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SYSTEMATIC REVIEW

Predictors of gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis

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Abstract

Purpose: To systematically identify predictors of gastrointestinal (GI) bleeding in adult intensive care unit (ICU) patients.

Methods: We conducted a systematic review and meta-analysis of cohort studies including trial cohorts. We searched MEDLINE, EMBASE, and trial registries up to March 2019. Eligible studies assessed potential predictors of clinically important GI bleeding (CIB; primary outcome) or overt GI bleeding (secondary outcome), had > 20 events, and presented adjusted effect estimates. Two reviewers assessed study eligibility, extracted data, and assessed risk of bias and certainty of evidence using GRADE. We meta-analysed adjusted effect estimates if data from ≥ 2 studies were available.

Results: We included 8 studies (116,497 patients). 4 studies (including 74,456 patients) assessed potential predictors of CIB, and we meta-analysed 12 potential predictors from these. Acute kidney injury (relative effect [RE] 2.38, 95% confidence interval [CI] 1.07–5.28, moderate certainty) and male gender (RE 1.24, 95% CI 1.03–1.50, low certainty) were associated with increased incidence of CIB. After excluding high risk of bias studies, coagulopathy (RE 4.76, 95% CI 2.62–8.63, moderate certainty), shock (RE 2.60, 95% CI 1.25–5.42, low certainty), and chronic liver disease (RE 7.64, 95% CI 3.32–17.58, moderate certainty) were associated with increased incidence of CIB. The effect of mechanical ventilation on CIB was unclear (RE 1.93, 0.57–6.50, very low certainty).

Conclusions: We identified predictors of CIB and overt GI bleeding in adult ICU patients. These findings may be used to identify ICU patients at higher risk of GI bleeding who are most likely to benefit from stress ulcer prophylaxis.

Keywords: Stress ulcer prophylaxis, Gastrointestinal bleeding, Meta-analysis, Predictors, Critical care, Prognosis

Introduction

Gastrointestinal (GI) stress ulceration is a well-recognized condition that affects critically ill patients in the intensive care unit (ICU) and has been associated with increased morbidity and mortality [1, 2]. It has been thought for decades that mechanical ventilation for more than 48 h and coagulopathy are the strongest, and possibly the only, predictors of clinically important GI bleeding (CIB) [2, 3], which is usually defined as overt GI bleeding (visual evidence of GI bleeding) with affection of haemodynamics, haemoglobin levels, or transfusion requirements. In a recent large cohort study, coagulopathy was associated with higher incidence of CIB, while mechanical ventilation was not [4]. In that study, other predictors of CIB were identified, i.e., number of comorbidities, need for renal replacement therapy, and chronic liver disease [4]. Furthermore, while crude mortality was increased in patients with CIB, this association was not

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significant after adjustment for potential confounders related to severity of illness [4].

Providing stress ulcer prophylaxis (SUP) in the ICU is a topic of ongoing debate. Although SUP is commonly prescribed in the ICU [4], there have been concerns about potential harms including pneumonia, *Clostridioides difficile* infection and myocardial ischemia [5, 6]. The recent Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial showed that proton pump inhibitors (PPIs) reduce both overt GI bleeding and CIB, with no effect on mortality and infectious complications [7]. A recent meta-analysis confirmed these findings, although the effects on CIB and serious adverse events were less certain [8]. The remaining uncertainty about the safety of using SUP warrants careful selection of patients who may benefit the most from prophylaxis (i.e., those at highest risk of bleeding).

In this systematic review and meta-analysis of cohort studies and randomised clinical trials (RCTs), we aimed to identify and summarise predictors of CIB and overt GI bleeding in adult ICU patients. We hypothesised that we could identify clinically relevant predictors of CIB and overt GI bleeding.

Take-home message

We identified and summarised predictors of clinically important and overt GI bleeding in adult ICU patients. The findings will help clinicians and guideline developers to identify high-risk patients who are likely to benefit the most from stress ulcer prophylaxis.

Methods

This systematic review and meta-analysis was conducted in accordance with recent recommendations [9] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10] [completed checklist included in the Electronic Supplementary Material (ESM)]. The review was conducted according to a pre-specified internal protocol, which was not published or prospectively registered.

Data sources and searches

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) on March 12–14th 2019 using relevant search terms and filters to identify studies of prognosis. The search was conducted by a medical librarian and the electronic search strategy is presented in the ESM. No restriction on year of publication or language was used. For included studies that were secondary publications of another study (e.g., secondary cohort studies based on RCTs), we also obtained the original publications. For two trial registrations without available data, we attempted to contact authors once and excluded both entries, as no response was obtained.

Study selection and eligibility criteria

We included retrospective and prospective cohort studies including RCT cohorts assessing potential predictors of GI bleeding in adult ICU patients. Adult patients were defined by the included studies; if no definition was provided, we included studies if at least 80% of the included population were at least 18 years of age. ICUs were defined according to the included studies. To decrease confounding, uncertainty, and chance findings, studies with 20 or fewer GI bleeding events and studies that did not report multivariable adjusted estimates for at least one of the outcomes of interest were excluded.

For studies in languages not spoken by any of the authors, we used Google Translate (Google LLC, CA, USA) to assess eligibility [11]. Studies reported as abstracts only and records without any data presented were excluded.

Two reviewers (AG and LZ) independently and in duplicate screened titles and abstracts, followed by full-text screening of potentially eligible studies using a standardised screening form and the Covidence platform (https://www.covidence.org; Veritas Health Innovation, Melbourne, Australia). Discrepancies were solved through consensus or by involvement of a third reviewer (MHM or WA).

Data extraction, risk of bias assessments, and certainty of evidence

We extracted the following data from eligible studies: study type, countries, period of enrolment, setting, number of centres, enrolment criteria, age, gender, severity of illness, use of SUP (medication used, route of administration and dose), definitions of overt/any GI bleeding and CIB, duration of follow-up, number of patients and events, potential predictors [including effect estimates and confidence intervals (CIs) and/or *P* values] and analytic strategy including the covariates adjusted for. We did not contact study authors for any additional data, as this was not deemed necessary for any of the included studies.

We assessed risk of bias in the included studies using the Quality In Prognosis Studies (QUIPS) tool [12]. The domains patient selection, study attrition, measurement of prognostic factors, outcome measurement, study confounding, and statistical analysis and reporting were rated as low, moderate, or high risk of bias. We classified studies with 5 or 6 low risk of bias domains as overall low risk of bias; studies with 2 or more high risk of bias domains as overall high risk of bias; and all other studies as overall moderate risk of bias [13].

