Current multivariate risk scores in patients undergoing non-cardiac surgery
Gian Francesco Mureddu

Italian Association of Cardiovascular Prevention and Rehabilitation (IACPR)

Abstract

Several indexes to predict perioperative cardiovascular risk have been proposed overtime. The most widely used is the Revised Cardiac Risk Index (RCRI) developed by Lee since 1999. It predicts major cardiac outcomes from five independent clinical determinants: history of ischemic heart disease, history of cardiovascular disease, heart failure, insulin-dependent diabetes mellitus, and chronic renal failure (i.e. serum creatinine >2 mg/dl). In external validation studies, the RCRI showed high negative predictive value in all groups of age, indicating that it may be used to identify people at low risk for perioperative adverse cardiovascular events in noncardiac surgery. However its accuracy is suboptimal in many clinical settings. More recently the National Surgical Quality Improvement Program database (NSQIP) has developed a new index to predict perioperative myocardial infarction (MI) or cardiac arrest (MICA) from a cohort of 211,410 patients (the Gupta index) and afterwards a universal surgical risk estimation tool has been developed, using standardized clinical data from 393 ACS-NSQIP hospitals in US (a cohort based on 1,414,006 patients), showing a good performance for mortality (C-statistic=0.944) and morbidity (C-statistic=0.816) as compared with procedure-specific models. Other risk scores include the Vascular events In noncardiac Surgery patients cOhort evaluatIon (VISION), which has evaluated cardiac complications in 15,065 patients, the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) and the large Preoperative Score to Predict Postoperative Mortality (POSPOM) that was built up from data collected in the National Hospital Discharge Data Base (NHDBB) including a cohort of 7,059,447 patients. In Italy a new risk index (the Orion score) built up from a cohort of 9000 patients generated four classes of major cardiovascular adverse events perioperative risk ranging from 1 (0.6%); 2 (2.4%); 3 (7.4%) and 4 (23.1%). The AUROC curves showed higher accuracy as compared to the RCRI score both in the derivation than in the validation cohort (AUROC=0.872 ± 0.028 vs 0.807 ± 0.037).

Thus, many risk indices are available nowadays. Despite the latest European guidelines recommended them for risk stratification (class I, level of evidence B), their use in clinical practice is still scarce.

Introduction

Worldwide, more than 200 million adults undergo major noncardiac surgery each year, and the number of such patients is increasing [1]. It has been estimated that are performed annually about 19 million surgery procedures in Europe, 30% of which in patients with cardiovascular comorbidities and hence at greater risk of complications [2]. Cardiovascular complications are still one of the most important causes of morbidity and mortality in patients undergoing non-cardiac surgery. It is estimated that major surgery is associated with an increased incidence of cardiac death (between 0.5 and 1.5%) and major cardiac complications (between 2% and 3.5%) [3]. This means more than 150,000 cardiac complications every year when referring to the European population. According to the US hospital discharges registry, the number of surgical procedures is constantly increasing and will affect mostly elderly people [4]. Hence, within the next 20 years, aging will have a significant impact on the perioperative management of most patients candidate to non-cardiac surgery [1,2,5]. The elderly represent a part of population particularly at risk, not only for the increasing incidence and lethality of coronary disease which occurs with increasing age [6], but also for the effects of aging on the myocardium. Perioperative acute myocardial infarction (MI), indeed have a higher mortality rate in the elderly. Since it is estimated that old people require surgery four times as often than the rest of the population, the relevance of proper cardiovascular risk stratification (RCV) is rising over time and the role of the cardiologist as a consultant in the departments of surgery is becoming crucial [1,2,3].

For this reason, given the population who will undergo cardiac surgery has been increasing overtime and given the increasing burden of potential comorbidities that population has been carrying on, predicting perioperative complications has become a rising need in clinical practice.

