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Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS): an international prospective cohort study establishing diagnostic criteria and prognostic importance

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Abstract

Background: We aimed to establish diagnostic criteria for bleeding independently associated with mortality after noncardiac surgery (BIMS) defined as bleeding during or within 30 days after noncardiac surgery that is independently associated with mortality within 30 days of surgery, and to estimate the proportion of 30-day postoperative mortality potentially attributable to BIMS.

Methods: This was a prospective cohort study of participants ≥45 yr old having inpatient noncardiac surgery at 12 academic hospitals in eight countries between 2007 and 2011. Cox proportional hazards models evaluated the adjusted relationship between candidate diagnostic criteria for BIMS and all-cause mortality within 30 days of surgery.

Results: Of 16 079 participants, 2.0% (315) died and 36.1% (5810) met predefined screening criteria for bleeding. Based on independent association with 30-day mortality, BIMS was identified as bleeding leading to a postoperative haemoglobin <70 g L^{-1}, transfusion of ≥1 unit of red blood cells, or that was judged to be the cause of death. Bleeding independently associated with mortality after noncardiac surgery occurred in 17.3% of patients (2782). Death occurred in 5.8% of patients with BIMS (161/2782), 1.3% (39/3028) who met bleeding screening criteria but not BIMS criteria, and 1.1% (115/10

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269) without bleeding. BIMS was associated with mortality (adjusted hazard ratio: 1.87; 95% confidence interval: 1.42–2.47). We estimated the proportion of 30-day postoperative deaths potentially attributable to BIMS to be 20.1–31.9%.
Conclusions: Bleeding independently associated with mortality after noncardiac surgery (BIMS), defined as bleeding that leads to a postoperative haemoglobin <70 g L^{-1}, blood transfusion, or that is judged to be the cause of death, is common and may account for a quarter of deaths after noncardiac surgery.
Clinical trial registration: NCT00512109.

Keywords: anaemia; mortality; noncardiac surgery; perioperative bleeding; postoperative outcome; transfusion

Editor's key points

- Current definitions of bleeding were developed without systematically considering the independent association of diagnostic criteria for bleeding with patient outcomes.
- A large data set of 16 079 participants in the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation study was analysed to establish diagnostic criteria for bleeding independently associated with mortality after noncardiac surgery (BIMS), and to estimate its incidence and prognostic importance.
- Based on independent association with 30-day mortality, BIMS was identified as bleeding leading to a postoperative haemoglobin <70 g L^{-1}, transfusion of ≥1 unit of red blood cells, or bleeding judged to be the cause of death.
- BIMS was common, occurring in 17% of participants, and was associated with mortality with an estimated 20–32% of 30-day postoperative deaths potentially attributable to BIMS.

More than 200 million people have major noncardiac surgery worldwide each year.[1] Despite innovations in safety, millions of these patients die within 30 days of surgery. Perioperative bleeding may represent a target in the effort to reduce perioperative mortality. Some patients may experience bleeding that, if not directly fatal, initiates a cascade of postoperative complications or further complicates a tumultuous postoperative course ending in death. Prior studies have shown that bleeding is associated with perioperative morbidity, mortality, and resource use[2–6]; however, it remains unclear what kind of bleeding independently increases risk of mortality in noncardiac surgery. Current definitions of bleeding[7,8] were developed without systematically considering the independent association of diagnostic criteria for bleeding with patient outcomes.[9]

We defined 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 performed this study to establish diagnostic criteria for BIMS, the incidence of BIMS, and the prognostic importance of BIMS in terms of the proportion of 30-day mortality that it explains.

Methods

The research ethics board at each site approved the study protocol before recruitment. All participants gave informed consent before taking part in the study.

We prespecified the current analyses in a published protocol written before undertaking the analyses.[10] Clinical prediction guides for BIMS are reported in an accompanying paper.[11]

Study design and eligibility criteria

The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) prospective international cohort study 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).[12–15] We enrolled patients aged ≥45 yr having inpatient noncardiac surgery during the day or night on weekdays or weekends through daily screening of patient lists in preoperative assessment clinics, surgical lists, lists in surgical wards and in ICUs, and in preoperative holding areas. In centres where surgical volume exceeded recruitment capacity, we recruited patients on randomly selected weeks or randomly selected surgical services proportional to the prevalence of the types of surgery at each centre. Participants answered a series of questions regarding their past medical and social history. Study personnel reviewed medical charts for additional history. Research personnel performed clinical evaluations, reviewed medical records, and noted outcome events throughout the hospital stay. Staff conducted a follow-up telephone interview with patients or their caregiver 30 days after surgery. If the interview suggested the possibility of an outcome, staff contacted primary care physicians to obtain further documentation. Data monitoring involved central data consistency checks and on-site monitoring for all centres.