The certainty of evidence was assessed as high, moderate, low, or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach adapted to studies of prognosis, where observational studies start as high certainty of evidence [14]. This assessment was based on risk of bias, consistency, precision, directness, and other concerns including publication bias (which we planned to assess by visual inspection of funnel plots if at least 10 studies were included [15]).

Two reviewers (AG and LZ) independently and in duplicate extracted data, assessed risk of bias, and assessed certainty of evidence using GRADE. Any discrepancies were resolved by consensus or through involvement of a third reviewer (MHM or WA).

Outcomes and predictors

The primary outcome was CIB during the ICU stay, based on definitions in the included studies. The secondary outcome was overt GI bleeding during the ICU stay, based on definitions in the included studies, including GI bleeding events without further specifications. For studies that only assessed potential predictors of CIB, we also included data for this outcome in the analyses of overt GI bleeding. We were primarily interested in upper GI bleeding, but as clinical differentiation of upper and lower GI bleeding is sometimes difficult without diagnostic endoscopy, we included any GI bleeding unless specifically stated that it was lower GI in origin.

We considered all reported potential predictors of GI bleeding, except all forms of pharmacologic SUP [including PPIs, histamine-2-receptor antagonists (H2RAs), sucralfate, and antacids], as this was beyond the scope of this review, and the effect of SUP has already been assessed in recent systematic reviews and meta-analyses of RCTs [8, 16].

Data synthesis and statistical analyses

Potential predictors reported in two or more included studies are presented in the main text; potential predictors assessed in only one study are presented in the ESM. When meta-analysis was not possible (due to different definitions, categorisations, or other dissimilarities), we qualitatively summarised potential predictors across studies.

We performed meta-analyses by extracting and pooling adjusted relative effect (RE) estimates and their standard errors using DerSimonian-Laird random effects models and the inverse variance method [9, 17]. Standard errors were calculated from 95% CIs or from effect estimates and P values [18]. Where $P < 0.001$ was reported, we assumed P to be exactly 0.001 to allow estimation [18]. If only P values reported as larger inequalities were available, results were not meta-analysed.

Statistical heterogeneity was addressed through consistency of point estimates and the extent of overlap of CIs. Heterogeneity was not assessed with I^2 statistics (although these are presented in the forest plots), as they are uniformly high and not useful in prognostic studies with large sample sizes and relatively precise estimates [14].

We conducted pre-specified subgroup analyses according to the effect measures used (hazard ratios [HRs] and odds ratios [ORs]), to assess if any systematic differences caused by the use of different effect measures were present [9]. Furthermore, we conducted pre-specified subgroup analyses according to overall risk of bias where this differed for studies included in the same meta-analysis, to assess the influence of risk of bias on the results [14]. Results from both the analyses including all studies and from studies adjudicated as overall moderate or low risk of bias (i.e., excluding high risk of bias studies) are presented in the evidence profiles.

All analyses were conducted using R version 3.5.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the *meta* package v. 4.9-5, which was also used for producing forest plots, and the *ggplot2* package v. 3.1.1. Two-sided P values < 0.05 and 95% CIs not including 1.00 were considered statistically significant.

Results

Study selection and characteristics

We screened 5352 abstracts and 143 full-text papers and included 8 studies including a total of 116,497 patients [2, 4, 5, 19–23] (Fig. 1). Four studies including 74,456 patients assessed potential predictors of CIB [2, 4, 19, 22]; 2 studies were prospective cohort studies [2, 4], 2 were secondary studies of RCTs [19, 20, 24, 25], and 4 were retrospective cohort studies [5, 21–23]. All studies were conducted in multiple centres. Inclusion criteria in most studies were broad; 1 study included neurocritically ill patients only [23], and 2 studies included patients mechanically ventilated for at least 24 [5] or 48 h [19]. More than 70% of the patients received SUP in all but 1 study, where only 30% received SUP [2]; in 3 studies, all patients received SUP [5, 19, 22], and enrolment in 2 of these studies was restricted to patients who received SUP for at least 2 [5] or 3 days [22].

Risk of bias was low in 1 study [19], moderate in 3 studies [2, 4, 20], and high in 4 studies [5, 21–23]. There was substantial variation in the analytic strategies used including the variables adjusted for, and in the definitions of some of the included predictors

(ESM). Additional study characteristics are presented in Table 1 and Tables S1-S8 in the ESM.

The incidences of CIB and overt GI bleeding in the included studies ranged from 0.6 to 2.8% and 1.3 to 12.8%, respectively.

Predictors assessed

We included a median of 8 potential predictors per study (range 2–21) in our meta-analyses and reported summary estimates for 12 potential predictors of CIB and 21 for overt GI bleeding (Tables 2, 3). All individual forest plots (including results from all subgroup analyses) and additional details are presented in the ESM.

Predictors of CIB

We performed meta-analyses of adjusted estimates for 12 potential predictors of CIB (Table 2 and Fig. 2). Acute kidney injury was associated with a statistically significant increase in the risk of CIB (3 studies [2, 4, 22], 484 events/73,379 patients, RE 2.38, 95% CI 1.07–5.28, moderate certainty). Male gender was also associated with a small increase in the risk of CIB (2 studies [4, 22], 451 events/71,127 patients, RE 1.24, 95% CI 1.03–1.50, low certainty). The effect of mechanical ventilation on CIB risk was unclear (3 studies [2, 4, 22], 484 events/73,379 patients, RE 1.93, 95% CI 0.57–6.50, very low certainty).

When high risk of bias studies were excluded, coagulopathy (2 studies [2, 4], 60 events/3286 patients, RE 4.76, 95% CI 2.62–8.63, moderate certainty), shock (2 studies [2, 4], 60 events/3286 patients, RE 2.60, 95% CI 1.25–5.42, low certainty), and chronic liver disease (1 study [4], 27 events/1034 patients, RE 7.64, 95% CI 3.32–17.58, moderate certainty) were associated with a statistically significant increase in risk of CIB.

The 95% CIs for all remaining potential predictors included both increased and decreased risk of CIB; the certainty of evidence was very low, low, or moderate for most potential predictors, primarily due to inconsistency or imprecision (Table 2).

Results from subgroup analyses according to the effect measures used are presented in the ESM; these estimates of subgroup effects are highly uncertain and difficult to interpret due to the low number of studies and the overlap between differences in effect measures and according to risk of bias adjudications.

