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Preoperative prediction of Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS): an international prospective cohort study

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Abstract

Background: Diagnostic criteria for Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS) have been defined as bleeding that leads to a postoperative haemoglobin <70 g L^{-1}, leads to blood transfusion, or is judged to be the direct cause of death. Preoperative prediction guides for BIMS can facilitate informed consent and planning of perioperative care.

Methods: In a prospective cohort study of 16 079 participants aged ≥45 yr having inpatient noncardiac surgery at 12 academic hospitals in eight countries between 2007 and 2011, 17.3% (2782) experienced BIMS. An electronic risk calculator for BIMS was developed and internally validated by logistic regression with bootstrapping, and further simplified to a risk index. Decision curve analysis assessed the potential utility of each prediction guide compared with a strategy of identifying risk of BIMS based on preoperative haemoglobin <120 g L^{-1}.

Results: With information about the type of surgery, preoperative haemoglobin, age, sex, functional status, kidney function, history of high-risk coronary artery disease, and active cancer, the risk calculator accurately predicted BIMS

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(bias-corrected C-statistic, 0.84; 95% confidence interval, 0.837–0.852). A simplified index based on preoperative haemoglobin <120 g L^{-1}, open surgery, and high-risk surgery also predicted BIMS, but less accurately (C-statistic, 0.787; 95% confidence interval, 0.779–0.796). Both prediction guides could improve decision making compared with knowledge of haemoglobin <120 g L^{-1} alone.

Conclusions: BIMS, defined as bleeding that leads to a postoperative haemoglobin <70 g L^{-1}, leads to blood transfusion, or that is judged to be the direct cause of death, can be predicted by a simple risk index before surgery.

Clinical trial registration: NCT00512109.

Keywords: mortality; noncardiac surgery; perioperative bleeding; prediction; risk index; transfusion

Editor's key points

- The diagnostic criteria for Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS) are defined as bleeding that leads to a postoperative haemoglobin <70 g L^{-1}, leads to blood transfusion, or is judged to be the immediate cause of death.
- Using data from a prospective study of 16 079 patients aged ≥45 yr having inpatient noncardiac surgery at 12 academic hospitals in eight countries between 2007 and 2011, an electronic risk calculator for BIMS was developed and internally validated.
- A risk calculator using information about the type of surgery, preoperative haemoglobin, age, sex, functional status, kidney function, history of high-risk coronary artery disease, and active cancer predicted BIMS.
- A simplified index based on preoperative haemoglobin <120 g L^{-1}, open surgery, and high-risk surgery also predicted BIMS, but less accurately.
- These preoperative prediction guides for BIMS should facilitate informed consent and planning of perioperative care.

More than 200 million people have major noncardiac surgery worldwide each year.[1] Significant bleeding and blood transfusion are common during and after surgery and are associated with perioperative morbidity, mortality, and resource use.[2–6] Clinical practice guidelines recommend preoperative evaluation of the risk of major bleeding, correcting preoperative anaemia when feasible, assuring that blood and blood components are available when significant blood loss or transfusion is expected, and using acute normovolaemic haemodilution for prophylaxis when major bleeding is expected.[7]

We define Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS) as bleeding that occurs either during or within the 30 days after surgery and that independently increases the 30-day probability of perioperative death. We have derived diagnostic criteria for BIMS based on their association with all-cause mortality within 30 days of noncardiac surgery.[8] The criteria include any one of: bleeding that leads to blood transfusion or a postoperative haemoglobin <70 g L^{-1}, or that is clinically judged to be the direct cause of death. BIMS diagnosed using these criteria is likely to be important to patients and clinicians, is associated with all-cause mortality within 30 days of noncardiac surgery, and may account for approximately one-quarter of deaths occurring within 30 days of major noncardiac surgery.[8] We undertook the current analysis to create clinical prediction guides for estimating a patient's risk of BIMS to aid informed consent and facilitate perioperative planning.

Methods

We published a protocol written before the analyses were undertaken.[9] Here we provide an abridged account of our methods focused on the third objective from that protocol: to create clinical prediction guides for estimating patients' risk of experiencing BIMS.

Study design and eligibility criteria

We conducted the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) prospective international cohort study that included 16 079 patients from 12 centres in eight countries throughout North and South America, Australia, Asia, and Europe from August 2007 to January 2011 (ClinicalTrials.gov NCT00512109). The research ethics board at each site approved the protocol before patient recruitment; all participants gave informed consent.

We have previously described VISION enrolment and data collection.[10–13] Study personnel asked eligible and consenting participants aged ≥45 yr who had inpatient noncardiac surgery a series of questions regarding their past medical and social history, and reviewed their medical charts for additional history. Research personnel performed clinical evaluations, reviewed medical records, and noted outcome events throughout the hospital stay. Research staff conducted a follow-up telephone interview with patients or their caregiver 30 days after surgery and contacted primary care physicians to obtain further documentation if the interview suggested the possibility of an outcome. Personnel performed central data consistency checks and on-site monitoring to ensure data integrity in all centres.

