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ORIGINAL ARTICLE

Addition of biomarker panel improves prediction performance of American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) calculator for cardiac risk assessment of elderly patients preparing for major non-cardiac surgery: a pilot study

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Abstract

Background Number of elderly patients subjected to extensive surgical procedures in the presence of cardiovascular morbidities is increasing every year. Therefore, there is a need to make preoperative diagnostics more accurate.

Aims To evaluate the usefulness of American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) calculator as a predictive tool in preoperative assessment of cardiovascular risk in elderly patients.

Methods This prospective pilot study included 78 patients who were being prepared for extensive non-cardiac surgeries under general anaesthesia. Their data have been processed on the interactive ACS NSQIP calculator. Blood sampling has been performed 7 days prior to surgery, and serum has been separated. Clinical, novel, and experimental biomarkers [hsCRP, H-FABP, and Survivin (BIRC5)] have been measured in specialized laboratories.

Results Mean age of included patients was 71.35 ± 6.89 years. In the case of heart complications and mortality prediction, hsCRP and ACS NSQIP showed the highest specificity and sensitivity with AUC, respectively, 0.869 and 0.813 for heart complications and 0.883 and 0.813 for mortality. When combined with individual biomarkers AUC of ACS NSQIP raised, but if we combined all three biomarkers with ACS NSQIP, AUC reached as much as 0.920 for heart complications and 0.939 for mortality.

Discussion ACS NSQIP proved to reduce inaccuracy in preoperative assessment, but it cannot be used independently, which has already been proved by other authors.

Conclusions Our results indicate that ACS NSQIP represents an accurate tool for preoperative assessment of elderly patients, especially if combined with cardiac biomarkers.

Keywords Period · Preoperative; survivin protein · Human; H-FABP · Human; hsCRP · Human

Background

Preoperative risk assessment received clinical significance after it became clear that morbidity after non-cardiac procedures increases mortality. Risk for perioperative complications depends on the patient's preoperative condition, comorbidities and urgency, extensiveness, type, and duration of the surgical procedure [1]. In Europe, about 30% of patients are subjected to extensive surgical procedures in the presence of cardiovascular comorbidities. Around the world, these types of operations are associated with the level of mortality between 0.8 and 1.5% and as high as 42% of these events are caused by cardiovascular complications [1].

It is the fact that patients' age has impact on postoperative complications due to significant comorbidities, with cardiovascular diseases being the most prevalent. Therefore, older patients have to be considered with a great caution. Estimations say that the number of patients

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undergoing surgery will increase by 25% by 2020. Age alone seems not to increase the risk of complications [1, 2].

Elderly people have physiological changes that impair their functional reserve and make them vulnerable to complications and mortality. Frail elderly patients are more likely to experience postoperative complications such as: delirium, pneumonia, infectious complications, postoperative venous thromboembolism, urinary tract infections, etc. In addition, researches have shown that this population spends more time in hospital and is more frequently discharged to long-term care facilities. Many methods for risk stratification do not meet the need of elderly population and cannot measure their physiological reserves appropriately [3–6]. To overcome these obstacles, clinicians are advised to use comorbidity scales for elderly patients. Among others, Cumulative Illness Rating Scale for Geriatrics (CIRS-G) is considered to be a comprehensive "gold standard" for rating of total burden of disease in older people. It relies on evaluation and clinical data and is derived for medical record, current examinations and tests, and interviews with patients [7, 8].

Anaesthetic perioperative cardiovascular risk assessment involves clinical signs and experience, assessment of the functional status by determining metabolic equivalents (MET), and several cardiac risk indices (Goldman, Detsky and Lee) [1, 9–11]. Contemporary methods include interactive calculators, such as the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) calculator for predicting intraoperative/postoperative myocardial infarction and cardiac arrest [12, 13]. This method is considered a guiding principle in decision-making both in the preoperative and surgical treatment [12, 14].

High-sensitivity C-reactive protein (hsCRP), a specific cardiac biomarker, had been introduced into clinical practice much earlier [15, 16], while heart-type fatty acid-binding protein (H-FABP) is a novel cardiac biomarker [17, 18]. Survivin (BIRC5) is a member of the inhibitors of apoptosis proteins (IAP) family, and it decides whether the cell will enter the apoptotic process or not [19–21]. We have already confirmed the possible use of survivin (BIRC) as a novel cardiac biomarker in our previous study [22]. In this study, we used hsCRP and ACS NSQIP as standards, H-FABP is included as a novel and prospective cardiac biomarker, and survivin (BIRC5) is added as an experimental biomarker.

Due to the fact that there are a growing number of elderly patients who undergo extensive non-cardiac procedures and already have existing comorbidities, it is necessary to simplify the preoperative preparation of patients and find the most efficient panel of biomarkers and risk scores [23].

Aim

The aim of our study was to evaluate the usefulness of ACS NSQIP calculator in preoperative assessment of cardiovascular risk, to compare it with experimental and clinical cardiac biomarkers and evaluate their combined use in diagnostics and prognostics.

Methods

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

This prospective pilot study included a total of 78 patients preparing for major non-cardiac surgeries. All of the included patients were admitted in one of the surgical clinic of the Clinical Center in Niš, Serbia in the period between October 1st and December 31st 2013. Inclusion criteria were: extensive non-cardiac surgery (abdominal, orthopaedic, or thoracic surgery), general anaesthesia, age above 55 years, and at least one of the selected cardiovascular risk factors (hypertension, hyperlipidemia, smoking, diabetes mellitus, and positive family history for heart disease). Exclusion criteria were emergency surgical procedures and inability to understand and sign an informed consent. All included patients signed the informed consent. This study was approved by the local ethics committee.

Surgical procedures

Included patients were being prepared for one of the non-cardiac procedures in general anaesthesia. Surgical procedures were performed according to clinical standards of our institution. The largest number of operations belonged to abdominal and orthopaedic surgeries with four thoracic and one endocrine surgeries.

The American College of Surgeons Surgical Risk Calculator (ACS NSQIP)

The ACS Surgical Risk Calculator (ACS NSQIP) estimates the chance of an unfavourable postoperative outcome. We calculated ACS NSQIP score for each patient individually using interactive web calculator, available at http://riskcalculator.facs.org/RiskCalculator/. The parameters that need to be inserted are presented in Table 1. Provided risk percentages are only estimates.

Cumulative illness rating scale for geriatrics (CIRS-G)

To adjust our results with patients' comorbidities, we calculated the CIRS-G score through online interactive calculator (http://farmacologiaclinica.info/scales/CIRS-G/). The final total score has been calculated for each patient individually through their medical history and interview.

