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A prospective observational study of preoperative natriuretic peptide testing in adult non-cardiac surgical patients in hospitals in Western Cape Province, South Africa

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Background. International guidelines recommend risk stratification to identify high-risk non-cardiac surgical patients. It is also recommended that all patients aged ≥45 years with significant cardiovascular disease should have preoperative natriuretic peptide (NP) testing. Abnormal preoperative B-type NPs have a strong association with postoperative cardiac complications. In South African hospitals, it is not known how many patients with significant cardiovascular disease scheduled for intermediate- to high-risk surgery will have raised NPs.
Objectives. To determine the prevalence of abnormal (raised) NPs in non-cardiac surgical patients with cardiac clinical risk factors. A secondary objective was to develop a model to identify surgical patients who may benefit from preoperative NP screening.
Methods. The inclusion criteria were patients aged ≥45 years presenting for elective, non-obstetric, intermediate- to high-risk non-cardiac surgery with at least one of the following cardiovascular risk factors: a history of ischaemic heart disease or peripheral vascular disease (coronary equivalent); a history of stroke or transient ischaemic attack; a history of congestive cardiac failure; diabetes mellitus currently on an oral hypoglycaemic agent or insulin; and serum creatinine level >175 µmol/L (>2.0 mg/dL). Blood samples for N-terminal-prohormone B-type NP (NT-proBNP) were collected before induction of anaesthesia. The preoperative prognostic threshold for abnormal (raised) NT-proBNP was ≥300 pg/mL. A generalised linear mixed model was used to determine the association between the risk factors and an abnormal NT-proBNP level.
Results. Of 172 patients, 63 (37%) had an elevated preoperative NT-proBNP level. The comorbidities independently associated with elevated preoperative NT-proBNP were coronary artery disease or peripheral vascular disease, congestive cardiac failure, and a creatinine level >175 µmol/L.
Conclusions. We strongly recommend that non-cardiac surgical patients aged ≥45 years undergoing intermediate- or high-risk non-cardiac surgery with a history of coronary artery disease/peripheral vascular disease, congestive cardiac failure or elevated creatinine have preoperative NP testing as part of risk stratification.

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Every year ~230 million adults around the world undergo major non-cardiac surgery.[1] The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study highlighted the incidence of perioperative cardiac complications in patients with cardiovascular comorbidities. The findings showed that in patients aged ≥45 years, the 30-day mortality rate was 2%,[2] and 8% had significant myocardial injury that contributed to subsequent morbidity.[3]

Current guidelines emphasise the need to identify high-risk non-cardiac surgical patients through preoperative risk stratification.[4] However, widely used clinical risk stratification tools such as the Revised Cardiac Risk Index (RCRI) do not perform as well as cardiovascular biomarkers, specifically natriuretic peptides (NPs).[5] Raised preoperative B-type NPs have a strong association with postoperative cardiac complications. This has been shown in observational studies and meta-analyses, and has been the impetus for including B-type NP screening for high-risk surgical patients.[6,7]

Some preoperative international guidelines, such as the Canadian Cardiovascular Society (CCS) guidelines on perioperative cardiovascular risk assessment, advocate that all patients aged ≥45 years who have 'significant cardiovascular disease' and present

for intermediate- to high-risk surgery should have preoperative NP testing.[4] 'Significant cardiovascular disease' is defined as a history of coronary artery disease, cerebrovascular disease, peripheral artery disease, congestive heart failure or severe pulmonary hypertension, or a severe obstructive intracardiac abnormality (severe aortic stenosis, severe mitral stenosis, or severe hypertrophic obstructive cardiomyopathy).[4]

The rationale for the present study was that in the South African (SA) context, it is unknown how many patients with significant cardiovascular disease scheduled for intermediate- to high-risk surgery will have raised NPs. This information is necessary to inform appropriate preoperative screening protocols for patients at risk of cardiovascular events following non-cardiac surgery. Indiscriminate preoperative NP testing would be inappropriate in a resource-limited environment. A data-informed approach to preoperative NP screening may reduce costs and focus efforts on those patients at greatest cardiovascular risk in the perioperative period.