The VISION study collected data to address multiple objectives, including to investigate the relationship between bleeding and mortality. A potentially important bleeding event was captured when the local investigators, from documentation by the clinical team, suspected bleeding and found that this bleeding either (i) caused a decrease in haemoglobin of at least 30 g L^{-1} from the level before the bleeding event; (ii) led to transfusion of red blood cells, plasma, platelets, or cryoprecipitate; (iii) led to reoperation for reasons of bleeding; or (iv) was thought to be the cause of death. These screening criteria were designed to prevent capturing events largely caused by iatrogenic haemodilution.

Statistical analyses

We used Stata MP version 14.2 (Stata Statistical Software, College Station, TX, USA) for these analyses. Where specified in Fig 1, we imputed missing data using single stochastic conditional imputation. Supplementary Box S1 lists all variables included in the imputation model. We excluded patients

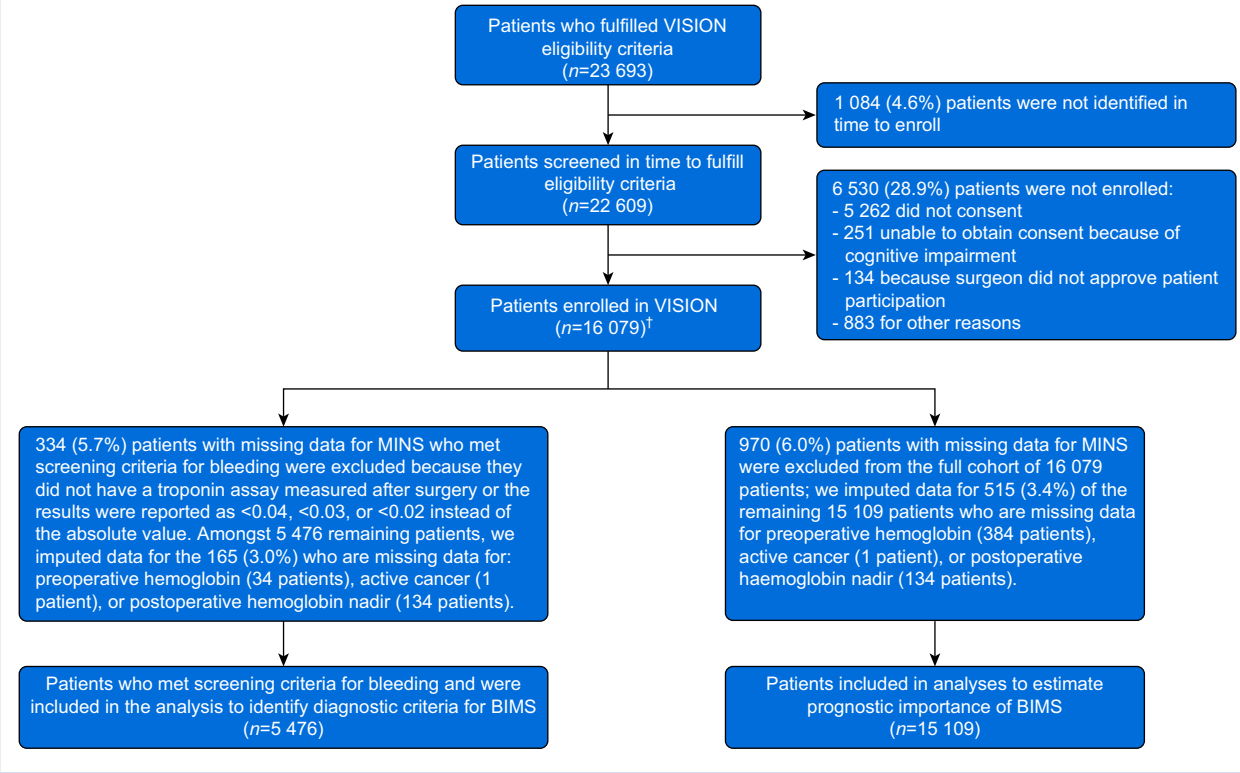

Fig. 1. Participant flow. *Fifty-three (0.3%) patients did not complete the 30-day follow-up; they were censored at their date of hospital discharge. BIMS, bleeding independently associated with mortality after noncardiac surgery; MINS, myocardial injury after noncardiac surgery; VISION, Vascular Events In Noncardiac Surgery Patients Cohort Evaluation.

who were missing troponin values necessary to diagnose myocardial injury after noncardiac surgery (MINS)[13] because we adjusted for MINS in our analyses.