Risk scores for stratification: advantages and limits

Over the past thirty years several indexes of perioperative clinical risk have been proposed. These scores have been based on multivariate analyses of observational studies that have linked the clinical characteristics of patients undergoing non cardiac surgery with perioperative morbidity and mortality for cardiac complications. The scores developed by Lee (i.e. the Revised Cardiac Risk Index, RCRI) [7], Goldman
The RCRI [6], which is still considered by many clinicians as the best currently available one, was developed using prospective data collected on 2893 unselected patients undergoing non-cardiac surgery (and validated in other 1422) and followed post-operatively. The RCRI that has been used since 1999, was built up to predict five major cardiac outcomes: post-operative myocardial infarction, pulmonary oedema, ventricular fibrillation or cardiac arrest, and complete heart block. Major cardiac complications occurred in 56 (2%) of 2893 patients assigned to the derivation cohort. The Lee index contains five independent clinical determinants of major perioperative cardiac events: history of ischemic heart disease, history of cardiovascular disease, heart failure, insulin-dependent diabetes mellitus, and chronic renal failure (i.e. serum creatinine >2 mg/dl). High-risk surgery is the sixth factor included in the index. All factors contribute equally (each a point) to determine a score on the basis of which the risk of complications is classified as very low (class I, risk=0.4%), low (class II, risk=0.9%), moderate (class III, risk=6.6%) or high (class IV, risk=11%). The area under the ROC (receiver operating characteristic) curve was 0.81, indicating that the index was effective in discriminating between patients who will develop major adverse cardiac events in the perioperative period, from those who will not. However, patients included in the RCRI cannot be considered as a cohort at medium surgical risk, usually including unselected and patients without heart disease as it had been developed mainly using cohorts of patients who underwent orthopedic (35%), vascular (21%) or thoracic surgery (12%). Moreover, several studies of external validation suggested that the Lee index had a suboptimal predictive ability in patients presenting multiple risk factors. A systematic review of 24 studies including over 790,000 patients found that the Lee index discriminated moderately well between patients at low risk vs patients at high risk for cardiac events after mixed noncardiac surgery, but its performance was hampered when predicting cardiac events after vascular surgery or predicting death [11].

The Vascular Study Group of the new England (VSGNE) studied 10,081 patients who underwent elective carotid endarterectomy (CEA; n=5293), lower extremity bypass (LEB; n=2673), endovascular abdominal aortic aneurysm repair (EVAR; n=1005), or open infrarenal abdominal aortic aneurysm repair (OAAA; n=1110) from 2003 to 2008. The RCRI predicted risk after CEA reasonably well but largely underestimated risk after LEB, EVAR, and OAAA for low- and higher-risk patients. Across all VSGNE patients, the RCRI underestimated cardiac complications by 1.7- to 7.4-fold (predicted values) based on observed event rates of 2.6%, 6.7%, 11.6%, and 18.4% for patients with 0, 1, 2, and >3 risk factors respectively. In this study a derivation cohort of 8208 was used to develop a new cardiac risk prediction model specifically for vascular surgery patients. The ability of the model to predict cardiac complications was assessed within a validation cohort of 1873 patients (validation cohort). In multivariate analysis of the VSGNE cohort, independent predictors of adverse cardiac events were increasing age (OR=1.7 to 2.8), smoking (OR=1.3), insulin-dependent diabetes (OR=1.4), coronary artery disease (OR=1.4), CHF (OR=1.9), abnormal cardiac stress test (OR=1.2), long-term -blocker therapy (OR=1.4), chronic obstructive pulmonary disease (OR=1.6), and creatinine >1.8 mg/dl (OR=1.7). Prior cardiac revascularization was protective (OR=0.8). The new model showed good calibration (r=0.99, p<0.001) and discrete discrimination ability (AUROC=0.71). The VSG Cardiac Risk Index (VSG-CRI) identified six categories of risk ranging from 2.6% to 14.3% (score of 0-3 to 8). However, the VSG-CRI is limited to predicts in-hospital cardiac events only in patients undergoing vascular surgery [12].

