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Research Article

Risk assessment tools for predicting transfusion in surgery: a systematic review and meta-analysis

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Abstract

Background: United Kingdom blood shortages necessitate better prediction of surgical blood requirement. We sought to assess the predictive accuracy of tools designed to identify those patients requiring blood transfusion within the perioperative period.

Methods: We searched the Cochrane library, EMBASE, MEDLINE, ClinicalTrials.gov and WHO trials portal, 2000–July 2023. We included studies that developed and/or validated prediction tools for blood requirement during the early perioperative period (48 hours). Risk of bias was evaluated using the Prediction model Risk Of Bias Assessment Tool. We pooled area under receiver operating curve and calibration data via random effects meta-analysis. We evaluated certainty of evidence of any estimates using the Grading of Recommendations Assessment, Development and Evaluation framework. We used meta-regression to describe associations between included variables/tool characteristics with tool accuracy.

Results: We included 50 papers, describing 67 unique prediction tools. Most tools were at high risk of bias, with limited external validation. Discrimination (area under receiver operating curve) of prognostic models ranged from 0.49 to 0.96. Only two surgery-specific tools, the McClusky Index (liver transplant surgery) and Papworth Bleeding Risk Score (cardiothoracic surgery), had sufficient data to enable pooling of discrimination measures. The McClusky Index's pooled area under receiver operating curve: 0.74 (95% CI 0.61 to 0.84) and Bleeding Risk Score's area under receiver operating curve: 0.68 (95% CI 0.49 to 0.82) were both rated 'very low' certainty by Grading of Recommendations Assessment, Development and Evaluation. Pooling calibration data was not possible for any prediction tools. Meta-regression suggested that fewer included variables, longer time from surgery and independent validation studies were all associated with lower accuracy.

Limitations: There were insufficient studies to assess overall tool performance via meta-analysis in other surgical subgroups beyond cardiothoracic surgery and liver transplant. Our study population is also predominantly made up of elective surgeries which may make our results less generalisable to emergency settings.

Future work: Implementation and cost-effectiveness studies are needed to evaluate how promising tools could be applied to clinical practice and the economic impact such tools could have upon the service.

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Conclusions: Despite the availability of multiple potential tools, available data suggest none are currently suitable for predicting blood transfusion in surgical practice. Our summary of the data comes with caveats around the quality of the included papers and the limited number of tools with more than one reported external validation.
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Introduction

Despite temporal reductions in the use of blood resources in the UK NHS,[1] an amber alert for blood shortages was issued in 2022, leading to cancellation of elective surgery and raising serious concerns over blood availability.[2] A series of patient blood management measures are described in the latest National Institute for Health and Care Excellence (NICE) blood transfusion guidelines.[3] Despite this, reports suggest that there is still room to optimise blood resource use.[4]

Multicomponent prediction tools are mathematical models that link a series of predictors to the probability of a certain outcome.[5] Using these tools to predict which patients would need transfusion before surgery offers several potential advantages: avoiding unnecessary cross-matching, targeting pre- or perioperative blood saving strategies, and rationalising administration of pharmacological products such as tranexamic acid.[6] Despite many tools for predicting surgical blood loss having been described, at present none are routinely used.

Previous reviews[7–9] have cast doubt on the accuracy and clinical usefulness of blood loss prediction tools; however, they have tended to describe tool test accuracy in isolation, prohibiting identification and selection of optimal tools where multiple exist. A broad evaluation of multicomponent prediction tools for blood loss, including a description of direct tool comparisons, is lacking.

The objective of this review was to determine to what extent multicomponent prediction tools can predict the need for transfusion during and immediately following various types of surgery, and whether any of the existing tools could be suitable for clinical use.

Study design and methods

This systematic review was registered in PROSPERO (www.crd.york.ac.uk/PROSPERO/view/CRD42023467613). We followed best practice for conduct and reporting of evidence synthesis for prediction tools[10] developing our question using the PICOTS format (see *Appendix 1*, *Table 7*).

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), EMBASE (Ovid SP), MEDLINE (Ovid SP), ClinicalTrials.gov and WHO trials portal: International Clinical Trials Registry Platform (ICTRP) using a search strategy devised for each database by an information scientist. The search aimed to identify any studies reporting the development or evaluation of transfusion prediction tools. We ran the search in July 2023. The full search strategy can be found in *Appendix 2*, *Table 8*.

The search was limited to human studies published in peer reviewed scientific journals in English. We included studies published from January 2000, to ensure included data are relevant to contemporary surgical practice. Where papers described development of a prediction tool, forward citation searches were conducted to check for independent publications validating the tool.

Retrieved records were deduplicated and, after a first assessment, imported into Covidence software (Veritas Health Innovation, Melbourne, VIC, Australia). Two researchers (Abril Seyahian, Martin Taylor-Rowan) independently screened titles and abstracts against eligibility criteria. Disagreements were resolved through discussion with recourse to a third reviewer as needed (Terry J Quinn).

The full texts of potentially includable studies identified in title and abstract screening were retrieved. One reviewer assessed the full text of all articles (Abril Seyahian) and a second reviewer assessed 20% (Martin Taylor-Rowan).

Inclusion criteria

We included studies that attempted to create a prediction tool for blood transfusion or blood loss within the perioperative period. Initial scoping suggested there would be insufficient studies to focus on specific surgical subgroups. Therefore, our definition of surgery included emergency and elective surgery, paediatric and obstetric procedures. We did not include interventional radiological procedures. We defined the period of interest as the first 48 hours following surgery (inclusive of the intraoperative period). There is no consensus on what constitutes

the 'perioperative' period, and we chose a period that should allow for assessment of all blood loss that is directly attributable to the surgery, as opposed to later complications. Where a study simply referenced the 'peri-operative period' without specific timing, study authors were contacted. If no clarification was provided, these studies were excluded.

To be included, tools needed to have evidence of at least one validation exercise – internal validation or external validation. If the original tool development paper was excluded, for example for predicting outcome at the wrong time, subsequent validation papers may still have been included if they met our inclusion criteria.

Prediction tools included were both generic and designed for particular surgical interventions. Tools were required to include more than two predictor variables that were plausibly independent of each other. We excluded studies describing a prognostic factor in isolation or studies that described the association of multiple variables with blood loss or transfusion but that did not attempt to create a model for clinical use.[6,7,11–14]

Outcomes of interest

To speak to our inclusions of interest that is, transfusion and blood loss, we had a primary outcome of 'transfusion required in the perioperative period'. We chose this because of its clinical relevance, and because the dichotomous nature of the outcome avoids issues[15] associated with estimating absolute surgical blood loss.

We had various secondary outcomes relating to blood loss: absolute volume of perioperative blood loss (ml), number of perioperative blood transfusions, levels of postoperative haemoglobin (as an absolute value or as a proportion of patients below a threshold), clinically significant bleeding (as defined by study authors) and bleeding causing death or other harm (prolonged length of stay or need for higher level of care in the postoperative period).

We also aimed to compare tools to one another. While techniques allow for indirect comparisons of predictive accuracy across tools, the ideal is to directly compare tools in a common data set to avoid the introduction of confounding factors in the analysis. Where papers presented direct comparative analyses, we extracted these data and presented them separately.

Data extraction

One reviewer extracted data from all the included studies (Abril Seyahian) which was then cross-checked by a second reviewer (Martin Taylor-Rowan). Only published data were extracted. Unpublished data were not sought to ensure that all data utilised had been peer reviewed.

Extracted data included study specific data, surgery details, baseline patient data, operation details (such as the use of tranexamic acid during surgery, autologous blood saving, operation time), model data (variables considered for the model, variables included in the model), performance measures and outcome measures. We made no assumptions about surgical approach or urgency based on the operation described.