Statistical analyses

We used Stata MP version 14.2 (StataCorp, College Station, TX, USA) and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria) for all analyses. We summarised categorical data using proportions and continuous data using means and standard deviations.

Approach to missing data

We imputed missing data using single stochastic conditional imputation with logistic regression for binary variables and predicted mean matching for continuous variables.

Supplementary Box S1 in the Supplementary material lists all variables included in the imputation model.

Outcome variable

The outcome variable was BIMS, defined as bleeding that occurred either during or within 30 days after surgery and that independently increased the 30-day probability of death. The diagnostic criteria for BIMS are any one of: bleeding that leads to a blood transfusion, postoperative haemoglobin value <70 g L^{-1}, or that is clinically judged to be the direct cause of death.[8]

Predictor variables

Predictor variables included age, preoperative estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,[14] preoperative haemoglobin, sex, a preoperative haemoglobin-by-sex interaction term, requirement of assistance with activities of daily living, recent high-risk coronary artery disease, history of congestive heart failure, hypertension, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, active cancer, thoracic aorta reconstruction surgery, aorto-iliac reconstruction surgery, peripheral vascular reconstruction surgery, extracranial cerebrovascular surgery, endovascular aortic aneurysm repair, complex visceral resection general surgery, partial or total colectomy or stomach surgery, other intra-abdominal surgery, head and neck resection of non-thyroid tumour, pneumonectomy, lobectomy or other thoracic surgery, urogenital or gynaecologic visceral resection, urogenital or gynaecologic cytoreductive surgery, non-radical hysterectomy, radical hysterectomy, radical prostatectomy, transurethral prostatectomy, major hip or pelvic surgery, internal fixation of femur, knee arthroplasty, above knee amputation, lower leg amputation, craniotomy, major spine surgery, only other low risk surgery, urgent/emergent surgery, and use of open (*vs* endoscopic) surgical technique. Variable definitions are provided in the Supplementary material.

Development and internal validation of clinical prediction guides for BIMS

We first constructed a candidate logistic regression model that included all preoperative and surgical predictor variables with BIMS as the outcome variable. We used a preoperative eGFR value of 5 ml min^{-1} 1.73 m^{-2} calculated using the CKD-Epi equation for patients who were receiving dialysis preoperatively.[14] We modelled continuous variables (age, preoperative haemoglobin, and eGFR) using restricted cubic spline functions to allow for non-linearity in their relationship with BIMS. We simplified the model through backward elimination with a *P*-

