



How can we identify the high-risk patient?

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Purpose of review

Accurate and early identification of high-risk surgical patients allows for targeted use of perioperative monitoring and interventions that may improve their outcomes. This review summarizes current evidence on how information from the preoperative, operative, and immediate postoperative periods can help identify such individuals.

Recent findings

Simple risk indices, such as the Revised Cardiac Risk Index or American Society of Anesthesiologists Physical Status scale, and online calculators allow risk to be estimated with moderate accuracy using readily available preoperative clinical information. Both specific specialized tests (i.e., cardiopulmonary exercise testing and cardiac stress testing) and promising novel biomarkers (i.e., troponins and natriuretic peptides) can help refine these risk estimates before surgery. Estimates of perioperative risk can be further informed by information acquired during the operative and immediate postoperative periods, such as risk indices (i.e., surgical Apgar score), individual risk factors (i.e., intraoperative hypotension), or postoperative biomarkers (i.e., troponins and natriuretic peptides).

Summary

Preoperative clinical risk indices and risk calculators estimate surgical risk with moderate accuracy. Although novel biomarkers, specialized preoperative testing, and immediate postoperative risk indices show promise as methods to refine these risk estimates, more research is needed on how best to integrate risk information from these different sources.

Keywords

biomarkers, clinical risk indices, exercise testing, postoperative complications, preoperative risk assessment

INTRODUCTION

Major surgery imposes physiological stresses that can cause significant morbidity and mortality in the perioperative period. This morbidity and mortality tends to occur in a relatively small proportion of surgical patients. For example, the United Kingdom has an overall rate of perioperative mortality of 2%, but 80% of these deaths occur in a small subset of high-risk surgical procedures. This subgroup constitutes only 12% of the surgical population [1].

As perioperative risk appears to be concentrated within a small subgroup of surgical patients, identifying these individuals early through perioperative risk stratification has important value. Nonetheless, there remain several challenges to effectively identify these high-risk patients. First, most perioperative risk stratification methods were designed to predict a certain type of event, typically death or specific complications. The prognostic accuracy of a risk-stratification tool is not necessarily transferable across different postoperative events. For example, the Revised Cardiac Risk Index (RCRI) was designed to predict major cardiac complications after noncardiac surgery [2]. Although it discriminates moderately well between patients with varying risks for cardiac complications, it poorly performs at predicting postoperative mortality [3]. Second, clinicians have to consider prognostic accuracy, simplicity, ease of access, and cost when selecting a particular approach for risk stratification, especially in the case of biomarkers and specialized testing. Even in the case of clinical risk indices, which are the most inexpensive risk stratification approach, an

Curr Opin Crit Care 2015, 21:328-335

DOI:10.1097/MCC.00000000000216

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Volume 21 • Number 4 • August 2015

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KEY POINTS

- Most episodes of postoperative mortality and major morbidity occur within a relatively small subgroup of surgical patients.
- The ASA-PS classification, RCRI, and American College of Surgeons risk calculator facilitate moderately accurate preoperative estimation of surgical risk using readily available clinical information.
- Measurement of natriuretic peptides and cardiac troponins before surgery can further help inform estimates of perioperative risk, as can CPET and cardiac stress testing.
- Immediately after surgery, patients' expected postoperative risks can be further informed using the surgical Apgar score and serial biomarkers (troponins and natriuretic peptides).
- Further research is needed to determine how best to integrate perioperative risk estimates from different sources such as clinical risk indices, biomarkers, and specialized testing.

optimal risk index must be accurate at predicting outcomes, and also simple enough for widespread implementation [4]. Third, the timing of evaluation is crucially important, as information regarding perioperative risk needs to be available early enough to influence clinical decision making.

IDENTIFICATION OF HIGH-RISK PATIENTS PRIOR TO SURGERY

Accurate and timely preoperative identification of high-risk patients provides opportunities to better inform patients about expected risks, make selective referrals to medical specialists before surgery, order further specialized preoperative investigations, initiate preoperative interventions intended to decrease perioperative risk, and arrange for appropriate levels of postoperative care. In select cases wherein a patient is deemed to be at very high risk, consideration might be given to canceling the planned surgery and opting for alternative nonoperative or less-invasive treatments. Importantly, perioperative risk is influenced by both patient-level (e.g., age and comorbidity) and surgery-level risk factors. For example, predictors of postsurgical mortality in the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) cohort study included nonelective surgery, select procedures, increased age, and specific comorbidities (Table 1) [5].