Risk-of-bias assessment

Risk of bias (RoB) was independently assessed by two reviewers (Abril Seyahian, Martin Taylor-Rowan) using Prediction model Risk Of Bias Assessment Tool (PROBAST). Final ratings were based on consensus, with recourse to a third reviewer (Terry J Quinn) where needed. We created data visualisations to present RoB at study level and in aggregate.[16]

Data synthesis

We described results of our search using a Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram, and tabulated details of all included tools. We created tables describing the component items of each prediction tool, with one table including all items as described in the paper and one table collating items under common themes.

Where possible we described accuracy of prediction tools in terms of discrimination [area under receiver operating curve (AUROC) and calibration (Observed events to Expected events (O:E ratio)]. Where AUROC and O:E ratio standard errors were missing, we estimated standard error from either a confidence interval (CI), or total sample size and number of observed events using the metamisc R package.[17] If these data were unavailable, where possible, a standard error was estimated using a previously described formula[18] and AUROC estimated by 0.5 (sensitivity + specificity).[19]

Where the same tool and same outcomes were assessed in three or more independent studies, random-effects meta-analyses of measures (with standard error) were conducted to obtain pooled estimates with 95% confidence intervals for individual prediction tools. Meta-analyses were conducted on logit transformed values and used statistical software R 4.2.3 (The R Foundation for Statistical Computing, Vienna, Austria)[20] with the metamisc[17] and metafor[21] packages for producing forest plots (with original units). A funnel plot including all studies was generated to evaluate publication bias.

This research article should be referenced as follows:
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A meta-regression was conducted considering any prediction tool to assess if selected factors had an impact on model discrimination overall. Factors considered were (1) whether the data set was for development, internal validation, or external validation, (2) timing of the outcome (intraoperative, 24 hours, or 48 hours), and (3) number of components in the prediction tool. Factors were considered separately and together. Meta-regressions were conducted separately for studies that considered any transfusion and massive transfusion, where massive transfusion was defined as ≥ 6 units.[22] Some studies developed and conducted external validations on different tools using the same data set. In order to ensure overinterpretation was avoided, through inclusion of such data but assuming estimates were independent, a sensitivity analysis was also conducted, where for studies with more than one tool, only the simplest (fewest number of components) tool was included.

We evaluated the certainty of evidence of any summary statistics via the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[23] There is currently no consensus guidance on the application of GRADE to prognostic modelling studies. Therefore, we adopted an approach outlined in a previous review,[24] which takes the standard GRADE approach and applies to clinical prediction, and supplemented this with more recently published guidance.[25]

Involvement of key interest holders

Members of our evidence synthesis unit's patient and public involvement group along with colleagues working in surgery, haematology or within the national blood transfusion service provided feedback throughout the review process. We held online meetings with clinicians, public contributors and national blood transfusion service and used these meetings to refine the review questions and outcomes of interest, to sense-check the preliminary results and to aid with the clinical and policy interpretation of the final analyses.

Results

Fifty papers met our inclusion criteria (*Figure 1*), of which 42 described development of prediction tools. A total of 67 unique prediction tools were identified, 56 development exercises were performed within included papers, 47 internal validations were performed, and 36 tools were externally validated. One included paper was subsequently found to have been retracted and was excluded from analyses.

Studies overview

Included studies were from various countries and included various surgeries (see *Appendix 3*, *Table 9*) Only 18 papers considered our primary outcome of transfusion as a binary outcome.[26–43]

Twenty-eight papers looked at transfusion during the intraoperative period, 16 papers considered the first 24 hours after surgery (including or excluding the intraoperative period) and the remaining 6 papers considered transfusions within 48 hours of surgery (including or excluding the intraoperative period) (see *Appendix 3*, *Table 9*).

For secondary outcomes, 16 studies reported absolute volume blood loss,[31,33,39,44–56] 22 studies reported number of blood transfusions,[30,33,34,36,38–40,44,49,50,53,56–66] 5 studies reported postoperative haemoglobin[44,50,53,56,58] and 1 study reported discharge haemoglobin,[34] 8 studies reported clinically significant bleeding,[46–48,52,54,55,67,68] and 6 studies reported bleeding causing death or other harm.[33,42,44,54,64,68]

Models and variables

Over 200 distinct variables were considered across the 67 unique models. We created 19 categories to classify these variables (see *Appendix 4*, *Table 10*). Most models contained five variables, while the average number of variables per model was seven. The largest number of variables contained within a model was 22.[60] The most commonly included variables were related to full blood count (n = 47 tools), surgery (n = 43) and demographics (n = 35).

Performance of the included models

Discrimination (AUROC) ranged from 0.67 to 0.96 in development studies, from 0.69 to 0.96 in internal validation studies, and from 0.49 to 0.94 in external validation studies. Study details can be seen in *Appendix 3*, *Table 9*. Calibration data were not suitable for synthesis. In the majority (n = 25) of the included studies, there was no description of calibration. Calibration was assessed via visual examination of calibration plots in just 17 studies. The Hosmer–Lemeshow test was the most commonly used statistical test to assess calibration (11 studies). Five studies employed the Hosmer–Lemershow test alone to assess calibration despite the potential for bias in this approach.

Direct comparisons between prediction tools

A total of four papers made direct comparisons between prediction tools. It was not possible to pool result from these papers in a meta-analysis. However, the results reported from the individual studies are detailed below and shown in *Figure 2*.

