REVIEW

Examining Risk: A Systematic Review of Perioperative Cardiac Risk Prediction Indices

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Abstract

Objective: To conduct a systematic review of published cardiac risk indices relevant to patients undergoing noncardiac surgery and to provide clinically meaningful recommendations to physicians regarding the use of these indices.
Methods: A literature search of articles published from January 1, 1999, through December 28, 2018, was conducted in Ovid (MEDLINE), PubMed, Embase, CINAHL, and Web of Science. Publications describing models predicting risk of cardiac complications after noncardiac surgery were included and citation chaining was used to identify additional studies for inclusion.
Results: Eleven risk indices involving 2,910,297 adult patients were included in this analysis. Studies varied in size, population, quality, risk of bias, outcome event definitions, risk factors identified, index outputs, accuracy, and clinical usefulness. Studies considered 6 to 83 variables to develop their models. Among the identified models, the factors with the highest predictiveness for adverse cardiac outcomes included congestive heart failure, type of surgery, creatinine, diabetes, history of stroke or transient ischemic attack, and emergency surgery. Substantial data from the large studies also supports advancing age, American Society of Anesthesiology physical status classification, functional status, and hypertension as additional risks.
Conclusion: The risk indices identified generally fell into two groups — those with higher accuracy for predicting a narrow range of cardiac outcomes and those with lower accuracy for predicting a broader range of cardiac outcomes. Using one index from each group may be the most clinically useful approach. Risk factors identified varied widely among studies. In addition to judicious use of predictive indices, reasoned clinical judgment remains indispensable in assessing perioperative cardiac risk.

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A 78-year-old woman presents to your primary care clinic for preoperative cardiac risk assessment before elective knee replacement surgery. Her medical history includes obesity (body mass index, 38 kg/m^2), osteoarthritis, smoking, chronic obstructive pulmonary disease, a myocardial infarction (MI) 2 years ago, ischemic cardiomyopathy (left ventricular ejection fraction, 38%), type 2 diabetes mellitus (hemoglobin A1c, 9.6%, on insulin, with normal renal function), hyperlipidemia, mild aortic stenosis, hypertension, atrial fibrillation, and a transient ischemic attack (TIA) 6 years ago. She is sedentary but independent in her activities of daily living. Given her general poor health and comorbidities, you are concerned that the cardiac risk of this surgery might be unacceptably high.

You are accustomed to using the Revised Cardiac Risk Index (RCRI)[1] to risk stratify patients before surgery, and you determine that the patient is in RCRI class IV, which corresponds to a 9.1% risk of perioperative MI, ventricular arrhythmia, cardiac arrest, pulmonary edema, or complete heart block. You also use the more recently published online risk calculator by Gupta et al.[2] This calculator returns a cardiac risk of 0.8% for MI or cardiac arrest.

This scenario, in which different perioperative cardiac risk indices produce what appear to be substantially different risks for

From the Core Educator Faculty, Department of Medicine, Massachusetts General Hospital, Boston (D.E.W., S.J.K., A.N., J.L.G.); and the Treadwell Virtual Library, Massachusetts General Hospital, Boston, (L.L.P.).

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ARTICLE HIGHLIGHTS

- Worldwide, myocardial infarction and other perioperative cardiac events complicate 10 million noncardiac surgeries annually. Risk indices have been developed to aid clinicians in the preoperative assessment of their patients' cardiac risk before surgery. However, different indices often yield widely varying risk estimates, leading to uncertainty about how to advise patients and surgical colleagues.
- In this systematic review, the authors review the methodologies of 11 cardiac risk indices for noncardiac surgery and offer recommendations for their use and interpretation. The National Surgery Quality Improvement Program–based risk indices, which are derived from large numbers of patients, have high predictive accuracy, but the risk estimates they produce do not address the full spectrum of clinically relevant perioperative cardiac risks, and may not provide an adequate picture of the likelihood of potential complications to patients and clinicians.
- Despite its age and slightly lower predictive accuracy, the Revised Cardiac Risk Index is the only index identified in this review that has been both internally and externally validated, and it is being used for patient stratification in other perioperative management studies. Therefore, it remains one of the most useful indices.
- The authors recommend a two-part approach to preoperative cardiac risk stratification. First, use a high-accuracy National Surgery Quality Improvement Program-based risk index to get an accurate estimate of the risk of the most immediately life-threatening cardiac outcomes. Second, use an index such as the Revised Cardiac Risk Index to get an estimate of a broader range of risks.

the same patient, occurs frequently, and may cause significant confusion for clinicians. In this systematic review, we identify clinically usable, preoperative models for predicting the risk of cardiac complications in patients undergoing noncardiac surgery. We compare the identified indices, explain why they return differing risk estimates for the same patient, and offer guidance on how to use and interpret their results.

METHODS AND LITERATURE SEARCH

This systematic review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[3]

Literature searches were conducted by a medical librarian (L.L.P.) in the Ovid (MEDLINE), PubMed, Embase, CINAHL, and Web of Science databases in September 2015, May 2017, and December 2018 for English language articles published from January 1, 1999, through December 28, 2018. The year 1999 was chosen to include the RCRI[1] with the knowledge that some older studies[4,5] would be excluded — these studies have been supplanted by the RCRI, the oldest index still in wide use. The search strategy included free-text synonyms and controlled vocabulary for the concepts of risk models, the perioperative period, and cardiac complications. The full Ovid (MEDLINE) search strategy is available (Supplemental Table 1). Animal research, editorials, and conference abstracts were excluded using limits. In databases that use controlled vocabulary, studies classified as cardiac surgery articles were excluded from the search. Identified citations were screened independently by two authors, with disagreements resolved by a third author. Full text review was conducted independently by two authors, with disagreements resolved by discussion.