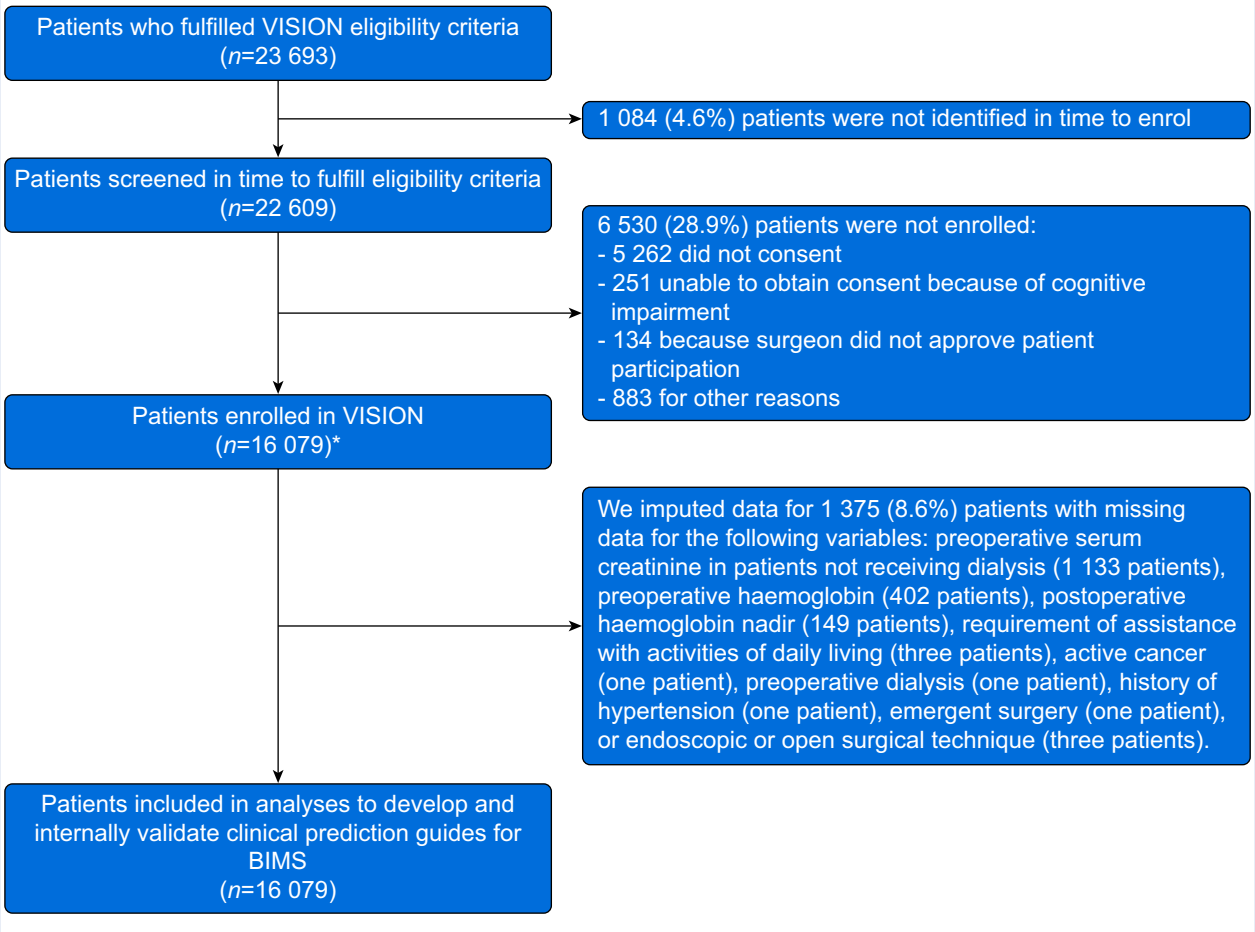

Fig 1. Participant flow. *A total of 53 (0.3%) patients did not complete the 30-day follow-up; they were censored at their date of hospital discharge. BIMS, bleeding independently associated with mortality after noncardiac surgery.

Table 1 Cohort characteristics. Data are presented as *n* (%), unless otherwise indicated.

Variables	All patients	No BIMS	BIMS
	16 079 (100)	13 297 (82.7)	2782 (17.3)
Age (yr), mean (SD)	64.8 (11.9)	63.7 (11.5)	69.7 (12.2)
eGFR (ml min^{-1} 1.73 m^{-2}), mean (SD)	78.7 (23.1)	80.4 (21.8)	70.8 (27.4)
Preoperative haemoglobin (g L^{-1}), mean (SD)	131.0 (18.9)	133.9 (17.4)	117.0 (19.5)
Women, *n* (%)	8316 (51.7)	6730 (50.6)	1586 (57.0)
Preoperative haemoglobin in women (g L^{-1}), mean (SD)	126.5 (16.3)	128.9 (15.0)	116.1 (17.4)
Preoperative haemoglobin in men (g L^{-1}), mean (SD)	135.8 (20.2)	139.0 (18.1)	118.1 (21.9)
Requires assistance with ADLs	932 (5.8)	586 (4.4)	346 (12.4)
Recent high-risk CAD	190 (1.2)	112 (0.8)	78 (2.8)
History of CHF	761 (4.7)	541 (4.1)	220 (7.9)
History of hypertension	8172 (50.8)	6489 (48.8)	1683 (60.5)
History of stroke	770 (4.8)	558 (4.2)	212 (7.6)
History of PVD	858 (5.3)	613 (4.6)	245 (8.8)
History of COPD	1337 (8.3)	1051 (7.9)	286 (10.3)
Active cancer	4222 (26.3)	3382 (25.4)	840 (30.2)
Major vascular surgery	521 (3.2)	380 (2.9)	141 (5.1)
Thoracic aorta reconstruction	27 (0.2)	16 (0.1)	11 (0.4)
Aorto-iliac reconstruction	137 (0.9)	67 (0.5)	70 (2.5)
Peripheral vascular reconstruction	200 (1.2)	149 (1.1)	51 (1.8)
Extracranial cerebrovascular surgery	96 (0.6)	90 (0.7)	6 (0.2)
Endovascular aortic aneurysm repair	70 (0.4)	61 (0.5)	9 (0.3)
Major general surgery	3210 (20.0)	2534 (19.1)	676 (24.3)
Complex visceral resection	399 (2.5)	266 (2.0)	133 (4.8)
Partial or total colectomy or stomach surgery	1081 (6.7)	772 (5.8)	309 (11.1)
Other intra-abdominal surgery	1607 (10.0)	1378 (10.4)	229 (8.2)
Head and neck resection	270 (1.7)	216 (1.6)	54 (1.9)
Major thoracic surgery	398 (2.5)	356 (2.7)	42 (1.5)
Pneumonectomy	15 (0.1)	13 (0.1)	2 (0.1)
Lobectomy	172 (1.1)	158 (1.2)	14 (0.5)
Other thoracic surgery	224 (1.4)	197 (1.5)	27 (1.0)
Major urogenital surgery	1978 (12.3)	1688 (12.7)	290 (10.4)
Visceral resection	441 (2.7)	323 (2.4)	118 (4.2)
Cytoreductive surgery	146 (0.9)	96 (0.7)	50 (1.8)
Hysterectomy	664 (4.1)	593 (4.5)	71 (2.6)
Radical hysterectomy	139 (0.9)	103 (0.8)	36 (1.3)
Radical prostatectomy	283 (1.8)	248 (1.9)	35 (1.3)
Transurethral prostatectomy	419 (2.6)	397 (3.0)	22 (0.8)
Major orthopaedic surgery	3266 (20.3)	2120 (15.9)	1146 (41.2)
Major hip or pelvic surgery	1368 (8.5)	857 (6.4)	511 (18.4)
Internal fixation of femur	421 (2.6)	228 (1.7)	193 (6.9)
Knee arthroplasty	1336 (8.3)	959 (7.2)	377 (13.6)
Above knee amputations	70 (0.4)	34 (0.3)	36 (1.3)
Lower leg amputation	74 (0.5)	43 (0.3)	31 (1.1)
Major neurosurgery	930 (5.8)	743 (5.6)	187 (6.7)
Craniotomy	457 (2.8)	382 (2.9)	75 (2.7)
Major spine surgery	473 (2.9)	361 (2.7)	112 (4.0)
Low risk surgery only	5916 (36.8)	5560 (41.8)	356 (12.8)
Urgent/emergent surgery	2313 (14.4)	1782 (13.4)	531 (19.1)
Open surgical technique	12939 (80.5)	10324 (77.6)	2615 (94.0)