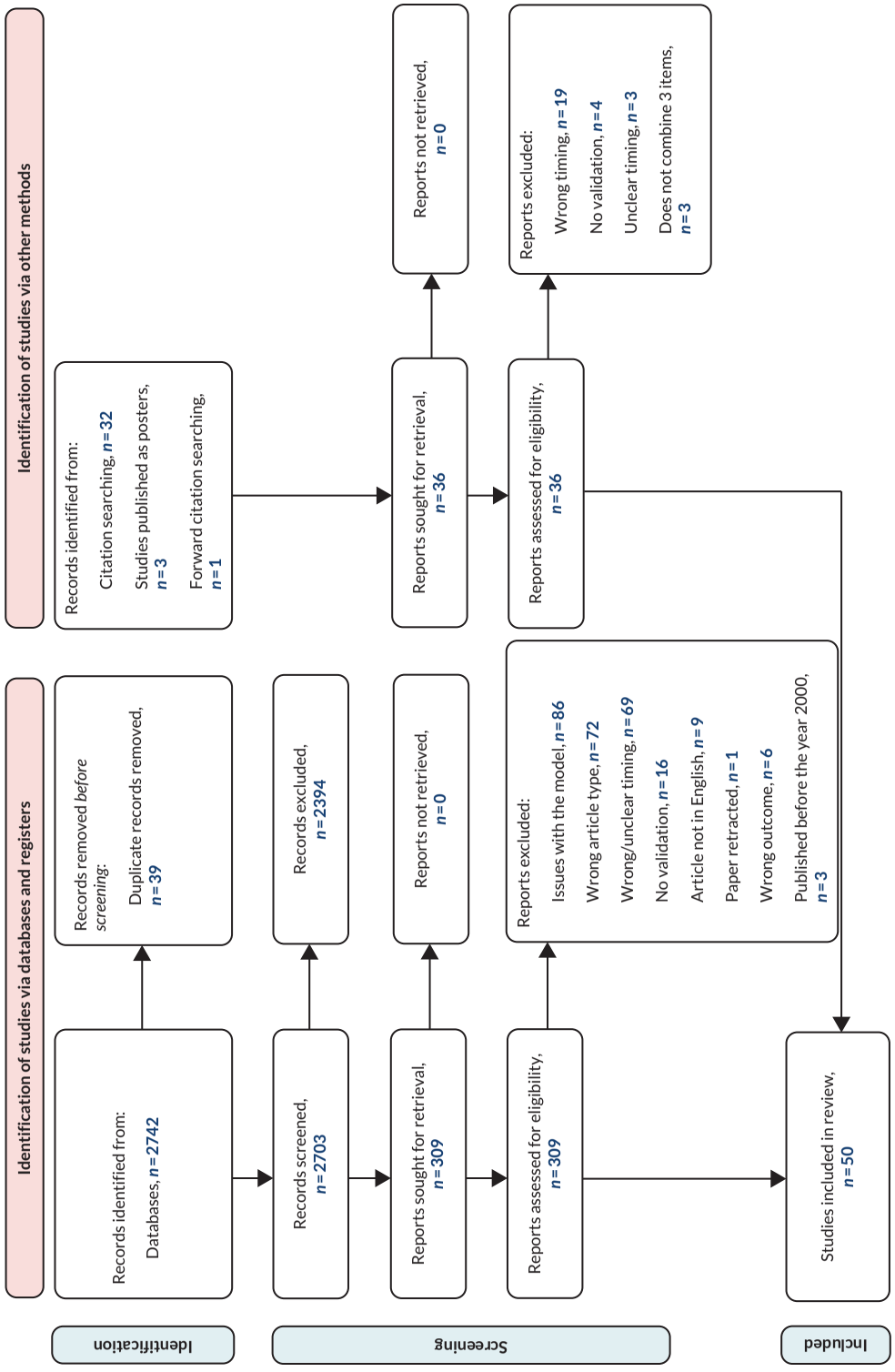

FIGURE 1 PRISMA diagram.

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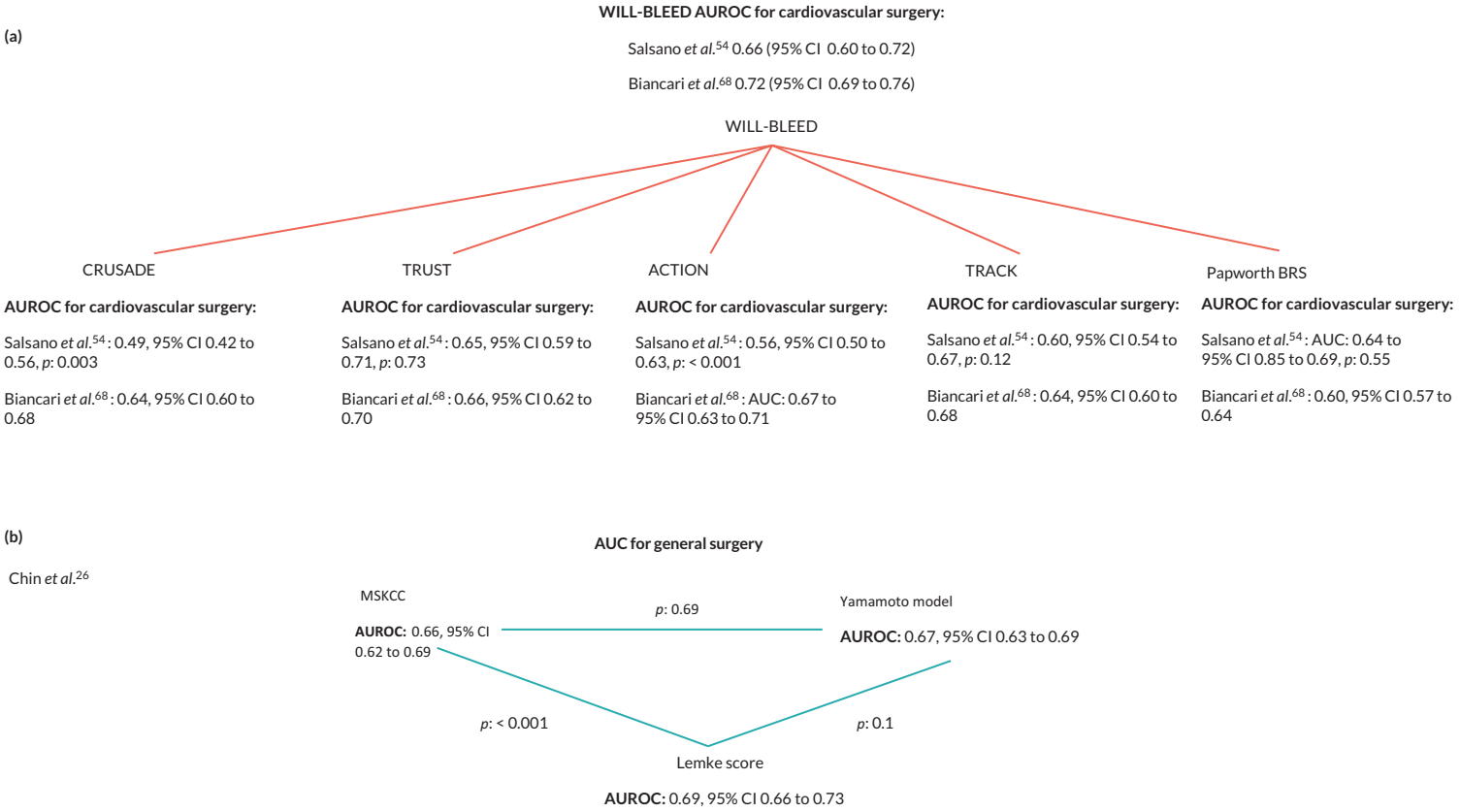

FIGURE 2 Individual study comparisons of different bleeding risk scores for cardiovascular surgery against WILL-BLEED (a). Individual study comparison of three models predicting transfusion risk for general surgery (b). AUROC, area under the curve; BRS, Bleeding Risk Score.

Biancari *et al.*[68] and Salsano *et al.*[54] directly compared six scores for bleeding risk in cardiovascular surgery. Both studies concluded that the WILL-BLEED score outperformed others (see *Figure 2*).

Chin compared three tools for liver transplant: Lemke transfusion risk score,[69] MSKCC nomogram[70] and Yamamoto model.[43] Only the Lemke score showed good calibration[26] (see *Figure 2*).

In orthopaedic surgery, Carabini *et al.*[56] compared their prediction tool to the Predictive Model of Transfusion in Spine Surgery (PMTSS). The authors reported a significant difference favouring their new prediction tool (difference in AUROC: −0.25; 99% CI −0.40 to −0.10). Calibration was not assessed for either model.[56]

Prediction tools with external validation

Of the included tools, 12 had been validated in independent data sets.[27,43,48,62,68–75] In general, tool performance was poorer in external validation studies than in the original development studies (*Table 1*).

Risk-of-bias analysis

Fifty one out of 56 tool development studies were rated as high RoB in at least 1 domain, while 43 out of 48 tool validation studies were rated high RoB in at least 1 domain (*Tables 2* and *3*). Common issues within both development and external validation studies were around analyses (*Figures 3* and *4*). Applicability concerns were often around outcomes for both development and validation studies (*Figure 5*).

TABLE 1 Meta-regression results regarding discrimination (AUROC) of prediction tools for any transfusion

Type of regression	Factor/variable		Group AUROC estimate	Coefficient[a]	Test of statistical significance[b]
Factors considered independently	Type of data set	Development (*n* = 30)	0.82 (95% CI 0.79 to 0.85)	N/A	*p* = 0.001
		Internal validation (*n* = 9)	0.85 (95% CI 0.79 to 0.89)	N/A	
		External validation (*n* = 27)	0.74 (95% CI 0.69 to 0.78)	N/A	
	Timing	Intraoperative (*n* = 30)	0.83 (95% CI 0.80 to 0.86)	N/A	*p* = 0.004
		24 hours (*n* = 22)	0.79 (95% CI 0.75 to 0.83)	N/A	
		48 hours (*n* = 14)	0.72 (95% CI 0.65 to 0.78)	N/A	
	Number of components in model	N/A	0.05 (95% CI 0.02 to 0.08)	*p* < 0.001	
Factors considered together	External validation (vs. development)	N/A	−0.38 (95% CI −0.68 to −0.09)	*p* = 0.011	
	Internal validation (vs. development)	N/A	0.05 (95% CI −0.37 to 0.46)	*p* = 0.831	
	24 hours (vs. intraoperative)	N/A	−0.29 (95% CI −0.59 to 0.01)	*p* = 0.058	
	48 hours (vs. intraoperative)	N/A	−0.50 (95% CI −0.85 to −0.14)	*p* = 0.006	
	Number of components in model	N/A	0.050 (95% CI 0.02 to 0.07)	*p* = 0.001	

a This represents the increase in AUROC per unit increase [e.g. for number of components in model, the coefficient represents the increase in AUROC per additional component (on logit scale)].
b When considering a categorical factor on its own, this is a joint test of significance; otherwise, it is a test of significance regarding the regression variable.