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

Table 1 ACS NSQIP, surgical risk calculator. Patients and surgical information needed to be entered in an online interactive calculator

Procedure	(select)	Are there other potential appropriate treatment options	Other surgical options Other non-operative options None
Age	Under 65 years 65–74 years 75–84 years 85 years or older	Diabetes	None Oral Insulin
Sex	Female Male	Hypertension requiring medication	No Yes
Functional status	Independent Partially dependent Totally dependent	Previous cardiac event	No Yes
Emergency case	No Yes	Congestive heart failure in 30 days prior to surgery	No Yes
ASA class	I Healthy patient II Mild systemic disease III Severe systemic disease IV Severe systemic disease/ constant threat to life V Moribund/ not expected to survive surgery	Dyspnea	None With moderate exertion At rest
Wound class	Clean Clean/contaminated Contaminated Dirty/infected	Current smoker within 1 year	No Yes
Steroid use for chronic condition	No Yes	History of severe COPD	No Yes
Ascites within 30 days prior to surgery	No Yes	Dialysis	No Yes
Systemic sepsis within 48 h prior to surgery	None SIRS Sepsis Septic shock	Acute renal failure	No Yes
Ventilator dependent	No Yes	Height	(in)
Disseminated cancer	No Yes	Weight	(lbs)

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 Elx800G (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-enhanced 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 (H-FABP, 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 interquartile range. 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 all the three biomarkers and ACS NSQIP as predictors of heart complications and mortality. The area under the curve (AUC) and the most appropriate cut-off value for all three biomarkers were determined. *P* value below 0.05 was considered a statistically significant result. To assess interaction between variables, binary logistic regression model has been performed, and to control for CIRS-G score, hierarchical logistic regression has been used. Predicted values for variables have been used to assess ROC curves. All results were statistically processed in the program SPSS 10.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) for Windows.

Results

A total of 78 patients, whose main characteristics are presented in Table 2, were included in the study. Elderly patients (>65 years according the definition of the World Health Organization) counted 72 patients (92.31%). Accurate data regarding the age of patients are presented in Table 3. ACS NSQIP score marked as "above average" was present in 32 patients (41.03%). Most patients had two or more cardiovascular risk factors (73.08%), while 79.49% of patients were taking some type of cardiovascular therapy.

During our follow-up, a total of 14 patients (17.95%) have died, of which 13 (92.86%) were subjected to one of extensive abdominal surgeries and 1 (7.14%) patient was subjected to extensive orthopaedic procedure. All the deceased patients belonged to the age group >65 years (Table 3). Out 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. As much as, 13 patients (92.86%) had NSQIP risk scored as above average ($P=0.0001$). The average number of days spent in the intensive care was 10 ± 7 days. Duration of the follow-up was defined as the primary endpoint, which is the in-hospital all-cause mortality and secondary endpoint, which is total hospital stay.

Patients, who deceased were older, had preoperative dyspnoea, were taking HSS/Clopidogrel therapy, and had survivin (BIRC5)>4.00 pg/ml, higher value of H-FABP and hsCRP (Table 2).

A hierarchical binary logistic regression was performed to assess effect of CIRS-G on accuracy of all the biomarkers and ACS NSQIP score in prediction of postoperative heart complications and mortality. Total CIRS-G score had mean of 6.67 ± 2.20 for all included patients and there was no statistical significance between the groups, for either heart complications or mortality ($P>0.05$).

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 three biomarkers had higher values in the deceased patients when compared to those who survived (Table 2).

When it comes to the prediction of heart complications (cardiac arrest, myocardial infarction), hsCRP showed the higher AUC=0.869 (95% CI, $P=0.0001$, 0.781–0.957), besides ACS NSQIP with AUC=0.813 (95% CI, $P=0.0001$, 0.704–0.921) (Fig. 1). All the models were statistically significant. Hierarchical binary logistic regression showed that CIRS-G alone was not statistically significant for prediction of heart complications, $\chi^2 = 1.912$, $P>0.05$. Survivin did not add to statistical significance of the model, but hsCRP and H-FABP did with, respectively, $\chi^2 = 19.936$, $P<0.0001$; $\chi^2 = 9.508$, $P=0.009$. Those biomarkers correctly classified 85.9 and 82.1% of cases. The increase of hsCRP and H-FABP serum levels was associated with higher chance of the development of heart complications. ACS NSQIP significantly added to the model accuracy with $\chi^2 = 23.442$, $P<0.0001$. It explained 41.6% of the variance and correctly classified 83.3% of cases. Class 3 of NSQIP was 36.48 times more likely to develop cardiac complications than class 1 (Fig. 2).

Table 2 Basic characteristics of patients involved in our study

	All patients	Survivors	Deceased	*P*-value survivors versus deceased
n[a] (%)	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	$\mathbf{P=0.034}$
BMI[b] median (IQR[c])	25.35 (22.97–28.15)	25.90 (23.10–28.67)	24.05 (22.50-25.47)	$P=0.146$
CAD[d], *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)	$P=0.349$
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)	$\mathbf{P=0.023}$
NSQIP (mortality prediction), *n* (%)				$\mathbf{P=0.0001}$
Risk is below average	41 (52.56)	40 (62.5)	1 (7.14)	$\mathbf{P=0.0001}$
Risk is average	5 (6.41)	5 (7.81)	0 (0)	$P=0.283$
Risk is above average	32 (41.03)	19 (29.69)	13 (92.86)	$\mathbf{P=0.0001}$
Hgb (g/dl) median (IQR)	11.9 (10.87–13.00)	11.9 (10.72–12.90)	12.1 (11.35–13.47)	$P=0.249$
Creatinine (mg/dl) median (IQR)	1.02 (0.84–1.19)	1.03 (0.85–1.20)	1.00 (0.83–1.16)	$P=0.787$
Survivin (pg/ml) median (IQR)	4.56 (0.11–9.28)	2.33 (0.11–6.78)	9.55 (6.22–21.22)	$\mathbf{P=0.020}$
H-FABP (µg/l) median (IQR)	7.32 (4.35–10.80)	6.63 (4.12–8.73)	11.95 (7.18–16.70)	$\mathbf{P=0.001}$
hsCRP (mg/l) median (IQR)	11.35 (2.83–35.20)	7.10 (2.29–22.16)	68.13 (25.07–114.62)	$\mathbf{P=0.0001}$

Statistically significant data are bolded

[a]Number

[b]Body mass index

[c]Inter-quartile range

[d]Coronary artery disease

Table 3 Frequency distribution of the age of all the included patients and deceased patients only

Age	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89
Number of patients, *n*[a] (%)	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)

[a]Number

The addition of ACS NSQIP to each of the biomarker by logistic regression showed similar increase of AUC (H-FABP, survivin (BIRC5) and hsCRP) with the addition of 0.155, 0.127, and 0.111, respectively. Adjustment with comorbidity score did not detract the ROC curves (Fig. 3). Combination of all three biomarkers was empowered by the addition of ACS NSQIP, resulting in the final AUC as high as 0.920 (95% CI, $P=0.0001$, 0.841–0.998). Even after