The RCRI performance in different age groups, has been also investigated in a large population study from the Danish National Patient Registry [13]. All individuals ≥25 years who underwent major elective noncardiac surgery in Denmark (from January 1, 2005, to November 30, 2011) were followed up for the 30-day risk of major adverse cardiovascular events (ischemic stroke, myocardial infarction, or cardiovascular death). The accuracy of the RCRI (C statistic) was highest among the age group from 56 to 65 years (0.772) and lowest for those aged >85 years (0.683). The sensitivity of RCRI class >1 (i.e., in patients presenting with >1 risk factor) was similar among age groups (59%, 71%, 64%, 66%, and 67% in patients aged ≤55, 56 to 65, 66 to 75, 76 to 85, and >85 years, respectively). The negative predictive value was >98%, indicating that RCRI may be used to identify people at low risk for perioperative adverse cardiovascular events in noncardiac surgery in all groups of age.

New developed risk scores

More recently, a new perioperative risk index has been proposed, on the basis of an observational study conducted in 2007 by the American College of Surgeons (ACS). Data from 250 hospitals were collected in a prospective database (the National Surgical Quality Improvement Program database) (NSQIP) for a total of 211,410 patients [14,15]. Among these, 1371 subjects (0.65%) developed a perioperative myocardial infarction (MI) or cardiac arrest. In the multivariate logistic regression, five predictors of perioperative MI or cardiac arrest were identified: the type of surgery, a reduced functional capacity (functional state of dependence), an increase in serum creatinine, a high risk category according to the American Society of Anesthesiology [16], and an advanced age. This risk model was validated on the 257,385 cases collected in the following year (2008) with a very similar performance (area under the ROC curve=0.884 and 0.874, respectively). In contrast when the Lee index was applied at the National Surgical Quality Improvement Program data set of 2008, the predictive power was lower (AUROC=0.747). Stepwise Logistic Regression analysis showed that among non surgery-related factors, a totally dependent functional status (adjusted OR=2.79, 95% IC: 2.36-3.30) or a partially dependent functional status (adjusted OR=1.92, 95% IC: 1.65-2.23), were the major independent predictors of outcome, together with an abnormal serum creatinine (>1.5 mg/dl) (adjusted OR=1.84, 95% IC: 1.63-2.09). A risk calculator, is also available on the web in the form of an interactive spreadsheet that allows the clinician to enter the patient’s data and provides an estimated probability percentage of MICA based on the validated model (Figure 1).

Afterwards a universal surgical risk estimation tool has been developed, using standardized clinical data from 393 ACS-NSQIP hospitals in US (based on 1,414,006 patients). A regression model was developed to predict 8 outcomes based on the preoperative risk factors Based on 21 preoperative factors [17] (demographics, comorbidities, procedure). Subspecialties included general surgery, gynecology, neurosurgery, orthopaedics, otolaryngology, plastic surgery, cardiothoracic surgery, urology, and vascular surgery. The universal model was compared with procedure-specific models. The universal surgical risk calculator model had good performance for mortality (C-statistic=0.944) and morbidity (C-statistic=0.816).

The Vascular events In noncardiac Surgery patients eObort evaluaIion (VISION) study is a large, international, prospective study evaluating cardiac complications in 15,065 patients aged 45 years or older who underwent in-patient noncardiac surgery [18]. Myocardial injury after noncardiac surgery (MINS) was defined as prognostically relevant myocardial ischemia defined as a peak troponin T (TnT) values of 0.04 μg/l or greater in the first 3 days after surgery. Patients with troponin T level above the upper limit of the laboratory range were assessed for

[Monaldi Archives for Chest Disease 2017; 87:848]
**Perioperative Myocardial Infarction or Cardiac Arrest Risk Calculator**