Objectives

To describe the prevalence of and associations with abnormal (raised) NPs in patients with clinical risk factors for cardiovascular disease undergoing intermediate- and high-risk surgery.

Methods

This was a prospective, observational study conducted in seven public sector hospitals in Western Cape Province, SA. Paarl, Victoria, Mitchells Plain, George, Worcester and New Somerset hospitals are secondary-level hospitals and Groote Schuur Hospital is a tertiary-level hospital. Ethics approval was provided by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (ref. no. 463/2019) and the trial was registered on ClinicalTrials.gov (ref. no. NCT 04114032). Approval was granted by the Western Cape Department of Health and the individual hospitals to conduct the study (provincial approval ref. no. WC_201909_006).

The primary objective was to determine the prevalence of abnormal (raised) NP levels in patients with clinical risk criteria. Abnormal (raised) NP levels were defined according to the NP thresholds associated with major adverse cardiac events following non-cardiac surgery, with an N-terminal-prohormone B-type NP (NT-proBNP) level >300 ng/L.[6] The secondary objective was to develop a model to identify surgical patients who may benefit from preoperative NP screening. The inclusion criteria were patients aged ≥45 years presenting for elective, non-obstetric, intermediate- to high-risk non-cardiac surgery with at least one of the following cardiovascular risk factors: a history of ischaemic heart disease or peripheral vascular disease (coronary equivalent); a history of stroke or transient ischaemic attack; a history of congestive cardiac failure; diabetes mellitus currently on an oral hypoglycaemic agent or insulin; and serum creatinine level >175 µmol/L (>2.0 mg/dL). Intermediate-risk surgery is defined as having a 30-day risk of cardiovascular death or non-fatal myocardial infarction of 1 - 5%, and high-risk surgery as exceeding 5%.[8] Emergency and day-case surgery were excluded. Patients were screened on the afternoon before surgery and provided written informed consent during preoperative anaesthesia assessment. Baseline demographic and clinical data included age, gender, preoperative haemoglobin, white cell count and serum creatinine. If a preoperative electrocardiogram was done, a copy was kept as a source document.

Blood samples for NT-proBNP testing were collected in theatre before induction of anaesthesia on insertion of the intravenous cannula for vascular access. The specimens were couriered to PathCare Laboratories and analysed within 2 hours of the blood specimen being drawn. The team in theatre were blinded to the NT-proBNP result, since this was only available postoperatively. However, elevated NT-proBNP results that were of prognostic importance for postoperative cardiovascular events were declared to the surgeons postoperatively, and they were advised to do troponin screening for 3 days. The reporting of results to surgeons postoperatively would allow for institution of supportive strategies (e.g. management of tachycardia,[9] optimisation of haemoglobin if necessary,[10] administration of aspirin and statin therapy)[11] and monitoring for progression to myocardial infarction, and cardio-vascular risk modification could be advocated following discharge.

In order to evaluate the association between five clinical risk factors and an abnormal (raised) NT-proBNP level in a binary logistic regression model, a sample that included at least 50 patients with an abnormal level would be required. To ensure that we fulfilled this requirement, we estimated the sampling cohort as follows. Based on previous observational studies in the Western Cape, we expected to screen ~800 elective surgical patients in all centres over a 4-week period, of whom we expected that 160 would fulfil clinical and surgical criteria for NP testing, and that of these ~65 would have abnormal (raised) NPs. The sample size was derived on an estimated prevalence of a raised NP level of 40% (95% confidence interval (CI) 33 - 48). Sixty-five patients with raised NPs would provide sufficient power to allow for a regression that included the five clinical risk factors of the RCRI, and would not violate the 10 events (raised NPs) per variable rule.[12]