Analysis for Objective 1: establishing diagnostic criteria for BIMS

We restricted the analysis for this objective to patients who met screening criteria for potentially important bleeding. If a patient experienced more than one bleeding episode, we evaluated only the first episode in all analyses.

We studied the association between five candidate BIMS diagnostic criteria as the independent variables (Supplementary Table S1) and time (in days) to death occurring up to 30 days after surgery as the dependent variable using iterative shared (by study centre) frailty multivariable Cox regression models. These models were adjusted for the variables listed in Supplementary Table S1, which included preoperative patient characteristics, surgical factors (i.e. type and timing of surgery), and postoperative complications (i.e. sepsis, pulmonary embolism, stroke, and MINS) that occurred before the day of the bleeding event.

Candidate criteria considered for inclusion in the diagnostic criteria for BIMS were selected for their potential relationship with mortality, ability to reflect severity of bleeding, and ease of ascertainment. They were assessed using the algorithm in Supplementary Fig S1, with factors being introduced into multivariable models in the following order: (i) the patient underwent reoperation for reasons of bleeding, (ii) the number of units of red blood cells transfused, (iii) the lowest (nadir) postoperative haemoglobin, (iv) the absolute decrease in haemoglobin from the preoperative value, and (v) the relative (percentage) decrease in haemoglobin from the preoperative value. Supplementary Table S2 provides rationale for this order. If a candidate criterion was significantly associated with mortality, we retained it in the model and added the next candidate criterion for testing to determine its independent association with mortality beyond that of the criteria already retained; if not significantly associated with mortality, we removed it from the model before testing the next candidate.

We predefined BIMS as bleeding that met any of the bleeding criteria that were retained in the multivariable model, and bleeding that was thought to be the cause of death by the patient's clinical team. We included the latter because massive bleeding may lead to death before other criteria could be met. In a prespecified sensitivity analysis, we repeated the analysis to identify diagnostic criteria for BIMS after adjusting for additional types of surgery (i.e. major vascular surgery, major thoracic surgery, major orthopaedic surgery, and major urological or gynaecological surgery).

Analysis for Objective 2: estimating the prognostic importance of BIMS

We performed this analysis in all patients (i.e. whether they met bleeding criteria or not). We estimated the independent association between BIMS (as a time-varying covariate) and 30-day mortality in a shared frailty Cox regression model. The model was adjusted for the same adjustment variables used in the BIMS diagnostic criteria selection models, with

Table 1 Cohort characteristics. ADL, 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 cause of death during or within 30 days after noncardiac surgery); CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; MINS, myocardial injury after noncardiac surgery; PE, pulmonary embolism; PVD, peripheral vascular disease

Variable	All patients, *n* (%)	Patients who did not fulfil predefined screening criteria for bleeding, *n* (%)	Patients who fulfilled predefined screening criteria for bleeding, *n* (%)
n	16 079 (100)	10 269 (63.9)	5810 (36.1)
Age (yr)			
45–64	8205 (51.0)	5743 (55.9)	2462 (42.4)
65–74	3990 (24.8)	2417 (23.5)	1573 (27.1)
≥75	3884 (24.2)	2109 (20.5)	1775 (30.6)
Preoperative haemoglobin (g L^{-1})			
≥140	5741 (35.7)	3699 (36.0)	2042 (35.1)
120–139	6430 (40.0)	4317 (42.0)	2113 (36.4)
100–119	2893 (18.0)	1791 (17.4)	1102 (19.0)
<100	1015 (6.3)	462 (4.5)	553 (9.5)
Requires assistance with ADL	932 (5.8)	455 (4.4)	477 (8.2)
Recent high-risk CAD	190 (1.2)	96 (0.9)	94 (1.6)
History of stroke	770 (4.8)	459 (4.5)	311 (5.4)
History of PVD	858 (5.3)	471 (4.6)	387 (6.7)
History of COPD	1337 (8.3)	756 (7.4)	581 (10.0)
Active cancer	4222 (26.3)	2497 (24.3)	1725 (29.7)
Major vascular surgery	521 (3.2)	255 (2.5)	266 (4.6)
Major general surgery	3210 (20.0)	1946 (19.0)	1264 (21.8)
Major thoracic surgery	398 (2.5)	279 (2.7)	119 (2.0)
Major urogenital surgery	1978 (12.3)	1227 (11.9)	751 (12.9)
Major orthopaedic surgery	3266 (20.3)	910 (8.9)	2356 (40.6)
Major neurosurgery	930 (5.8)	533 (5.2)	397 (6.8)
Urgent/emergent surgery	2313 (14.4)	1502 (14.6)	811 (14.0)
Death within 30 days postoperatively	315 (2.0)	115 (1.1)	200 (3.4)
MINS within 30 days postoperatively			
None	13 912 (92.1)	9124 (94.7)	4788 (87.4)
Before bleeding	219 (1.4)	509 (5.3)	219 (4.0)
After bleeding	978 (6.5)	0 (0.0)	469 (8.6)
Sepsis within 30 days postoperatively			
None	15 200 (94.5)	10 077 (98.1)	5123 (88.2)
Before bleeding	141 (0.9)	192 (1.9)	141 (2.4)
After bleeding	738 (4.6)	0 (0.0)	546 (9.4)
PE within 30 days postoperatively			
None	15 979 (99.4)	10 247 (99.8)	5732 (98.7)
Before bleeding	11 (0.1)	22 (0.2)	11 (0.2)
After bleeding	89 (0.6)	0 (0.0)	67 (1.2)
Stroke within 30 days postoperatively			
None	15 987 (99.4)	10 239 (99.7)	5748 (98.9)
Before bleeding	16 (0.1)	30 (0.3)	16 (0.3)
After bleeding	76 (0.5)	0 (0.0)	46 (0.8)