Preoperative functional capacity

Evaluation of functional capacity or exercise capacity is highly emphasized in perioperative risk

assessment. For example, in the American College of Cardiology and American Heart Association clinical practice guidelines, a patient's estimated functional capacity is a key determinant of whether further specialized preoperative cardiac testing is recommended [6]. This emphasis on functional capacity is likely based on extrapolation from studies of preoperative exercise stress testing or cardiopulmonary exercise testing (CPET). In previous studies, patients performing more than four to six metabolic equivalents (METs) on objective exercise testing had low perioperative risk [7^{*},8,9].

By comparison, perioperative physicians typically estimate patients' functional capacity subjectively by enquiring about their activities of daily living. Although a few studies have shown patients' self-reported inability to perform four to five METs to be associated with increased risks of perioperative complications [10,11], the magnitude of this association is weak. For example, poor self-reported functional capacity had a positive likelihood ratio of 1.3 and negative likelihood ratio of 0.62 for predicting complications [10]. By comparison, likelihood ratios greater than 2 or less than 0.5 are recommended for providing even minimal additional information [12]. This weak prognostic accuracy might be explained, in part, by the inherent subjectivity associated with physicians' judgment of patients' functional capacity. Indeed, recent research showed poor agreement between physicians' subjective estimate of preoperative functional capacity and the results of validated objective questionnaires such as the Duke Activity Status Index [13[•]]. These data point to the need for more standardized and accurate approaches to assess preoperative functional capacity in usual clinical practice.

Clinical risk indices using preoperative information

Several preoperative scoring systems have been developed to estimate risks of mortality or complications after surgery. A commonly used index is the American Society of Anesthesiologists Physical Status (ASA-PS) classification, which assigns a score of I–V based on a patient's overall health status [14]. Despite its simplicity, the ASA-PS classification scheme has moderately good performance in predicting death [15[°],16] and some complications after surgery [17,18,19[°],20]. The classification scheme also has limitations. Specifically, it has moderate interrater reliability at best [19[°]], does not incorporate surgeryspecific risks, and has diminished accuracy in settings with high overall mortality rates [15[°]].

The **RCRI** is a simple and widely used index for predicting major cardiac complications after

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Table 1. Association of preoperative characteristics with mortality within 30 days after major noncardiac surgery [5]

Age	
Age	
45–64 years	Reference group
74 years to 76 years	1.67 (1.18–2.36)
75 years and older	3.03 (2.20-4.18)
Urgent or emergent surgery	4.62 (3.57–5.98)
Operative procedure	
Major intra-abdominal or head-and-neck surgery	3.25 (1.64-6.45)
Craniotomy or multilevel spine surgery	3.72 (1.68-8.20)
Major vascular surgery	2.38 (1.04-5.47)
Comorbid disease	
Recent high-risk coronary artery disease ^a	3.12 (1.71–5.68)
History of heart failure	1.60 (1.09–2.36)
History of stroke	2.01 (1.42-2.84)
History of peripheral arterial disease	2.13 (1.47-3.10)
Chronic obstructive pulmonary disease	2.15 (1.61–2.89)
Active cancer ^b	2.38 (1.79–3.18)

^aAcute myocardial infarction, acute coronary syndrome, or severe (Canadian Cardiovascular Society Class 3 or 4) angina within 6 months before surgery. ^bActive treatment (chemotherapy, radiation, or surgery) for cancer within 6 months before surgery, known metastatic disease, or planned surgery for cancer.