Citations were excluded if they met any of the following criteria: (1) not a risk index or was a topic review; (2) not a broad surgical population (defined by representing multiple types of surgery); (3) cardiac outcomes not studied in the model; (4) population size fewer than 500; (5) only a single factor examined in the model (Figure 1). Five studies were excluded for other reasons. Two were excluded due to reliance on intraoperative factors.[6,7] One was excluded because the methodology of the database it relied on did not count MIs as events if the patients who had them underwent revascularization.[8] One[9] was excluded because the paper does not include sufficient data on a risk index presented therein, and one[10] was excluded because the senior author was fired over allegations of scientific misconduct.[11]

Data were extracted using a spreadsheet designed for this purpose by three authors

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(D.E.W., J.L.G., S.J.K.). Where necessary, authors of included studies were contacted for clarifying information. Study quality and risk of bias were assessed by three authors (D.E.W., J.L.G., S.J.K.) using techniques adapted from published literature.[12-14]

This was an unfunded project.

RESULTS

The search identified 8832 unique citations. Screeners selected 182 articles for full text review. From this collection, 10 articles were selected for analysis.[1,2,15-22] Citation chaining, the process of finding studies that reference each other as described by Ellis,[23] identified one additional article for inclusion (Figure 1).[24]

The 11 identified risk indices together include 2,910,297 patients, representing 17,925 cardiac events or 0.0062 events/patient. The indices varied in study design and populations, operating characteristics, types and classification of surgical procedures included, definitions of and surveillance for primary cardiac outcomes being predicted, risk factors identified, risk model outputs, and event and mortality rates. Study quality and risk of bias also varied.

Study Designs and Populations

All included studies represented adult patients (mean age, 55−74 y), which, excluding the two Veterans Affairs−based studies (Kumar et al[20] and Davenport et al[15]), were evenly balanced by sex (Table 1). The studies can be classified as either moderate in size (approximately 500 to 10,000 patients; mean, 4000 patients) or large (>100,000 patients; mean, 577,000 patients).

Five studies (Davenport et al,[15] Gupta et al,[2] Bilimoria et al,[24] Kheterpal et al,[17] and Alrezk et al[19]) were conducted using National Surgical Quality Improvement Program (NSQIP) data, which was collected by trained nurses at sites across the United States using established protocols.[25] The study from Andersson et al[22] was conducted using data from Denmark's government registry of health care−related variables.[26]

The RCRI from Lee et al[1] — and modifications and validations thereof — comprised five of the six non-NSQIP studies. The model from Weber et al [21] added troponin measurements to the RCRI, Davis et al[16] substituted glomerular filtration rate for creatinine (Cr), Andersson et al[22] stratified patients by age, and Kopec et al[18] added N-terminal pro B-type natriuretic peptide (NT-proBNP) and troponin.

The number of variables examined in the multivariate models of the 11 studies varied approximately 14-fold (Figure 2A).

Two of the indices were validated only internally,[20,24] and five were not validated.[16-18,21,22] Only the index from Lee et al[1] was both internally and externally validated. The remaining three studies were externally validated (Table 2).[2,15,19] Three studies (Kumar et al,[20] Weber et al,[21] and Kopec et al[18]) specifically enrolled patients at higher cardiac risk. One study (Alrezk et al.[19]) created a submodel focusing on older patients (≥65 y). Although this author published the full model from the total population, only the geriatric substudy is available in usable form. As such, only the results of the substudy are reported here.

Operating Characteristics of the Models

The area under the receiver operating characteristic curve (AUROC), a measure of the discrimination of the risk indices,[27] was very good (0.83−0.90) for the three large NSQIP studies (Davenport et al,[15] Gupta et al[2], and Bilimoria et al[24]), and good (0.70−0.79) for the remaining studies (Figure 2B). Only four studies (Davenport et al,[15] Gupta et al,[2] Bilmoria et al,[24] and Alrezk et al[19]) reported the calibration of their models, which was good in each case (Supplemental Table 2).

Surgical Procedures and Classification

Although all studies included a wide range of noncardiac surgeries, methods of categorizing them differed (Table 1). In 9 of 11 studies, surgeries were divided into a range of 3 to 21 different categories, whereas in Bilimoria et al[24] procedures were assigned to 1557 categories using Current Procedural Terminology codes. Surgical urgency was also heterogeneous, with four of the studies (Kumar et al,[20] Davenport et al,[15] Kheterpal et al,[17] and Gupta et al[2]) including emergency surgeries whereas the studies from Lee et al,[1]

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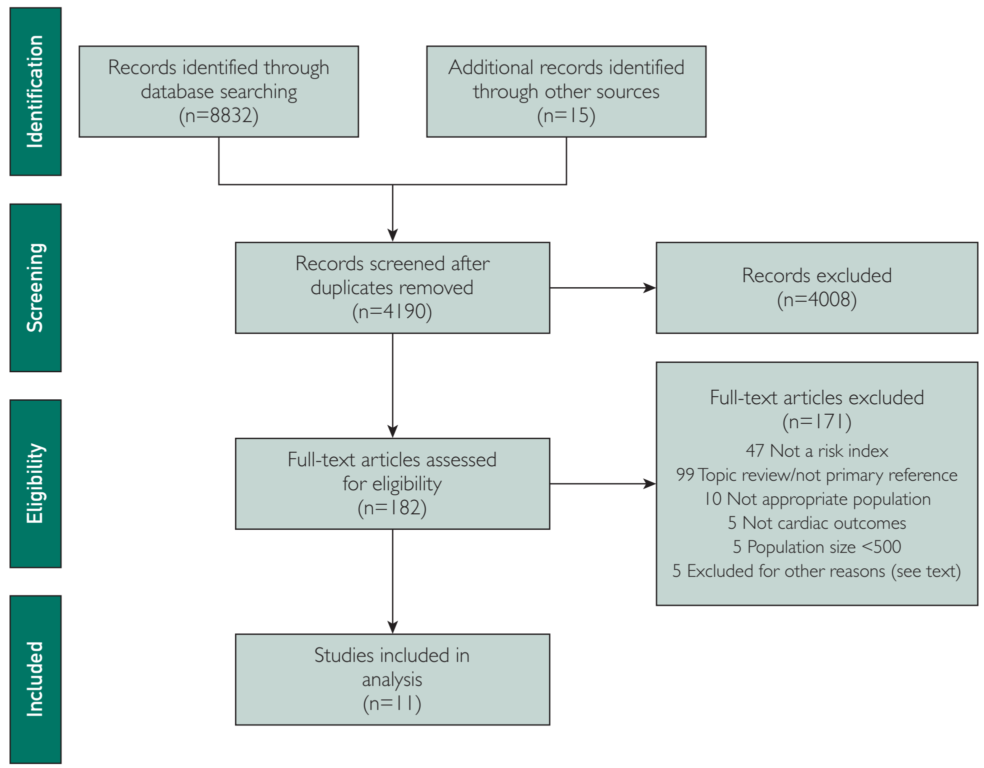