<table>
<thead>
<tr>
<th>Age</th>
<th>Enter actual age in years</th>
<th>Estimated risk probability for perioperative MICA: 1.23%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA Class</td>
<td>Enter</td>
<td>1-5 for American Society of Anesthesiologists' Class</td>
</tr>
<tr>
<td>Creatinine (preoperative)</td>
<td>Enter</td>
<td>2 for missing value</td>
</tr>
<tr>
<td>Functional Status (preoperative)</td>
<td>Enter</td>
<td>1 for patients with totally dependent functional status</td>
</tr>
<tr>
<td>Procedure</td>
<td>Enter</td>
<td>1 for Aneurysm</td>
</tr>
</tbody>
</table>

**Authors:**
- Paltiel K Gupta, MD
- Hamra Gupta, MD
- Alkhalef Sunbarm, MD
- Monu Kaurkohal, MAMS
- Xiang Fung, PhD
- Wallsten Niller, MD
- Dannia | (Zabernolos), MD
- Claire B Hurtle, MD
- Inabkis | (Zapewv), MD
- Joston M (Ohmning, MD
- Tharam | (Zamec), MD
- R Armitage Force, MD, PhD
- Snavd M | (Zamzok), MD
- Aryan N | (Zamzol), MD

**Methodology:**

**Figure 1. NSIQP_MICA Calculator (from ref. #15) ACS NSQIP PUF.** In the figure is shown the case of a 60 years old man who has a severe COPD and hence in ASA Class III (the patient has severe systemic disease that is not incapacitating) and shows values of serum creatinine <1.5 mg/dl, who has a preoperative totally independent functionally state and will undergo aortic surgery. The estimated risk of MICA is 1.23%. Available at: [http://www.acsnsqip.org/puf/docs/ACS_NSQIP_Participant_User_Data_File_User_Guide.pdf](http://www.acsnsqip.org/puf/docs/ACS_NSQIP_Participant_User_Data_File_User_Guide.pdf)
ischemic features (i.e. ischemic symptoms and electrocardiography findings). An age of 75 years or older, ST elevation or a new left bundle branch block, and anterior ischemic EKG findings were found to be the independent predictors of 30-day mortality among patients who showed MINS. The new-MINS based score was able to predict 30-day mortality on the basis of: age 75 yr or older (1 point), ST elevation or new left bundle branch block (2 points), and anterior ischemic electrocardiographic findings (1 point). Patients with a score=0 had an expected 30-day mortality rate of 5.2%, those with a score=1, of 10.2%, those with a score=2, 19.0%, those with a score=3, of 32.5% and those with a score=4, of 49.8%, respectively.

After the experience of the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) scoring system for predicting the probability of in-hospital mortality after surgery [19] has been widely validated but have considerable limitations since it includes a number of risk factors collected at discharge (operative blood loss and the presence of malignancy) that precludes its preoperative use, the Preoperative Score to Predict Postoperative Mortality (POSPOM) study was built up to develop and validate a surgical risk score based on preoperative information, for predicting in-hospital mortality [20]. From January 1, 2010, to December 31, 2010, data related to all surgeries requiring anesthesia were collected from all centers performing more than 500 operations in France and collected in the National Hospital Discharge Data Base (NHDBB). From the entire cohort of 7,059,447 patients, 1,551,619 patients were excluded since they underwent low risk interventions (ophthalmologic, obstetric, or endoscopic procedure not requiring anesthesia) or from center with less than 500 cases/year activity. The remaining population (n=5507.834) was divided into a derivation cohort (2,717,902 pts; 479 centers) and a validation cohort (2,789,932 pts, 479 centers).