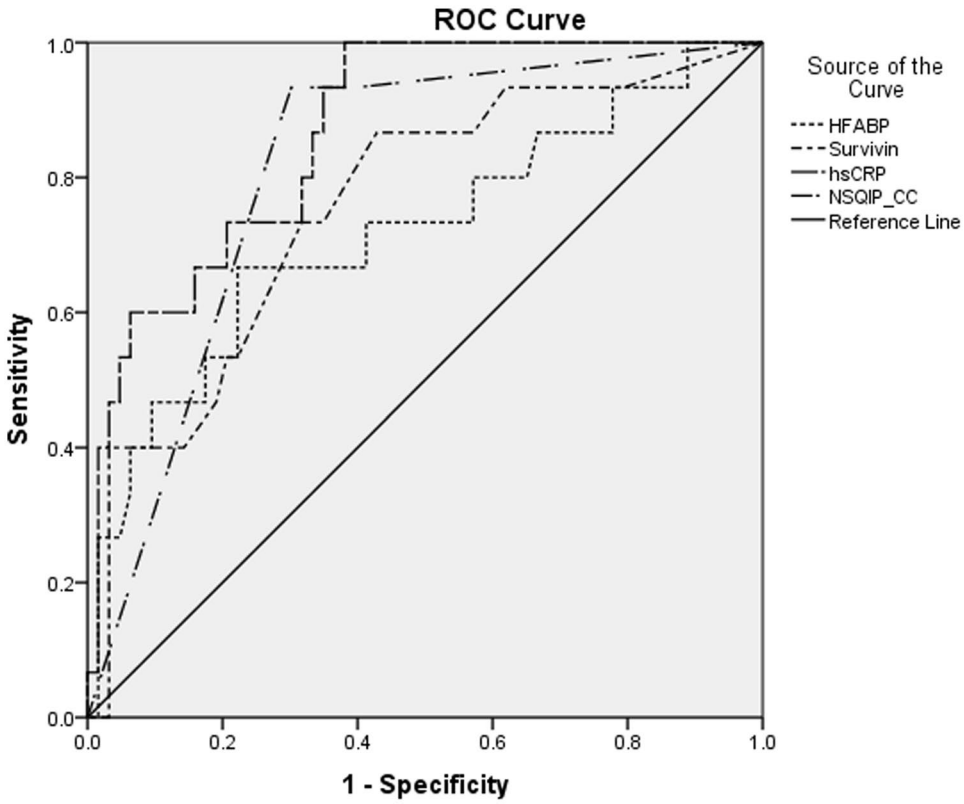

Fig. 1 All of the observed factors presented on ROC curve, considering heart complications. Survivin (BIRC5): AUC = 0.758 (95% CI, *P* = 0.002, 0.620–0.859). H-FABP: AUC = 0.720 (95% CI, *P* = 0.009, 0.561–0.878). hsCRP: AUC = 0.869 (95% CI, *P* = 0.0001, 0.781–0.957). ACS NSQIP_CC (ACS NSQIP for cardiac complications): AUC = 0.813 (95% CI, *P* = 0.0001, 0.704–0.921)

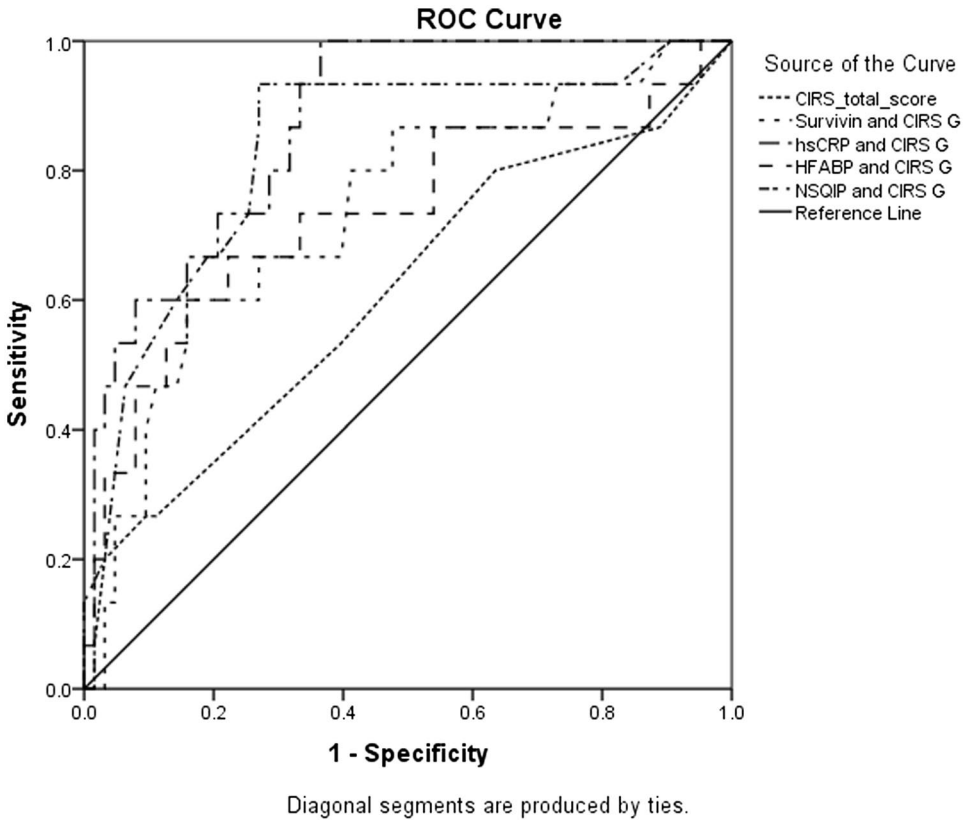

Fig. 2 ROC curves for all the biomarkers and ACS NSQIP when adjusted with CIRS-G, and CIRS-G alone when it comes to heart complications. CIRS-G: AUC = 0.610 (95% CI, *P* = 0.189, 0.439–0.780). Survivin and CIRS-G: AUC = 0.739 (95% CI, *P* = 0.004, 0.595–0.883). hsCRP and CIRS-G: AUC = 0.873 (95% CI, *P* < 0.0001, 0.788–0.958). H-FABP and CIRS-G: AUC = 0.732 (95% CI, *P* = 0.005, 0.570–0.895). NSQIP and CIRS-G: AUC = 0.835 (95% CI, *P* < 0.0001, 0.716–0.954)