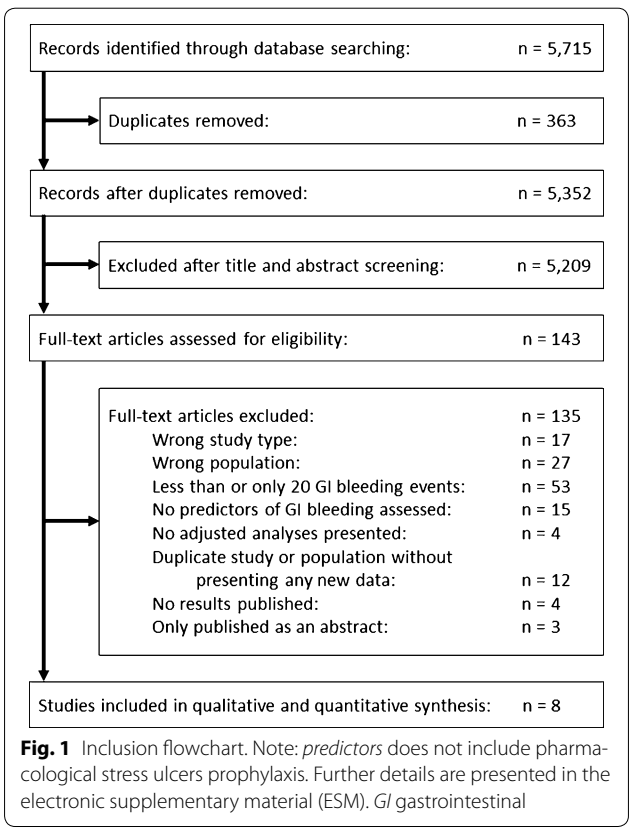

Fig. 1 Inclusion flowchart. Note: *predictors* does not include pharmacological stress ulcers prophylaxis. Further details are presented in the electronic supplementary material (ESM). *GI* gastrointestinal

Predictors of overt GI bleeding

We performed meta-analyses of adjusted estimates for 21 potential predictors of overt GI bleeding (Table 3 and Figure S1 in the ESM); 8 predictors were associated with a statistically significant increase in the risk of overt GI bleeding: coagulopathy (4 studies [2, 4, 5, 22], 2069 events/108,691 patients, RE 2.13, 95% CI 1.31–3.45, moderate certainty), shock (4 studies [2, 4, 5, 22], 2069 events/108,691 patients, RE 1.34, 95% CI 1.03–1.74, low certainty), sepsis (3 studies [2, 5, 22], 2020 events/107,657 patients, RE 1.16, 95% CI 1.02–1.32, moderate certainty), acute hepatic failure (4 studies [2, 5, 20, 22], 2096 events/108,531 patients, RE 1.76, 95% CI 1.13–2.74, moderate certainty), chronic liver disease (3 studies [4, 5, 22], 2036 events/106,439 patients, RE 2.16, 95% CI 1.25–3.71, moderate certainty), acute kidney injury (4 studies [2, 4, 5, 22], 2069 events/108,691 patients, RE 1.90, 95% CI 1.20–3.02, moderate certainty), male gender (4 studies [4, 5, 21, 22], 2094 events/110,878 patients, RE 1.18, 95% CI 1.07–1.31, low certainty), and acute myocardial infarction (2 studies [5, 22], 1987 events/105,405 patients, RE 1.65, 95% CI 1.41–1.93, low certainty). The effect of mechanical ventilation was unclear (5 studies [2, 4, 21–23], 764 events/79,234 patients, RE 1.11, 95% CI 0.64–1.91, very low certainty).

When high risk of bias studies were excluded, coagulopathy (2 studies [2, 4], 82 events/3286 patients, RE 4.14, 95% CI 2.69–6.90, moderate certainty), shock (2 studies [2, 4], 82 events/3286 patients, RE 2.56, 95% CI 1.44–4.54, low certainty), and chronic liver disease (1 study [4], 49 events/1034 patients, RE 4.51, 95% CI 2.30–8.85,

Table 1 Overview of included studies

Study	Study type	Population	Stress ulcer prophylaxis	CIB definition or overt GI bleeding definition if CIB not defined	Patients/ events (*n*)	Potential predictors included[a]	Overall risk of bias
Cook et al. [2]	Prospective cohort, 4 centres in Canada	Medical–surgical ICU patients without GIB at baseline. 48.5% were cardiac surgical patients	30% received stress ulcer prophylaxis	Overt GI bleeding (haematemesis, gross blood or "coffee grounds" material in a nasogastric aspirate, haematochezia or melaena) complicated by one of the following within 24 h after the onset of bleeding (in the absence of other causes): a spontaneous decrease of more than 20 mmHg in the systolic blood pressure; an increase of more than 20 beats per minute in the heart rate, or a decrease of more than 10 mm Hg in the systolic blood pressure measured on sitting up; or a decrease in the haemoglobin level of more than 2 g per decilitre (1.2 mmol per litre) and subsequent transfusion, after which the haemoglobin did not increase by a value defined as the number of units transfused minus 2 g per decilitre	Patients: 2252 Overt GIB: 100 (4.4%)[b] CIB: 33 (1.5%)	10	Moderate
Cook et al. [19]	RCT cohort, 16 centres in Canada	ICU patients expected to be ventilated for > 48 h, who had no GIB and did not die or get discharged in the first 48 h	100% received stress ulcer prophylaxis (RCT randomised patients in a 1:1 ratio to ranitidine or sucralfate)	Overt GI bleeding (haematemesis, nasogastric aspirate containing blood or coffee-grounds material, melaena, or haematochezia) plus one of the following four features, in the absence of other causes: a) a spontaneous decrease in systolic or diastolic blood pressure of ≥ 20 mmHg within 24 h of upper gastrointestinal bleeding; b) an increase in pulse rate of 20 beats/min and a decrease in systolic blood pressure of 10 mmHg on orthostatic change; c) a decrease in haemoglobin of ≥ 2 g/dL (20 g/L) in 24 h and transfusion of 2 units of packed red blood cells within 24 h of bleeding; or d) failure of the haemoglobin to increase by at least the number of units transfused minus 2 g/dL (20 g/L) (i.e., if 8 g/dL [80 g/L] haemoglobin and 4 units of packed cells were infused, the bleed would be considered important if the haemoglobin did not increase by ≥ 2 g/dL [20 g/L] to 10 g/dL [20 g/L])	Patients: 1077 Overt GIB: 30 (2.8%)[b] CIB: 30 (2.8%)	2	Low
Ellison et al. [20]	RCT cohort, 6 centres in USA	Medical–surgical ICU patients with an expected stay > 2 days and no GIB at baseline	74% received stress ulcer prophylaxis	NR Overt GI bleeding was defined as haematemesis, grossly bloody nasogastric tube drainage, or upper GI bleeding requiring transfusion	Patients: 874 Overt GIB: 76 (8.7%) CIB: NR	3	Moderate