A generalised linear mixed model using a logit link was used to identify independent risk factors for the binary outcome. These included a one-level and a hierarchical two-level model to account for the expected correlation in outcomes within hospitals. We excluded patients with missing values for potential risk predictors, and only used complete case analysis as <1% of the dataset was incomplete for a potential clinical risk predictor.[13] Results are reported as adjusted odds ratios with 95% CIs. All the RCRI factors were entered into the models, with the exception of the type of surgery, as all patients were scheduled for intermediate- or high-risk surgery. The potential independent predictors entered into the model were a history of ischaemic heart disease or peripheral vascular disease (coronary equivalent); a history of stroke or transient ischaemic attack; a history of congestive cardiac failure; diabetes mellitus currently on an oral hypoglycaemic agent or insulin; and serum creatinine level >175 µmol/L (>2.0 mg/dL). The independent variables associated with an abnormal NP level would be used to build a model to predict which patients should undergo preoperative NP testing prior to intermediate or major surgery.

Continuous data are reported as mean and standard deviation (SD) or median and interquartile range, and categorical data as number and percentage. The Statistical Package for the Social Sciences version 24 (SPSS Inc., USA) was used for data analysis.

Results

The patients recruited into the study are shown in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram in Fig. 1. The trial was extended to 8 consecutive weeks in each hospital over the months beginning October 2019 to end of March 2020 in order to reach the sample size required for the study. The study was stopped because of the curtailment of elective surgery during the COVID-19 pandemic lockdown, with 63/172 patients (37%) with an abnormal (raised) NT-proBNP level, 2 patients fewer than our target. The baseline patient characteristics are set out in Table 1.

Only one preoperative creatinine value was missing from the data set, since no renal function test was done for the patient pre-operatively.

The prevalence of abnormal (raised) NT-proBNP in patients with clinical risk criteria was 37%. Table 2 shows recruitment across the study sites. The highest recruiting sites were Groote Schuur, Paarl and Victoria hospitals.

The comorbidities that were independently associated with elevated NT-proBNP in the generalised linear mixed model were coronary artery disease (and coronary equivalent, peripheral vascular disease), congestive cardiac failure, and a creatinine level >175 µmol/L (Table 3).