FIGURE 1. Preferred reporting items for systemic reviews and meta-analyses (PRISMA) 2009 flow diagram.

Andersson et al,[22] and Kopec et al[18] only included patients undergoing elective surgeries.

Cardiac Outcome Definitions and Identification

The definition of cardiac outcome events varied among the 11 studies (Table 1). All studies included both Q-wave and non–Q-wave MIs (including troponin elevations) except that from Davenport et al,[15] which only included Q-wave MIs. Similarly, all studies except Kopec et al[18] identified cardiac arrest. Other outcomes differed by trial, variably including ventricular dysrhythmias, pulmonary edema, acute coronary syndrome, heart failure, or heart block.

The studies also varied by method of outcome identification and duration of follow-up (Table 1). Only three of the studies (Lee et al,[1] Kumar et al,[20] and Kopec et al[18]) found cardiac events by active surveillance — the rest identified outcomes that came to clinical attention. Outcomes for the NSQIP trials were measured at 30 days. Andersson et al[22] tracked cardiovascular mortality for 30 days, but MI and stroke only in hospital. The remaining trials included endpoints during the index hospitalization only.

Risk Factors Identified

There was striking heterogeneity of risk factors identified (Supplemental Tables 2 and 3, Figure 3), and there were important differences between the small and the large studies. The small and large studies were generally in agreement in identifying congestive heart failure (CHF), type of surgery, Cr, diabetes, history of stroke or TIA, and emergency surgery as risk factors (Figures 3A and B, top cluster).

The small and large studies generally disagreed about a second group of risk factors (Figures 3A and B, middle cluster). All the

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small studies found prior MI/coronary artery disease (CAD) to be a risk factor for perioperative cardiac events. The four large NSQIP studies (Davenport et al,[15] Gupta et al,[2] Bilimoria et al,[24] and Alrezk et al[19]) did not find prior cardiac disease (generally defined in those studies as recent heart failure or angina or a history of coronary revascularization) to be a risk factor, but the large Danish national database trial (Andersson et al[22]) did. The large studies, but not the smaller ones, tended to find age, American Society of Anesthesiologists (ASA) physical status classification, dependent functional status, and hypertension to be risk factors.

Cardiac rhythm other than sinus and preoperative elevations in troponin and NT-proBNP were examined only in small studies (Figures 3A and B, bottom cluster). Troponin was found to be predictive in both studies in which it was examined, and NT-proBNP in one of the two studies.

Figure 3C shows the number of studies that find each risk factor predictive or not. No two indices produced the same set of risk factors (Supplemental Table 3).

Risk Model Outputs

Risk estimates from Gupta et al,[2] Bilimoria et al,[24] and Alrezk et al[19] are obtained from online risk calculators, whereas the rest use point scoring systems with assignment of risk classes.

Event Rates and Mortality

The event rate varied from 0.5% (Andersson et al[22] and Alrezk et al[19]) to 8.1% (Kumar et al[20]). Among the studies that provided information on mortality, the percentage of patients with events who died ranged from 8.8% to 69% (Supplemental Table 2).

Study Quality and Risk of Bias

An evaluation of study quality and risk of bias is summarized in Supplemental Table 4. The primary issues affecting the quality and risk of bias among this group of studies were: (1) a lack of clear delineation of the percent of missing follow-up data and how it was handled; and (2) the lack of blinding in some of the smaller studies with respect to reviewers knowing outcomes at the time of data extraction. From the perspective of usefulness of the models, four have external validation (Table 2, Supplemental Table 2), two are validated internally, and five are not validated. Only the index from Lee et al[1] is internally and externally validated. Four studies (Kheterpal et al,[17] Kumar et al,[20] Weber et al,[21] and Kopec et al[18]) show a risk of overfitting based on lower numbers of events per variable (Supplemental Table 2). Data are not sufficient to determine this ratio in Lee et al.[1]

DISCUSSION

We undertook this review having been challenged by how meaningfully to interpret risk estimates generated by the available perioperative cardiac risk indices. This challenge stems from the fact that the indices often yield widely disparate results for the same patient as the opening case demonstrates. To explore this problem and learn how to make the most out of the available data, we systematically reviewed the literature on cardiac risk indices currently used for patients undergoing noncardiac surgical procedures.

The 11 indices we identified showed substantial variability in patient and surgical risk factors, patient populations, operating characteristics, quality and risk of bias, as well as event type and event definitions, the use of active event surveillance, and the duration of patient surveillance and follow-up. These differences appear to explain the variability in risk that they each predict for a given patient.