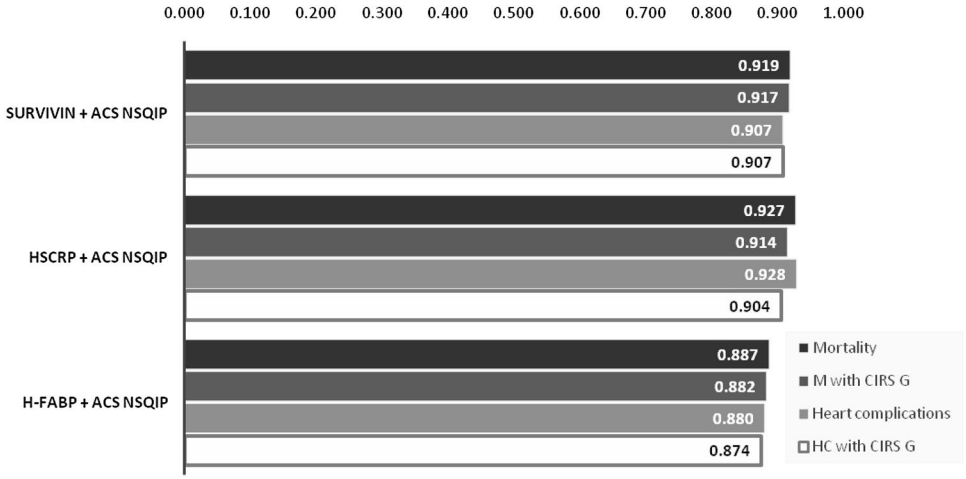

Fig. 3 AUC values for the addition of ACS NSQIP to each biomarker and their adjustment for CIRS-G

the adjustment with CIRS-G total score, hsCRP and ACS NSQIP retained their statistical significance and correlation with heart complications. Statistical model also retained statistical significance with $\chi^2 = 37.602$, $P < 0.0001$ and correct classification of as much as 91% of cases and AUC = 0.923 (Fig. 4) (Table 4).

ROC curves for all three biomarkers and NSQUIP score showed that they can be used as predictors of mortality (Fig. 5). Among them, hsCRP showed the greatest AUC of 0.883 (95% CI, $P = 0.0001$, 0.797–0.969), followed by ACS NSQUIP of AUC = 0.813 (95% CI, $P = 0.0001$, 0.702–0.924). All of the models were statistically significant except CIRS-G, with $\chi^2 = 2.628$, $P > 0.05$. However, biomarkers added to statistical significance of the model, respectively (Survivin (BIRC5), hsCRP and H-FABP): $\chi^2 = 6.283$, $P < 0.05$; $\chi^2 = 21.390$, $P < 0.0001$; $\chi^2 = 11.999$, $P < 0.005$. ACS NSQIP also added to the model accuracy with correct classification of 82.1% of cases and class 3 being 28.85 times more likely to develop mortality (Fig. 6).

Combination of biomarkers with ACS NSQIP resulted in significant increase of AUC for each of them individually (Fig. 3). When we use all three biomarkers combined, we get the AUC = 0.914 (95% CI, $P = 0.0001$,

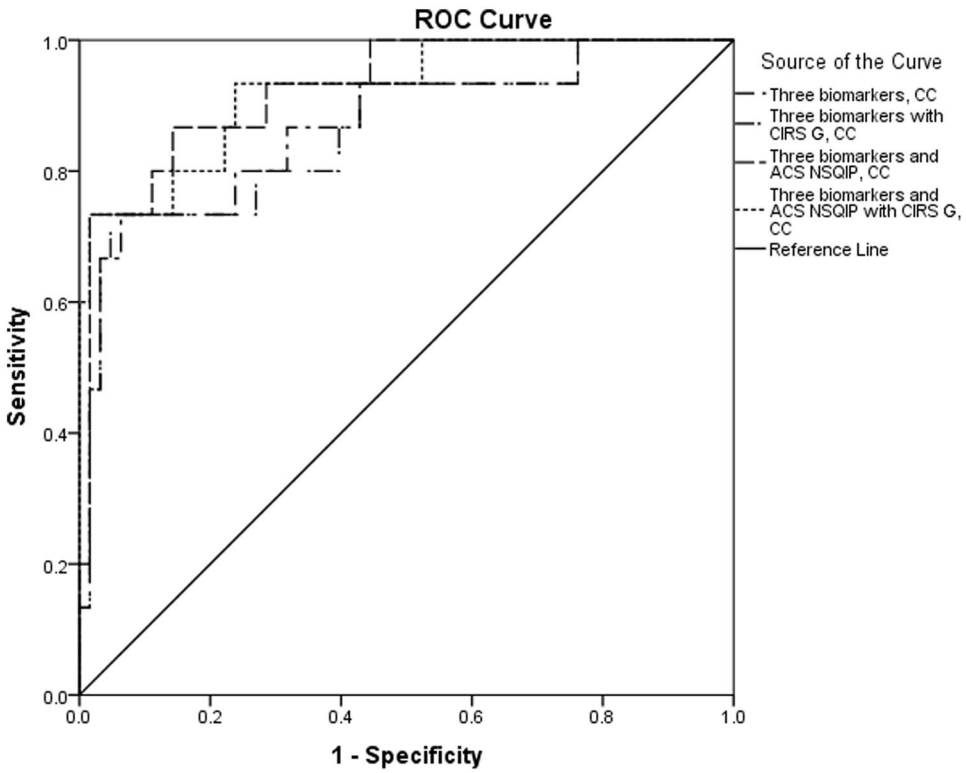

Fig. 4 Three biomarkers and NSQIP when compared to CIRS-G when it comes to heart complications: Three biomarkers: AUC = 0.868 (95% CI, $P < 0.0001$, 0.754–0.981). Three biomarkers with CIRS-G: AUC = 0.861 (95% CI, $P < 0.0001$, 0.744–0.978). Three biomarkers and ACS NSQIP: AUC = 0.926 (95% CI, $P < 0.0001$, 0.855–0.997). Three biomarkers and ACS NSQIP with CIRS-G: AUC = 0.923 (95% CI, $P < 0.0001$, 0.845–1.000)

Table 4 Results of hierarchical binary logistics for heart complications

	χ^2	P	R^2	Correct classification (%)
Heart complications				
Three biomarkers	28.834	<0.0001	0.495	91
Three biomarkers with CIRS-G	28.879	<0.0001	0.496	91
Three biomarkers and ACS NSQIP	36.381	<0.0001	0.597	91
Three biomarkers and ACS NSQIP with CIRS-G	37.602	<0.0001	0.613	91