The preoperative risk calculator (Table 4) shows that the presence of coronary artery disease/peripheral vascular disease is associated
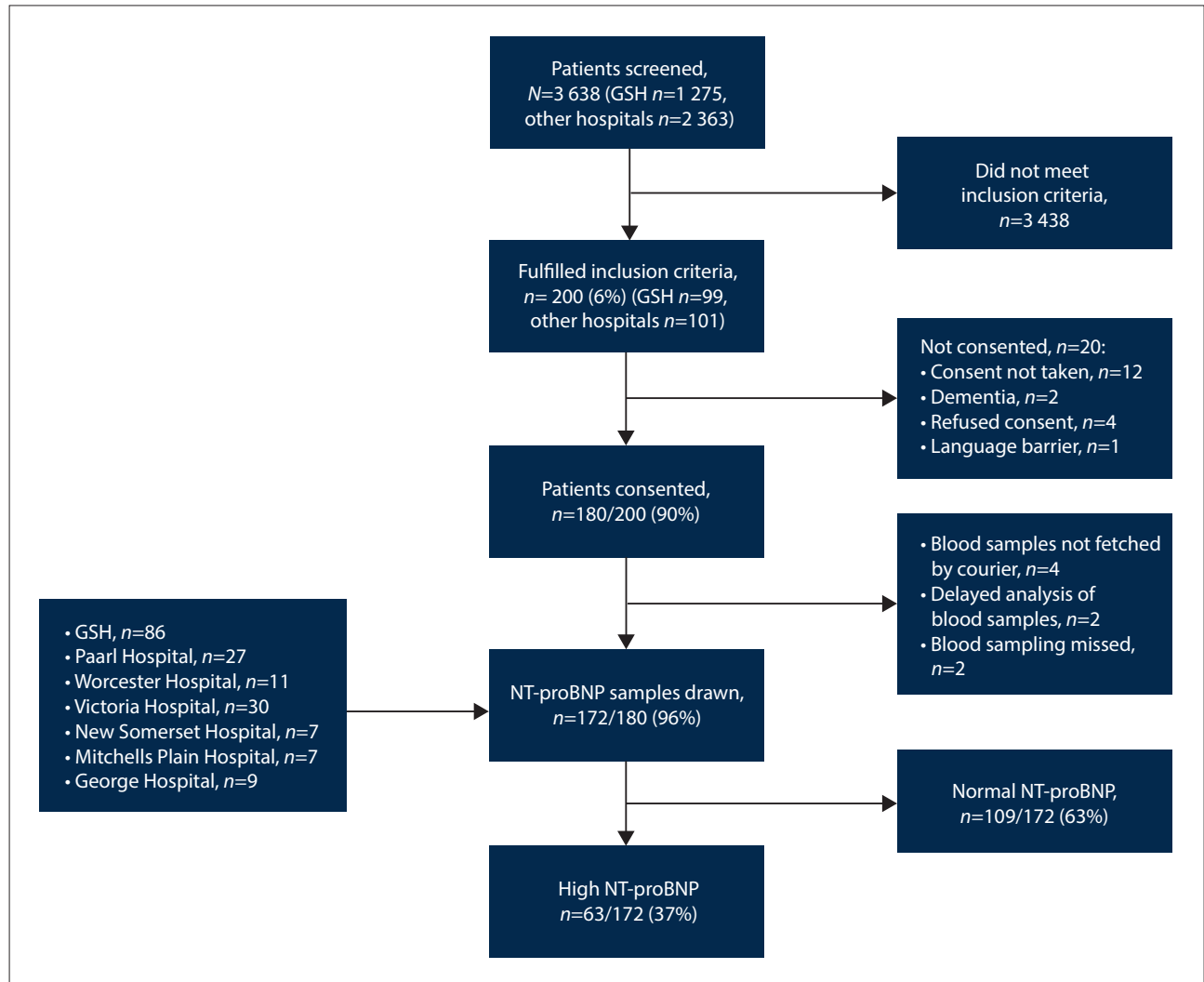

Fig. 1. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram. (NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; GSH = Groote Schuur Hospital.)

Table 1. Baseline characteristics of patients

	Whole cohort (N=172)	High NT-proBNP* (N=63; 37%)	Normal NT-proBNP (N=109; 63%)	p-value
Age (years), mean (SD)	63.5 (9.8)	65.4 (10.2)	62.4 (9.4)	0.0523
Gender female, n (%)	92 (54)	28 (44)	64 (59)	0.0423
Comorbidity, n (%)				
CAD/PVD	76 (44)	33 (52)	43 (39)	0.1087
CCF	17 (10)	12 (19)	5 (9)	0.0033
Diabetes mellitus	97 (56)	35 (56)	62 (57)	0.8886
Stroke/TIA	25 (15)	5 (5)	20 (18)	0.0739
Creatinine >175 µmol/L	15 (8.7)	10 (16)	5 (5)	0.3340

NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; SD = standard deviation; CAD/PVD = coronary artery disease/peripheral vascular disease; CCF = congestive cardiac failure; TIA = transient ischaemic attack.
*High NT-proBNP >300 ng/L.

Table 2. Patient recruitment characteristics per hospital

Hospital	Patients for elective surgery, N	Patients fulfilling study inclusion criteria (RCRI ≥1), n (%)	Raised NT-proBNP, n (%)	No consent, no blood sample taken, n
Groote Schuur	1 275	99 (8)	33 (33)	13
Paarl	431	27 (6)	10 (37)	0
Worcester	264	12 (5)	1 (8)	1
Victoria	483	37 (8)	11 (30)	6
New Somerset	486	13 (3)	2 (15)	4
Mitchells Plain	206	2 (1)	0	0
George	493	10 (2)	6 (60)	1

RCRI = Revised Cardiac Risk Index; NT-proBNP = N-terminal-prohormone B-type natriuretic peptide.

