalje studije sa većim brojem pacijenata.

Ključne reči: survivin, srčani morbiditet: pre-operativni faktori, osetljivost, specifičnost, peri-operativni risk za MI

Introduction

Percentage of non-cardiac surgeries in patients with cardiovascular comorbidity in Europe is as high as 30%. Extensive non-cardiac surgeries are associated with a mortality degree of 0.8 to 1.5% in the general population, with serious cardiovascular complications being reported between 1.7 and 3.5%. About 42% of the mortality is caused by cardiovascular complications (1).

Perioperative cardiovascular (CVS) risk assessment includes clinical signs and clinical experience, but also several risk scores, such as Goldman, Detsky, and most recently introduced revised Lee score (1, 2–4). Further assessment methods have been developed by the American Society of Anesthesiologists, the so called ASA score (5). Contemporary methods include interactive calculators, such as the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) calculator (6).

The fact is that age of the patient has impact on postoperative complications due to significant comorbidities, with cardiovascular diseases being the most prevalent. Therefore, elderly patients have to go through cautious preoperative assessment (1).

Cardiovascular biomarkers are needed in order to make preoperative assessment more accurate. High sensitivity C-reactive protein (hsCRP) has been introduced into clinical practice much earlier as a cardiac biomarker (7), while heart-type fatty acid binding protein (H-FABP) is a novel accurate cardiac biomarker (8, 9). Apoptosis plays a key role in the pathogenesis of different cardiovascular diseases, together with necrosis. It may be initiated by the activation of the first and stopped by deactivation of one of the downstream caspases, therefore a new challenge is to determine the »point of no return«. Survivin (BIRC5) is a member of the inhibitors of apoptosis proteins (IAP) family, which bind to caspases, inhibit them and decide whether the cells enters the apoptotic process or not (10–12). In contrast to other IAPs, survivin (BIRC5) is highly specific to fetal tissue and is usually not present in the adult serum (13), except in the case of tumor or autoimmune disease. Survivin (BIRC5) represents an already confirmed tumor biomarker by many studies. Apart from this, recent studies indicate that it is sensitive to the existence of previous ischemic heart disease since it is activated in the process of tissue repair and angiogenesis (10, 13).

The aim of our study was to evaluate the usefulness of survivin (BIRC5) as a new cardiac biomarkers in the preoperative assessment of cardiovascular risk in comparison with the already confirmed and clinically accepted cardiac biomarkers (hsCRP and H-FABP) and the relevant clinical risk index (revised Lee score) in elderly patients.

Materials and Methods

Ethical approval for this study (Ethical Committee No 01-6481-26) was provided by the Ethical Committee of Medical School, University in Niš, Niš, Serbia (Chairperson Prof. dr Borislav Kamenov) on 24 September 2013.

Annex to this approval (Ethical Committee No 12-6316-2/3) was provided by the Ethical Committee of Medical School, University in Niš, Niš, Serbia (Chairperson Prof. dr Vladmila Bojanić) on 16 June 2016.

Patients

Research was conducted as a prospective pilot study involving patients preparing for major non-cardiac surgeries. A total of 78 patients were operated in one of the surgical clinic of the Clinical Center in Nis, Serbia 2013 (starting from October 1st, ending December 31st). Inclusion criteria were: extensive

non-cardiac surgery (abdominal, orthopedic, endocrine and thoracic surgery), general anesthesia, an age >55 years and at least one of the selected cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking and positive family history for heart disease). Exclusion criteria were emergency surgical procedures and inability to understand and sign an informed consent. Postoperative cardiac complications were defined as one of the following: hypertension, arrhythmias, myocardial infarction and heart failure. Cause of mortality has been considered only if it was the consequence of one of the postoperative cardiovascular complications, and it manifested as cardiac arrest. The duration of the follow-up was specified as the primary endpoint, which is the in-hospital all-cause mortality and secondary endpoint, which is total hospital stay. All patients included in the study signed the informed consent. This study was approved by the local ethics committee of center in which it was conducted.

Surgical procedures

Patients who were included in the study were being prepared for one of the non-cardiac procedures in general anesthesia. Surgical procedures were performed according to clinical standards of our institution. The largest number of operations belonged to abdominal and orthopedic surgeries with a small number of thoracic (4) and endocrine (1) surgeries.

Revised cardiac index (Lee index)

We calculated the Lee index for each patient individually using interactive web calculator, available at https://www.mdcalc.com/revised-cardiac-risk-index-pre-operative-risk. Briefly, the following parameters were being entered: a high-risk surgery (intraperitoneal, intrathoracic), history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin-dependent diabetes mellitus, preoperative creatinine > 176.8 mmol/L.

Laboratory assessment

Blood sampling was performed within 7 days prior to surgery from the antecubital vein into serum Vacutainer tubes without additives. After centrifugation, the serum was separated and frozen at -70 °C until analyzes. Analyzes were done after collecting all the samples in the Scientific Research Center for Biomedicine, Medical School, University in Niš and in the Center for Medical Biochemistry, Clinical Center in Niš. Researchers in these institutions were not aware of any of the patient's identity and pathology.