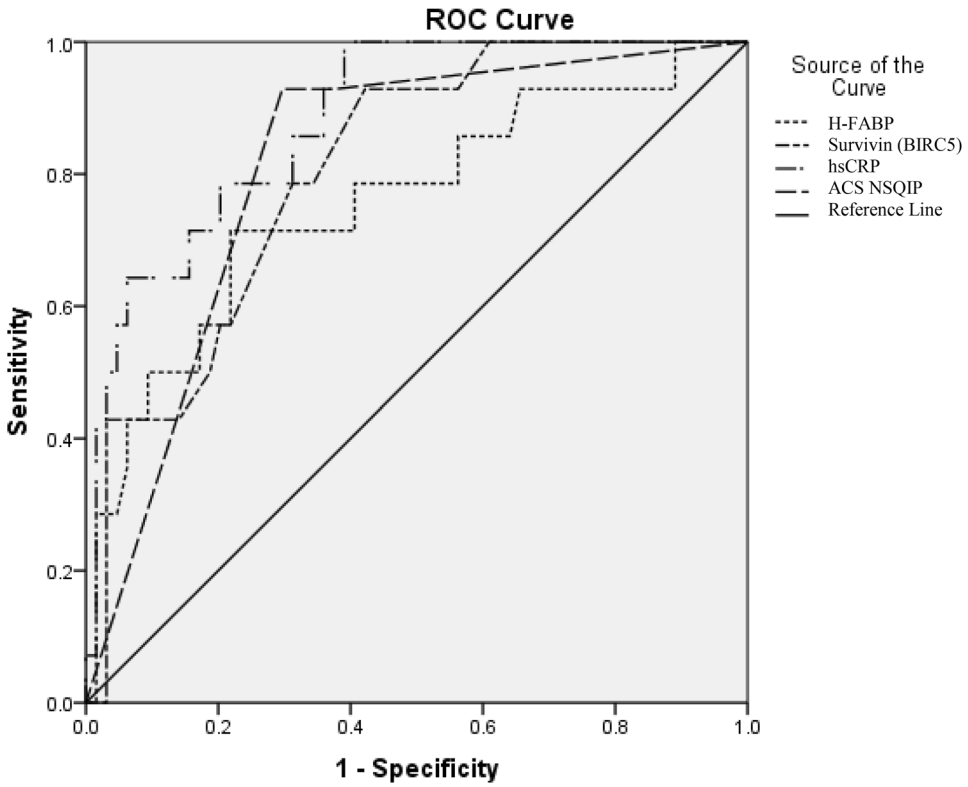

Fig. 5 All of the observed factors presented on ROC curve, considering postoperative mortality. Survivin (BIRC5): AUC = 0.807 (95% CI, $P = 0.0001$, 0.698–0.917). H-FABP: AUC = 0.758 (95% CI, $P = 0.003$, 0.607–0.924). hsCRP: AUC = 0.883 (95% CI, $P = 0.0001$, 0.797–0.969). ACS NSQIP: AUC = 0.813 (95% CI, $P = 0.0001$, 0.702–0.924)

0.836–0.992), and if we add NSQUIP, we get AUC = 0.939 (95% CI, $P = 0.0001$, 0.870–1.000), which makes this combination accurate in the mortality prediction, with $\chi^2 = 38.686$, $P < 0.0001$, and correct classification of 92.3% of cases. Adjustment of this model with CIRS-G score did not detract the model specificity and sensitivity, nor to the accuracy of ROC curve (Fig. 7) (Table 5).

Discussion

The aim of this pilot study was to examine the individual and combined values of three cardiac biomarkers [hsCRP, which has long been used in clinical practice, H-FABP, which presents new cardiac biomarker and survivin (BIRC5) which is still in the experimental stage] and interactive calculator ACS NSQIP in predicting postoperative morbidity and mortality of elderly patients. The main finding of our study is that ACS NSQIP adds to specificity and sensitivity of biomarkers and that it certainly should be used in the preoperative cardiovascular risk assessment in elderly population. In addition, our findings indicate that comorbidities assessed through CIRS-G score do not interfere with efficiency of hsCRP, H-FABP, and ACS NSQIP. In addition, the specificity and sensitivity of combined model which includes all of the investigated variables are not reduced.

Perioperative mortality and morbidity are the result of cardiovascular complications after non-cardiac surgeries. Formal and documented assessment of perioperative risk is rarely conducted [24]; therefore, every anaesthesiologist must assess the risk of specific patient's perioperative

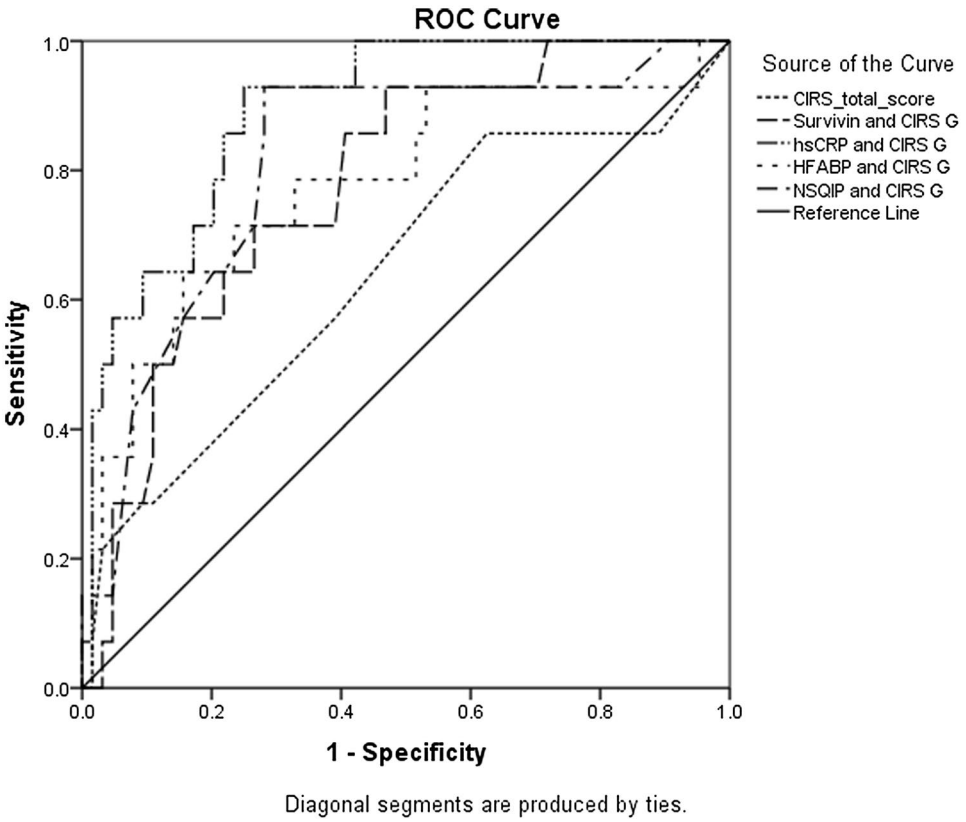

Fig. 6 ROC curves for all the biomarkers when adjusted to CIRS-G and CIRS-G alone when it comes to mortality. CIRS-G: AUC = 0.640 (95% CI, $P = 0.104$, 0.468–0.811). Survivin and CIRS-G: AUC = 0.778 (95% CI, $P = 0.001$, 0.656–0.901). hsCRP and CIRS-G: AUC = 0.892 (95% CI, $P < 0.0001$, 0.812–0.971). H-FABP and CIRS-G: AUC = 0.777 (95% CI, $P = 0.001$, 0.628–0.925). ACS NSQIP and CIRS-G: AUC = 0.814 (95% CI, $P < 0.0001$, 0.688–0.940)