Table 1 (continued)

Study	Study type	Population	Stress ulcer prophylaxis	CIB definition or overt GI bleeding definition if CIB not defined	Patients/events (*n*)	Potential predictors included[a]	Overall risk of bias
Krag et al. [4]	Prospective cohort, 97 ICUs in 11 countries	Acutely admitted patients from primarily mixed ICUs without GIB at baseline	73% received acid suppressants on at least one day in the ICU, 56% did on the day of ICU admission	Clinically important GI bleeding: overt bleeding (haematemesis, coffee ground emesis, melaena, haematochezia, or bloody nasogastric aspirate) and at least one of the following features within 24 h of overt bleeding in the absence of other causes (clinical evaluation): (1) decrease in blood pressure of 20 mmHg or more, (2) start of/increase of vasopressor of 20% or more, (3) decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l), (4) transfusion of two or more units of red blood cells during the bleeding episode	Patients: 1034 Overt GIB: 49 (4.8%) CIB: 27 (2.6%)	14	Moderate
Kumar et al. [21]	Retrospective cohort, 2 ICUs in USA	Medical ICU patients without GIB at baseline	79% received stress ulcer prophylaxis on the first 24 h in the ICU	NR Overt GI bleeding was identified using billing diagnoses and indications in endoscopy database; suspected events confirmed by chart review	Patients: 4439 Overt GIB: 58 (1.3%) CIB: NR	6	High
Lilly et al. [22]	Retrospective cohort of data repository, multiple centres in USA	ICU patients with risk factors for stress ulcers who were treated with H2RA/PPI for at least 3 days in the ICU and had no GIB at baseline or within the first 3 days	100% received stress ulcer prophylaxis for at least 3 days	GI bleeding and occurrence of any of the following: (1) an absolute reduction in systolic blood pressure by at least 20 mmHg; (2) reduction in diastolic blood pressure by at least 10 mmHg; (3) heart rate increase by at least 20 beats/min; or (4) administration of a blood transfusion Episodes of GI bleeding were defined through the ICD-9 code 578 that encompassed haematemesis, blood in stool, and unspecified bleeding. Only one code entry was required to define a bleeding episode	Patients: 70,093 Overt GIB: 424 (0.6%)[b] CIB: 424 (0.6%)	21	High
MacLaren et al. [5]	Retrospective cohort of database, 71 hospitals in USA	Patients were ventilated for at least 24 h and received H2RA/PPI for at least 48 h without GIB at baseline	100% received stress ulcer prophylaxis for at least 2 days	NR GI haemorrhage identified through ICD-9 codes	Patients: 35,312 Overt GIB: 1563 (4.6%) CIB: NR	21	High
Wei et al. [23]	Retrospective cohort, 12 hospitals in China	Neurocritically ill patients with GCS $\leq$ 10 within 24 h of lesion/admission without GIB at baseline	78.8% received a PPI and 9.2% received a H2RA on inclusion	CIB defined (ESM), but only 10 events and no data on associations between potential predictors and CIB presented Overall upper GI bleeding included any overt stress ulcer bleeding (defined as haematemesis), red blood or "hemoccult positive coffee grounded" materials in a nasogastric aspirate, or melena (or haematochezia or hemoccult positive stool likely with upper GI origin) with or without clinically significant complications	Patients: 1416 Overt GIB: 182 (12.9%) CIB: 10 (0.7%)[c]	4	High

Overview of the included studies; detailed study characteristics and risk of bias assessments are available in the electronic supplementary material (ESM)

CIB clinically important [gastrointestinal] bleeding, *GCS* Glasgow Coma Scale, *GIB* gastrointestinal bleeding, *H2RA* histamine-2-receptor antagonist, *ICU* intensive care unit, *NR* not reported, *PPI* proton pump inhibitor, *RCT* randomised clinical trial

[a] Potential predictors included is the number of potential predictors included in this review (not in the original study), including both potential predictors included in the qualitative and quantitative analyses

[b] This study either only presented CIB events or only assessed potential predictors of CIB; the number of events for CIB are consequently used in the applicable meta-analyses of overt/any GI bleeding

[c] No potential predictors for CIB were presented in this study, and these events are not included in any analyses

Table 2 GRADE evidence profile for potential predictors of CIB

Potential predictor	Number of studies	Quality assessment					Effect[a]			Certainty of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision[b]	Other considerations[c]	Number of events	Number of patients	Relative effect estimate (95% CI)	
Clinically important gastrointestinal bleeding—all studies regardless of risk of bias										
Mechanical ventilation	3	Not serious[d]	Serious[e]	Not serious[e]	Very serious[b]	None	484	73,379	1.93 (0.57–6.50)	Very low
Coagulopathy	3	Not serious[f]	Serious[f]	Not serious	Serious[b]	None	484	73,379	2.82 (0.94–8.50)	Low
Shock[g]	3	Not serious[d]	Not serious	Serious[h]	Serious[b]	None	484	73,379	1.70 (0.91–3.17)	Low
Sepsis	2	Not serious[d]	Not serious	Not serious	Very serious[b]	None	457	72,345	1.20 (0.69–2.07)	Low
Acute hepatic failure	2	Not serious[d]	Not serious	Not serious	Serious[b]	None	457	72,345	1.36 (0.85–2.18)	Moderate
Chronic liver disease	2	Not serious[f]	Serious[f]	Not serious	Very serious[b]	None	451	71,127	3.16 (0.59–16.90)	Very low
Acute kidney injury[j]	3	Not serious[d]	Not serious	Serious[h]	Not serious	None	484	73,379	2.38 (1.07–5.28)	Moderate
Enteral nutrition	2	Not serious[f]	Serious[f]	Not serious	Very serious[b]	None	454	71,170	0.63 (0.17–2.37)	Very low
Use of steroids/immunosuppression	3	Not serious[d]	Not serious	Not serious	Serious[b]	None	484	73,379	1.18 (0.82–1.70)	Moderate
Use of anticoagulants	3	Very serious[j]	Not serious	Not serious	Serious[b]	None	484	73,379	0.89 (0.69–1.15)	Very low
Cancer	2	Not serious[d]	Not serious	Not serious	Serious[b]	None	451	71,127	1.29 (0.94–1.78)	Moderate
Male gender	2	Very serious[j]	Not serious	Not serious	Not serious	None	451	71,127	1.24 (1.03–1.50)	Low
Clinically important gastrointestinal bleeding—moderate–low risk of bias studies only[k]										
Mechanical ventilation	2	Not serious	Serious[e]	Not serious[e]	Very serious[b]	None	60	3286	4.09 (0.37–45.67)	Very low
Coagulopathy	2	Not serious	Not serious	Not serious	Serious[b]	None	60	3286	4.76 (2.62–8.63)	Moderate
Shock[g]	2	Not serious	Not serious	Serious[h]	Serious[b]	None	60	3286	2.60 (1.25–5.42)	Low
Sepsis	1	Not serious	Not serious	Not serious	Very serious[b]	None	33	2252	2.00 (0.74–5.37)	Low
Acute hepatic failure	1	Not serious	Not serious	Not serious	Very serious[b]	None	33	2252	1.60 (0.70–3.67)	Low
Chronic liver disease	1	Not serious	Not serious	Not serious	Serious[b]	None	27	1034	7.64 (3.32–17.58)	Moderate
Acute kidney injury[j]	2	Not serious	Not serious	Serious[h]	Serious[b]	None	60	3286	3.26 (0.78–13.63)	Low
Enteral nutrition	1	Not serious	Not serious	Not serious	Serious[b]	None	30	1077	0.30 (0.13–0.68)	Moderate
Use of steroids/immunosuppression	2	Not serious	Not serious	Not serious	Very serious[b]	None	60	3286	1.39 (0.71–2.71)	Low
Use of anticoagulants	2	Not serious	Not serious	Not serious	Very serious[b]	None	60	3286	1.42 (0.65–3.10)	Low
Cancer	1	Not serious	Not serious	Not serious	Very serious[b]	None	27	1034	1.36 (0.28–6.54)	Low
Male gender	1	Not serious	Not serious	Not serious	Very serious[b]	None	27	1034	0.85 (0.39–1.87)	Low