Survivin (BIRC5) in serum was determined by Enzyme-linked immunosorbent assay (ELISA) method which implies a quantitative sandwich enzyme immunoassay technique. The kit we used was Quantikine Human Survivin ELISA Kit, R & D Systems, Minneapolis, MM, USA (DSVOO), and it was commercially available. After implementation of the protocol recommended by the manufacturers, optical density was read on DIAREADER EIx800G (DIALAB, Austria). Results were then calculated from a standard curve which was constructed from the parametric logistic curve and were presented in pg/mL.

hsCRP was measured by latex-anhanced turbidimetric immunoassay (CRP Latex, and Beckmann Coulter, Nyon, Switzerland) on the AU480 biochemical analyzer (Beckman Coulter and International SA, Nyon, Switzerland). Assay range was 0.2–160 mg/L. H-FABP was measured by immunoturbidimetric method (HFABP, Reagents Randox, Crumlin, UK). Assay range was 0.747–120 ng/mL.

Statistics

All the results related to continuous variables are expressed as median with inter quartile range. In order to evaluate the difference between the two groups the T-test for independent samples was used, and if the groups were inhomogeneous the Mann-Whitney U test was used. Receiver operating characteristic (ROC) curves were constructed to evaluate the effectiveness of survivin (BIRC5) compared to the other two biomarkers and revised Lee index as a predictor of mortality. The area under the curve (AUC) and the most appropriate cut-off value for survivin (BIRC5) were determined. In order to assess interaction between variables binary logistic regression model has been performed. P value below 0.05 was considered a statistically significant result. All results were statistically processed in the program SPSS 10.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) for Windows.

Results

The study included a total of 78 patients whose main characteristics are presented in *Table I*. A total of 72 patients (92.31%) belonged to the group of elderly patients (>65 years according the definition of the World Health Organization). Accurate data regarding the age of patients are presented in the Table II. A Lee index of 1 was present in the majority of patients, 37 (47.43%), of 2 in 14 (17.95%) patients and 3 in 11 (14.10%) patients. Most patients had two or more cardiovascular risk factors (73.08%) while 79.49% of patients were taking some type of cardiovascular therapy.

During the stay on the Surgery department a total of 14 patients (17.95%) have died, of which 13 (92.86%) were subjected to one of extensive abdom-

Table I Basic characteristics of patients involved in our study. Values are number (n), percent (%) and median (IQR range).

	All patients	Survivors	Deceased	P-value survivors vs. deceased
n (%)	78	64 (82.05)	14 (17.95)	
Female gender, n (%)	41 (52.56)	33 (51.56)	8 (57.14)	P=0.709
Age AM±SD	71.35±6.89	70.57±6.67	74.86±6.97	P=0.034
BMI* median (IQR)	25.35 (22.97–28.15)	25.90 (23.10–28.67)	24.05 (22.50–25.47)	P=0.146
CAD**, n (%)	25 (32.05)	18 (28.12)	7 (50)	P=0.115
Dyspnoea (NYHA II-IV), n (%)	60 (76.92)	47 (73.43)	13 (92.86)	P=0.061
Angina pectoris (CCS) (II-IV), n (%)	23 (29.49)	16 (25)	7 (50)	P=0.195
Atrial fibrillation, n (%)	10 (12.82)	8 (12.5)	2 (14.29)	P=0.859
Diabetes mellitus, n (%)	23 (29.49)	20 (31.25)	3 (21.43)	P=0.472
Insulin dependent, n (%)	6 (7.69)	6 (9.37)	0 (0)	P=0.236
Hypertension, n (%)	61 (78.20)	51 (79.69)	10 (71.43)	P=0.504
Hyperlipidemia, n (%)	13 (16.67)	12 (18.75)	1 (7.14)	P=0.294
Active smoker, n (%)	12 (15.38)	11 (17.19)	1 (7.14)	P=0.349
Malignancy, n (%)	44 (56.41)	34 (53.12)	10 (71.43)	P=0.211
Aspirin/clopidogrel, n (%)	23 (29.49)	17 (26.56)	6 (42.86)	P=0.065
Beta-blocker, n (%)	41 (52.56)	34 (53.12)	7 (50)	P=0.835
ACE-inhibitor/AT-antagonist	45 (57.69)	37 (57.81)	8 (57.14)	P=0.964
Diuretics, n (%)	13 (16.67)	10 (15.62)	3 (27.43)	P=0.495
Nitrates, n (%)	8 (10.26)	7 (10.94)	1 (7.14)	P=0.676
OAT	8 (10.26)	6 (9.37)	2 (14.28)	P=0.589
HSS/Clopidogrel	16 (20.51)	10 (15.62)	6 (42.86)	P=0.023
Lee index 0 n (%) 1 2 ≥3	 16 (20.51) 37 (47.43) 14 (17.95) 11 (14.10)	 15 (23.44) 31 (48.43)1 2 (18.75) 6 (9.37)	 1 (7.14) 6 (42.86) 2 (14.29) 5 (35.71)	P=0.028 P=0.174 P=0.709 P=0.698 P=0.011
Hgb (g/L) median (IQR)	119 (108.7–130.0)	119 (107.2–129.0)	121 (113.5–134.7)	P=0.249
Creatinine (g/L) median (IQR)	0.0102 (0.0084–0.0119)	0.0103 (0.0085–0.0120)	0.01 (0.0083–0.0116)	P=0.787
Survivin (pg/mL) median (IQR)	4.56 (0.11–9.28)	2.33 (0.11–6.78)	9.55 (6.22–21.22)	P=0.020
H-FABP (μg/L) median (IQR)	7.32 (4.35–10.80)	6.63 (4.12–8.73)	11.95 (7.18–16.70)	P=0.001
hsCRP (mg/L) median (IQR)	11.35 (2.83–35.20)	7.10 (2.29–22.16)	68.13 (25.07–114.62)	P=0.0001
Survivin >4.00 pg/mL, n %	40 (51.28)	27 (42.19)	13 (92.86)	P=0.001

* BMI; Body mass index; **CAD; coronary artery disease

Table II Frequency distribution of the age of all the included patients and deceased patients only. Values are number (n) and percent (%).