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TABLE 2 Risk of bias and applicability assessment for development studies

	Risk of bias				Applicability			Overall	
Author, year	1. Participants	2. Predictors	3. Outcome	4. Analysis	1. Participants	2. Predictors	3. Outcome	Risk of bias	Applicability
Alghamadi, 2006[27]	+	+	+	–	+	+	+	–	+
Biancari, 2017[68]	+	+	+	–	+	+	–	–	–
Booth, 2022[28]	?	–	+	–	+	+	+	–	+
Cao, 2022[29]	?	+	+	–	+	+	–	–	–
Carabini, 2014[56]	?	–	–	–	+	+	–	–	–
Chen, 2022[76]	?	+	–	–	+	+	–	–	–
Covin, 2003 – FFP transfusion model[30]	?	+	+	–	?	+	–	–	–
Covin, 2003 – platelet transfusion model[30]	?	+	+	–	?	+	–	–	–
Covin, 2003 – RBC transfusion model[30]	?	+	+	–	?	+	–	–	–
Cywinski, 2014 > 20 units CART analysis[66]	?	?	?	–	+	+	–	–	–
Cywinski, 2014 > 20 units[66]	?	+	?	–	+	+	–	–	–
Cywinski, 2014 > 30 units CART analysis[66]	?	?	?	–	+	+	–	–	–
Cywinski, 2014 > 30 units analysis[66]	?	+	?	–	+	+	–	–	–
Engel, 2021[31]	+	–	–	–	+	+	+	–	+
Feng, 2021 – Model 1[65]	+	+	+	–	+	+	+	–	+
Feng, 2021 – Model 2[65]	+	+	+	–	+	+	–	–	–
Gao, 2020[49]	?	+	?	–	+	+	–	–	–
Greiff, 2015 – locally developed model 1[47]	+	+	+	+	+	+	–	+	–
Greiff, 2015 – locally developed model 2[47]	+	+	+	+	+	+	–	+	–
Greiff, 2015 – locally developed model 3[47]	+	+	+	+	+	+	–	+	–
Greiff, 2015 – locally developed model 4[47]	+	+	+	+	+	+	–	+	–

TABLE 2 Risk of bias and applicability assessment for development studies (*continued*)

	Risk of bias				Applicability			Overall	
Author, year	1. Participants	2. Predictors	3. Outcome	4. Analysis	1. Participants	2. Predictors	3. Outcome	Risk of bias	Applicability
Guo, 2021[32]	–	+	+	–	+	+	–	–	–
Huang, 2021[33]	?	–	+	–	+	+	–	–	+
Huang, 2015[77]	?	+	+	–	+	+	+	–	+
Jalali, 2020[78]	+	–	+	–	+	+	–	–	–
Karkouti, 2001[34]	+	+	+	–	+	+	+	–	+
Karkouti, 2006[79]	+	+	+	–	+	+	–	–	–
Kim, 2017[57]	+	–	+	–	+	+	–	–	–
Li, 2023[80]	?	+	+	–	+	+	–	–	–
Liu, 2021[36]	?	–	+	–	+	+	+	–	+
Lou, 2022[37]	+	+	+	+	+	+	+	+	+
Massicotte, 2009[58]	?	–	–	–	+	+	–	–	–
Massicotte, 2018[50]	+	–	–	–	+	+	–	–	–
Mathai, 2012[51]	+	–	–	–	+	+	–	–	–
McCluskey, 2006[62]	+	+	+	–	+	+	–	–	–
Metcalf, 2018[81]	+	+	?	–	+	+	–	–	–
Nie, 2021 – femoral fracture model[63]	?	+	+	–	+	+	–	–	–
Nie, 2021 – posterior lumbar model[63]	?	+	+	–	+	+	–	–	–
Paiva, 2021[38]	?	+	+	–	+	+	–	–	–
Park, 2022[52]	?	–	–	–	+	+	–	–	–
Pennington, 2021 (IOBL)[39]	+	+	+	–	+	+	–	–	–
Pennington, 2021 (transfusion)[39]	+	+	+	–	+	+	+	–	+
Pennington, 2020[82]	?	–	–	–	+	+	–	–	–
Pustavoitau, 2017[83]	+	+	+	–	+	+	–	–	–
Pustavoitau, 2020 – ModRI[64]	+	+	+	–	+	+	–	–	–
Shah, 2010[40]	+	+	+	–	+	+	+	–	+

continued

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TABLE 2 Risk of bias and applicability assessment for development studies (*continued*)

	Risk of bias				Applicability			Overall	
Author, year	**1. Participants**	**2. Predictors**	**3. Outcome**	**4. Analysis**	**1. Participants**	**2. Predictors**	**3. Outcome**	**Risk of bias**	**Applicability**
Shen, 2021[44]	?	+	+	–	+	–	–	–	–
van Klei, 2001[41]	?	+	+	–	+	+	+	–	+
Vuylsteke, 2011[48]	+	+	+	–	+	+	–	–	–
Wang, 2022[84]	?	+	+	–	+	+	+	–	+
Yamamoto, 2011[55]	?	+	–	–	+	+	–	–	–
Yamamoto, 2014[43]	?	+	+	–	+	+	–	–	–
Yin, 2021 CT-based clinical-RN1[46]	?	?	?	–	+	+	–	–	–
Yin, 2021 CT-based clinical-RN2[46]	?	?	?	–	+	+	–	–	–
Yin, 2021 CTE-based clincal-RN2[46]	?	?	?	–	+	+	–	–	–
Yin, 2021 CTE-based clinical-RN1[46]	?	?	?	–	+	+	–	–	–

CART, Classification and Regression Tree; FFP, fresh-frozen plasma; RBC, red blood cell.

TABLE 3 Risk of bias and applicability assessment for validation studies

	Risk of bias				Applicability			Overall	
Author, year	1. Participants	2. Predictors	3. Outcome	4. Analysis	1. Participants	2. Predictors	3. Outcome	Risk of bias	Applicability
Alghamadi, 2006[27]	+	+	+	–	+	+	+	–	+
Biancari, 2017 – ACTION[68]	+	?	+	–	+	+	–	–	–
Biancari, 2017 – CRUSADE[68]	+	+	+	–	+	+	–	–	–
Biancari, 2017 – Papworth[68]	+	+	+	–	+	+	–	–	–
Biancari, 2017 – TRACK[68]	+	+	+	–	+	+	–	–	–
Biancari, 2017 – TRUST[68]	+	+	+	–	+	+	–	–	–
Carabini, 2014[56]	?	–	–	–	+	+	–	–	–
Carabini, 2014 – PMTSS[56]	?	+	+	–	+	+	–	–	–
Chen, 2022[76]	?	+	–	–	+	+	–	–	–
Chin, 2022 – MSKCC[26]	+	+	+	?	+	+	–	?	–
Chin, 2022 – TRS[26]	+	+	+	?	+	+	–	?	–
Chin, 2022 – Yamamoto[26]	+	+	+	?	+	+	–	?	–
Escoresca Ortega, 2008[59]	?	+	+	–	+	+	–	–	–
Gao, 2020[49]	?	+	?	–	+	+	–	–	–
Greiff, 2015 – Papworth bleeding alt out[47]	+	+	+	–	+	+	–	–	–
Greiff, 2015 – Papworth bleeding risk[47]	+	+	+	–	+	+	–	–	–
Guo, 2021[32]	–	+	+	–	+	+	–	–	–
Justo, 2021[61]	+	+	+	–	+	+	–	–	–
Karkouti, 2001[34]	+	+	+	–	+	+	+	–	+
Karkouti, 2006[79]	+	+	+	–	+	+	–	–	–
Kim, 2017[57]	+	–	+	–	+	+	–	–	–
Leff, 2019 (all transfusions)[35]	+	+	+	–	+	+	–	–	–
Leff, 2019 (RBC transfusions)[35]	+	+	+	–	+	+	–	–	–
Li, 2023[80]	?	+	+	–	+	+	–	–	–

continued

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TABLE 3 Risk of bias and applicability assessment for validation studies (*continued*)