ADLs, activities of daily living; BIMS, bleeding independently associated with mortality after noncardiac surgery (bleeding that led to any red blood cell transfusion, postoperative haemoglobin <70 g L^{-1}, or that was thought to be the immediate cause of death during or within 30 days after noncardiac surgery); CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate based on CKD-Epi equation; OR, odds ratio; PVD, peripheral vascular disease; SD, standard deviation.

value criterion for removal of $P>0.10$.[15] All surgical types were forced into the final model. We repeated the modelling and backward elimination procedure in each of 1000 bootstrap samples and tested each resultant version of the model on the original data, reporting model discrimination using bias-corrected C-statistic and model calibration with a calibration curve. We judged discrimination performance as poor ($0.50 \leq$C-statistic<0.70), acceptable ($0.70 \leq$C-statistic<0.80), excellent ($0.80 \leq$C-statistic<0.90), or outstanding (≥ 0.90).[16] We also reported other complementary performance measures including Nagelkerke's R^2, Brier score, and Somers' D.[17] We used this model to develop a web-based risk calculator for BIMS.

We further simplified the model into a risk index consisting of three equally-weighted risk factors that stratified patients into three risk groups for BIMS. We combined the types of surgery that significantly increased the risk of BIMS ($P<0.05$) into one 'high-risk surgery' variable. We then selected the three variables that made the greatest contribution to the prediction of BIMS for inclusion into the simplified risk index: preoperative haemoglobin, high-risk surgery, and open surgical approach. We prespecified dichotomising preoperative haemoglobin (<120 g L^{-1} *vs* ≥120 g L^{-1}) for use in the simplified index and, in *post hoc* receiver operating characteristics curve analysis, we confirmed that this threshold provided the highest C-statistic.