Age	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89
Number of patients, n (%)	2 (2.56)	1 (1.28)	3 (3.85)	24 (30.77)	23 (29.49)	17 (21.79)	6 (7.69)	2 (2.56)
Deceased, n (%)	0 (0)	0 (0)	0 (0)	3 (21.43)	3 (21.43)	5 (35.71)	2 (14.29)	1 (7.14)

Table III Type of surgery and mortality. The distribution of different surgical procedures for patients and deceased patients; The number and percentage of deceased patients who had surviving (BIRC5) levels in serum above and below the cut-off value. Values are number (n) and percent (%).

		Deaths n (%)		
n (%)		Total	Survivin (BIRC5)>4	Survivin (BIRC5) 4
Abdominal	48 (61.54)	13 (27.08)	12/26 (46.15)	1/22 (4.54)
Orthopedy	25 (32.05)	1 (4)	1/9 (11.11)	0/16 (0)

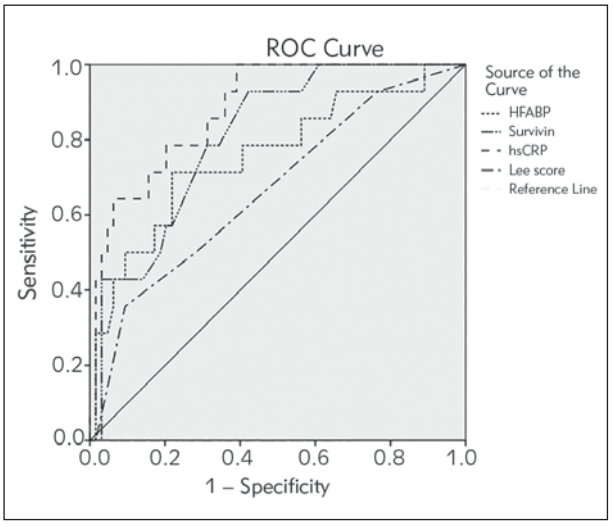

Figure 1 ROC curve of survivin (BIRC5), hsCRP, H-FABP and the revised Lee index in relation to postoperative mortality.

H-FABP: AUC=0.758 (95% CI, P<0.005, 0.607–0.909); Survivin (BIRC5): AUC=0.807 (95% CI, P<0.0005, 0.698–0.917); hsCRP: AUC=0.883 (95% CI, P<0.0005, 0.797–0.969); Revised Lee score: AUC=0.666 (95% CI, P>0.05, 0.507–0.826)

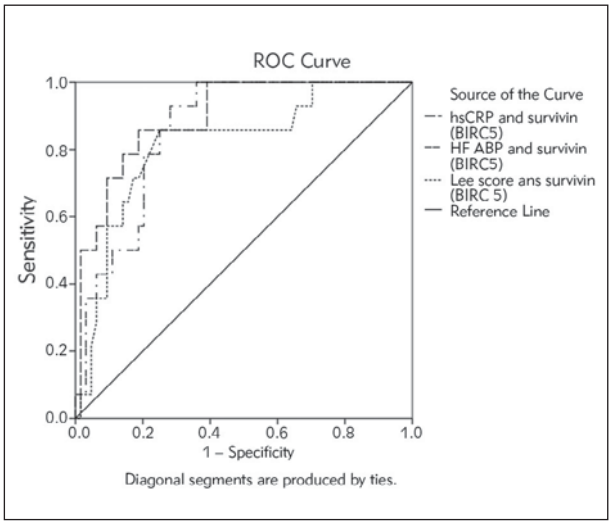

Figure 2 ROC curve showing combination of survivin (BIRC5) with other predictors.

Survivin (BIRC5) and hsCRP, AUC=0.896 (95% CI; P<0.0005; 0.815–0.977); Survivin (BIRC5) and H-FABP, AUC=0.857 (95% CI, P<0.0005, 0.772–0.942); Survivin (BIRC5) and revised Lee score, AUC=0.814 (95% CI, P<0.0005, 0.690–0.939)

inal surgeries and 1 (7.14%) patient was subjected to extensive orthopedic procedure (*Table III*). All the deceased patients belonged to the age group >65 years (*Table II*). Of the total number of deceased patients 7 (50%) had some form of coronary artery disease, 11 (78.57%) had two or more cardiovascular risk factors, while 12 (85.71%) were taking a cardiovascular therapy. The average number of days spent in the intensive care was 10 ± 7 days. Average number of postoperative days until the final excites was 10 ± 6 dana.

Patients who deceased were older, had preoperative dyspnea, were taking HSS/Clopidogrel therapy, had higher Lee score (P <0.05 for the score 3), had survivin (BIRC5)> 4:00 pg/mL, higher value of H-FABP and hsCRP.