postoperative complications (i.e. MINS, sepsis, pulmonary embolism, and stroke) treated as time-varying covariates. We estimated the percentage of deaths potentially attributable to BIMS (i.e. the population attributable risk fraction), to other perioperative complications, and to patient and surgical characteristics independently associated with mortality. We repeated this analysis without adjustment for MINS, sepsis, pulmonary embolism, or stroke because, for some patients, these complications may be the result of bleeding or its management. Population attributable risk fractions that are adjusted and unadjusted for these complications provide minimum and maximum estimates of the percentage of 30-day mortality potentially attributable to BIMS.

We tested the proportional hazards assumption using tests of Schoenfeld residuals. If these tests suggested violation ($P<0.05$) for any variables in the multivariable model, we added interactions terms between the affected variables and post-operative day to the model, and compared the hazard ratios in our prespecified model to this extended model in a sensitivity analysis to determine if violations appreciably impacted the results.

We separately estimated the incidence and adjusted association of BIMS with 30-day mortality in the following predefined subgroups: age <75 *vs* ≥75 yr, preoperative haemoglobin <120 *vs* ≥120 g L^{-1}, men *vs* women, known coronary artery disease *vs* no known coronary artery disease, and those with *vs* without recent high-risk coronary artery disease. We interpreted a subgroup effect as significant if BIMS was significantly positively associated with mortality (adjusted hazard ratio [aHR] >1.0; $P<0.05$) in one of the subgroups but not the other, and there was a statistically significant test of interaction ($P<0.01$).

In *post hoc* analyses, we compared the adjusted association between each of the following types of BIMS and 30-day perioperative mortality: BIMS occurring intraoperatively or on the day of surgery *vs* BIMS occurring on postoperative Days 1–30; BIMS occurring intraoperatively, on the day of surgery, or on

postoperative Day 1 *vs* BIMS occurring on postoperative Days 2–30; and BIMS occurring at the surgical site *vs* BIMS occurring elsewhere.

We performed *post hoc* sensitivity analyses of the association between BIMS and mortality in response to reviewer comments by (i) adjusting for preoperative estimated glomerular filtration rate (eGFR), (ii) assuming all patients with missing data regarding MINS experienced MINS before BIMS, and (iii) assuming that no patients with missing data regarding MINS experienced MINS before BIMS.

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.

Characteristics of perioperative bleeding

Table 2 summarises the characteristics of perioperative bleeding. Of the 16 079 patients, 36.1% (5810) met our predefined screening criteria for bleeding within 30 days of surgery. Most of the bleeding events occurred before or on the third postoperative day (87.6%; 5089/5810 patients). Only one unit of red blood cells was transfused in 4.1% of all patients (654/16 079 patients), two units in 8.1% (1305/16 079 patients), and three or more units were transfused in 5.0% (802/16 079 patients). Postoperative haemoglobin reached a nadir of 70–79 g L^{-1} in 7.0% (1121/16 079 patients), 60–69 g L^{-1} in 2.0% (327/16 079 patients), and <60 g L^{-1} in 0.7% (116/16 079 patients). Bleeding led to reoperation in 0.7% (106/16 079 patients).