	Risk of bias				Applicability			Overall	
Author, year	1. Participants	2. Predictors	3. Outcome	4. Analysis	1. Participants	2. Predictors	3. Outcome	Risk of bias	Applicability
Lou, 2022[37]	+	+	+	+	+	+	–	+	–
Massicotte, 2009[58]	?	–	–	–	+	+	–	–	–
Mathai, 2012[51]	+	–	–	–	+	+	–	–	–
Nie, 2021 – femoral fracture model[63]	?	+	+	–	+	+	–	–	–
Nie, 2021 – posterior lumbar model[63]	?	+	+	–	+	+	–	–	–
Priem, 2022 – Nomogram A[53]	+	–	–	–	+	+	–	–	–
Priem, 2022 – Nomogram B[53]	+	–	–	–	+	+	–	–	–
Priem, 2022 – Nomogram C[53]	+	–	–	–	+	+	–	–	–
Pustavoitau, 2017[83]	+	+	+	–	+	+	–	–	–
Pustavoitau, 2020 – McCluskey[64]	+	+	+	–	+	+	–	–	–
Saber, 2018[67]	+	+	–	–	+	+	–	–	–
Salsano, 2020 – ACTION[54]	+	?	+	–	+	+	–	–	–
Salsano, 2020 – CRUSADE[54]	+	+	+	–	+	+	–	–	–
Salsano, 2020 – PAPWORTH[54]	+	+	+	–	+	+	–	–	–
Salsano, 2020 – TRACK[54]	+	+	+	–	+	+	–	–	–
Salsano, 2020 – TRUST[54]	+	+	+	–	+	+	–	–	–
Salsano, 2020 – WILL-BLEED[54]	+	?	+	–	+	+	–	–	–
Vlot, 2022[42]	+	+	+	+	+	+	+	+	+
Wang, 2022[84]	?	+	+	–	+	+	+	–	+
Yamamoto, 2011[55]	?	+	–	–	+	+	–	–	–
Yin, 2021 CT-based clinical-RN1[46]	?	?	?	–	+	+	–	–	–
Yin, 2021 CT-based clinical-RN2[46]	?	?	?	–	+	+	–	–	–
Yin, 2021 CTE-based clinical-RN2[46]	?	?	?	–	+	+	–	–	–
Yin, 2021 CTE-based clinical-RN1[46]	?	?	?	–	+	+	–	–	–

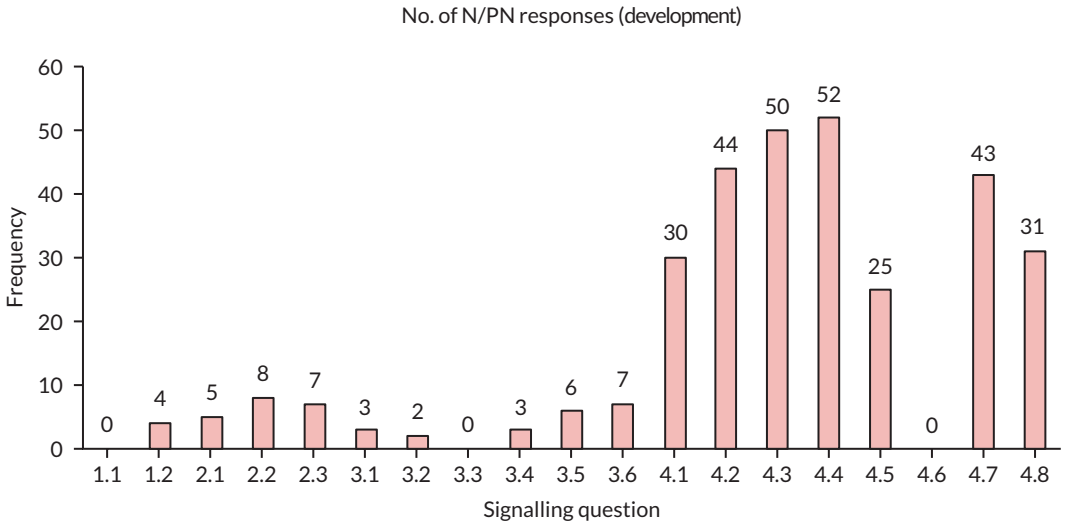

FIGURE 3 Frequency each signalling question was answered N/PN for development studies. N, No; PN, Probably no.

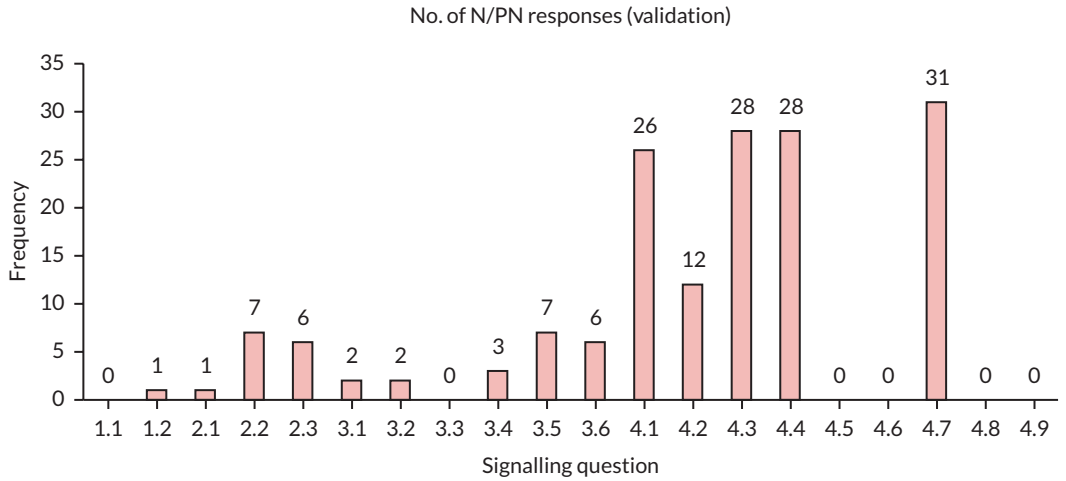

FIGURE 4 Frequency each signalling question was answered N/PN for validation studies. N, No; PN, Probably no.