For the entire population median hsCRP was 11.35 mg/L, H-FABP 7.32 μg/L and survivin (BIRC5) 4.56 pg/mL. All the three biomarkers had higher values in the deceased patients when compared to those who survived. None of the biomarkers had statistical

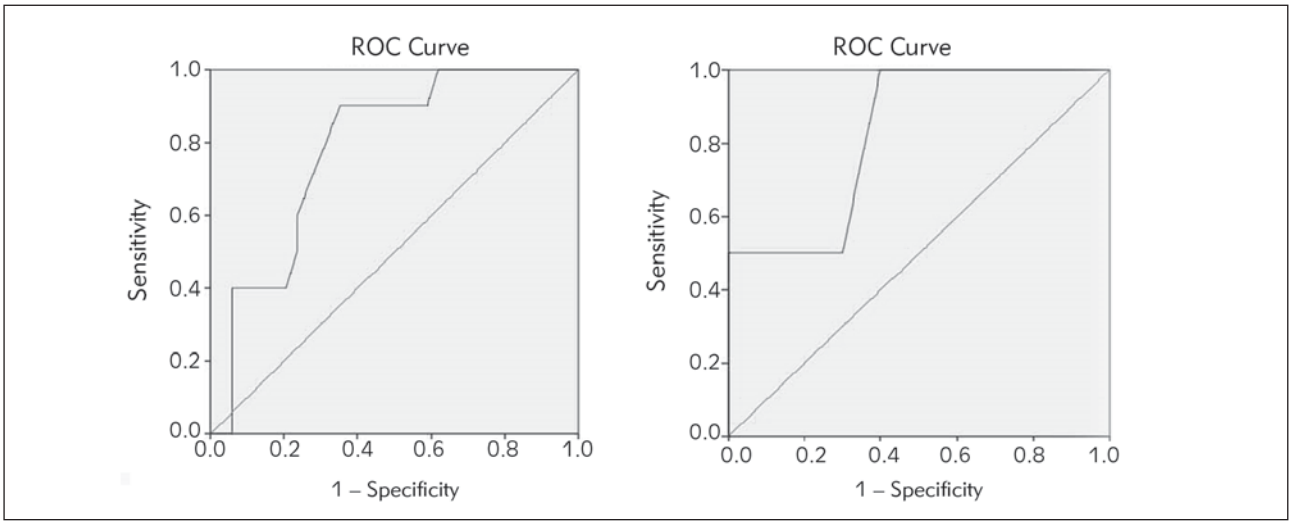

Figure 3 Comparative review of ROC curves in patients with and without malignancy.

A) ROC curve that describes the relationship of survivin (BIRC5) value and death in the group of patients with some type of malignancy. AUC=0.782. B) ROC curve that describes the relationship of survivin (BIRC5) and death in the group of patients without malignancy. AUC=0.825.

significance when it comes to preoperative cardiovascular comorbidities.

ROC curves for all three biomarkers as predictors of intrahospital mortality showed significant AUC (*Figure 1*). The highest AUC was of hsCRP, AUC = 0.883, while survivin (BIRC5) showed AUC = 0.807, greater than both H-FABP and revised Lee index. Survivin (BIRC5) in combination with the other two biomarkers and revised Lee score showed that survivin (BIRC5) increases the mortality prediction of both biomarkers and revised Lee score (*Figure 2*). The model of hsCRP and HFABP were statistically significant, with respectively 2=21.285, P<0.0005 and 2=10.477, P<0.005. The models explained 39.2% and 20.6% of the variance and correctly classified 82.1% and 84.6% of cases. Patients with higher hsCRP and HFABP had a higher chance for postoperative mortality. Addition of survivin (BIRC5) maintained the statistical significance of both models, with respectively 2=23.803, P<0.0005 and 2=17.125, P<0.0005, correct classification of 88.5% and 85.9% of the patients and explanation of 43.1% and 32.3% of the variance.

Since there is no clinically accepted cut-off value for survivin (BIRC5) we determined the most appropriate, which was 4 pg/mL. Of the total number of patients, 40 (51.28%) had a value of survivin (BIRC5) > 4 pg/mL. Thirteen patients (92.86% of the total number of deceased patients) belonged to this group of patients, with P<0.005.

When it comes to malignancy, a total of 44 (56.41%) of our patients had some form of malignancy. In order to prove that the presence of tumor does not affect the significance of survivin (BIRC5) as a cardiac biomarker we divided the patients into two groups, patients with and without tumor. In the group of patients with tumor, value of survivin (BIRC5) showed P>0.05 in the prediction of postoperative mortality, AUC=0.782 (95% CI, P=0.007, 0.639–0.928), with the cut-off value 6.22 pg/mL. In the group of patients without tumor value of survivin (BIRC5) showed P<0.05, AUC=0.825 (95% CI, P<0.05, 0.629–1.000), with the cut-off value 4 pg/mL (*Figure 3*).

Discussion

The aim of this pilot study was to examine the independent and additive value of survivin (BIRC5) in identifying the patients who are at a high risk to develop cardiac postoperative complications. The key finding of our study is that survivin (BIRC5) as an already confirmed tumor and autoimmune biomarker has an important prediction when it comes to postoperative mortality. It also has an important additive value to already confirmed biomarkers (hsCRP and H-FABP) and revised Lee score. The most important thing is that when it comes to the prediction of postoperative mortality survivin (BIRC5) is independent of the presence of tumor.

Cardiovascular complications after non-cardiac surgeries represent a major cause of postoperative morbidity and mortality. Every anesthesiologist and surgeon would have to ask themselves the following questions: what is the risk of developing cardiovascular complications and mortality and how can that be alleviated or prevented? There is the fact that it is pretty challenging to distinguish between changes in physiology caused by aging and certain diseases that are very common in elderly. Elderly patients are

extremely sensitive and therefore must be assessed preoperatively with high caution and must be informed about possible risks (14).