There are two important ways to view these studies. They can be evaluated by their predictive accuracy, or by the clinical relevance of the variables analyzed and complications predicted. By the first metric, predictive accuracy, the large NSQIP studies are clearly superior, but clinicians may criticize their "gut validity" for not including relevant factors such as diagnosed cardiac disease. By the second metric, the smaller, lower accuracy studies retain some important advantages due to the breadth of clinically relevant outcomes they predict. Hence, we will examine the strengths and limitations of the larger, higher accuracy

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TABLE 1. Study Designs and Populations[a]

	Davenport et al[15]	Kheterpal et al[17]	Gupta et al[2]	Bilimoria et al[24]	Alrzek et al[19]	Lee et al[1]	Kumar et al[20]	Weber et al[21]	Davis et al[16]	Andersson et al[22]	Kopec et al[18b]
Number of centers	142	1	183[c], 211[d]	393	NS	1	1	8	2	NS	1
Prospective vs retrospective	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Prospective
Patients (n)	D: 91,572 V: 91,497	7740	D: 211,410 V: 257,385	1,403,137[e]	D: 210,914 V: 172,905	D: 2893 V: 1422	1000	979	9519	447,352	572
Follow-up period	30 d	30 d	30 d	30 d	30 d	Index hospitalization only	Index hospitalization only	Index hospitalization only	Index hospitalization only	30 days[f]	Post-operative days 1-3
Age, mean (y)	60	NS	55	NS	74	66[g]	66	69	66	55	65
Female (%)	20	49	57	57	58	52	1	46	49	57	38
Patient population; years of study; region	NSQIP; 2002-2004; USA	NSQIP, general, vascular, and urological surgeries; 2002-2007; single center, Michigan	NSQIP; 2007-2008[h]; USA	NSQIP; 2009-2012 [h]; USA	NSQIP; 2012-2013, USA Excludes patients <65 years old	Elective, noncardiac, non-emergent surgeries in patients ≥50 years old expected to stay ≥2 d; 1989-1994; Massachusetts	Noncardiac surgeries in VA patients with known or suspected cardiac disease; 1992-1995; Texas	Noncardiac major surgeries in patients >55 years old with at least 1 cardiovascular risk factor; 2006-2009; Germany, Switzerland, Serbia, and Spain	Noncardiac, non-emergent surgeries in patients ≥50 years old expected to stay ≥2 days; 2008-2010; Ontario, Canada	Danish National Patient Registry; 2005-2011; Denmark	Elective, noncardiac, non-laparoscopic, major surgeries under general anesthesia in patients with known CAD or multiple risk factors; 2008-2011; Missouri
Types of surgeries	39% abdominal, 18% vascular, 25% hernia, 12% "integumentary and musculoskeletal," ∼6% other	General, vascular, urologic (including emergent and aortic)	21 surgical groupings, by anatomical region	Surgeries covering 1557 CPT codes; trauma and transplant surgeries excluded	19 surgical groupings, by anatomical region (excludes cardiac surgery)	35% orthopedic, 21% vascular, 11% abdominal, 12% thoracic, 20% other[i]	25% vascular, 23% general, 19% orthopedic, 14% urologic, 18% other	26% abdominal, 26% vascular, 11% gynecologic, 8% orthopedic/trauma, 29% other	14% abdominal, 24% orthopedic, 11% thoracic, 5% vascular, 47% other	40% orthopedic, 16% abdominal, 12% gynecologic, 8% urologic, 6% neurosurgery, 6% vascular, 12% other[j]	33% vascular, 34% orthopedic, 9% gynecologic, 9% urologic, 8% ENT, 7% neurosurgery
Surgical urgency (emergent, urgent, semi-urgent, elective)	11% emergent, 62% inpatient, balance NS	12% emergent, balance NS	NS	All, except trauma and transplant surgeries	All except emergent and cardiac surgeries	Elective	4% emergent, balance NS	Emergent surgeries excluded	Urgent and emergent surgeries excluded	Elective	Elective
Surgical risk	NS	22% high risk[k]	NS	NS	NS	31% high risk[l]	7% very high risk (aortic), 37% high risk, 22% intermediate risk, 34% low risk	NS	26% high risk[l]	NS	NS
Definition of cardiac outcome event	Q-wave MI, cardiac arrest requiring resuscitation	Q-wave MI, NSTEMI, cardiac arrest requiring CPR, new cardiac dysrhythmia	MI (Q-wave MI and troponin elevation >3 times ULN), cardiac arrest	MI, cardiac arrest	MI (STEMI/Q-wave MI or troponin elevation >3 times ULN or physician diagnosis of MI), cardiac arrest	MI, pulmonary edema, VF or primary cardiac arrest, complete heart block	Cardiac death, MI, pulmonary edema, cardiac arrest, nonfatal VT and VF, unstable angina pectoris, new or worsened CHF[m]	All-cause mortality, MI, cardiac arrest or VF, need for CPR, acute decompensated heart failure	MI, pulmonary edema, primary cardiac arrest	Nonfatal MI or ischemic stroke, cardiovascular mortality	MI

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TABLE 1. Continued

	Davenport et al[15]	Kheterpal et al[17]	Gupta et al[2]	Bilimoria et al[24]	Alrzek et al[19]	Lee et al[1]	Kumar et al[20]	Weber et al[21]	Davis et al[16]	Andersson et al[22]	Kopec et al[18b]
Active postoperative event surveillance	No	No	No	No	No	Post-op CK and, if elevated, CK-MB immediately after surgery, at 8PM on the day of surgery, and on the next 2 mornings; ECG in recovery room and on post-operative days 1, 3, and 5	Post-operative ECG, then ECG, CK, CK-MB daily through post-operative day 6	No	No	No	ECG, hs-TnT, NT-proBNP for 3 days
No of variables examined in multivariate model	83	18	43	32	43	NS	15	8	6	6	8

[a]CAD = coronary artery disease; CK = creatine kinase; CK-MB = creatinine kinase—muscle/brain test; CPR = cardiopulmonary resuscitation; CPT = current procedural terminology; D = derivation set; ECG = electrocardiogram; ENT = ear nose, and throat; hs-TnT = high-sensitivity troponin T; MI = myocardial infarction; NS = not specified; NSQIP = National Surgical Quality Improvement Program; NSTEMI = non—ST-elevation myocardial infarction; NT-proBNP = N-terminal pro B-type natriuretic peptide; ULN = upper limit of normal; V = validation set; VA = Veterans Affairs; VF = ventricular fibrillation; VT = ventricular tachycardia.