GRADE evidence profile for all meta-analysed potential predictors of CIB. Of note, observational studies start with an overall high rating in GRADE for prognosis [14]

CI confidence interval, *GRADE* Grading of Recommendations Assessment, Development and Evaluation approach

[a] Relative effect estimates contain combined estimates of both hazard ratios and odds ratios. The number of events and number of patients are as presented in the included studies; some analyses may contain fewer events/patients due to missing data, however, this was not clearly described in most of the included studies

[b] We considered imprecision as not serious for analyses where the 95% CI did not include 1.00 and at least 100 events were included, serious if the 95% CI overlapped 1.00 or less than 100 events were included, and very serious if the 95% CI overlapped both 0.75 and 1.33

[c] Other considerations included publication bias. We planned to assess publication bias by visual inspection of funnel plots where more than 10 studies were included; this was not done as only 8 studies were included (of which only 4 assessed predictors of CIB), however, we have no reason to suspect publication bias. We did not find reason to rate up the certainty of evidence for any potential predictors

[d] Studies at high risk of bias contributed substantially to this analysis (according to the study weights in the meta-analysis) but did not affect the overall pooled estimate and the associated 95% confidence interval substantially

[e] Serious inconsistency was present for this predictor. Definitions of the predictor were different in the included studies; we are uncertain if this was the cause of heterogeneity and decided to rate down in the inconsistency domain only to avoid penalising twice

[f] Studies at high risk of bias contributed substantially to this analysis (according to the study weights in the meta-analysis), and effect estimates in high risk of bias studies seemed to be different from the other studies, leading to inconsistency. We rated down the certainty in the estimate for this predictor in the inconsistency domain, and not in the risk of bias domain, as the influence on the overall estimate from the high risk of bias studies was not considered large enough to penalise twice, and we are not certain that risk of bias was the only reason for inconsistency

[g] Shock includes hypotension, shock and use of circulatory support

[h] Rated down due to different definitions of the predictor in the included studies, and the GRADE assessment for this predictor was not already rated down in the inconsistency domain for this reason

[i] Acute kidney injury includes both acute kidney injury (acute renal failure) and use of renal replacement therapy

[j] Studies at high risk of bias contributed substantially to this analysis (according to the study weights in the meta-analysis) and their inclusion reversed the direction of the overall estimate compared to the overall estimate from the subgroup analysis excluding high risk of bias studies

[k] Analyses for studies adjudicated as overall moderate or low risk of bias are only presented where at least one study not rated as high overall risk of bias was present