The high mortality rate (17.95%) in our study can be partly explained by the fact that the patients included in our study belonged to old age (71.35 ± 6.89 years, $P<0.05$), that the study group is relatively small, that there was a great number of co-morbidities and that extensive non-cardiac surgeries carry a particularly high risk. All the deceased patients belonged to the group of patients over 65 years, while the highest percentage (35.71%) belonged to the group of 75–79 years. All of the patients who died were subjected to abdominal (92.86%), mostly radical, resections and orthopedic procedures (7.14%).

High mortality rate can also be explained by the fact that cancer incidence and mortality rate in Serbia have been increased since the year of 1999, and that mortality rate in people above 65 years of age is significantly higher than in other European countries. Elderly who live in rural areas have low monthly income, are separated from their family members and do not have an easy access to health care providers (15, 16).

Tzeng et al. (17) indicated that reduced physiological reserve of elderly patients leads to far greater risk of death after serious complications, and must therefore be assessed with a far greater caution considering their age and comorbidities +. Age cannot be considered as an individual risk factor but only in combination with comorbidities and the type of operation (18, 19). The only case when age can be considered as an independent risk factor is after 90 years of age (20). Lees et al. have conducted their research on 257 patients with the mean age of 72 years, with a conclusion that the degree of intrahospital mortality is as high as 12% and that mortality is associated with higher ASA class and more intrahospital complications (21). Hernandez et al. (22) have noted a mortality rate of 18.3% in a sample of patients with severe cardiovascular comorbidities. Both of these studies are in accordance with our results.

Although several clinical risk scores had been developed, currently the most commonly used in practice is the revised Lee score. The revised Lee score can be calculated by assessing six clinical and easily available patient data, based on which we get the results from 0 to 6 points (4). Several studies showed that Lee score is a useful tool for preoperative treatment of patients as well as that its great advantage is that it uses easily available patient data (23, 24). Our study showed that it is possible to distinguish patients who are at increased risk with the use of the revised Lee score, but the AUC showed only 0.666. Several studies have correlated with this result (25, 26).

The possibility to use H-FABP in clinical practice has already been confirmed (27). It is believed that elevated levels of this biomarker are associated with the risk of cardiovascular events and the occurrence of heart failure and death in the first 10 months after acute coronary syndrome (28). It is even considered more sensitive than hs-cTnT, cTnT, myoglobin, and CK-MB in some cases (29, 30). H-FABP has an important additive value to other predictive parameters and it has a significant role in the palette of cardiac biomarkers, however it is believed that there are more specific biomarkers which can be used in practice (27, 31, 32). This correlates with our findings since H-FABP showed lower AUC when compared to hsCRP and survivin (BIRC5).

Biomarker hsCRP had previously been confirmed as a predictor of morbidity and mortality, especially when combined with other cardiac biomarkers and clinical risk predictors (33). It may be used as an independent biomarker for cardiac complications, however, it is considered that it is most efficient when combined with NT-proBNP and TnI I (34). Our study points to the extremely high sensitivity and specificity of hsCRP with AUC=0.883, which is consistent with previous studies.

Correlation of survivin (BIRC5) levels and development of cardiac complications has not yet been studied. Survivin (BIRC5) participates in the process of angiogenesis by interacting with vascular endothelial growth factor VEGF (35). A positive feedback, which connects the expression of survivin (BIRC5) with the PI3K/Akt increased expression of β-catenin-Tcf/Lef, which is then followed by secretion of VEGF and final angiogenesis, has been proven (36). It is believed that survivin (BIRC5) is under the regulation of VEGF in the process of angiogenesis (37). In the first 24 hours after the occurrence of myocardial infarction significant changes in VEGF receptor sFlt-1 level may be expected but not changes in the level of VEGF itself, while significant changes in the levels of both molecules occur in patients with chronic myocardial infarction (38). This showed that the expression of survivin (BIRC5) persists longer, and that it can be used in preoperative diagnosis and prognosis of myocardial damage even if it did not happen recently.

Santini et al. (39) showed that survivin (BIRC5) is expressed in myocytes located in the peri-infarct zone in a far higher percentage in deceased patients than in controls, by immunohistochemistry. It is believed that myocardial expression of survivin (BIRC5) is associated with the cell survival in a surveillance infarction zone as well as that it can indicate a better remodeling after AMI. Ho et al. (40) have shown that survivin (BIRC5) directly affects the proliferation of Nkx2.5+ population of cardiomyoblasts and increases the viability of cultured cardiomyocytes. Survivin (BIRC5) possess potentially cytoprotective effects when it comes to doxorubicin-induced apoptosis of cardiomyocytes (41). All of this has identified survivin (BIRC5) as a new potential target protein in the treatment of post-infarction preservation and remodeling and as a novel potential cardiac biomarker (39).

It has previously been proved that the detection of survivin (BIRC5) in cell culture supernatant is possible after its transduction in the culture of mice cardio myoblasts in vitro, which proves that it can be detected in the serum of patients after an increased expression in myocardial tissue (42). Therefore, we have examined the level of survivin (BIRC5) in the serum of patients.

The level of survivin (BIRC5) showed a statistically significant difference between the group of deceased patients and the group of patients who survived. ROC-AUC has proved that survivin (BIRC5) can be used as a useful biomarker (cut-off value 4.00 pg/mL) in preoperative prediction of mortality with high sensitivity and specificity. After application of cut-off value, we found that survivin (BIRC5) is increased in half (51.28%) of patients. In deceased patients elevated levels of survivin (BIRC5) were found in 92.85% of cases (P=0.005). Clinical application of survivin (BIRC5) is still uncertain, since a greater number of patients is needed.