[b]A post hoc analysis of the VINO trial.[6]

[c]2007, derivation cohort.

[d]2008, validation cohort.

[e]1,414,006 patients screened. The authors excluded 10,869 due to representing CPT codes with 25 or fewer cases in the data set.

[f]For cardiovascular mortality; index hospitalization only for MI and stroke.

[g]Same age in derivation and validation cohorts.

[h]Excludes trauma and transplant patients.

[i]Derivation cohort.

[j]"Other" is condensed from 17 categories.

[k]Defined as intrathoracic, intra-abdominal, and supra-inguinal vascular surgeries, excluding hernia repairs.

[l]Defined as intrathoracic, intra-abdominal, and supra-inguinal vascular surgeries.

[m]"Serious" events, as defined in the study.

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and the smaller, lower accuracy studies separately.

The Higher Accuracy Studies

Strengths. The three studies with the highest AUROC (Gupta et al,[2] Davenport et al,[15] and Bilimoria et al[24]; AUROC, 0.85—0.90) offer excellent predictive accuracy, patient and hospital diversity, and improved surgical type specificity. These large NSQIP studies are further strengthened by their standardized, audited, clinician-driven data collection methodology[25,28] and a longer endpoint follow-up period of 30 days after discharge. Two of these indices (Gupta et al[2] and Bilimoria et al[24]) have online calculators.

Limitations. The advantages afforded by the large size of these studies come at a cost. Perhaps the biggest limitation of the NSQIP studies is their narrow definitions of cardiac events. Event definitions vary in the large NSQIP studies from Q-wave MI and cardiac arrest only (Davenport et al[15] and Bilimoria et al[24]) to broader definitions that also include troponin elevations (Gupta et al[2]). However, because of the lack of active event surveillance, only events that came to clinical attention were captured, so these indices only predict cardiac arrest and symptomatic MIs. It is therefore not surprising that the 30-day death rate of patients meeting criteria for a cardiac event in the index from Davenport et al[15] was 59%, and that from Gupta et al[2] was 61%. However, among perioperative MIs, many, if not most, are asymptomatic,[29-32] with two recent studies showing troponin elevations manifesting asymptomatically in 84.2%[33] and 93.1%[34] of subjects. If asymptomatic MIs and troponin elevations were of no prognostic consequence, the failure of risk indices to predict them would not be problematic. However, among the estimated 4.6 million patients worldwide annually who have asymptomatic perioperative myocardial injury due to ischemia that does not fulfill the universal definition of MI, the estimated 30-day mortality is 7.8%.[35] Hence, the NSQIP indices lead to underestimation of perioperative asymptomatic but clinically significant myocardial injury. They also do not predict the risk of perioperative CHF and ventricular or supraventricular arrhythmias, which also have clinical significance.[36]

A second major weakness of the large NSQIP studies is that the presence of CAD was established based upon chart review identifying patients who had undergone revascularization — patients with unrevascularized CAD would have been counted as not having CAD. This definition may partly explain why the three large NSQIP indices (Davenport et al,[15] Gupta et al,[2] and Bilimoria et al[24]) do not identify CAD as a risk factor for perioperative cardiac events — a finding that challenges clinical logic — whereas the other six non-NSQIP studies do (Kheterpal et al,[17] a small single center NSQIP study, did find CAD to be a risk factor). In addition, it is not clear why the NSQIP studies do not identify severe aortic stenosis, which has been shown to be a risk factor for cardiac events in noncardiac surgery.[37]

In summary, the majority of the large NSQIP studies have high predictive accuracy for a narrow spectrum of very serious outcomes.

The Lower Accuracy Studies

Strengths. Given the statistical strength of the majority of the large NSQIP studies, one might be tempted to abandon the indices generated by the lower accuracy studies. However, these studies have meaningful strengths of their own. The widely used RCRI and related studies make up four of the smaller, lower accuracy studies in this review (Lee et al,[1] Davis et al,[16] Kopec et al,[18] and Weber et al[21]) and one of the large ones (Andersson et al[22]). In addition to validating the original index (Davis et al[16] and Andersson et al[22]), these studies extend the RCRI from Lee et al[1] by showing slightly improved predictive value of adding cardiac biomarkers (Weber et al[21] and Kopec et al[18]), substituting a glomerular filtration rate definition in place of Cr (Davis et al[16]), and stratifying the RCRI by age (Andersson et al[22]). Although individually small (except Andersson et al[22]), these updated studies are further

Mayo Clin Proc. ■ November 2019;94(11):2277-2290 ■ https://doi.org/10.1016/j.mayocp.2019.03.008
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demonstration of the value of the RCRI and are hypothesis-generating regarding efforts to refine its components. The RCRI's impact on the perioperative literature extends beyond its use in predicting risk. For example, studies examining perioperative risk reduction strategies have stratified their patient populations by RCRI class, such as trials of the value of perioperative beta-blockade.[38,39] Thus, the RCRI not only predicts risk but can also guide risk reduction interventions.