Percentage of low/unclear/high concern ratings within each domain

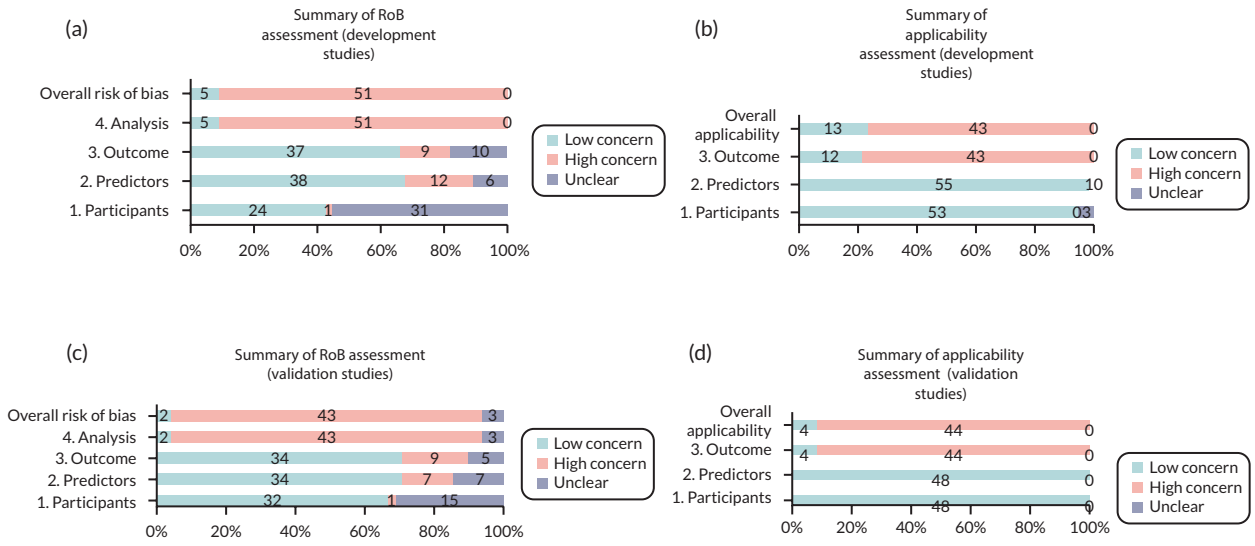

FIGURE 5 Summary of RoB assessment for development studies (a) and validation studies (c). Summary of applicability assessment for development studies (b) and validation studies (d). These figures show the proportion of studies that received specific ratings (low/unclear/high concern of bias) within our RoB assessment. The x axis is the percentage of low/unclear/high concern ratings within each domain. The Y axis is the name of the RoB domain.

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Meta-analysis

Data were highly heterogeneous across studies. Lack of external validations and variation in outcome measurement precluded producing individual prediction tool pooled estimates from most prediction tools. Only the McClusky Index and Papworth Bleeding Risk Score (BRS) had suitable data from three or more independent studies to warrant pooling (*Figure 6*).

Four studies[59,61,62,64] (1978 participants) assessed the McClusky index for predicting transfusion following massive blood loss, pooled AUROC: 0.74 (95% CI 0.61 to 0.84).

Three studies[47,54,68] (12,042 participants) assessed Papworth BRS for predicting transfusion following massive blood loss, pooled AUROC: 0.68 (95% CI 0.49 to 0.82).

No predictive models provided calibration statistics in a form that would enable pooling.

Data from all secondary outcomes were too heterogeneous to pool.

Meta-regression

When considering any prediction tool, combining measures of discrimination for any transfusion (n = 66) gave a pooled AUROC of 0.80 (95% CI 0.77 to 0.82) with between-study heterogeneity τ^2 = 0.42. Analyses (see *Table 1*) suggested later outcome assessment, fewer included variables in the model and validation cohorts all had lower discrimination (τ^2 reduced to 0.27 in combined model).

The sensitivity analysis where duplicate populations were removed (*Table 4*) gave similar results; however, statistical significance was reduced regarding some factors.

Association with discrimination was less clear for analyses limited to massive transfusion (n = 18) (*Table 5*).

GRADE

The certainty of evidence for the Papworth BRS was rated 'very low'. Similarly, certainty of evidence for the McClusky index was 'very low' (*Table 6*).

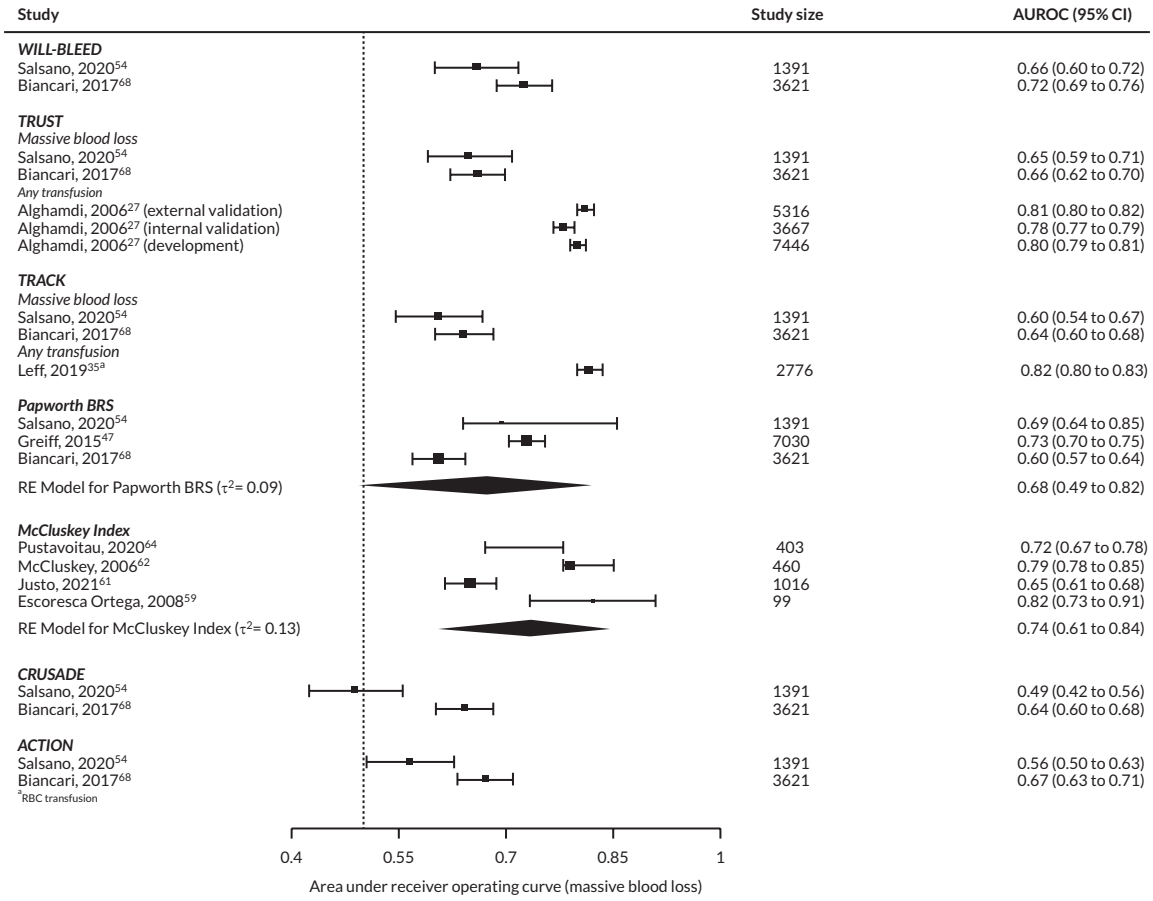

FIGURE 6 Forest plot of measures for discrimination of named prediction tools (where meta-analyses could be conducted, the size of squares indicate weightings). RBC, red blood cell.