Addition of survivin (BIRC5) to other predictors has been assessed with hierarchical binary logistic regression and it proved to be significant in the case of H-FABP and revised Lee score (addition to model significance and increase in AUC). Only AUC value of hsCRP does not change significantly (0.013), which supports the results of other studies that hsCRP can be used independently. Other studies have also confirmed the dependence of revised Lee score and H-FABP and necessity to add other non-invasive method of assessment with the aim of precise identification of patients in increased risk (26). Roshanov et al. (43) have launched the so-called VISION study in January 2017. with the aim of anew revision of Lee score since estimated level of glomerular filtration is considered to be a more appropriate parameter for the assessment of renal function than the level of serum creatinine.

We have found the data of survivin (BIRC5) being present in the endometrium of women during normal menstrual cycle, namely during the secretory phase (43). We believe that our results are not compromised by this since the average age of the women in our study was 71.36 ± 6.35 (53-87) years.

Survivin (BIRC5) is overexpressed in the majority of malignant cells but not in normal differentiated tissues (13, 44). For this reason, we have divided the patients into two groups: group of patients with and without the presence of a tumor. After comparing the mortality of patients with a value of survivin (BIRC5) in both groups, statistical significance was observed only in the group of patients without tumor. The area under the ROC curve has also shown that survivin (BIRC5) is a better predictor of mortality in the same group (AUC=0.825) with a cut-off value of 4 pg/mL and a very high sensitivity. It is evident that the limit values were higher in the group with tumor than in controls in previous studies, therefore we hope that future studies will demonstrate that lower levels of survivin (BIRC5) in serum indicate the likely absence of tumor. Levels of survivin (BIRC5) in serum in our study are in accordance with other studies (45, 46).

Most of our patients had colorectal carcinoma and expression of survivin (BIRC5) in tissues of these patients has already been confirmed by previous studies. With a specificity that normal, healthy tissues did not express this protein at all (47, 48). Many other studies in patients with tumors of different locations also confirmed elevated survivin (BIRC5) levels in patients' serum (46, 49). In the study by Goricar et al. (46) surviving showed level od 4.1 pg/mL at diagnosis, but patients with progressive disease had significantly higher surviving levels before chemotherapy which is in accordance to our results. Other study has also confirmed that surviving level in the advanced stage of different carcinoma locations hits higher levels (49–51). These deviations in serum levels can be explained by the fact that there are many specificities about tumors that can affect the serum levels of this protein.

There is a strong association between survivin (BIRC5) expression and perineural invasion, venous invasion and lymph nodes status, but not with the tumor size, age, gender, or tumor location (52, 53). Survivin (BIRC5) levels were also found to be higher in muscle-invasive tumors than in non-muscle invasive tumors and in poorly differentiated tumors than in moderately differentiated tumors (54). The median overall survival of patients with normal survivin (BIRC5) serum levels (control group) has been to be longer that that of elevated serum surviving (BIRC5) group (53).

Certainly, we suggest that the survivin (BIRC5) should not be used as an independent biomarker since its specificity for tumor and autoimmune diseases is strong. It should be used only in combination with highly specific cardiac biomarkers or as a part of the cardiac palette since it has a strong additive ability.

We have to point out that this is only a pilot study and that more extensive studies are needed in order to determine the specificity and sensitivity of survivin (BIRC5) and its cut-off value. However, we do consider this study significant for the fact that we have proved for the first time the relationship between the value of survivin (BIRC5) in the serum of patients and the prediction of postoperative mortality as a result of cardiovascular complications.

Acknowledgements. Acknowledgements relating to this article: Assistance with the study: We would like to thank Miodrag Krstić, Master Engineer of Electrical Engineering and Computer Science, for his assistance in statistical analyses of data.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