Diagnostic criteria for BIMS

Supplementary Table S2 summarises the results of our analyses to identify diagnostic criteria for BIMS. Two of the candidate criteria met our prespecified requirements to become diagnostic criteria for BIMS: bleeding that led to transfusion of red blood cells (aHR with 30-day mortality: 2.01; 95% confidence interval [CI]: 1.29–3.11; P=0.002) and bleeding that led to a postoperative haemoglobin <70 g L^{-1} (aHR with 30-day mortality: 1.71; 95% CI: 1.14–2.57; P=0.01). The results remained consistent in the prespecified sensitivity analysis that adjusted for additional types of surgery (Supplementary

Table 2 Characteristics of bleeding. 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 cause of death during or within 30 days after noncardiac surgery); pRBCs, packed red blood cells

Variable	All patients, *n* (%)	Any bleeding, *n* (%)	Non-BIMS bleeding, *n* (%)	BIMS, *n* (%)
All patients	16 079 (100)	5810 (36.1)	3028 (18.8)	2782 (17.3)
Timing of bleeding				
Intra- or postoperative operating theatre day	2268 (14.1)	2268 (39.0)	831 (27.4)	1437 (51.7)
Postoperative Day 1	1572 (9.8)	1572 (27.1)	1009 (33.3)	563 (20.2)
Postoperative Day 2	809 (5.0)	809 (13.9)	549 (18.1)	260 (9.3)
Postoperative Day 3	440 (2.7)	440 (7.6)	305 (10.1)	135 (4.9)
Postoperative Days 4–30	721 (4.5)	721 (12.4)	334 (11.0)	387 (13.9)
Reoperation for bleeding	106 (0.7)	106 (1.8)	27 (0.9)	79 (2.8)
pRBCs transfused (units)				
0	13 318 (82.8)	3049 (52.5)	3028 (100.0)	21 (0.8)
1	654 (4.1)	654 (11.3)	0 (0.0)	654 (23.5)
2	1305 (8.1)	1305 (22.5)	0 (0.0)	1305 (46.9)
≥3	802 (5.0)	802 (13.8)	0 (0.0)	802 (28.8)
Postoperative haemoglobin nadir (g L^{-1})				
≥80	14 515 (90.3)	4246 (73.1)	2905 (95.9)	1341 (48.2)
70–79	1121 (7.0)	1121 (19.3)	123 (4.1)	998 (35.9)
60–69	327 (2.0)	327 (5.6)	0 (0.0)	327 (11.8)
<60	116 (0.7)	116 (2.0)	0 (0.0)	116 (4.2)
Absolute decrease in haemoglobin from preoperative baseline (g L^{-1})				
<30	11 318 (70.4)	1049 (18.1)	99 (3.3)	950 (34.1)
30–39	1967 (12.2)	1967 (33.9)	1423 (47.0)	544 (19.6)
40–49	1334 (8.3)	1334 (23.0)	878 (29.0)	456 (16.4)
50–59	839 (5.2)	839 (14.4)	436 (14.4)	403 (14.5)
≥60	621 (3.9)	621 (10.7)	192 (6.3)	429 (15.4)
Relative decrease in haemoglobin from preoperative baseline (%)				
<30	13 284 (82.6)	3015 (51.9)	1809 (59.7)	1206 (43.4)
30–39	1828 (11.4)	1828 (31.5)	1004 (33.2)	824 (29.6)
≥40	967 (6.0)	967 (16.6)	215 (7.1)	752 (27.0)
Bleeding thought to be the cause of death	13 (0.1)	13 (0.2)	0 (0.0)	13 (0.5)
Location of bleeding (multiple were possible)				
Surgical site bleeding	5263 (32.7)	5263 (90.6)	2791 (92.2)	2472 (88.9)
Intracranial	14 (0.1)	14 (0.2)	6 (0.2)	8 (0.3)
Intraspinal or epidural	4 (<0.1)	4 (0.1)	3 (0.1)	1 (<0.1)
Retroperitoneal	18 (0.1)	18 (0.3)	5 (0.2)	13 (0.5)
Gastrointestinal	139 (0.9)	139 (2.4)	27 (0.9)	112 (4.0)
Genitourinary	45 (0.3)	45 (0.8)	16 (0.5)	29 (1.0)
Respiratory	10 (0.1)	10 (0.2)	5 (0.2)	5 (0.2)
Other	503 (3.1)	503 (8.7)	200 (6.6)	303 (10.9)

Table S2). 'Bleeding that was thought to be the cause of death by the patient's clinical team' was then added as a third diagnostic criterion for BIMS.