TABLE 4 Meta-regression results regarding discrimination (AUROC) of prediction tools for any transfusion with duplicated populations removed (sensitivity analysis)

Type of regression	Factor/variable		Group AUROC estimate	Coefficient[a]	Test of statistical significance[b]
Factors considered independently	Type of data set	Development (*n* = 25)	0.84 (95% CI 0.81 to 0.87)	N/A	*p* = 0.339
		Internal validation (*n* = 9)	0.85 (95% CI 0.79 to 0.89)	N/A	
		External validation (*n* = 14)	0.80 (95% CI 0.75 to 0.85)	N/A	
	Timing	Intraoperative (*n* = 25)	0.77 (95% CI 0.70 to 0.83)	N/A	*p* = 0.093
		24 hours (*n* = 14)	0.85 (95% CI 0.81 to 0.87)	N/A	
		48 hours (*n* = 9)	0.84 (95% CI 0.79 to 0.88)	N/A	
	Number of components in model		N/A	0.06 (95% CI 0.03 to 0.08)	*p* < 0.001
Factors considered together	External validation (vs. development)		N/A	−0.13 (95% CI −0.47 to 0.21)	*p* = 0.456
	Internal validation (vs. development)		N/A	−0.77 (95% CI −0.47 to 0.31)	*p* = 0.701
	24 hours (vs. intraoperative)		N/A	−0.17 (95% CI −0.50 to 0.16)	*p* = 0.311
	48 hours (vs. intraoperative)		N/A	−0.33 (95% CI −0.71 to 0.06)	*p* = 0.096
	Number of components in model		N/A	0.05 (95% CI 0.03 to 0.08)	*p* < 0.001

N/A, not applicable.
a This represents the increase in AUROC per unit increase [e.g. for number of components in model, the coefficient represents the increase in AUROC per additional component (on logit scale)].
b When considering a categorical factor on its own, this is a joint test of significance; otherwise, it is a test of significance regarding the regression variable.

TABLE 5 Meta-regression results regarding discrimination (AUROC) of prediction tools for massive transfusion

Type of regression	Factor/variable	Group AUROC estimate	Coefficient[a]		Test of statistical significance[b]
Factors considered independently	Type of data set		Estimate not reported due to lack of significance		*p* = 0.756
	Timing	Intraoperative (*n* = 13)	0.77 (95% CI 0.74 to 0.81)	N/A	*p* = 0.015
		24 hours (*n* = 4)	0.84 (95% CI 0.78 to 0.89)	N/A	
		48 hours (*n* = 1)	0.65 (95% CI 0.50 to 0.77)	N/A	
	Number of components in model		Estimate not reported due to lack of significance		*p* = 0.755

N/A, not applicable.
a This represents the increase in AUROC per unit increase [e.g. for number of components in model, the coefficient represents the increase in AUROC per additional component (on logit scale)].
b When considering a categorical factor on its own, this is a joint test of significance, otherwise, it is a test of significance regarding the regression variable.

TABLE 6 Summary of findings

Review question: To what extent are multicomponent prediction tools able to predict need for transfusion during and immediately following surgery?

Population: Surgical patients

Setting: Emergency and elective surgery, including obstetrics

Intervention (model)**:** Multicomponent prediction tools

Comparison: (if available) other multicomponent prediction tools

Outcome: Transfusion

TABLE 6 Summary of findings (*continued*)

	Pooled AUROC	No. of participants	Certainty of evidence (GRADE)	Pooled calibration	Certainty of evidence (GRADE)	Comments
McClusky Index	0.74 (95% CI 0.61 to 0.84)	1978 (Four studies)	⊕⊖⊖⊖ Very low [a,b,c,d]	N/A	N/A	Findings restricted to studies included in our primary meta-analysis evaluating the ability of the McClusky Index to predict need for blood transfusion following massive blood loss. Pooling of calibration data was not possible
Papworth BRS	0.68 (95% CI 0.49 to 0.82)	12,042 (Three studies)	⊕⊖⊖⊖ Very low [a,b,c,d,e]	N/A	N/A	Findings restricted to studies included in our primary meta-analysis evaluating the ability of the Papworth BRS to predict need for blood transfusion following massive blood loss. Pooling of calibration data was not possible.

N/A, not applicable.
a Downgraded 1 point due to high RoB in all included studies.
b Downgraded 1 point due inconsistency in AUROC point estimate.
c Downgraded 1 point for indirectness due to applicability concerns apparent within all included studies.
d Downgraded 1 point due to publication bias.
e Downgraded 1 point for imprecision due to confidence intervals crossing 0.5.

Discussion

Principal findings

We identified several tools designed to predict blood transfusion during the perioperative period. Unfortunately, most tools lack substantive external validation and are at high RoB. Thus, the reported prognostic accuracies are likely overly optimistic. Only the McClusky Index and Papworth BRS had sufficient data for quantitative synthesis, and our meta-analysis indicates that relying on either tool to gauge need for transfusion in liver transplant or cardiothoracic surgery, respectively, would lead to large numbers of misclassifications, resulting in either inappropriate cross-matching of blood or patients not having immediate access to required blood products.

Direct comparisons between tools were sparse; only the WILL-BLEED tool was compared against other tools in more than one study, and while a performance advantage was reported for use in cardiovascular surgery, the overall predictive accuracy reported in individual studies was still inadequate (AUROC: 0.65–0.72).

Strengths and weaknesses of studies

Various factors contributed to the low quality of evidence we observed. Reporting was problematic, few studies clearly described the surgical approach used, or other factors that could influence predictive accuracy, such as population characteristics (e.g. adult or paediatric), pre-surgical or intraoperative interventions (e.g. cell salvage), or timing of transfusion. Moreover, the analysis approach adopted by most studies did not follow best practice,[85] increasing risk of model overfitting, while key aspects of model performance such as calibration were either not evaluated or assessed using suboptimal methods.[7]

The methodological issues identified in the included studies are not unique to the surgical setting.[86] A recent review highlighted that bleeding risk prediction tools typically lack accuracy and are at high RoB.[86] Similarly, Gianola *et al.* evaluated blood loss prediction tools for trauma and concluded that most tools were at unclear RoB.[87]

There was considerable variability in the variables included within models, yet certain factors considered highly related to transfusion requirements (e.g. pre-surgical haemoglobin) were not always included in prediction tools. This likely reflects a general uncertainty regarding the most important factors for predicting transfusion, with over-reliance on statistical selection techniques and insufficient use of clinical expertise and available evidence in choice of component variables.

Implications for research and practice

The available data do not suggest a predictive tool suitable for use in clinical practice. A fundamental question that cannot currently be answered is if new tools are needed. It is unclear if any new tool would reach a threshold for clinical utility by employing existing methods.

Our review highlights aspects of study design that could be improved in future studies that seek to develop new tools, or further validate existing prognostic tools, for blood transfusion or blood loss.

Firstly, researchers should refer to established guidance[88,89] when planning, conducting and reporting prognostic modelling studies. Secondly, researchers should also ensure that any promising tool is externally validated and compared with other tools to establish generalisability and optimal tool selection.

Thirdly, feasibility of tool usage needs to be considered, for example tools requiring more than 22 distinct variables before a prediction can be made would seem impractical for most settings. We would encourage researchers to involve end users (i.e. clinicians) in all stages of the development of a prediction tool to ensure that they are suitable for clinical implementation at scale.

Lastly, implementation and cost-effectiveness studies are particularly needed to evaluate how promising tools could be applied to clinical practice and the economic impact such tools could have upon the service. It is crucial that this is conducted within the context of clinical acumen. At present, many tools are not compared against clinician-based judgements of blood requirements, which prohibits our ability to determine what improvements prognostic tools could add to clinical practice.

Patient and public involvement or community engagement

We worked with multidisciplinary interest holders throughout the review. The input from clinicians, policy makers and public contributors ensured the review was relevant to contemporary practice, assessed the face validity of the findings and contributed to discussions around the interpretation of the review analyses. All groups agreed that the tools we had included in the review were not yet ready for clinical implementation at scale; this unanimous assessment gives us confidence in our conclusions around the need for a differing approach to risk assessment.

Equality diversity and inclusion

Considerations around equality, diversity and inclusion are central to the work we produce in our evidence synthesis group. The prognostic utility of a multi-item prediction tool will differ across differing populations and characteristics of particular interest include age, sex and ethnicity – as these can influence both need for surgery and haemostasis. The original research papers rarely offered disaggregated data on these characteristics, and the variables did not consistently feature in the risk scores developed. It is not clear if this is because data were not collected, the tool developers did not think these issues were important, or they were found to not have an important association with blood loss or transfusion. All our included studies were conducted in industrialised countries. Our results do not necessarily extrapolate to other healthcare contexts where surgical approaches, bleeding risk and availability of blood may all differ.