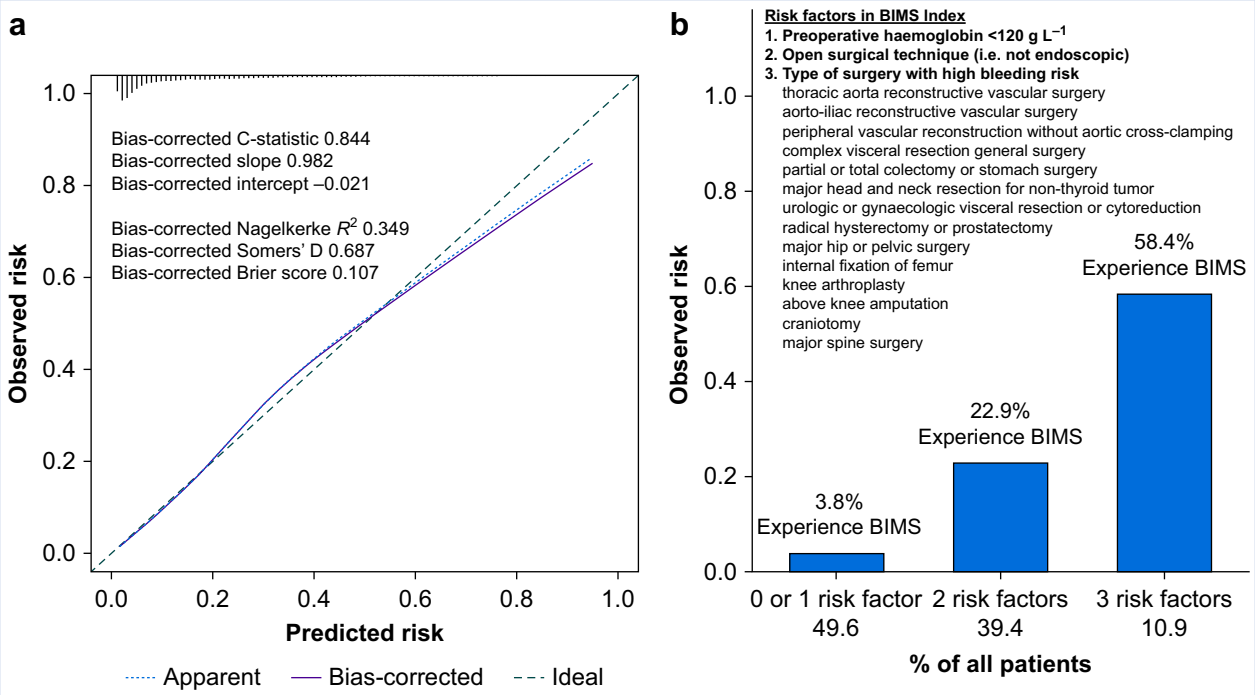

Fig 2. Performance of the BIMS risk calculator and simple BIMS risk index. (a) Performance of the BIMS risk calculator. The dashed 'ideal' line represents perfect agreement between predicted and observed risks. When the calibration curve is above the ideal line, observed risks are higher than predicted risks. When the curve is below the ideal line, observed risks are lower than the predicted risks. Internal validation in 1000 bootstrap iterations revealed minimal risk of statistical overfitting bias. There was excellent discrimination (bias-corrected C-statistic 0.844 [95% CI, 0.837–0.852]; apparent C-statistic 0.847 [95% CI, 0.839–0.854]) and calibration (i.e. strong agreement between predicted risks and observed event proportions, bias-corrected slope 0.982 [95% CI, 0.980–0.983; ideal slope 1.0], and bias-corrected intercept −0.021 [95% CI, −0.017 to −0.023; ideal intercept 0]). Bias-corrected Nagelkerke R^2 0.349 (95% CI, 0.335–0.370); bias-corrected Somers' D 0.688 (95% CI, 0.674–0.705); bias-corrected Brier score 0.107 (95% CI, 0.104–0.110). Estimates are based on 16 079 patients and 2782 BIMS events. (b) Risk predicted by the simplified BIMS risk index. This simplified risk index had good discrimination (C-statistic, 0.787; 95% CI, 0.779–0.796). Not shown: Patients with no risk factors were 12.2% of total and 1.8% (95% CI, 1.3%–2.5%) of them experienced BIMS; patients with one risk factor were 37.4% of total and 4.5% (95% CI, 4.0%–5.0%) of them experienced BIMS. BIMS, bleeding independently associated with mortality after noncardiac surgery (bleeding that led to any red blood cell transfusion, postoperative haemoglobin <70 g L^{-1}, or that was thought to be the immediate cause of death during or within 30 days after noncardiac surgery); CI, confidence interval.

We reported the C-statistic for this risk index and determined the proportion of patients in each risk class and the incidence of BIMS across the risk classes. We performed DeLong's test to compare C-statistics between the risk calculator and the simplified risk index.[18] We also performed a sensitivity analysis estimating the discrimination and calibration performance of our clinical prediction guides in the subset of patients who were not missing any predictor or outcome data.

Estimating potential clinical benefit

We used decision curve analysis to estimate the clinical net benefit that we could expect when using each prediction guide compared with an approach where all patients are treated according to the same policy irrespective of their predicted risk.[19,20] Net benefit is the difference between the proportion of patients who had true positive predictions (i.e. predicted to be at 'high risk' and developed BIMS) and the proportion of patients who had false positive predictions (i.e. predicted to be at 'high risk' but did not develop BIMS), where that difference is adjusted for the relative value that decision makers place on true positives relative to false positives. Decision curve analysis is based on the assumption that the threshold risk of BIMS (referred to as the 'minimum clinically important risk' [MCIR]) reflects how a decision maker (patient or clinician) weighs the relative harms of a false positive and a false negative prediction. Because clinicians may estimate the risk of major bleeding based on preoperative haemoglobin values alone, we also estimated the expected net benefit when patients with preoperative haemoglobin <120 g L^{-1} are treated differently from patients with haemoglobin ≥120 g L^{-1}. The Supplementary material provides further details about the decision curve analysis methods.

Sample size

BIMS occurred in 2782 patients in our dataset.[8] Simulation studies suggest that this number of events would allow us to evaluate 100–200 predictor variables without significant risk of statistical overfitting bias[21,22]; we evaluated 41.