Table 3 GRADE evidence profile for potential predictors of overt GI bleeding

Potential predictor	Number of studies	Quality assessment					Effect[a]			Certainty of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision[b]	Other considerations[c]	Number of events	Number of patients	Relative effect estimate (95% CI)	
Overt gastrointestinal bleeding[d]—all studies regardless of risk of bias										
Mechanical ventilation	5	Serious[e]	Serious[f]	Not serious[f]	Very serious[b]	None	746	79,234	1.11 (0.64–1.91)	Very low
Coagulopathy	4	Not serious[g]	Serious[g]	Not serious	Not serious	None	2069	108,691	2.13 (1.31–3.45)	Moderate
Shock[h]	4	Serious[e]	Not serious[i]	Serious[i]	Not serious	None	2069	108,691	1.34 (1.03–1.74)	Low
Sepsis	3	Serious[e]	Not serious	Not serious	Not serious	None	2020	107,657	1.16 (1.02–1.32)	Moderate
Acute hepatic failure	4	Not serious[g]	Serious[g]	Not serious	Not serious	None	2096	108,531	1.76 (1.13–2.74)	Moderate
Chronic liver disease	3	Serious[e]	Not serious[j]	Not serious	Not serious	None	2036	106,439	2.16 (1.25–3.71)	Moderate
Acute kidney injury[k]	4	Not serious[g]	Serious[g]	Not serious[l]	Not serious	None	2069	108,691	1.90 (1.20–3.02)	Moderate
Chronic renal failure	3	Serious[e]	Not serious[j]	Not serious	Very serious[b]	None	1764	37,762	1.01 (0.58–1.75)	Very low
Use of steroids/immunosuppression	3	Not serious[m]	Not serious	Not serious	Serious[b]	None	506	73,379	1.23 (0.86–1.75)	Moderate
Transplants	2	Not serious[m]	Not serious	Not serious	Serious[b]	None	1596	37,564	1.61 (0.80–3.24)	Moderate
Use of anticoagulants	5	Very serious[n]	Not serious[j]	Not serious	Serious[b]	None	2251	110,107	0.87 (0.60–1.26)	Very low
Use of antiplatelets	2	Very serious[o]	Very serious[p]	Not serious	Very serious[b]	None	1987	105,405	1.00 (0.57–1.75)	Very low
Cancer	3	Not serious[m]	Very serious[p]	Not serious	Very serious[b]	None	549	72,001	0.98 (0.37–2.61)	Very low
Male gender	4	Very serious[n]	Not serious[j]	Not serious	Not serious	None	2094	110,878	1.18 (1.07–1.31)	Low
Acute myocardial infarction	2	Very serious[o]	Not serious	Not serious	Not serious	None	1987	105,405	1.65 (1.41–1.93)	Low
Heart failure	2	Not serious[m]	Not serious	Not serious	Serious[b]	None	1612	36,346	1.09 (0.96–1.24)	Moderate
Treatment with NSAID/ASA	2	Serious[e]	Not serious	Not serious	Very serious[b]	None	473	71,127	0.86 (0.48–1.55)	Very low
Thrombolysis	2	Very serious[n]	Not serious	Not serious	Serious[b]	None	473	71,127	0.87 (0.62–1.23)	Very low
Neurologic injury	2	Very serious[o]	Not serious	Not serious	Serious[b]	None	1987	105,405	1.11 (0.97–1.28)	Very low
Trauma/surgery	2	Very serious[o]	Serious[q]	Not serious	Very serious[b]	None	1987	105,405	0.74 (0.31–1.76)	Very low
Previous ulcer or UGIB	2	Very serious[o]	Serious[q]	Not serious	Very serious[b]	None	1745	36,728	0.31 (0.03–3.05)	Very low
Overt gastrointestinal bleeding[d]—moderate–low risk of bias studies only[r]										
Mechanical ventilation	2	Not serious	Serious[s]	Not serious[s]	Very serious[b]	None	82	3286	4.24 (0.43–42.09)	Very low
Coagulopathy	2	Not serious	Not serious	Not serious	Serious[b]	None	82	3286	4.14 (2.49–6.90)	Moderate
Shock[h]	2	Not serious	Not serious	Serious[t]	Serious[b]	None	82	3286	2.56 (1.44–4.54)	Low
Sepsis	1	Not serious	Not serious	Not serious	Very serious[b]	None	33	2252	2.00 (0.74–5.37)	Low
Acute hepatic failure	2	Not serious	Not serious	Not serious	Serious[b]	None	109	3126	3.10 (0.77–12.51)	Moderate
Chronic liver disease	1	Not serious	Not serious	Not serious	Serious[b]	None	49	1034	4.51 (2.30–8.85)	Moderate
Acute kidney injury[k]	2	Not serious	Serious[l]	Not serious[l]	Serious[b]	None	82	3286	3.46 (0.78–15.41)	Low
Chronic renal failure	1	Not serious	Not serious	Not serious	Very serious[b]	None	49	1034	1.94 (0.72–5.24)	Low
Use of steroids/immunosuppression	2	Not serious	Not serious	Not serious	Serious[b]	None	82	3286	1.52 (0.83–2.76)	Moderate
Transplants	1	Not serious	Not serious	Not serious	Very serious[b]	None	33	2252	1.50 (0.57–3.95)	Low
Use of anticoagulants	2	Not serious	Not serious	Not serious	Serious[b]	None	82	3286	1.79 (0.93–3.44)	Moderate
Cancer	2	Not serious	Very serious[p]	Not serious	Very serious[b]	None	125	1908	0.83 (0.11–6.13)	Very low
Male gender	1	Not serious	Not serious	Not serious	Very serious[b]	None	49	1034	0.80 (0.44–1.45)	Low
Heart failure	1	Not serious	Not serious	Not serious	Very serious[b]	None	49	1034	1.15 (0.37–3.58)	Low

Table 3 (continued)

Potential predictor	Number of studies	Quality assessment					Effect[a]			Certainty of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision[b]	Other considerations[c]	Number of events	Number of patients	Relative effect estimate (95% CI)	
Treatment with NSAID/ASA	1	Not serious	Not serious	Not serious	Very serious[b]	None	49	1034	0.41 (0.10–1.73)	Low
Thrombolysis	1	Not serious	Not serious	Not serious	Very serious[b]	None	49	1034	1.49 (0.17–12.98)	Low

GRADE evidence profile for all meta-analysed potential predictors of overt GI bleeding. Of note, observational studies start with an overall high rating in GRADE for prognosis [14]

ASA acetylsalicylic acid, *CI* confidence interval, *GRADE* Grading of Recommendations Assessment, Development and Evaluation approach, *NSAID* non-steroidal anti-inflammatory drug, *UGIB* upper gastrointestinal bleeding

[a] Effect estimates contain combined estimates of both hazard ratios and odds ratios. The number of events and number of patients are as presented in the included studies; some analyses may contain fewer events/patients due to missing data, however, this was not clearly described in most of the included studies

[b] We considered imprecision as not serious for analyses where the 95% CI did not include 1.00 and at least 100 events were included, serious if the 95% CI overlapped 1.00 or less than 100 events were included, and very serious if the 95% CI overlapped both 0.75 and 1.33

[c] Other considerations included publication bias. We planned to assess publication bias by visual inspection of funnel plots where more than 10 studies were included; this was not done as only 8 studies were included, however, we have no reason to suspect publication bias. We did not find reason to rate up the certainty of evidence for any potential predictors

[d] Overt gastrointestinal bleeding used estimates from studies with gastrointestinal bleeding events with no clear definition, with a definition for overt or any bleeding, or if none of those were available, the same numbers and estimates as for clinically important gastrointestinal bleeding. Only one study assessed potential predictors of both overt and clinically important gastrointestinal bleeding [4]

[e] Rated down as studies at high risk of bias substantially affected the overall point estimate compared to studies not at high risk of bias

[f] Serious inconsistency was present for this predictor, and this was not completely explained by risk of bias, for which we already rated down. Definitions of the predictor were different in the included studies; we are uncertain if this was the cause of the remaining heterogeneity and decided to rate down in the inconsistency domain and not in the indirectness domain to avoid penalising twice

[g] Studies at high risk of bias contributed substantially to this analysis (according to the study weights in the meta-analysis), and effect estimates in high risk of bias studies seemed to be different from the other studies. However, this potential predictor was already rated down due to inconsistency and the influence on the overall estimate from the high risk of bias studies was not large enough to penalise twice

[h] Shock includes hypotension, shock and use of circulatory support

[i] Some inconsistency was present, which seemed to be explained by risk of bias, and in addition, some differences in how the predictor was defined in the included studies were present. As most inconsistency seemed explained by the risk of bias, for which we already rated down, we did not rate down in inconsistency here, but instead rated down for indirectness

[j] Some inconsistency appears to be present, but this was in studies at high risk of bias and this predictor was already rated down due to risk of bias and was thus not penalised twice

[k] Acute kidney injury includes both acute kidney injury (acute renal failure) and use of renal replacement therapy