Table 3. Multivariable association with a prognostically important elevated NT-proBNP

Comorbidities (predictors)	p-value	OR	95% CI
CAD/PVD	0.006	3.295	1.410 - 7.698
CCF	0.001	8.016	2.293 - 28.020
Stroke/TIA	0.195	0.455	0.137 - 1.504
Diabetes	0.080	2.099	0.914 - 4.817
Creatinine >175 µmol/L	0.001	8.901	2.422 - 32.713

NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; OR = odds ratio: CI = confidence interval; CAD/PVD = coronary artery disease/peripheral vascular disease; CCF = congestive cardiac failure; TIA = transient ischaemic attack.

Table 4. Preoperative risk calculator

Preoperative variables from derivation model	Coefficients	Probability of high NT-proBNP, %
Baseline	−3.570	3
CAD/PVD	1.192	8
CCF	2.081	18
Creatinine >175 µmol/L	2.186	20

NT-proBNP = N-terminal-prohormone B-type natriuretic peptide; CAD/PVD = coronary artery disease/peripheral vascular disease; CCF = congestive cardiac failure.

with an 8% probability of a high NT-proBNP level, congestive cardiac failure with a 18% probability, and elevated creatinine with a 20% probability. The baseline probability in the cohort is 3%. The risk equation to derive the probability of high NT-proBNP appears alongside, below Table 4.

Discussion

The main finding of this study was that of SA patients aged ≥45 years with clinical cardiovascular risk factors scheduled for intermediate- or high-risk non-cardiac surgery, 1 in 3 will have an abnormal (raised) NT-proBNP level. In addition, patients with a history of congestive cardiac failure or a creatinine level >175 µmol/L have a >15% probability of a high preoperative NT-proBNP level. Previous studies have shown that high preoperative NPs are prognostic of perioperative cardiovascular complications.

Study strengths and limitations

The strengths of this study are that it was a prospective, pragmatic study, which provides information for preoperative risk stratification of SA surgical patients scheduled for intermediate- and high-risk non-cardiac surgery. In the SA resource-limited environment, these findings suggest that it is justifiable to conduct preoperative NP testing in patients with coronary artery disease/peripheral vascular disease, congestive cardiac failure, and an elevated creatinine level scheduled for intermediate- and high-risk surgery.

Risk equation:

$$p = \frac{1}{1+e^{-\,(-3.570+(CAD/PAD)+(CCF)+(CREATININE))}}$$

$$p = \frac{1}{1+e^{-\,(-3.570+1.192+2.081+2.186)}}$$

Since we recruited patients who already had at least one of the RCRI risk factors, this patient cohort represents a high-risk group.

A further strength of this study is that it was a multicentre study that included hospitals serving different demographic areas. Controlling for the hospital clusters suggests that the findings are robust and generalisable to patients from different healthcare facilities in the Western Cape. Furthermore, controlling for the clusters may explain the difference between the lack of association of diabetes mellitus with an abnormal NT-proBNP level on univariate analysis, but not on multivariate analysis.

The weakness of the study is that we did not follow up these patients for cardiovascular outcomes. However, a large observational cohort study suggests that an abnormal (raised) preoperative NP level is an important independent predictor of postoperative cardiovascular morbidity and mortality.[14] We therefore believe that our findings are of clinical relevance in preoperative cardiovascular risk stratification in SA.

Studies have also shown that the addition of NP testing to existing clinical risk indices, such as the RCRI, improves prognostic performance. However, clinical risk factors are not equally weighted and some clinical risk factors may have a greater impact on patient outcomes. In our study, three of the five traditional preoperative cardiovascular risk factors, coronary artery disease/peripheral vascular disease, congestive cardiac failure and elevated creatinine, were found to be independently associated with NP elevation. This study supports the CCS guidelines in using clinical risk predictors as a screening tool to identify which patients should have preoperative NP screening.