Results

Figure 1 summarises the flow of participants through the study; Table 1 describes their characteristics. We completed

30-day follow-up for 99.7% of 16 079 patients; the other 53 patients (0.3%) were censored at the time of hospital discharge.

BIMS occurred in 17.3% of patients (2782 of 16 079 patients; 95% confidence interval [CI], 16.7%–17.9%). Among them, 99.2% (2761 of 2782 patients) received a red blood cell transfusion (95% CI, 98.8%–99.5%), 15.9% had a documented postoperative haemoglobin <70 g L^{-1} (442 of 2782 patients; 95% CI, 14.6%–17.3%), and 0.5% (13 of 2782 patients; 95% CI, 0.3%–0.8%) had bleeding that was judged as the immediate cause of death.

BIMS risk calculator

Of the 41 candidate predictor variables evaluated, 35 were retained in the final model after the backward elimination procedure (Supplementary Table S1). These represent nine information items: seven preoperative patient characteristics (preoperative haemoglobin, age, sex, functional status, kidney function, history of recent high-risk coronary artery disease, and active cancer), the type of surgery, and the use of an open *vs* endoscopic or endovascular surgical approach.

Preoperative haemoglobin concentration was the strongest predictor of BIMS. The relationship between preoperative haemoglobin and BIMS (Supplementary Fig. S1a) was non-linear (*P*-value for non-linearity <0.001), with the risk of BIMS increasing more rapidly with lower haemoglobin concentrations. This relationship differed quantitatively in men compared with women (*P*-value for interaction=0.03), with lower haemoglobin concentrations conferring a higher risk of BIMS in men than in women.

The relationship between kidney function (eGFR) and BIMS was also non-linear (*P*-value for nonlinearity <0.001), with the risk of BIMS only increasing with eGFR<80 ml min^{-1} 1.73 m^{-2} (Supplementary Fig. S1b). The risk of BIMS increased linearly with age (*P*-value for non-linearly=0.90, Supplementary Fig. S1c).

The final model predicted BIMS accurately (Fig. 2a). Internal validation across 1000 bootstrap samples showed excellent discrimination (bootstrap bias-corrected C-statistic, 0.844; 95% CI, 0.837–0.852). The apparent C-statistic before bias correction with bootstrapping was 0.847 (95% CI, 0.839–0.854). Calibration was excellent with strong agreement between predicted and observed risk throughout a wide range of predicted risks. These findings suggest that the risk of statistical overfitting bias is negligible. Bias-corrected Nagelkerke R^2 was 0.349 (95% CI, 0.335–0.370); Somers' D 0.688 (95% CI, 0.674–0.705); Brier score 0.107 (95% CI, 0.104–0.110). The full equation is available in Supplementary Box S2 and has been