In the derivation cohort, 29 potential predictors were evaluated for. Of these, only 17 entered the final logistic model: age, ischemic heart disease, cardiac arrhythmia or heart blocks, chronic heart failure or cardiomyopathy, peripheral vascular disease, dementia, cerebrovascular disease, hemiplegia, chronic obstructive pulmonary disease, chronic respiratory failure, chronic alcohol abuse, cancer, diabetes, transplanted organ(s), chronic dialysis, chronic renal failure, and type of surgery. POSPOM score values less than or equal to 20 were associated with a probability of in-hospital mortality less than or equal to 0.32% (i.e., less than the in-hospital mortality observed in the full population - the average risk); a POSPOM value of 25 equates to a probability of in-hospital mortality of 1.37% (i.e., about three times the average risk), and POSPOM values of 30 and 40 equate to probabilities of in-hospital mortality of, respectively, 5.65 and 20.51% (i.e., 10 and 40 times the average risk). Thus, POSPOM risk score is a robust tool for predicting in-hospital mortality in patients undergoing surgery showing good discrimination and calibration.

In Italy, recent observations have been reported by researchers from Cagliari (G. Brotzu Community Hospital). Preliminary unpublished data from a prospective observational case-control study (the Orion study), which enrolled during 1 year (2013-2014) about 9000 patients who underwent cardiac preoperative counseling [21]. The primary aim of this study was to reclassify the perioperative cardiac risk in a contemporary unselected population. The preliminary analysis of the data have identified four independent variables of risk at the multivariate logistic analysis: high surgical risk (classified according to the latest ESC guidelines) [1], severe renal failure (defined as a GFR <30 ml/min), a history of heart failure (in subject aged <75 years), and older age (≥75 years) in absence of heart failure. Thus, the new risk score (Orion score) generated four classes of major cardiovascular adverse events perioperative risk ranging from 1 (0.6%); 2 (2.4%); 3 (7.4%) and 4 (23.1%). The AUROC curves comparing the sensitivity and specificity between the updated cardiac risk score and the Lee risk score (RCRI) showed higher accuracy of the new Orion score as compared to the Lee score both in the derivation cohort (AUROC=0.791±0.029 vs 0.739±0.032) and in the validation cohort (AUROC=0.872±0.028 vs 0.807±0.037).

Comments and Conclusions

The European guidelines on the management of patients undergoing non cardiac surgery [2] published in 2014, recommended using clinical risk indices for perioperative risk stratification (class I, level of evidence B) and among these indicates both the Revised Cardiac Risk Index (RCRI) and the National Surgical Quality Improvement Program (NSQIP-MICA). This indication comes from the fact that the NSQIP and Lee risk index models provide complementary prognostic perspectives and can help the clinician in the decision-making process. However, despite this strong recommendation risk scores are not widely used yet in clinical practice. One explanation probably lies in the fact that the same guidelines do not fit clearly the risk scores (Lee or MICA) in the decision-making algorithms. The guidelines-based risk scores are not widely used yet in clinical practice. One explanation probably lies in the fact that the same guidelines do not fit clearly the risk scores (Lee or MICA) in the decision-making algorithms. Take the case of a 60-year-old male who has to undergo aortic surgery (high risk). As it underwent a hip implant, his functional capacity is less than 4 METS (or not quantifiable) (step 4). At this point, the guidelines recommend (step 6) to look at the number of risk factors (the RCRI predictors), rather than a risk score as a percentage: if they are <2 than it we can proceed with surgery without further investigation, if ≥3 the clinician must consider non-invasive testing.

Furthermore, a number of other gaps in evidence do exist. The number of elderly patients undergoing non-cardiac surgery is growing as a result of the increased longevity of the general population in Italy. Data on elderly patients undergoing non cardiac surgery are scarce. Other end-points such as heart failure (HF) and atrial fibrillation (AF) have gained importance particularly in cohorts of elderly patients [22]. The risk score proposed by the guidelines do not refer to elderly patients. In conclusion, as also the European (ESC/ESA) pointed out, the development of new studies that clarify the “gap” in the evidence is needed. The new risk scores highlight the importance of stratifying the risk for other factors including age, comorbidity, and surgical complexity. The systematic use of risk ratings can help caregivers to guide clinical practice on the needs and on the new cardiovascular epidemiology, particularly in relation to outcome of elderly patients.

References

15. ACS NSQIP PUF. http://surgicalriskcalculator.com/miocardiarrest