Using these diagnostic criteria, BIMS affected 17.3% of patients (2782/16 709 patients). Amongst them, 99.2% (2761/2782 patients) received red blood cell transfusion, 15.9% had a documented postoperative haemoglobin <70 g L^{-1} (442/2782 patients), and 0.5% (13/2782 patients) had bleeding judged as the cause of death. The proportion of patients who experienced BIMS based on only one of the three criteria was 83.8 % (2332/2782 patients) for transfusion, 0.7% (20 patients) for a postoperative haemoglobin <70 g L^{-1}, and only one patient had bleeding judged as the cause of death as the sole criterion for BIMS.

Prognostic importance of BIMS

Death occurred within the first 30 days after surgery in 2.0% (315/16 079 patients). All patients who had BIMS met the VISION screening criteria for bleeding by requirement. Of the patients who had BIMS, 5.8% (161/2782 patients) died within 30 days of surgery compared with 1.3% (39/3028 patients) of patients who met the screening criteria for bleeding but not the criteria for BIMS (i.e. non-BIMS bleeding), and 1.1% (115/10 269 patients) of those who did not have a bleeding event. After adjusting for preoperative patient characteristics, surgical factors, and other postoperative complications, BIMS was independently associated with 30-day mortality (aHR: 1.87; 95% CI: 1.42–2.47; P<0.001) and had a population attributable risk fraction of 20.1% for 30-day mortality (95% CI: 11.2–28.1%) (Fig 2). The population attributable risk fraction for BIMS increased to 31.9% for 30-day mortality (95% CI: 26.9–36.5%) when adjusted for preoperative patient characteristics and surgical factors, but not adjusted for the other perioperative complications.

Testing of the proportional hazards assumption suggested statistically significant violations for active cancer (P=0.005), major general surgery (P=0.004), and major neurosurgery (P=0.005). Sensitivity analysis interacting these variables with time did not appreciably change the results from the prespecified approach (Supplementary Table S3).

No prespecified subgroup analysis met our criteria for significance (Fig 3). *Post hoc* analyses did not find that the association between BIMS and 30-day mortality differed according to when BIMS occurred or whether BIMS occurred at a surgical or non-surgical site (Supplementary Table S4). The association between BIMS and mortality remained similar to our prespecified analysis in the sensitivity analysis adjusting for preoperative eGFR (aHR: 1.85; 95% CI: 1.40–2.45; P<0.001).

A similar proportion of patients with and without bleeding was excluded from the analysis because of missing MINS data (5.7% [636 patients without bleeding] compared with 6.2% [334 patients with bleeding]; P=0.26). Patients without MINS data had lower preoperative haemoglobin concentrations and were more likely to have functional dependence, require urgent or emergency surgery, and suffer postoperative complications (including BIMS) (Supplementary Table S5). The association between BIMS and mortality remained similar to our prespecified analysis in the sensitivity analyses assuming that all patients with missing data regarding MINS experienced MINS