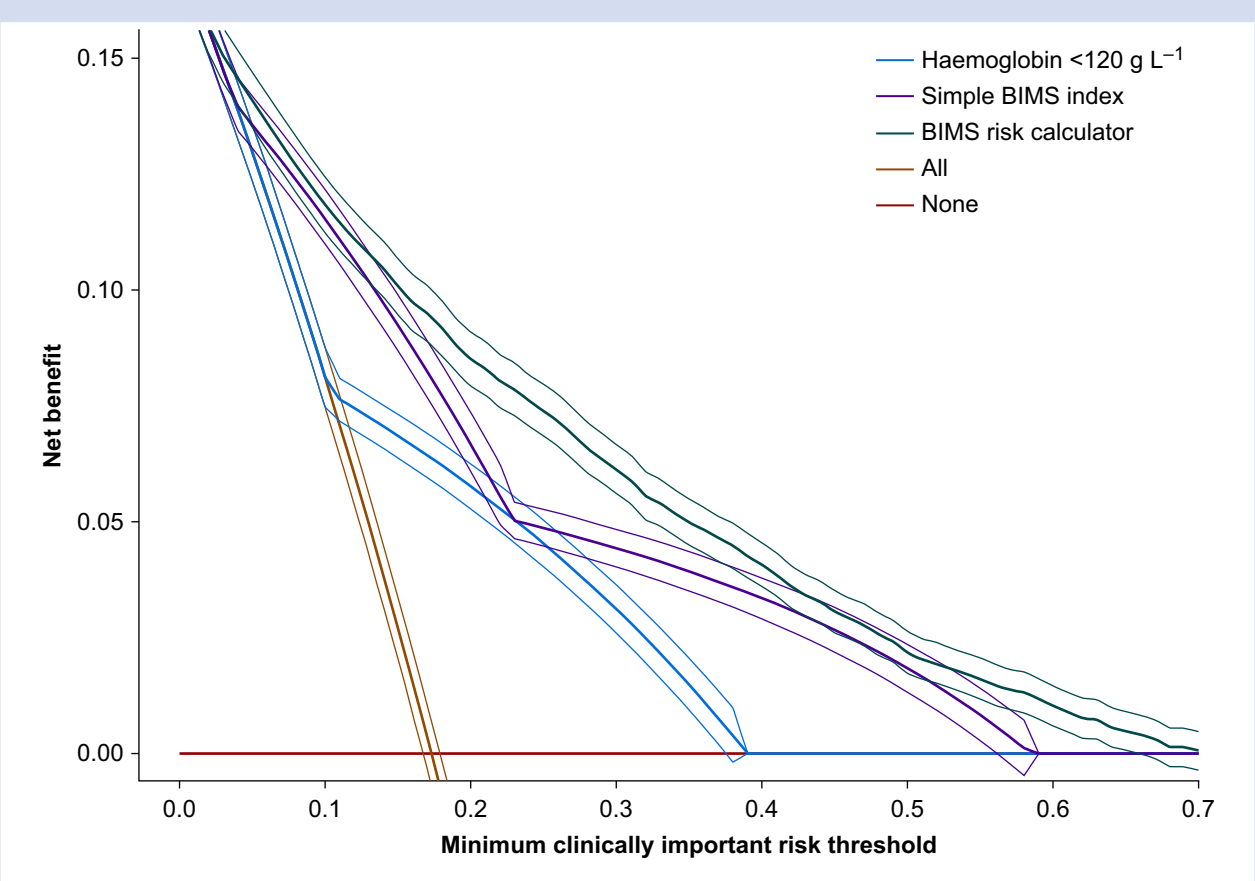

Fig 3. Decision curve analysis. For minimum clinically important risk thresholds >5%, decisions are better informed by the multivariable risk calculator and the simple risk index than by a haemoglobin threshold <120 g L^{-1} alone. The risk calculator is consistently more informative than the risk index when the minimum clinically important risk threshold is between 15% and 70%. Below minimum clinically important risk thresholds of 15%, the BIMS risk calculator and the simple risk index are similarly informative. Thick solid lines represent point estimates; thin solid lines represent 95% confidence intervals estimated across 1000 bootstrap samples. BIMS, bleeding independently associated with mortality after noncardiac surgery.

incorporated into a web-based risk calculator (http://perioperativerisk.com/BIMS).

BIMS risk index

We simplified the risk calculator to a risk index that divides patients into categories of risk for BIMS based on the sum of three risk factors. Supplementary Table S2 lists the relative contribution to the prediction of BIMS made by the variables considered for inclusion in the simplified BIMS risk index. The selected variables were preoperative haemoglobin <120 g L^{-1} (24.3% of patients; 95% CI, 23.6%–25.0%), open surgical approach (80.5%; 95% CI, 79.9%–81.0%), and high bleeding risk surgery (44.2%; 95% CI, 43.5%–45.0%). High bleeding risk surgery included any of: thoracic aorta reconstructive vascular surgery, aorto-iliac reconstructive vascular surgery, complex visceral resection, partial or total colectomy or stomach surgery, major head and neck resection of non-thyroid tumour, major urologic visceral resection, urologic cytoreductive surgery, radical hysterectomy, radical prostatectomy, major hip or pelvic surgery, internal fixation of femur, knee arthroplasty, above-knee amputation, craniotomy, and major spine surgery involving multiple levels of the spine. We selected these types of surgery because they were positively associated ($P<0.05$) with BIMS in the full candidate model described in Supplementary Table S1 and combined them into a single 'high-risk surgery' variable.

BIMS occurred in 3.8% (95% CI, 3.4–4.3) of patients with none or one of these risk factors, 22.9% (95% CI, 21.9–23.9) of patients with two risk factors, and 58.4% (95% CI, 56.1–60.7) of patients with all three risk factors (Fig. 2b). This simplified risk index had acceptable discrimination (C-statistic, 0.787; 95% CI, 0.779–0.796), but this was lower than the risk calculator ($P<0.001$).

The models performed similarly in the subset of patients without missing data as they did in the main analysis where missing data were imputed (Supplementary Fig. S2).

Clinical net benefit

Decision curve analysis suggested that using either the BIMS risk calculator or simplified risk index would lead to greater net benefit (i.e. net true positive predictions adjusted for preference-weighted false positive predictions) for decision makers whose MCIR threshold lies above 5% (i.e. one patient with BIMS for every 20 patients having surgery) than using preoperative haemoglobin <120 g L^{-1} alone. That is, all but the most risk-averse decision makers would be better served using these multivariable prediction guides than basing decisions on haemoglobin <120 g L^{-1} alone (Fig. 3). Compared with the simple BIMS risk index, the BIMS risk calculator leads to a greater net benefit for decision makers whose MCIR threshold is greater than 15%. For decision makers who are more risk-averse (i.e. those who would alter their decisions at lower risk thresholds), the simple BIMS risk index provides similar net benefit to the risk calculator (Fig. 3).