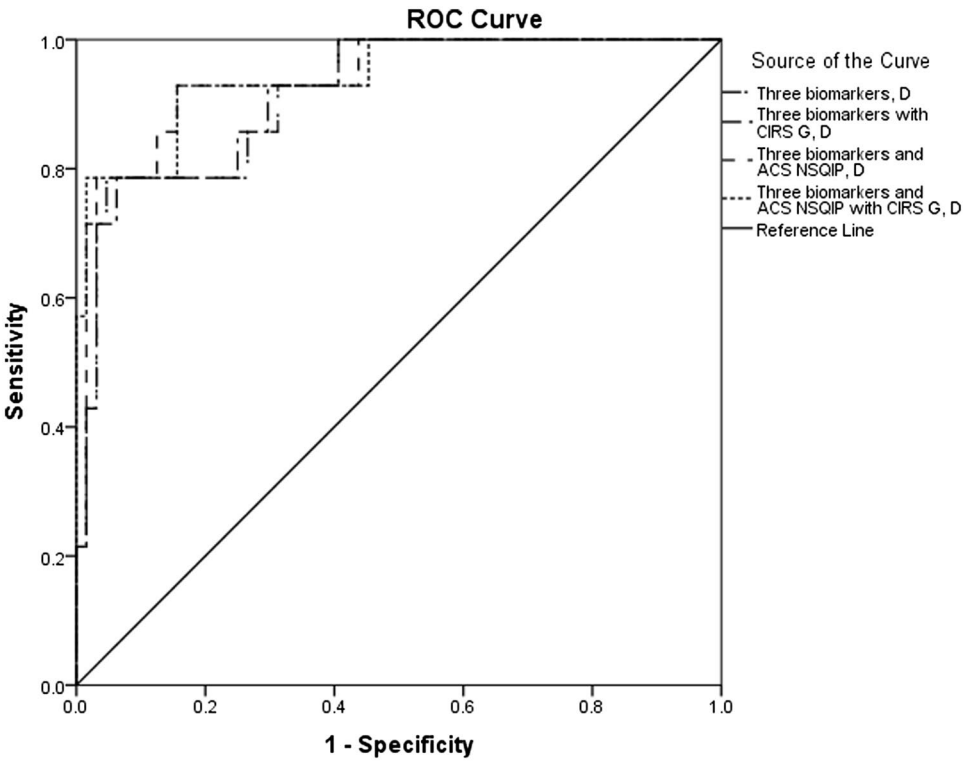

Fig. 7 Three biomarkers and NSQIP when compared to CIRS-G and when it comes to mortality. Three biomarkers: AUC = 0.914 (95% CI, $P < 0.0001$, 0.836–0.992). Three biomarkers with CIRS-G: AUC = 0.915 (95% CI, $P < 0.0001$, 0.839–0.991). Three biomarkers and ACS NSQIP: AUC = 0.939 (95% CI, $P < 0.0001$, 0.872–1.000). Three biomarkers and NSQIP with CIRS-G: AUC = 0.942 (95% CI, $P < 0.0001$, 0.874–1.000)

Table 5 Results of hierarchical binary logistics for mortality

	χ^2	P	R^2	Correct classification (%)
Mortality				
Three biomarkers	33.705	<0.0001	0.575	92.3
Three biomarkers with CIRS-G	33.712	<0.0001	0.575	92.3
Three biomarkers and ACS NSQIP	38.686	<0.0001	0.641	92.3
Three biomarkers and ACS NSQIP with CIRS-G	39.085	<0.0001	0.646	92.3

cardiovascular complications and the patient himself must be informed of the possible risks [25]. Since it is challenging to distinguish between changes in physiology caused by aging and certain diseases that are very common in elderly, the clinician must take preoperative assessment of elderly patients with high caution [26].

The high mortality rate in our study (17.95%) can be partly explained by the fact that the patients included in our study belong to the old population 71.35 ± 6.89, with $P < 0.05$. All the deceased patients belonged to the group of patients older than 65 years of age [which is, according to the World Health Organization (WHO) the definition of elderly population]. The highest percentage of deceased (35.71%) belonged to the group between 75 and 79 years. Those were people with a large number of comorbidities and they have been prepared for major non-cardiac surgeries that carry a particularly high risk. Patients who died were subjected to abdominal (92.86%) and orthopaedic procedures (7.14%). Most abdominal operations were radical surgical resections, which can compromise outcome and even lead to death in elderly patients who are unfit or frail [27]. In addition, the fact is that the number of included patients was relatively small.

The higher mortality rate can also be justified by the fact that there were many politics and socio-economic turbulences in Serbia, including immigration and wars during the 90s. Studies show that cancer incidence and mortality in Serbia have been increasing and that it is alarmingly higher than in the majority of European regions [28, 29]. Mortality rate in Serbia in people above 65 years of age is significantly higher than in other European countries [30]. We also have to highlight the fact that people who live in rural areas have low monthly income and are isolated from their family members [31]. Visits to the health care providers are more often paid by the urban, more educated, and richer population of elderly people [32].

When we compare our results with other studies that included elderly patients, we can find correlation. Tzeng et al. indicated that reduced physiological reserve of elderly patients leads to far greater risk of death and serious complications. Therefore, they must be assessed with a far greater caution considering their age and comorbidities [33]. Age below 90 years cannot be considered as an individual risk factor but only in combination with comorbidities and the type of operation [1, 34–36]. Lees et al. have conducted their research on patients of mean age 72 years with a conclusion that the degree of intrahospital mortality is as high as 12% and that mortality is associated with a higher ASA class and more intrahospital complications [37]. A mortality rate of 18.3% was noted in a sample of patients with severe cardiovascular comorbidities [38]. Postoperative mortality in elderly patients with colorectal cancer was as high as 15.6% [39]. Asouhiou et al. reported mortality as high as 16% in patients above 70 years of age undergoing major elective orthopaedic surgeries [26]. Study conducted by Jakobson et al. indicated that age above 70 years, ASA $\geq$ III, revised cardiac risk index $\geq$3, duration of surgery >130 min, and positive fluid balance >1300 ml after the first postoperative day can be identified as independent risk factors for complication development [40].