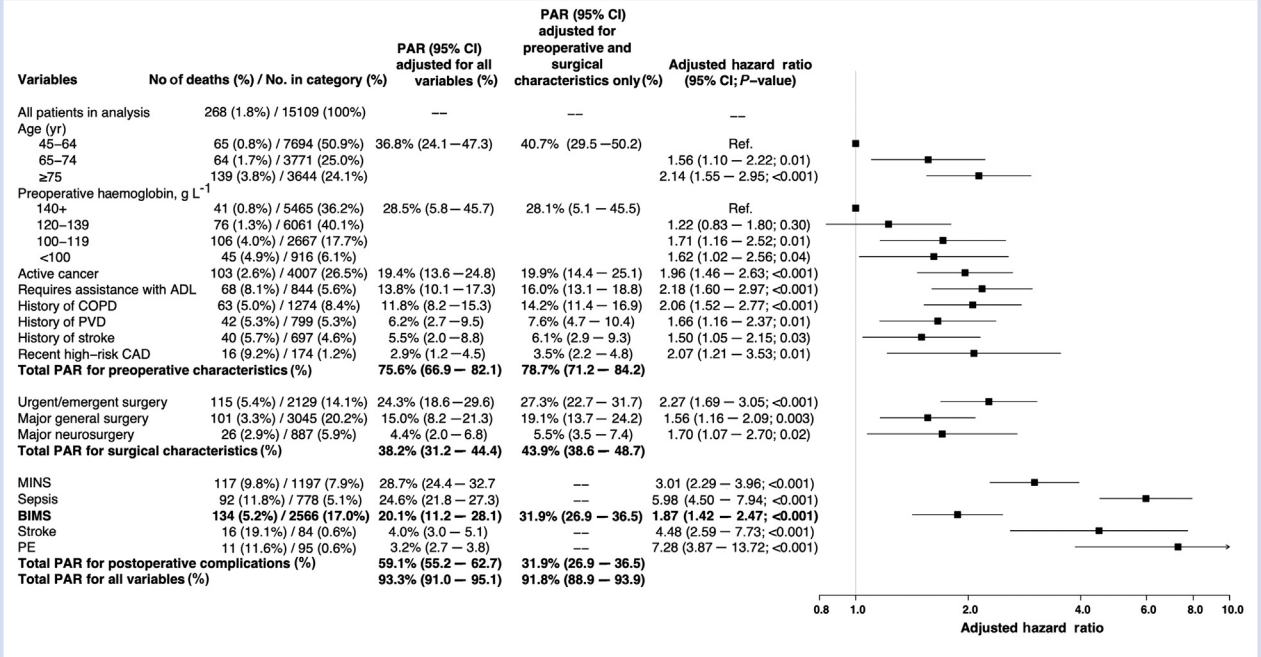

Fig. 2. Association of preoperative patient characteristics, surgical characteristics, bleeding independently associated with mortality after noncardiac surgery (BIMS), and other postoperative complications with 30-day all-cause perioperative death. Only patients with available data for myocardial injury after noncardiac surgery (MINS) were included in this analysis (n=15 109). BIMS is bleeding that led to any red blood cell transfusion, postoperative haemoglobin <70 g L^{-1}, or that was thought to be the cause of death during or within 30 days after noncardiac surgery. ADL, activities of daily living; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; PAR, population attributable risk fraction; PE, pulmonary embolism; PVD, peripheral vascular disease.

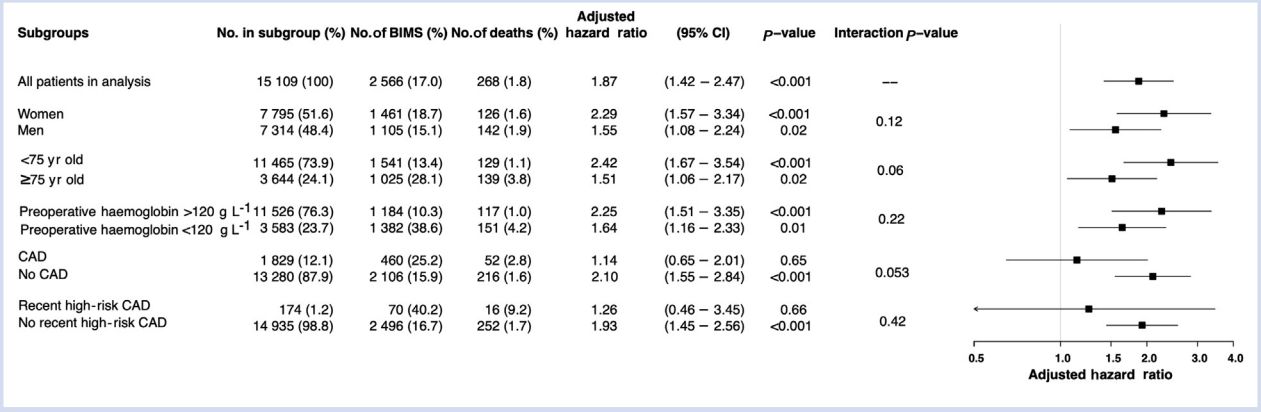

Fig. 3. Prespecified subgroup analyses for the relationship between bleeding independently associated with mortality after noncardiac surgery (BIMS) and 30-day all-cause perioperative death. Analyses were adjusted for preoperative patient characteristics, surgical characteristics, and other postoperative complications. Only patients with available data for myocardial injury after noncardiac surgery were included in these analyses (n=15 109). BIMS is bleeding that led to any red blood cell transfusion, postoperative haemoglobin <70 g L^{-1}, or that was thought to be the cause of death during or within 30 days after noncardiac surgery. CAD, coronary artery disease; CI, confidence interval.

before BIMS (aHR: 2.09; 95% CI: 1.62–2.68; P<0.001), and analyses assuming that no patients with missing data regarding MINS experienced MINS before BIMS (aHR: 2.06; 95% CI: 1.60–2.66; P<0.001).