noncardiac surgery. It incorporates six equally weighted components: coronary artery disease, heart failure, cerebrovascular disease, renal insufficiency, diabetes mellitus, and high-risk surgical procedures [2]. Despite being developed in 1999, it still discriminates moderately well between individuals with varying perioperative cardiac risk [3,21^{••},22]. It also has important limitations. Although the RCRI discriminates between individuals with differing perioperative cardiac risk, it does not accurately predict an individual patient's absolute risk of cardiac complications [23], possibly because of the increased sensitivity of contemporary biochemical tests for postoperative myocardial infarction (MI). In addition, some components of the index, such as diabetes mellitus, may warrant elimination as they provide minimal associated prognostic information [22]. Other components might require modification to better optimize their definitions. For example, renal insufficiency could be better defined using estimated glomerular filtration rate [22], whereas categories of surgical procedure risk could incorporate more levels of operative complexity [24]. Finally, the index may need to incorporate several other prognostically important risk factors including increased age, peripheral arterial disease, and functional capacity [3,24]. Importantly, any future changes to the RCRI must ensure that the index retains the inherent simplicity that led to its widespread uptake into clinical practice.

More recently, online web-based risk calculators have facilitated implementation of more complex

risk prediction tools into clinical practice while minimizing the need for additional cumbersome bedside calculations. The key example of this emerging group of indices is the American College of Surgeons risk calculator (http://riskcalculator.facs.org) [25]. This risk calculator implements a series of clinical prediction models developed using the National Surgical Quality Improvement Program (NSQIP) registry. These models have moderate-togood accuracy at predicting a range of postoperative events, such as death, cardiac complications, pneumonia, and acute kidney injury [25]. The NSQIP risk calculators also have limitations. Although the prediction models were derived in a very large multicenter observational dataset, they have yet to undergo external validation, especially in settings outside the United States. In addition, some prediction models are limited by the manner in which the NSQIP registry ascertains the relevant outcomes. For example, routine postoperative troponin surveillance was not implemented in all participating sites [26], thereby leading to potentially significant underreporting of postoperative MI rates [27^{••},28]. Finally, many of the prediction models incorporate the ASA-PS classification, which has limited interrater reliability [19[•]].

Preoperative biomarkers

Biomarkers are measurable markers of organ dysfunction that can independently predict postoperative complications or augment prognostic

information from clinical risk indices. Two preoperative biomarkers, in particular, have been extensively examined for predicting perioperative risk. They are cardiac troponins and natriuretic peptides, which include B-type natriuretic peptide (BNP) and N-terminal-pro-BNP (NT pro-BNP).

Natriuretic peptides are secreted by the myocardium into the circulation in response to ischemia [29] and stretching of the atrial or ventricular walls [30]. They are powerful markers of cardiovascular risk in nonsurgical patients, including individuals who are at risk for coronary artery disease, have coronary artery disease, or have heart failure [31]. Several systematic reviews indicate that preoperative BNP and NT pro-BNP are independent predictors of cardiac complications (i.e., nonfatal MI and cardiac death) after noncardiac surgery [32,33]. Furthermore, an individual patient data metaanalysis of preoperative BNP or NT pro-BNP in vascular surgery found the biomarkers to significantly improve risk prediction when combined with the **RCRI** [34]. Both low and elevated preoperative levels help identify patients with differing postoperative risks (Table 2) [35^{••}].

Another promising, albeit less studied, preoperative biomarker for predicting risk after noncardiac surgery is high-sensitivity cardiac troponin. Measurement of cardiac troponins, which are released in response to myocardial injury, is integral to the rapid diagnosis of MI [36]. High-sensitivity assays now allow for detection of low levels of circulating troponins in individuals without manifestations of acute coronary syndromes. In the nonoperative setting, elevated resting levels of circulating troponins **predict** the development of coronary artery disease, heart failure, and mortality [37,38]. Emerging research now demonstrates that 20% of patients undergoing major noncardiac surgery have elevated high-sensitivity troponin concentrations before surgery [39]. These findings have major implications for interpretation of any elevated postoperative troponin concentration. Furthermore, elevated preoperative high-sensitivity troponin concentrations are associated with increased risks of postoperative MI or mortality [40,41] and augment the predictive information from the RCRI [41].