References

1. The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. Eur Heart J 2014; 35: 2383–431.
2. Goldman L. Cardiac risk and complications of noncardiac surgery. Ann Intern Med 1983; 98(4): 504–13.
3. Detsky AS, Abrams HB, McLaughlin JR, Drucker DJ, Sasson Z, Johnston N et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1986; 1: 211–9.
4. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100(10): 1043–9.
5. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol 2007; 50: 1707–32.
6. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmjecik TE, Ko CY et al. Development and Evaluation of the Universal ACS NSQIP Surgical Risk Calculator: A Decision Aid and Informed Consent Tool for Patients and Surgeons. J Am Coll Surg 2013; 217(5): 833–42.
7. Klingenberg R, Aghlmandi S, Räber L, Gencer B, Nanchen D, Heg D et al. Improved risk stratification of patients with acute coronary syndromes using a combination of hsTnT, NT-proBNP and hsCRP with the GRACE score. Eur Heart J Acute Cardiovasc Care 2016 (DOI: 10.1177/2048872616684678).
8. Hamza M, Demerdash S, Ibrahim M. Heart-type fatty acid-binding protein as a diagnostic biochemical marker for early detection of myocardial infarction, Acta Cardiol 2016; 71(5): 537–41.
9. Janković RJ, Marković DZ, Sokolović DT, Zdravković I, Sorbello M. Clinical indices and biomarkers for perioperative cardiac risk stratification: an update. Minerva Anestesiol 2017; 83(4): 392–401.
10. Sanhueza C, Wehinger S, Castillo Bennett J, Valenzuela M, Owen GI, Quest AFG et al. The twisted survivin connection to angiogenesis. Mol Cancer 2015; 14: 198.
11. Lee PJH, Rudenko D, Kuliszewski MA, Liao C, Kabir MG, Connelly KA et al. Survivin gene therapy attenuates left ventricular systolic dysfunction in doxorubicin cardiomyopathy by reducing apoptosis and fibrosis. Cardiovasc Res 2014; 101: 423–33.
12. Delvaeye M, De Vriese A, Zwerts F, Betz I, Moons M, Autiero M et al. Role of the 2 zebrafish survivin genes in vasculo-angiogenesis, neurogenesis, cardiogenesis and hematopoiesis. BMC Dev Biol 2009; 9: 25.
13. Dobrzycka B, Mackowiak-Matejczyk B, Terlikowska KM, Kulesza-Bronczyk B, Kinalski M, Terlikowksi SJ et al. Prognostic significance of pretreatment VEGF, survivin, and Smac/DIABLO serum levels in patients with serous ovarian carcinoma. Tumour Biol 2015; 36(6): 4157–65.
14. Maddox TM. Preoperative cardiovascular evaluation for noncardiac surgery. Mt Sinai J Med 2005; 72(3): 185–92.
15. Mihajlović J, Pechlivanoglou P, Miladinov-Mikov M, Živković S, Postma MJ. Cancer incidence and mortality in Serbia 1999–2009. BMC Cancer 2013; 13: 18.
16. Urošević J, Odović G, Rapaić D, Davidović M, Trgovčević S, Milovanović V. Quality of life of the elderly in urban and rural areas in Serbia Kvalitet ivota starih u urbanoj i ruralnoj sredini u Srbiji. Vojnosanit Pregl 2015; 72: 968–74.
17. Tzeng CWD, Cooper AB, Vauthey JN, Curley SA, Aloia TA. Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. HPB 2014; 16: 459–68.
18. Latkauskas T, Rudinskait G, Kurtinaitis J Janciauskiene R, Tamelis A, Saladyinskas Z et al. The impact of age on post-operative outcomes of colorectal cancer patients undergoing surgical treatment. BMC Cancer 2005; 5: 153.
19. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg 2006; 203: 865–77.
20. D'Apuzzo MR, Pao AW, Novicoff WM, Browne JA. Age as an independent risk factor for postoperative morbidity and mortality after total joint arthroplasty in patients 90 years of age or older. J Arthroplasty 2014; 29: 477–80.
21. Lees MC, Merani S, Tauh K, Khadaroo RG. Perioperative factors predicting poor outcome in elderly patients following emergency general surgery: a multivariate regression analysis. Can J Surg 2015; 58: 312–7.
22. Hernandez AF, Whellan DJ, Stroud S, Sun JL, O'Connor CM, Jollis JG. Outcomes in heart failure patients after major noncardiac surgery. J Am Coll Cardiol 2014; 44: 1446–53.
23. Hoftman N, Prunean A, Dhillon A, Danovitch GM, Lee MS, Gritsch HA et al. Revised Cardiac Risk Index (RCRI) is a useful tool for evaluation of perioperative cardiac morbidity in kidney transplant recipients. Transplantation 2013; 96(7): 639–43.
24. Davis C, Tait G, Carroll J, Wijeysundera DN, Beattie WS. The Revised Cardiac Risk Index in the new millennium: a single-centre prospective cohort re-evaluation of the original variables in 9,519 consecutive elective surgical patients. Can J Anaesthesiol 2013; 60(9): 855–63.
25. Dover M, Tawfick W, Hynes N, Sultan S. Cardiac risk assessment, morbidity prediction, and outcome in the vascular intensive care unit. Vasc Endovasc Surg 2013; 47(8): 585–94.

26. Bae MH, Jang SY, Choi WS, Kim KH, Park SH, Lee JH et al. A new revised cardiac risk index incorporating fragmented QRS complex as a prognostic marker in patients undergoing noncardiac vascular surgery. Am J Cardiol 2013; 112(1): 122–7.

27. Niizeki T, Takeishi Y, Arimoto T, Takabatake T, Nozaki N, Hirono O et al. Heart-type fatty acid-binding protein is more sensitive than troponin T to detect the ongoing myocardial damage in chronic heart failure patients. J Cardiac Fail 2007; 13(2): 120–7.

28. Thielmann M, Pasa S, Holst T, Wendt D, Dohle DS, Demircioglu E et al. Heart-Type Fatty Acid Binding Protein and Ischemia-Modified Albumin for Detection of Myocardial Infarction After Coronary Artery Bypass Graft Surgery. Ann Thorac Surg 2017; 104(1): 130–7.

29. Willemsen RT, Van Severen E, Vandervoort PM Grieten L, Buntinx F, Glatz JF, et al. Heart-type fatty acid binding protein (H-FABP) in patients in an emergency department setting, suspected of acute coronary syndrome: optimal cut-off point, diagnostic value and future opportunities in primary care. Eur J Gen Pract 2015; 21(3): 156–63.

30. Sari M, Kilic H, Karakurt Ariturk O, Yazihan N, Akdemir R. Diabetic patients have increased perioperative cardiac risk in heart-type fatty acid-binding protein-based assessment. Med Princ Pract 2015; 24(1): 53–7.

31. Banu S, Tanveer S, Manjunath CN. Comparative study of high sensitivity troponin T and heart-type fatty acid-binding protein in STEMI patients. Saudi J Biol Sci 2015; 22(1): 56–61.

32. Jeong JH, Seo YH, Ahn JY Kin KH, Seo JY, Kim M et al. The prognostic value of serum levels of heart-type fatty acid binding protein and high sensitivity C-reactive protein in patients with increased levels of amino-terminal pro-B type natriuretic peptide. Ann Lab Med 2016; 36(5): 420–6.