Although the AUROC of the studies in this group is lower (0.70—0.79) than the majority of the large NSQIP studies, most of them consider cardiovascular outcomes besides just symptomatic MI and cardiac arrest (e.g., biomarker elevation, stroke, arrhythmias, and CHF) that might be important to clinicians and patients. Also, in some of the studies with smaller patient populations (Lee et al,[1] Kumar et al,[20] and Kopec et al[18]), active surveillance could be undertaken to identify events that were asymptomatic though prognostically meaningful. The reported risks from these indices, therefore, may be more clinically relevant to the question of broader and longer-term cardiac risk.

A unique feature of one of the lower accuracy studies (Alrezk et al[19]) is that it is focused on geriatric patients. Within that study, the authors compared the accuracy of this model with that of the models from Gupta et al[2] and Lee et al[1] as applied to geriatric patients. They found that their model performed better than the other two in this population.

Limitations. First, the biggest weakness of this group of studies is that they have lower AUROCs, and therefore only moderate predictive accuracy. Second, smaller size and numbers of events in most of these studies limit their ability to discriminate differing risk among various surgical procedures. Third, except Kheterpal et al[17] and Alrezk et al,[19] the studies only captured events that occurred in the index hospitalization, potentially leading to an underestimation of relevant risk. Fourth, risk in the highest risk category in some of the studies is relatively low; in Kheterpal et al,[17] the highest risk category has a risk of 3.6% whereas in the RCRI, it is 9.1%. However, we know from earlier studies[5,40] and from the NSQIP indices that risk in some patients can greatly exceed these numbers. Finally, as with the large NSQIP studies, the smaller studies do not find severe aortic stenosis to be a risk factor for cardiac events in noncardiac surgery. In some (e.g., Lee et al[1]), this may be due to inadequate numbers of patients with aortic stenosis undergoing surgery.

In summary, the smaller studies have lower predictive accuracy but encompass a broader array of cardiac outcomes that may be prognostically relevant.

Which Risk Factors are Most Important?

Given that no two risk indices identified the same set of risk predictors, which are most important? For several risk factors, the small and large studies agree; for others, the small and large studies do not agree. A third group of risk factors will require more study.

A history of CHF was found to be predictive in all studies, small and large, except one (Gupta et al[2]). Similarly, type of surgery, elevated preoperative Cr, diabetes, emergency surgery, and history of stroke/TIA were found to be risk factors in most of the small and large studies.

The presence of CAD was predictive in all studies except the large NSQIP studies — we believe this is due to how CAD was defined in these studies, as discussed above, and it stands to reason that CAD is an important risk factor for perioperative cardiac events.

The studies diverged on the importance of advancing age, ASA physical status classification, dependent functional status, and hypertension, which were not supported by the small studies, but all found strong support among the large ones, leading us to conclude that they are all relevant predictors. For age (the mean in the small studies was 65-69), these studies may simply not have had enough older patients to detect increasing risk with advancing age.

Cardiac rhythm other than sinus, particularly atrial fibrillation, was examined in

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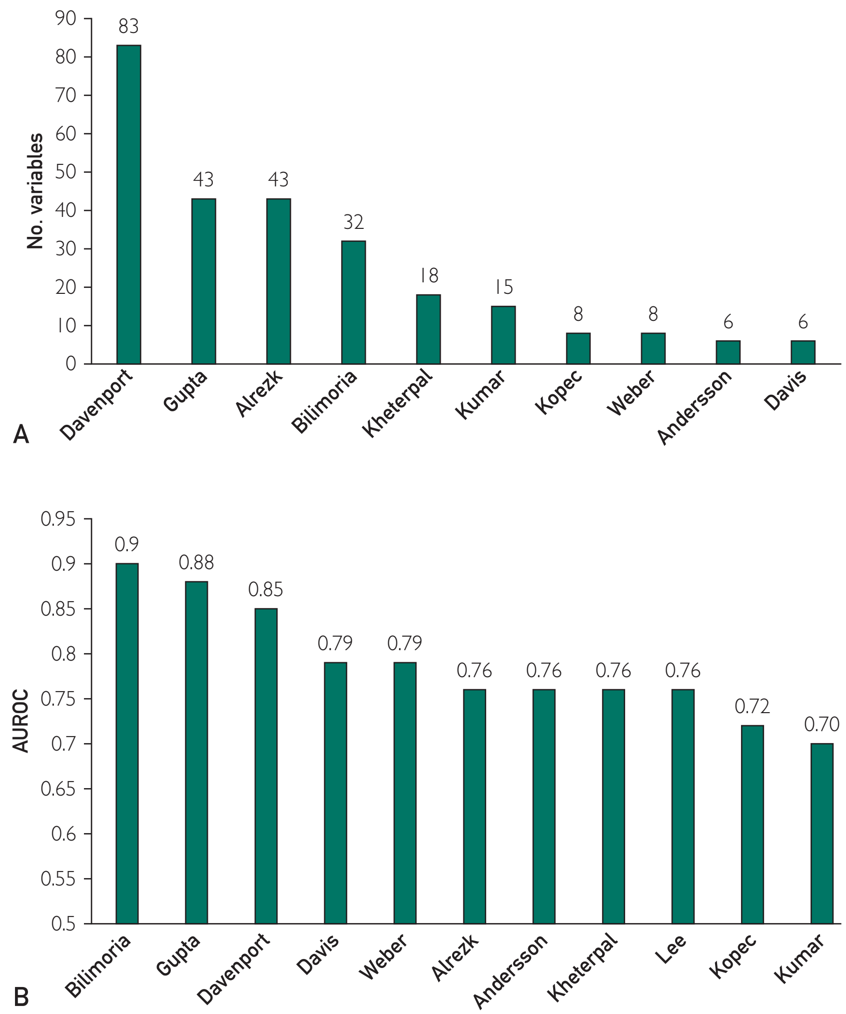

FIGURE 2. Number of variables analyzed in studies (A) (note: this information was not provided in Lee et al[1]). Area under the receiver operating characteristics curve (AUROC) (B).

four small studies but no large ones. This is of interest because rhythm other than sinus was found to be a predictive factor in early perioperative cardiac risk indices[4,5] (not included here due to their age). Newer literature also suggests that atrial fibrillation is predictive of perioperative cardiac events[41] (not included here because it was not a risk index per se). Further investigation of atrial fibrillation in a large study is needed. Elevated preoperative troponin was predictive in the two small studies in which it was assessed, and NT-proBNP was predictive in one of two small studies. Since these are easily obtainable laboratory tests that might be valuable, further study in large patient cohorts is needed.