Discussion

Principal findings

BIMS defined as bleeding that results in a red blood cell transfusion, a postoperative haemoglobin <70 g L^{-1}, or immediate death, is common, but its incidence varies with preoperative patient characteristics and type of surgery. With information about the type of surgery and six commonly known preoperative patient characteristics (age, functional status, preoperative haemoglobin, kidney function, recent history of high-risk coronary artery disease, and active cancer), we developed a web-based risk calculator accessible on desktop and mobile devices (www.perioperativerisk.com/BIMS) that accurately estimated risk of BIMS with negligible evidence of overfitting bias. An index of three preoperative factors (preoperative haemoglobin <120 g L^{-1}, open surgery, and surgery with a high risk-of-bleeding) also predicted BIMS with acceptable performance.

Strengths and weaknesses of the study

This prospective study used systematic monitoring of perioperative complications and attention to data quality which included central data consistency checks and on-site monitoring to ensure adherence to variable definitions. The study included a large sample from multiple countries and a variety of urgent and elective surgical procedures, nearly complete 30-day follow-up, little missing data that were imputed to minimise bias, and rigorous statistical methods to maximise the predictive value of commonly available preoperative information.

Our prediction guides for BIMS performed well but have yet to be externally validated. However, these guides represent a large sample from 12 centres in eight countries, strengthening our confidence in their generalisability. In contrast, previous studies that have attempted to predict perioperative bleeding in noncardiac surgery have been small and often limited to a single centre and type of surgery.[23–29] Our data do not directly inform risk in patients younger than 45 yr, but we do not have reason to believe that the simplified BIMS risk index would not predict in younger patients.

Our clinical prediction guides should not supplant clinical expertise for assessing the risk of bleeding. For example, we did not collect information regarding the history of bleeding, coagulopathy, liver disease, or platelet count or function. Surgeon experience and the varying complexities of a surgical procedure (both expected preoperatively and experienced intraoperatively) within the same general category can influence bleeding risk. Variation in transfusion practices will also influence the proportion of patients who meet the diagnostic criteria for BIMS. Despite these challenges, it was possible to predict BIMS in this international study conducted over several years.

Preoperative haemoglobin was the strongest predictor of BIMS. Although we dichotomised haemoglobin at <120 g L^{-1} in the simplified BIMS risk index, there was a continuous relationship between preoperative haemoglobin and risk of BIMS without a true threshold value. This dichotomisation reduces prediction performance but is avoided with use of the full risk calculator.

Implications for practice

Prediction of BIMS can inform healthcare providers and patients about the risks of surgery. Specialised surgeons who perform a limited number of procedures may have more confidence in estimating the bleeding risk associated with these procedures, but may still find use for quantitative tools when communicating risks to patients. Such tools, however, may be particularly helpful for anaesthesiologists, haematologists, cardiologists, and general practitioners involved in preoperative assessment and perioperative care.

Prediction of BIMS could direct measures to prevent it. Practice guidelines for perioperative blood management recommend measures to reduce the risk of major bleeding and blood transfusion.[7] Selecting patients appropriately for preoperative risk optimisation requires estimating their risks;

however, the values and preferences of decision makers (patients and clinicians) vary. For example, risk-averse decision makers may be willing to delay surgery until preoperative anaemia is corrected, while others may place greater value on prompt surgery while accepting a higher risk of BIMS. Compared with using a preoperative haemoglobin threshold of <120 g L^{-1} to identify patients at high risk of BIMS, using either one of these clinical prediction guides would provide more informative predictions in all patients except those who would consider a predicted risk of BIMS ≥5% to be high risk.

Conclusions

This large, international, prospective cohort study demonstrated that BIMS, defined as bleeding that leads to blood transfusion, postoperative haemoglobin concentration <70 g L^{-1}, or that is clinically judged to be the direct cause of death, can be accurately predicted before surgery based on the type of surgery and specific patient characteristics. Our prediction guides should not supersede clinical judgement and may underestimate the risk in patients with coagulopathy, liver disease, and low platelet counts or impaired platelet function.

Authors' contributions

Statistical analysis, full access to all the data, responsibility for the integrity of the data and the accuracy of the data analysis: PSR
Study concept and design: PSR, JWE, MC, VT, FKB, CK, AL, RW, BMB, WS, GHG, MP, JS, AXG, MM, TVH, PAK, JdB, MW, DIS, YLM, TS, JHP, LT, MRIS, RM, SR, PJD
Acquisition, analysis, or interpretation of data: all authors
Drafting of the manuscript: PSR
Critical revision of the manuscript for important intellectual content: all authors
Accountable for all aspects of the work: all authors
Approved the version to be published: all authors

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Appendix A. Supplementary data

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