33. Scrutinio D, Guido G, Guida P Passantino A, Angiletta D, Santoro D et al. Combined use of high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide for risk stratification of vascular surgery patients. Ann Vasc Surg 2014; 28(6): 1522–9.

34. Harutyunyan MJ, Mathiasen AB, Winkel P Gotze JP, Hansen JF, Hildebrandt P, et al. High-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide in patients with stable coronary artery disease: a prognostic study within the CLARICOR Trial. Scand J Clin Lab Invest 2011; 71(1): 52–62.

35. Ozisik K, Ozisik P, Yildirim E, Misirlioglu M, Tuncer S. Expression of antiapoptotic survivin and aven genes in rat heart tissue after traumatic brain injury. Transplant Proc 2006; 38: 2784–7.

36. Fernández JG, Rodríguez DA, Valenzuela M, Calderon C, Urzua U, Munroe D et al. Survivin expression promotes VEGF-induced tumor angiogenesis via PI3K/Akt enhanced β-catenin/Tcf-Lef dependent transcription. Mol Cancer 2014; 13: 209.

37. Ma ACH, Lin R, Chan PK, Leung JC, Chan LY, Meng A et al. The role of survivin in angiogenesis during zebrafish embryonic development. BMC Dev Biol 2007; 7: 50.

38. Ghaffarzadeh M, Ghaedi H, Alipoor B, Omrani MD, Kazerouni F, Shanaki M, Labbaf A, Pashaiefar H, Rahimipour A. Association of mir-149 (rs2292832) variant with the risk of coronary artery disease. J Med Biochem 2017; 36: 251–8.

39. Santini D, Abbate A, Scarpa S, Vasaturo F, Biondi-Zoccai GG, Bussani R, et al. Surviving acute myocardial infarction: survivin expression in viable cardiomyocytes after infarction. J Clin Pathol 2004; 57: 1321–4.

40. Ho YS, Tsai WH, Lin FC, Huang WP, Lin LC, Wu SM, et al. Cardioprotective actions of TGF RI inhibition through stimulating autocrine/paracrine of survivin and inhibiting Wnt in cardiac progenitors. Stem Cell 2015; 34(2): 445–55.

41. Lee BS, Kim SH, Jin T, Choi EY, Oh J, Park S, et al. Protective effect of survivin in doxorubicin-induced cell death in H9c2 cardiac myocytes. Korean Circ J 2013; 43: 400–7.

42. Lee PJH, Rudenko D, Kuliszewski MA, Liao C, Kabir MG, Connelly KA et al Survivin gene therapy attenuates left ventricular systolic dysfunction in doxorubicin cardiomyopathy by reducing apoptosis and fibrosis. Cardiovasc Res 2014; 101(3): 423–33.

43. Roshanov PS, Walsh M, Devereaux PJ, MacNeil SD, Lam NN, Hildebrand AM et al. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after non-cardiac surgery: rationale and plan for analyses of the VISION study. BMJ Open 2017; 7(1): e013510.

44. Duan L, Hu X, Jin Y, Liu R, You Q. Survivin protein expression is involved in the progression of non-small cell lung cancer in Asians: a meta-analysis. BMC Cancer 2016; 16: 276.

45. Noton EA, Colnaghi R, Tate S, Starck C, Carvalho A, Ko Ferrigno P et al. Molecular analysis of survivin isoforms: Evidence that alternatively spliced variants do not play a role in mitosis. J Biol Chem 2005; 281(2): 1286–95.

46. Goričar K, Kovac V, Franko A, Dodil-Fikfak M, Dolčan V. Serum survivin levels and outcome fo chemotherapy in patients with malignant mesothelioma. Dis Markers 2015; Article ID 316739.

47. Jiang ZM, Yao HR, Zhan J, Xie DR, Li HG. Expression and significance of survivin in colon cancer. Ai Zheng 2004; 23(11 Suppl): 1414–7.

48. Stanilov N, Miteva L, Mintchev N, Stanilova S. High expression of Foxp3, IL-23p19 and survivin mRNA in colorectal carcinoma. Int J Colorectal Dis 2009; 24(2): 151–7.

49. El-Attar HA, Kandil MH, El-Kerm YM, El-Ghandour MK. Comparison of serum survivin and alpha fetoprotein in Egyptian patients with hepatocellular carcinoma associated with hepatitis C viral infection. Asian Pac J Cancer Prev 2010; 11(4): 897–903.

50. Krepela E, Dankova P, Moravcikova E, Krepelova A, Prochazka J, Cermak J et al. Increased expression of inhibitor of apoptosis proteins, surviving and XIAP, in non-small cell lung carcinoma. International Journal of Oncology 2009; 35: 1449–62.

51. Dellala FD, Niyazoglub M, Gorara S, Ademoglua E, Candana Z, Bekdemira H et al. Serum surviving increases in prolactinoma. J Clin Med Res 2015; 7(4): 248–52.

52. Dong H, Qian D, Wang Y, Meng L, Chen D, Ji X et al. Survivin expression and serum levels in pancreatic cancer. World J Surg Oncol 2015; 13:189.

53. Ren YQ, Zhang HY, Su T, Wang XH, Zhang L. Clinical significance of serum survivin in patients with pancreatic ductal adenocarcinoma. Eur Rev Med Pharmacol Sci 2014; 18(20): 3063–8.

54. Chen HA, Su CM, Hsieh HY, Tung CL, Hsu CD, Wang YH et al. Clinical significance of survivin expression in patients with urothelial carcinoma. Dis Markers; 2014: 574985.

Received: July 6, 2017

Accepted: August 27, 2017