Although numerous risk factors have been convincingly shown to independently predict perioperative cardiac risk, these risk factors are likely not be of equal weight. Although data on relative weight of various risk factors is one of the outputs of logistic regression modeling, information on the relative weight of the factors is not readily available from most of the studies. The relative importance of each variable was reported in Alrezk et al[19] —ASA physical status classification, surgical category, history of stroke, and elevated Cr; had the greatest impact.

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TABLE 2. Validation of the Included Studies

Validation Type	Risk index study
Internal and external	Lee et al[1]
Internal	Bilimoria et al[24] Kumar et al[20]
External	Alrezk et al[19] Davenport et al[15] Gupta et al[2]
None	Andersson et al[22] Davis et al[16] Kheterpal et al[17] Kopec et al[18] Weber et al[21]

In summary, we believe that CHF, CAD, type of surgery, elevated preoperative Cr, diabetes, emergency surgery, history of stroke/TIA, advancing age, ASA physical status classification, dependent functional status, and hypertension are definite significant risk factors for perioperative cardiac events. Preoperative cardiac rhythm other than sinus may be predictive, and preoperative troponin and NT-proBNP are promising but need more study.

How and When to Use the Various Indices

Given the wide differences among these indices, how should clinicians use them to advise patients contemplating noncardiac surgery? We recommend the following approach: First, to get an accurate estimate of the chance of very serious events that could occur in the perioperative period (symptomatic MI and cardiac arrest), use either of the NSQIP online risk calculators from Gupta et al[2] or Bilimoria et al.[24] Although the tool presented by Gupta et al[2] is easier to use, the calculator from Bilimoria et al[24] has the advantages of being derived from newer NSQIP data, having a slightly higher AUROC value, and providing risk estimates for several noncardiac outcomes. At this step, keep in mind that these NSQIP indices provide an accurate but incomplete picture of potential cardiac complications. The 0.8% cardiac risk that was derived for the case patient using the online calculator from Gupta et al[2] refers to symptomatic Q-wave MI, troponin elevation greater than 3 times the upper limit of normal, or cardiac arrest occurring during the index hospitalization or in the 30 days post-discharge. While perhaps appearing reassuringly low, this estimate is heavily weighted toward catastrophic events.

Second, after gaining the insight provided by a large NSQIP-based calculator, consider also using another index that provides a broader assessment of cardiac risk. Despite its age, we find the RCRI from Lee et al,[1] which is commonly used and has been both internally and independently validated, to be still the most useful of the smaller indices. The use of two indices differs from the approach recommended in the 2014 American College of Cardiology/American Heart Association Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery,[42] which advises choosing either of the risk indices from Lee et al,[1] Gupta et al,[2] or Bilimoria et al.[24] We believe that the RCRI and the NSQIP indices complement each other and recommend using two indices, especially for higher-risk patients. For geriatric patients, the index from Alrezk et al[19] may have increased accuracy. The case patient's risk was predicted to be approximately 9% using the RCRI. There was active surveillance with creatinine kinase—muscle/brain (CK-MB) test and electrocardiograms for these events in the study, so both asymptomatic and symptomatic events were identified, but 9% could still be an underestimate for the following reasons: (1) although the highest risk category in the RCRI is 9%, we know from other data[5,40,43] that risk in some patients greatly exceeds this; (2) events occurring post-discharge are not captured in the RCRI as they are in the NSQIP indices; and (3) assays of myocardial injury are now more sensitive than they were when the RCRI was developed, so if the RCRI were repeated using troponin in place of CK-MB, the reported risks would be higher (as borne out in Weber et al[21]).

Third, remember that each of these indices has limitations and that clinical judgment