Preoperative specialized testing

Additional specialized tests that might be performed before surgery to better inform perioperative risk estimation include resting echocardiograms, cardiac stress tests, and CPET. Preoperative resting echocardiography provides potentially important prognostic on cardiac function, including ventricular systolic dysfunction, ventricular diastolic dysfunction, valvular abnormalities, fixed wall motion abnormalities, and pulmonary hypertension. Limited available data indicate that preoperative systolic dysfunction is associated with elevated risks of perioperative death and cardiac complications [42–44]. Nonetheless, these findings may not improve risk prediction beyond that achieved with routine clinical examination alone [44]. Furthermore, resting ventricular function is not a proxy measure of functional capacity [45,46] in individuals who cannot exercise because of arthritis, obesity, or peripheral arterial disease. Finally, routine preoperative

Test **Measurement period** Concentration (pg/ml) Likelihood ratio for death or nonfatal MI BNP 0-99 Before surgery 0.58 1.38 100-250 ≥250 3.88 NT pro-BNP Before surgery 0-300 0.42 301-900 1.46 901-3000 2.68 >3000 4.97 BNP After surgery 0-250 0.58 251-400 1.37 >400 2.58 NT pro-BNP 0-300 After surgery 0.16 301-900 0.75 901-3000 1.79 >3000 3.28

Table 2. Prediction of 30-day death or nonfatal myocardial infarction after noncardiac surgery based on preoperative and postoperative measurement of natriuretic peptides [34,35^{••}]

BNP, B-type natriuretic peptide; MI, myocardial infarction; NT pro-BNP, N-terminal pro-B-type natriuretic peptide.

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echocardiography has not been associated with improved survival after major elective noncardiac surgery [47], although there may be some benefit for patients with cardiovascular risk factors who are undergoing hip fracture repair [48].

The prognostic value of information from cardiac stress testing has been extensively studied [49–51]. If exercise stress testing is performed, the ability to reach <u>seven or more METs</u> is indicative of low perioperative <u>cardiovascular risk</u>, whereas the failure to reach <u>four METs</u> predicts <u>increased</u> risk [8]. Reversible defects on cardiac stress imaging are indicative of increased perioperative cardiac risk, with greater extents of reversibility being associated with progressively increasing risk [50]. Isolated fixed defects on cardiac stress imaging are not predictive of increased perioperative risk [50].

In some regions, especially England, CPET is increasingly popular as a specialized test for preoperative risk assessment [52]. It provides an objective measure of cardiopulmonary fitness and predicts a range of perioperative complications aside from cardiac events, including pneumonia, respiratory failure, and infection. Several CPET-derived measurements, including the inability to exercise at all, low anaerobic threshold (<11 ml/kg/min), or low peak oxygen uptake (VO₂ peak), are predictive of increased risks of postoperative mortality and complications [7[•],53]. Despite these promising initial data, there remains a need for more robust high-quality research in this area, especially studies that recruit large heterogeneous generalizable samples from multiple sites and ensure that clinicians are blinded to CPET results [9,53,54].

IDENTIFYING HIGH-RISK PATIENTS IN THE INTRAOPERATIVE AND POSTOPERATIVE PERIOD

Despite recognition of the intraoperative and immediate postoperative period as being associated with significant physiologic derangements from both surgery and anesthesia, relatively few studies have evaluated how information from this period can help better identify high-risk surgical patients. Previous research has already pointed to the potential importance of intraoperative and immediate postoperative factors as risk indicators. For example, poor postoperative outcomes are associated with surgical procedures that are nonelective, involve more extensive tissue injury, and are longer in duration [5,16,55]. The duration of intraoperative hypotension (i.e., mean arterial blood pressure <55 mmHg) is also associated with increased risks of myocardial injury and acute kidney injury in a dose-dependent fashion [56].

Clinical risk indices using intraoperative and immediate postoperative information

Although intraoperative and immediate postoperative characteristics (e.g., duration of surgery) have been shown to be associated with postoperative outcomes [55], there has been comparatively little research on incorporating these characteristics into clinical risk indices. Two important examples of risk indices that have done so are the Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (P-POSSUM) score [57] and the surgical Apgar score [58].