When other risk scores are concerned, a greater or lesser efficiency of their application in practice has been demonstrated, depending on the conducted study [41]. However, ACS NSQIP proved to be a calculator that reduces the inaccuracy of the current methods for preoperative assessment. It also leads the prediction in the right way, especially in elderly patients, since it includes a higher number of patients' data and a greater number of laboratory measurements when compared to all other risk scores [42, 43]. The special advantage of this risk score is the possibility for the surgeon to correct the risk level in accordance with his experience [44]. However, the downside is the fact that it requires a large amount of data and, therefore, requires more time [45]. Research also found that it has a great imprecision considering the patients' self-assessment of mobility limitation [42].

Our study did not show ACS NSQIP to be an individual predictor of postoperative morbidity and mortality, since the addition of H-FABP, Survivin (BIRC5) and hsCRP increased AUC curve of this score for, respectively, 0.062, 0.072, and 0.111 in the case of morbidity and 0.068, 0.101, and 0.109 in the case of mortality. For example, the Systematic Coronary Risk Evaluation (SCORE) algorithm is shown to increase AUC after the

addition of hsCRP for only 0.006, which indicates a high autonomy in the preoperative assessment of mortality [46]. Certainly, one cannot minimize the importance of AUC NSQIP in predicting postoperative morbidity and mortality due to the fact that it significantly increases AUC of all the three biomarkers.

Modification of ACS NSQIP, preoperative predictor of mortality that accompanies the trend of ACS NSQIP showed AUC of up to 0.93, which is higher than the value in our results. Such a difference can be explained with a far greater of patients included in the study [47].

The possibility of predicting morbidity and mortality in our study was lower than in a number of other studies; however, this can be explained by the fact that their number of patients was higher, since those were mainly retrospective studies and by the fact that they often considered procedures which are not major non-cardiac extensive surgeries [13, 48–50]. Even if AUC of ACS NSQIP was lower than in our study, this risk score always showed superiority to other risk scores [51, 52].

The so-called 'multimarker approach' is increasingly popularized in the world, since it showed a great ability to predict postoperative cardiovascular complications [53, 54]. In the case of biomarkers that we investigated, a multimarker approach showed AUC of 0.914. If they are combined with the ACS NSQIP, AUC is as high as 0.939, which indicates almost a hundred percent of patient's risk stratification.

The limitation of our study is the fact that the number of patients is low and they could not be divided into groups. Therefore, we have provided the comorbidity CIRS-G total score, which indicated that preoperative comorbidities themselves did not directly cause postoperative morbidity and mortality. Our results can be confirmed by other studies, showing that CIRS-G is more suitable for 1-year mortality prediction in non-surgical elderly patients [8, 55]. Cardiac biomarkers hsCRP and H-FABP and ACS NSQIP retained their statistical significance as well as high specificity and sensitivity after adjustment to CIRS-G score. Only survivin (BIRC5) lost its statistical significance and had lower AUC after adjustment. This can be explained by the fact that survivin (BIRC5) is highly specific for cancer and, therefore, interacts with CIRS-G score, which is highly dependent of malignancy. We have already proved in our previous study that survivin (BIRC5) has even greater sensitivity and specificity in patients without present malignancy, AUC = 0.825, but despite this fact its limitation is that it cannot be used independently, without highly specific cardiac biomarkers [22]. Combination of three biomarkers with ACS NSQIP was not under the influence of CIRS-G total comorbidity score.

Conclusion

ACS NSQIP calculator is an accurate novel tool for preoperative assessment, but it cannot be used independently in practice, since cardiac biomarkers undoubtedly add to its specificity and sensitivity. Among three biomarkers that we have investigated, hsCRP has proved to be the most accurate. Since this is a pilot study, further research with a greater number of patients is needed to make clinically applicable conclusions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All included patients signed the informed consent.

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) (2014) 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. Eur Heart J 35:2383–2431
2. Kim SW, Han HS, Jung HW et al (2014) Multidimensional frailty score for the prediction of postoperative mortality risk. JAMA Surg 149:633–640
3. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G (2004) Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 59:255–263
4. Partridge JS, Harari D, Dhesi JK (2012) Frailty in the older surgical patient: a review. Age Ageing 41:142–147
5. Saxton A, Velanovich V (2011) Preoperative frailty and quality of life as predictors of postoperative complications. Ann Surg 253:1223–1229
6. Bollegala N, Jackson TD, Nguyen GC (2016) Increased postoperative mortality and complications among elderly patients with inflammatory bowel diseases: an analysis of the national surgical quality improvement program cohort. Clin Gastroenterol Hepatol 14:1274–1281
7. Borson S, Scanlan JM, Lessig M et al (2010) Comorbidity in aging and dementia: scales differ, and the difference matters. Am J Geriatr Psychiatry 18:999–1006
8. Kirkhus L, Jordhøy M, Šaltytė Benth J et al (2016) Comparing comorbidity scales: Attending physician score versus the Cumulative Illness Rating Scale for Geriatrics. J Geriatr Oncol 7:90–98