Discussion

Based on independent association with 30-day mortality in a large, international, prospective cohort study, we identified that bleeding that led to a postoperative haemoglobin <70 g L^{-1}, red blood cell transfusion, or was thought to be the cause of death as diagnostic criteria for BIMS. In addition, BIMS occurred in 17.3% of patients and was independently associated with mortality (aHR: 1.87); it may independently account for between 20.1% (with adjustment for other perioperative complications) and 31.9% (without adjustment for other perioperative complications) of deaths within 30 days after noncardiac surgery. These estimates for the mortality attributable to BIMS indicate the proportion of deaths that could potentially be avoided by preventing BIMS if the relationship between BIMS and mortality is causal.

Strengths and weaknesses of the study

We established pragmatic diagnostic criteria for BIMS by assessing features of perioperative bleeding that are reliably ascertained in clinical practice. The strengths of the study included its prospective design with systematic monitoring for perioperative complications; rigorous attention to data quality; a large sample from multiple continents representative of a variety of urgent and elective surgeries; nearly complete 30-day follow-up; little missing data that were imputed to minimise bias; and prespecification of statistical methods that included adjustment for many patient characteristics, surgical characteristics, and postoperative complications previously associated with perioperative mortality.

This study has several potential limitations. Residual confounding may have affected the BIMS diagnostic criteria or estimation of their prognostic importance. Results of subgroup analyses and sensitivity analyses with additional adjustment were consistent with the primary findings.

The BIMS diagnostic criteria may reflect a component of iatrogenic dilutional anaemia. We partially addressed this limitation by requiring that a bleeding event be accompanied by a haemoglobin decrement of at least 30 g L^{-1}, transfusion of blood products, reoperation for reasons of bleeding, or death thought to be attributable to bleeding.

We relied on belief of bleeding by local investigators and treating physicians combined with supportive parameters to diagnose bleeding. Consistent with other definitions of bleeding,[9,16] we focused on the consequences of bleeding (e.g. effect on haemoglobin and transfusion) as clinically relevant surrogates of bleeding and severity. As we have previously done in developing the diagnostic criteria for MINS,[13] we used risk of death as the endpoint with which to correlate these readily assessed surrogates of bleeding.

We did not capture the exact timing of transfusion or haemoglobin nadir, but required of the local investigators that these were associated with bleeding episodes. Variability in transfusion practice decreases the precision of estimates of association between bleeding and outcomes for all definitions of major bleeding that share this component.[17] Our large and diverse sample allowed us to identify acceptably precise estimates of association whilst avoiding bias toward the practice of a single centre or type of surgery. Although transfusion practice has become more restrictive, BIMS includes bleeding associated with haemoglobin <70 g L^{-1}, a common restrictive transfusion threshold.[18,19] Further, the strength of association between BIMS and mortality would increase if restrictive thresholds have made transfusion a more specific marker of major bleeding.

Correlation amongst indices of bleeding limited power to test their associations with mortality. For example, we may have been unable to detect independent associations between decreases in haemoglobin (absolute and relative) and mortality because decrements in haemoglobin are already captured by transfusion and the postoperative haemoglobin nadir. We

predefined the order in which candidate criteria would be tested based on their practicality, prioritising transfusion and haemoglobin nadir because they are easily identified. Non-fatal bleeding in critical anatomical locations may not meet the criteria for BIMS, but has important consequences and should be counted when assessing the total burden of bleeding in clinical practice or research.

Our data do not directly inform the diagnostic criteria, incidence, and prognostic importance of BIMS in patients younger than 45 yr old. Although probably less common, bleeding that meets these BIMS criteria would likely be prognostically meaningful in younger patients.

Implications for practice and research

Early recognition of severe bleeding (which may later meet the diagnostic criteria for BIMS) should prompt measures to attempt treatment and stop the bleeding. In this way, the findings of our study have the potential to reduce BIMS and death from bleeding. Ability to consistently diagnose BIMS and understand its consequences will help to plan clinical trials.

Conclusions

This large international prospective cohort study determined the diagnostic criteria for BIMS as bleeding that leads to a postoperative haemoglobin concentration <70 g L^{-1}, a blood transfusion, or that is clinically judged to be the cause of death. In addition, BIMS is common and may account for a quarter of deaths within 30 days of noncardiac surgery. Clinicians and researchers can use our findings to help identify prognostically important bleeding.

Authors' contributions

Study conception/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
Data acquisition/analysis/interpretation: all authors
Statistical analysis: PSR
Drafting of paper: PSR
Critical revision of paper for important intellectual content: all authors
PSR had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the version to be published.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.06.051.

Declarations of interest

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