The P-POSSUM score incorporates **18** variables, including several intraoperative characteristics (e.g., extent of surgery, total blood loss, and peritoneal soiling), into a complex set of mathematical equations for predicting morbidity and mortality. The tool has important limitations, including its inherent complexity for bedside application, as well as its tendency to overestimate or underestimate mortality and morbidity in some surgical populations. Nonetheless, the P-POSSUM score is one of the few predictive tools with consistent predictive accuracy across multiple validation studies [4].

In contrast, the surgical Apgar score is a very simple 10-point risk index that predicts postoperative morbidity and mortality based on three operative characteristics: tachycardia, hypotension, and estimated blood loss [58]. The score has now been validated across multiple institutions [59] and countries [60]. Although a poor surgical Apgar score does not provide insights into the specific mechanisms whereby a patient is at increased risk for postoperative mortality and morbidity, the index facilitates early postoperative identification of patients who warrant more intensive monitoring. This early identification has important potential value as 75% of patients who die after surgery do not receive any access to critical care resources [16].

Immediate postoperative biomarkers

Inroads are being made into using early postoperative biomarkers to further improve identification of surgical patients at elevated risk. Early postoperative elevations in troponin concentrations are consistently associated with increased mortality in noncardiac surgery [5,61,62°,63], independent of any preoperative risk factors. Importantly, this association is not just mediated by the occurrence of postoperative MI, which by definition entails an elevated troponin concentration [36]. Postoperative troponin elevations are associated with increased mortality even in the absence of a formal diagnosis of MI [27°], although this association is attenuated

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when concomitant renal impairment is present [64[•]]. Furthermore, as opposed to being only an indicator of postoperative cardiac events, troponin elevations also predict noncardiac death and complications [5,62[•]]. Routine early postoperative monitoring for troponin elevations will undoubtedly lead to increased identification of patients at risk for postoperative mortality, especially as less than 40% of patients with postoperative MI exhibit any typical cardiac symptoms such as chest pain or dyspnea [27^{••}]. Nonetheless, the appropriate clinical management of affected individuals has yet to be defined because the pathophysiological link between isolated postoperative troponin elevations (i.e., no concomitant diagnosis of MI) and mortality remains unclear.

Serial postoperative monitoring of natriuretic peptide levels may also help identify high-risk surgical patients. An individual patient data metaanalysis of 2179 patients in 18 noncardiac surgery studies found that postoperative BNP or NT pro-BNP concentrations improved prediction of death or MI at 30 days after surgery, even after accounting for both preoperative risk factors and preoperative BNP or NT pro-BNP levels [35^{••}]. Both low and elevated postoperative biomarkers levels (Table 2) appear to help identify patients with varying risk profiles after surgery [35^{••}]. An important remaining challenge is to better understand the pathophysiological link between elevated postoperative BNP or NT pro-BNP levels and mortality, which is a prerequisite to selecting appropriate interventions for affected patients.

CONCLUSION

Important progress has been made in preoperative identification of high-risk surgical patients. Longstanding and commonly used simple risk indices, such as the ASA-PS and RCRI, retain moderate predictive accuracy. Simultaneously, novel biomarkers and online risk calculators are allowing for a more rapid, accurate, and complex assessment of perioperative risk. Nonetheless, important challenges remain. More research is needed to improve assessment of preoperative functional capacity, define the appropriate use of specialized preoperative tests (e.g., CPET), and delineate how novel biomarkers should be integrated with conventional clinical risk indices. Future research must also develop methods to update estimates of risk obtained before surgery with information gathered from the operative and immediate postoperative periods, such as intraoperative clinical events (e.g., hypotension) and postoperative biomarkers. Overall, the improved ability to identify high-risk surgical patients will help ensure that limited, and potentially expensive,

perioperative monitoring and intervention resources are allocated to the relatively small subgroup of surgical patients who are most likely to benefit.

Acknowledgements

None.

Financial support and sponsorship

D.N.W. is supported in part by a New Investigator Award from the Canadian Institutes of Health Research. D.N.W. and W.S.B. are supported in part by Merit Awards from the Department of Anesthesia at the University of Toronto. W.S.B. is the Fraser Elliot Chair of Cardiac Anesthesia at the University Health Network.

Conflicts of interest

There are no conflicts of interest.

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