9. Goldman L (1983) Cardiac risk and complications of noncardiac surgery. Ann Intern Med 98:504–513
10. Detsky AS, Abrams HB, Forbath N et al (1986) Cardiac assessment for patients undergoing noncardiac surgery. Arch Intern Med 146:2131
11. Lee TH, Marcantonio ER, Mangione CM et al (1999) Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100:1043–1049
12. Bilimoria KY, Liu Y, Paruch JL et al (2013) 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 217:833–842
13. Gupta PK, Gupta H, Sundaram A et al (2011) Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 124:381–387
14. Cohen ME, Ko CY, Bilimoria KY et al (2013) Optimizing ACS NSQIP modeling for evaluation of surgical quality and risk: patient risk adjustment, procedure mix adjustment, shrinkage adjustment, and surgical focus. J Am Coll Surg 217:336–346
15. Rahman MM, Alam MM, Jahan NA et al (2016) Prognostic role of multiple cardiac biomarkers in newly diagnosed acute coronary syndrome patients. Mymensingh Med J 25:326–333
16. Klingenberg R, Aghlmandi S, Räber L et al (2016) 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. doi:10.1177/2048872616684678
17. Das UN (2016) Heart-type fatty acid-binding protein (H-FABP) and coronary heart disease. Indian Heart J 68:16–18
18. Janković RJ, Marković DZ, Sokolović DT et al (2016) Clinical indices and biomarkers for perioperative cardiac risk stratification: an update. Minerva Anestesiol. doi:10.23736/S0375-9393.16.11545-7
19. Sanhueza C, Wehinger S, Castillo Bennett J et al (2015) The twisted survivin connection to angiogenesis. Mol Cancer 14:198
20. Lee PJH, Rudenko D, Kuliszewski MA et al (2014) Survivin gene therapy attenuates left ventricular systolic dysfunction in doxorubicin cardiomyopathy by reducing apoptosis and fibrosis. Cardiovsc Res 101:423–433
21. Markovic D, Djordjevic VB (2013) Apoptosis regulation by inhibitors of programmed cell death. J Med Biochem 32:207–213
22. Marković D, Jevtović-Stoimenov T, Golubović M et al (2016) Significance of survivin (BIRC5) as a cardiac biomarker for the assessment of preoperative cardiovascular risk in nin-cardiac surgeries- surviving (BIRC5) as a novel cardiac biomarker. SJAIT 38:201–212
23. Hernandez AF, Newby LK, O'Connor CM (2004) Preoperative evaluation for major noncardiac surgery focusing on heart failure. Arch Intern Med 164:1729–1736
24. Tomlinson JH, Ramani Moonesinghe S (2016) Risk assessment in anaesthesia. Anaesth Intensive Care Med 17:486–491
25. Maddox TM (2005) Preoperative cardiovascular evaluation for noncardiac surgery. Mt Sinai J Med 72:185–192
26. Asouhidou I, Asteri T, Sountoulides P et al (2009) Early postoperative mortality in the elderly: a pilot study. BMC Res Notes 2:118
27. Chou WC, Liu KH, Lu CH et al (2016) To Operate or Not: Prediction of 3-Month Postoperative Mortality in Geriatric Cancer Patients. J Cancer 7.1:14–21
28. Mihajlović J, Pechlivanoglou P, Miladinov-Mikov M et al (2013) Cancer incidence and mortality in Serbia 1999–2009. BMC Cancer 13:18
29. Ashford MW, Gottstein U (2000) The impact on civilians of the bombing of Kosovo and Serbia. Med Confl Surviv 16:267–280
30. Marinkovic I, Radivojevic B (2016) Mortality trends and depopulation in Serbia. Geogr Pannonica 20:220–226
31. Urošević J, Odović G, Rapaić D et al (2015) Quality of life of the elderly in urban and rural areas in Serbia Kvalitet života starih u urbanoj i ruralnoj sredini u Srbiji. Vojnosanit Pregl 72: 968–974
32. Republic of Serbia, Ministry of Health (2014) Results of the national health survey of the Republic of Serbia 2013. Belgrade, Serbia, pp 91–93
33. Tzeng CWD, Cooper AB, Vauthey JN (2014) Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. HPB (Oxford) 16:459–468
34. Latkauskas T, Rudinskaitė G, Kurtinaitis J et al (2005) The impact of age on post-operative outcomes of colorectal cancer patients undergoing surgical treatment. BMC Cancer 5:153
35. Turrentine FE, Wang H, Simpson VB et al (2006) Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg 203:865–877
36. D'Apuzzo MR, Pao AW, Novicoff WM et al (2014) 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 29:477–480
37. Lees MC, Merani S, Tauh K et al (2015) Perioperative factors predicting poor outcome in elderly patients following emergency general surgery: a multivariate regression analysis. Can J Surg 58:312–317
38. Hernandez AF, Whellan DJ, Stroud S et al (2014) Outcomes in heart failure patients after major noncardiac surgery. J Am Coll Cardiol 44:1446–1453
39. Heriot AG, Tekkis PP, Smith JJ et al (2006) Prediction of postoperative mortality in elderly patients with colorectal cancer. Dis Colon Rectum 49:816–824
40. Jakobson T, Karjagin J, Vipp L et al (2014) Postoperative complications and mortality after major gastrointestinal surgery. Medicina (B Aires) 50:111–117
41. Yan AT, Yan RT, Tan M et al (2007) Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. Eur Heart J 28:1072–1078
42. Harris C, Kim S, Groban L (2015) How well does the NSQIP surgical calculator predict early adverse outcomes in plder noncardiac surgical patients with self-reported limitations in mobility? Gerontologist 55:192
43. Marković D, Stošić B, Savić S et al (2016) Improtance of biomarkers in preoperative evaluation of cardiovascular risk. Acta Med Med 55:70–75
44. Cohen ME, Bilimoria KY, Ko CY et al (2009) Development of an American College of Surgeons National Surgery Quality Improvement Program: morbidity and mortality risk calculator for colorectal surgery. J Am Coll Surg 208:1009–1016
45. Barnett S, Ramani Moonesinghe S (2011) Clinical risk scores to guide perioperative management. Postgrad Med J 87:535–541
46. Graversen P, Abildstrøm SZ, Jespersen L et al (2016) Cardiovascular risk prediction: can systematic coronary risk evaluation (SCORE) be improved by adding simple risk markers? Results from the Copenhagen City Heart Study. Eur J Prev Cardiol 23:1546–1556
47. Vaid S, Bell T, Grim R et al (2012) Predicting risk of death in general surgery patients on the basis of preoperative variables using American College of Surgeons National Surgical Quality Improvement Program Data. Perm J 16:10–17
48. Rivard C, Nahum R, Slagle E et al (2016) Evaluation of the performance of the ACS NSQIP surgical risk calculator in gynecologic oncology patients undergoing laparotomy. Gynecol Oncol 141:281–286
49. Basta MN, Bauder AR, Kovach S et al (2016) Assessing the predictive accuracy of the ACS NSQIP surgical risk calculator in open ventral hernia repair. Plast Reconstr Surg Glob Open 4:115

50. Hyder JA, Reznor G, Wakeam E et al (2016) Risk prediction accuracy differs for emergency versus elective cases in the ACS-NSQIP. Ann Surg 264:959–965
51. Madhavan S, Soong SL, Vishalkumar S et al (2016) A comparison, validation and improvisation of possum and ACS-NSQIP surgical risk calculator in patients undergoing hepatic resection. HPB (Oxford) 18:e157
52. Chung PJ, Carter TI, Burack JH et al (2015) Predicting the risk of death following coronary artery bypass graft made simple: a retrospective study using the American College of Surgeons National Surgical Quality Improvement Program database. J Cardiothorac Surg 10:62
53. Blankenberg S, McQueen MJ, Smieja M et al (2006) Comparative impact of multiple biomarkers and N-terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the heart outcomes prevention evaluation (HOPE) study. Circulation 114:201–208
54. Zethelius B, Berglund L, Sundström J et al (2008) Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med 358:2107–2116
55. Ritt M, Ritt JI, Sieber CC et al (2017) Comparing the predictive accuracy of frailty, comorbidity, and disability for mortality: a 1-year follow-up in patients hospitalized in geriatric wards. Clin Interv Aging 12:293–304