[l] Different definitions of the risk factor in the included studies, but this predictor was already rated down for inconsistency between studies and was hence not rated down in this domain

[m] Studies at high risk of bias contributed substantially to this analysis (according to the study weights in the meta-analysis) but did not affect the overall pooled estimate and the associated 95% confidence interval substantially

[n] Studies at high risk of bias contributed substantially to this analysis (according to the study weights in the meta-analysis) and their inclusion reversed the direction of the overall estimate compared to the overall estimate from the subgroup analysis excluding high risk of bias studies

[o] Rated down for risk of bias as only high risk of bias studies were included in this meta-analysis

[p] Very substantial inconsistency not explained by other factors present. Inconsistency with no or minimal overlap of confidence intervals and with estimates in opposite directions

[q] Inconsistency was present and was not explained by causes leading to rating down in other domains

[r] Analyses for studies adjudicated as overall moderate or low risk of bias are only presented where at least one study not rated as high overall risk of bias was present

[s] Serious inconsistency was present for this predictor. Definitions of the predictor were different in the included studies; we are uncertain if this was the cause of heterogeneity and decided to rate down in the inconsistency domain only to avoid penalising twice

[t] Rated down due to different definitions of the predictor in the included studies, and the GRADE assessment for this predictor was not already rated down in the inconsistency domain for this reason

moderate certainty) remained statistically significantly associated with overt GI bleeding.

The 95% CIs for all remaining potential predictors included both increased and decreased risk of overt GI bleeding; the certainty of evidence was very low, low or moderate for most potential predictors, primarily due to risk of bias, inconsistency, or imprecision (Table 3).

The interpretation of the results from subgroup analyses according to effect measures was uncertain for similar reasons as for CIB (ESM).

Predictors not included in the meta-analyses

Potential predictors not meta-analysed are presented in Table S9 in the ESM. Age was associated with increased risk of overt GI bleeding in 1 study [5], but not in any of the other studies [4, 21, 22]. Increased creatinine was associated with increased risk of CIB and overt GI bleeding in 2 studies [19, 21], and thrombocytopenia was associated with decreased CIB in 1 study [5], while no effect on overt GI bleeding was seen in another study [22].

Discussion

This is, to our knowledge, the first systematic review and meta-analysis to provide an overview of predictors of CIB and overt GI bleeding in adult ICU patients and will help clinicians, guideline developers, and investigators to identify adult ICU patients who may benefit the most from SUP.

The first large study on predictors of CIB in adult ICU patients, published 25 years ago, identified 2 independent predictors: mechanical ventilation (for more than 48 h) and coagulopathy [2], which have been highlighted as important predictors since [3]. In this systematic review, we found no clear association between mechanical ventilation and CIB or overt GI bleeding. This could be explained by the use of lung-protective mechanical ventilation (lower pressures and tidal volumes) in the setting of contemporary practice of critical care compared to decades ago [26, 27]. It could also be speculated that the results are unclear due to different definitions of the predictor (primarily related to the duration of mechanical ventilation) or differences in populations, as almost half the patients included in the aforementioned study were cardiac surgical patients [2].

We found that coagulopathy was a predictor of CIB in moderate–low risk of bias studies and for overt GI bleeding regardless of risk of bias. Coagulopathy was defined using biochemical variables in two studies (platelets < 50,000/mm^3 or international normalised ratio > 1.5 in both studies [2, 4], or partial thromboplastin time > 2 times the refence value in one study [2]) and using International Classification of Diseases (ICD)-9 codes in two studies [5, 22]. Enteral nutrition has also been mentioned as a possible protective factor [3]. Although enteral nutrition was associated with a decreased risk of CIB in 1 study not at high risk of bias [19], the pooled estimate (RE 0.63, 95% CI 0.17–2.37) suggests that this effect is unclear.

Acute kidney injury was associated with increased risk of CIB and overt GI bleeding in studies irrespective of risk of bias. Acute kidney injury was defined using biochemical variables and oliguria in 1 study [2] (creatinine clearance < 40 ml/min, urine output < 500 ml/day, or creatinine > 2.8 mg/dl [248 μmol/l]), as the need for renal replacement therapy on the first day of admission in 1 study [4], and according to ICD-9 codes in two studies [5, 22]. Additional identified predictors of overt GI bleeding included shock, sepsis, acute hepatic failure, chronic liver disease, and acute myocardial infarction. The identified predictors (except male gender) are all related to severity of illness and involved in mechanisms proposed to lead to stress-related GI bleeding in the critically ill, by being physiological stressors or by decreasing splanchnic perfusion or haemostatic competence [3].

Finally, our results indicate that male gender could be a predictor of both outcomes, but this could be a chance finding, and the point estimate from the 1 study not at high risk of bias [4] indicated a decreased although uncertain risk in males.

It is important to highlight that some analyses for overt GI bleeding included almost four times as many events as the corresponding analyses for CIB, leading to more precise estimates and thus more statistically significant predictors than for CIB.

The results of this systematic review and meta-analysis could prove useful for several reasons. First, the identification of patients at risk of CIB and overt GI bleeding may help clinicians consider, identify and prevent GI bleeding, which may improve outcomes. Second, as current knowledge on the potential adverse effects of SUP is uncertain [7, 8, 28], it may help clinicians target this intervention to patients who are most likely to benefit overall. The clinical applicability of these results, however, is somewhat hampered by most of the available evidence being from patients who received SUP, and it should be stressed that predictors of CIB and overt GI bleeding could be different in patients not receiving SUP.

Future research on this topic is needed, including studies conducted in populations not exposed to SUP or alternatively after adjustment for the use of SUP. All included studies assessed individual potential predictors; however, the cumulative risk of being exposed to multiple predictors or specific combinations of predictors may also be important [29]. Assessing the influence of simultaneous predictors and severity of illness on the risk of