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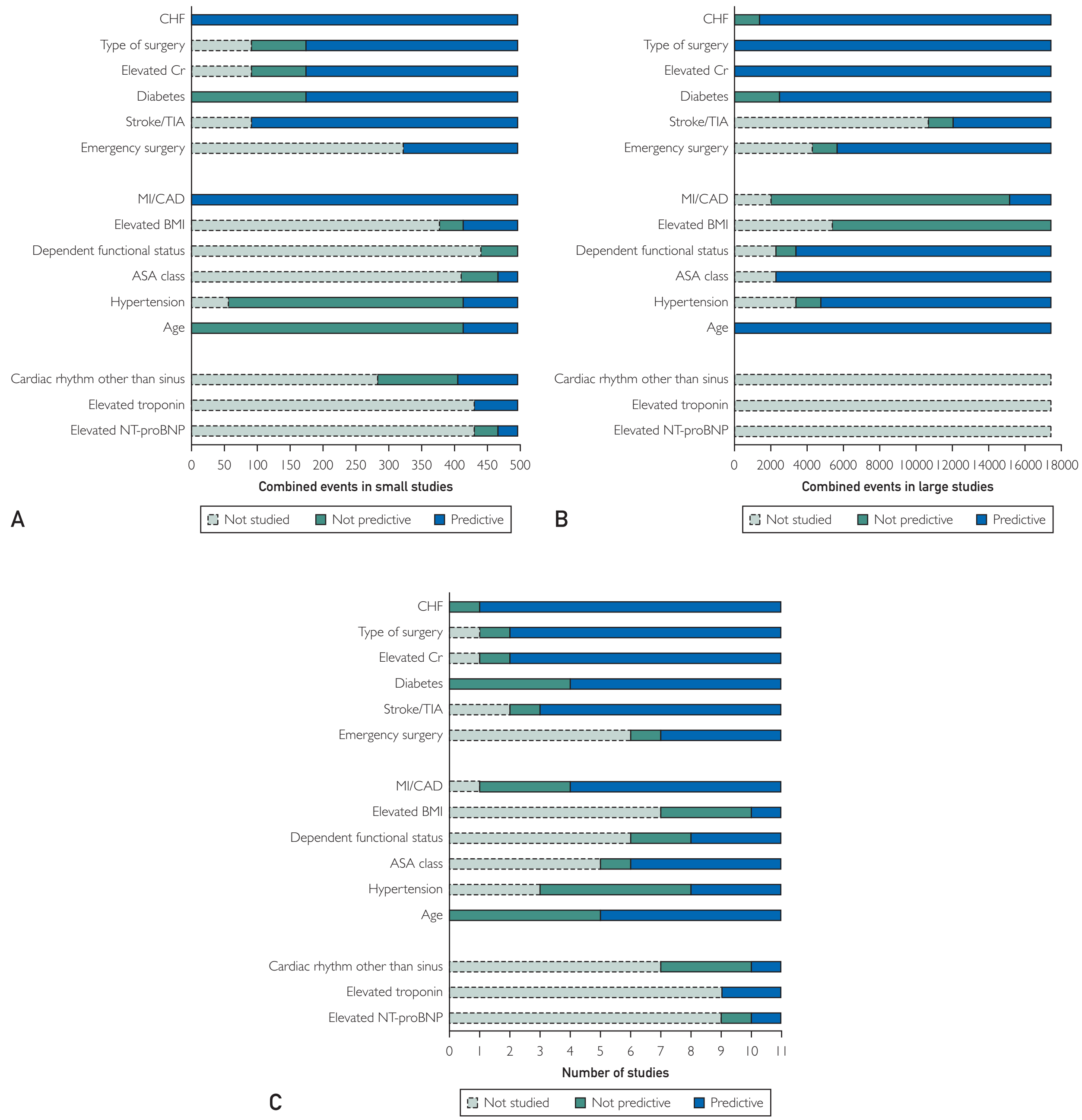

FIGURE 3. Predictiveness of risk factors in small (A) and large (B) studies, ascertained by the combined number of events in the studies. Predictiveness of risk factors in all studies (C), ascertained by whether risk factors were found to be predictive or not in particular studies. ASA = American Society of Anesthesiologists physical status classification; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; Cr = creatinine; NT-proBNP, N-terminal pro B-type natriuretic peptide; TIA = transient ischemic attack.

should always supplement and sometimes supersede what the indices predict. Given the overall morbidity of the case patient, we would consider her risk to be higher than either the index from Gupta et al[2] or the RCRI would predict and recommend a frank discussion of this information with the patient, using shared decision-making.

Mayo Clin Proc. ■ November 2019;94(11):2277-2290 ■ https://doi.org/10.1016/j.mayocp.2019.03.008
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Limitations of This Review

Our systematic review has several limitations. First, we only included English language studies published during or after 1999, the year in which the RCRI was published. We excluded indices derived from populations undergoing only one specific type of procedure (eg, hip fracture repair) as we wanted to identify models that had a sufficiently broad application. Further, our definition of a risk index may have been too limited. There are several published studies that look at a single variable (eg, a specific cardiac biomarker) as a predictor of perioperative cardiac risk. We excluded them, only including studies that considered two or more elements in the final model. Finally, because our goal was to identify studies that could be used preoperatively to estimate risk, we excluded studies with indices that relied on intraoperative variables.

CONCLUSIONS

Our systematic review identified 11 indices published since 1999 that can be used to estimate cardiac risk for patients undergoing noncardiac surgery. These studies are highly heterogeneous in their definitions of outcome events, risk factors identified, quality, risk of bias, and clinical usefulness.

The statistical strengths of the indices generated by the larger studies may, in specific situations, be eclipsed by the clinical breadth of the smaller ones. We recommend that clinicians become familiar with one of the large NSQIP indices such as Bilimoria et al[24] or Gupta et al[2] (Alrezk et al[19] may be more accurate in elderly patients), and one of the smaller studies, such as the time-tested and multiply-validated RCRI, and learn what they predict and what their operating characteristics and limitations are. When using these indices, clinical judgment remains of paramount importance.

At present, no single index combines the predictive ability of the large NSQIP indices, which are biased toward catastrophic outcomes, with the breadth of outcomes of the smaller indices. The field needs a large, prospective, multicenter study with comprehensive individualized data collection and outcome measurement that includes active surveillance for cardiac events, as well as pre- and postoperative measurement of cardiac biomarkers.

ACKNOWLEDGMENTS

The authors thank Joshua Metlay, MD, Farrin Manian, MD, Nancy Rigotti, MD, Mark Williams, MD, and Muthiah Vaduganathan, MD, for helpful discussions, and Sonya Alford for assistance.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AUROC** = area under receiver operator characteristic curve; **CAD** = coronary artery disease; **CHF** = congestive heart failure; **Cr** = creatinine; **MI** = myocardial infarction; **NSQIP** = National Surgical Quality Improvement Program; **RCRI** = Revised Cardiac Risk Index

Potential Competing Interests: The authors report no competing interests.

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