The cardiovascular disease burden per site in Table 2 can be used to plan for resource allocation and funding for NT-proBNP screening in high-risk patients.

Recommendations

Our recommendation is that surgical patients scheduled for intermediate- and high-risk non-cardiac surgery with a history of coronary artery disease/peripheral vascular disease, congestive cardiac failure or an elevated creatinine level should have preoperative NP testing done. We recommend that patients with an abnormal (raised) NT-proBNP level should also have postoperative troponin screening. Patients with a normal level do not require additional postoperative monitoring for cardiovascular events.[4] The small number of patients with a history of stroke or transient ischaemic attack would suggest that a larger study is required in order to determine whether a history of stroke or transient ischaemic attack is independently associated with an abnormal (raised) NT-proBNP level. Furthermore, the role of NT-proBNP screening on the basis of age alone remains uncertain in SA, where further research is needed. To understand the full implications of these findings for clinical practice in SA, a cost-effectiveness analysis would be beneficial.

Future research should focus on preoperative optimisation of patients with elevated NPs.

Conclusions

We recommend that SA surgical patients scheduled for intermediate- and high-risk non-cardiac surgery with a history of coronary artery disease/peripheral vascular disease, congestive cardiac failure or an elevated creatinine level have preoperative natriuretic testing done as part of risk stratification. We suggest that if these surgical patients have a history of stroke or transient ischaemic attack, they may also benefit from preoperative natriuretic testing. Patients with an abnormal (raised) NT-proBNP level should have postoperative troponin screening.

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: A modelling strategy based on available data. Lancet 2008;372(9633):139-144. https://doi.org/10.1016/s0140-6736(08)60878-8
2. Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012;307(21):2295-2304. https://doi.org/10.1001/jama.2012.5502
3. Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: A large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology 2014;120(3):564-578. https://doi.org/10.1097/aln.0000000000000113
4. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. Can J Cardiol 2017;33(1):17-32. https://doi.org/10.1016/j.cjca.2016.09.008
5. Ford MK, Beattie WS, Wijeysundera DN. Systematic review: Prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Ann Intern Med 2010;152(1):26-35. https://doi.org/10.7326/0003-4819-152-1-201001050-00007
6. Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: A systematic review and individual patient data meta-analysis. J Am Coll Cardiol 2014;63(2):170-180. https://doi.org/10.1016/j.jacc.2013.08.1630
7. Rodseth RN, Padayachee L, Biccard BM. A meta-analysis of the utility of pre-operative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. Anaesthesia 2008;63(11):1226-1233. https://doi.org/10.1111/j.1365-2044.2008.05574.x
8. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management: 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). Eur Heart J 2014;35(35):2383-2431. https://doi.org/10.1093/eurheartj/ehu282
9. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomised trials. Anesth Analg 2008;106(4):1039-1048. https://doi.org/10.1213/ane.0b013e318163f6a9
10. Karkouti K, Wijeysundera DN, Beattie WS; Reducing Bleeding in Cardiac Surgery Investigators. Risk associated with preoperative anemia in cardiac surgery: A multicenter cohort study. Circulation 2008;117(4):478-484. https://doi.org/10.1161/circulationaha.107.718353
11. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: A cohort study. Ann Intern Med 2011;154(8):523-528. https://doi.org/10.7326/0003-4819-154-8-201104190-00003
12. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II: Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48(12):1503-1510. https://doi.org/10.1016/0895-4356(95)00048-8
13. Steyerberg EW. Clinical Prediction Models. New York: Springer, 2010.
14. Duceppe E, Patel A, Chan MTV, et al. Preoperative N-terminal pro-B-type natriuretic peptide and cardiovascular events after noncardiac surgery: A cohort study. Ann Intern Med 2020;172(2):96-104. https://doi.org/10.7326/m19-2501