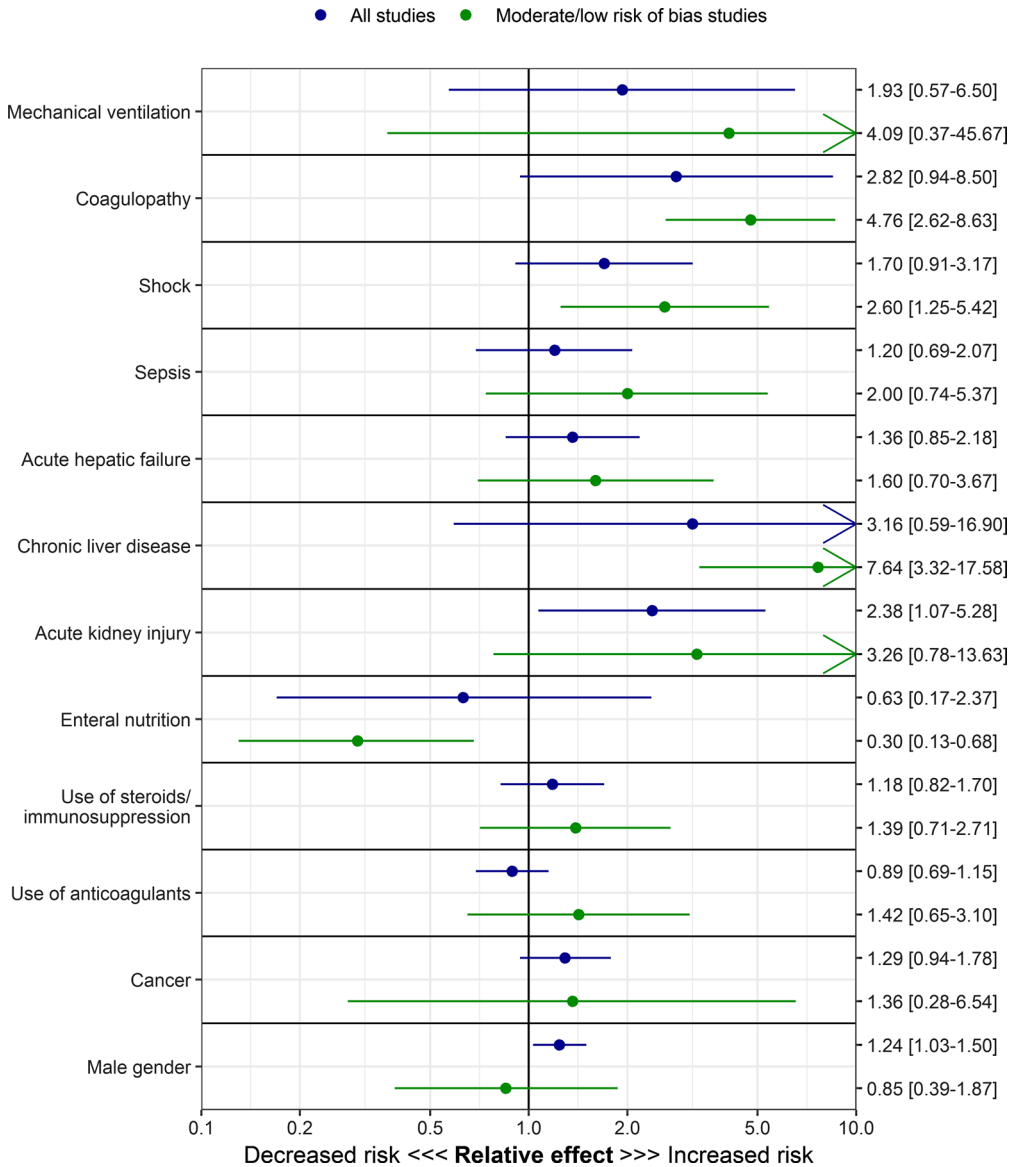

Fig. 2 Overview of potential predictors of clinically important GI bleeding. This figure presents all relative effects (points) with 95% confidence intervals (horizontal lines) for all included potential predictors of clinically important gastrointestinal (GI) bleeding. Arrows indicate values outside the plot (95% confidence interval smaller than 0.1 or larger than 10.0). Point estimates and 95% confidence intervals (in square brackets) are presented on the right side of the plot. Additional details can be found in Table 2 and the electronic supplementary material (ESM), where a similar figure for overt GI bleeding also can be found

CIB and overt GI bleeding could be useful, as could dedicated clinical prediction models [30].

Strengths and limitations of this review

This systematic review comes with several strengths. First, we performed a comprehensive and systematic literature search with no language or temporal restrictions. Second, our review was conducted according to recent recommendations for systematic reviews of prognostic factors [9], and study selection, data extraction, risk of bias assessments, and certainty of evidence assessments were performed independently and in duplicate using the QUIPS tool and the GRADE approach [12, 14]. Third, we included all potential predictors assessed in at least 2 studies, and when meta-analysis was not appropriate, we presented the results qualitatively. Fourth, we excluded studies with 20 or fewer events. While this led to exclusion of 53 studies (of which a substantial proportion likely

fulfilled multiple exclusion criteria), it also increased the confidence in the estimates presented, as studies with few events provide uncertain estimates and are at high risk of chance findings [31].

Our review also has limitations. First, the populations and potential predictors assessed were heterogenous, which may affect the interpretation and generalisability of the results. Second, as we only included adjusted estimates, the substantial variation in the used analytical strategies and adjustments may have affected the results. This is a common limitation in meta-analyses of prognostic factors and is hard to avoid; despite this obstacle, it is recommended to primarily focus on adjusted estimates [9]. Third, 3 of the studies presenting potential predictors for our secondary outcome (overt GI bleeding) may not have fulfilled the outcome and follow-up definitions completely; 1 study included a small proportion of lower GI bleeding [21], and in 2 studies, some events could have happened shortly after ICU discharge [5, 23] (details in ESM). Fourth, the evidence base was sparse with few events included in some of the analyses, which affects the certainty of evidence due to imprecision. Fifth, we meta-analysed different relative effect measures (ORs and HRs) together, which may have affected the summarised estimates [9]. As recommended [9], we presented separate summary estimates according to the effect measure used, but where differences were present, it was not possible to determine if this was due to a true heterogeneity or differences in effect measures used. Sixth, we did not estimate absolute risk differences for each potential predictor. This was not done due to several complicating factors, including the different effect estimates used, the varying event rates in the included studies, and the lack of baseline risks estimates from a population without any of the predictors, as most ICU patients will have one or more of the potential predictors assessed. Consequently, clinicians and guideline developers will have to estimate absolute risk differences based on these results and estimated baseline risks in the populations of interest. Seventh, there is a risk of chance findings due to the low event rate and the large number of analyses conducted. Finally, this review was undertaken in a short-time frame to inform the development of a guideline on the use of SUP; consequently, we did not register the review in PROSPERO or publish the protocol prior to conduct.

Conclusions

In this systematic review and meta-analysis of potential predictors of GI bleeding in adult ICU patients, we assessed 12 and 21 potential predictors of CIB and overt GI bleeding, respectively. Acute kidney injury, coagulopathy, shock, and chronic liver disease were consistently associated with increased risk of GI bleeding. These findings may help clinicians, guideline developers, and investigators to identify high-risk patients most likely to benefit from prophylactic acid suppression.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05751-6) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
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