Strengths and limitations of the review

We have performed a comprehensive review that follows best practice in conduct, analysis and reporting. Our review covers all areas of surgery, and presents quantitative synthesis with GRADE evaluation. As GRADE lacks consensus guidance on application to prognostic modelling, we modified the framework.

Nonetheless, there are important limitations to note.

Firstly, while our meta-analysis suggests that the McCluskey Index and Papworth Bleeding risk do not perform well in liver transplant surgery or cardiothoracic surgery, respectively, there were insufficient studies to assess overall tool performance in any other surgical subgroups.

Secondly, our review is restricted to studies that recorded transfusions occurring up to 48 hours post surgery, which may miss some surgery-related transfusions. We note that need for a transfusion in the first 48 hours is not synonymous with receiving a transfusion (the outcome assessed) and it is possible that outcomes were underscored.

Thirdly, the majority of evidence collated is in elective surgery only. Our results may therefore be less relevant to emergency surgery populations.

Lastly, we acknowledge that AUROC values may not be the most clinically informative metric, as they assume false positives and negatives are of equal importance. Misclassifications that result in the absence of required blood are arguably of greater consequence than misclassifications that result in available blood not being used. Studies should consider reporting additional performance metrics, such as positive and negative predictive values.

Conclusion

Available tools to determine risk of transfusion in patients undergoing surgery do not have the required accuracy, or strength of supporting evidence, to be routinely used in clinical practice. Efforts should be made to improve the quality of prediction research, ensuring it adheres to appropriate methods and available guidelines, while also considering clinicians' views on practicalities for implementation.

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Additional information

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Martin Taylor-Rowan (https://orcid.org/0000-0002-3027-5369): Funding acquisition, Data curation, Investigation, Writing – original draft.

Clareece Nevill (https://orcid.org/0000-0001-8305-2516): Data curation, Formal analysis.

Ryan Mullholland (https://orcid.org/0009-0008-7250-7464): Investigation.

Campbell Roxburgh (https://orcid.org/0000-0002-2649-6695): Supervision.

Susan Brunskill (https://orcid.org/0000-0002-0329-7677): Supervision.

Nicola Cooper (https://orcid.org/0000-0002-4486-2791): Conceptualisation, Funding acquisition, Project administration, Writing – reviewing and editing.

Anna Noel-Storr (https://orcid.org/0000-0003-3476-8432): Funding acquisition.

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Olivia Wu (https://orcid.org/0000-0002-0570-6016): Conceptualisation, Funding acquisition, Project administration, Writing – reviewing and editing.

Terry J Quinn (https://orcid.org/0000-0003-1401-0181): Conceptualisation, Funding acquisition, Project administration, Methodology, Writing – reviewing and editing.

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Data-sharing statement

All available data can be obtained by contacting the corresponding author.

Ethics statement

Not applicable as it is a systematic review that makes use of published data hence no permissions were needed.

Information governance statement

No personal information was handled in this study.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJAS1620.

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Study registration

This study is registered as PROSPERO CRD42023467613; www.crd.york.ac.uk/PROSPERO/view/CRD42023467613

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About this article

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List of abbreviations

AUROC	area under receiver operating curve
BRS	Bleeding Risk Score
CENTRAL	Central Register of Controlled Trials
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PMTSS	Predictive Model of Transfusion in Spine Surgery
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
RoB	risk of bias

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Appendix 1

TABLE 7 Review question

Population	Patients undergoing surgery
Intervention	Multicomponent prediction tools
Comparator	Other multicomponent prediction tools (if available)
Outcome	Dichotomous outcome 'transfusion required in the perioperative period'
Timing	During and immediately post-surgery (first 48 hours)
Setting	Emergency and elective surgery, including obstetrics

Appendix 2

TABLE 8 Full search strategies

Source	Search strategy	Hits retrieved
1. MEDLINE (Ovid SP) 1946–22 June 2023 Most recent stearch: 4 July 2023	1. "Bleeding Independently associated with Mortality".ti,ab. 2. BIMS.ti,ab. 3. "Transfusion Risk and Clinical Knowledge score".ti,ab. 4. (TRACK and ("blood loss" or bleed* or transfusion*)).ti,ab. 5. "Transfusion Risk Understanding Scor*".ti,ab. 6. (TRUST and ("blood loss" or bleed* or transfusion*)).ti,ab. 7. "Papworth Bleeding Risk Score".ti,ab. 8. BRiSc.ti,ab. 9. or/1-8 10. exp *Blood Loss, Surgical/ 11. ("blood loss" adj3 (surgery or surgical)).ti,ab. 12. *Blood Transfusion/ 13. "blood transfusion*".ab. 14. *Postoperative Complications/bl, co [Blood, Complications] 15. "postoperative transfusion".ti,ab. 16. *Postoperative Hemorrhage/ 17. "postoperative hemorrhag*".ab. 18. *Surgical Procedures, Operative/ae, bl, co, sn [Adverse Effects, Blood, Complications, Statistics & Numerical Data] 19. ("surgical procedure*" and (bleed* or "blood loss" or transfusion* or hemorrhag*)).ab. 20. *Preoperative Care/ae, bl, mt, sn [Adverse Effects, Blood, Methods, Statistics & Numerical Data] 21. "transfusion risk".ab. 22. *Erythrocyte Transfusion/ae [Adverse Effects] 23. or/10-22 24. *Prognosis/ 25. *Predictive Value of Tests/ 26. *Risk Assessment/ 27. *Risk Score/ 28. *Risk Factors/ 29. (risk profile or (risk adj2 model*)).ti,ab. 30. validat*.ti. 31. relative risk.ti,ab. 32. predict*.ti. 33. prognos*.ti,ab. 34. or/24-33 35. 23 and 34 36. 9 or 35 37. limit 36 to yr="2000 - 2024"	7097

TABLE 8 Full search strategies (*continued*)

Source	Search strategy	Hits retrieved
2. EMBASE (Ovid SP) 1996–2023 Week 24 Most recent search: 5 July 2023	1. "Bleeding Independently associated with Mortality".ti,ab. 2. BIMS.ti,ab. 3. "Transfusion Risk and Clinical Knowledge score".ti,ab. 4. (TRACK and ("blood loss" or bleed* or transfusion*)).ti,ab. 5. "Transfusion Risk Understanding Scor*".ti,ab. 6. (TRUST and ("blood loss" or bleed* or transfusion*)).ti,ab. 7. "Papworth Bleeding Risk Score".ti,ab. 8. BRiSc.ti,ab. 9. or/1-8 10. *bleeding/ 11. ("blood loss" adj3 (surgery or surgical)).ti,ab. 12. *blood transfusion/ 13. "transfusion risk".ab. 14. *Prognosis/ 15. *Predictive Value of Tests/ 16. *predictive value/ 17. *risk assessment/ 18. (risk profile or (risk adj2 model*)).ti,ab. 19. validat*.ti. 20. relative risk.ti,ab. 21. predict*.ti. 22. prognos*.ti,ab. 23. or/14-22 24. 10 or 11 or 12 or 13 25. 23 and 24 26. 9 or 25	10,323
3. CDSR Most recent search: 5 July 2023	#1 BIMS 11 #2 Transfusion Risk 6256 #3 blood transfusion 17887 #4 MeSH descriptor: [Blood Transfusion] this term only 2570 #5 MeSH descriptor: [Postoperative Hemorrhage] this term only 1760 #6 #1 or #2 or #3 or #4 or #5 19779 #7 MeSH descriptor: [General Surgery] explode all trees 506 #8 surgery 319185 #9 postoperative 160723 #10 #7 or #8 or #93 54686 #11 #6 and #10 with Cochrane Library publication date Between Jan 2000 and Jul 2023, in Cochrane Reviews 487 #12 prognosis 47162 #13 prognostic 24673 #14 MeSH descriptor: [Prognosis] explode all trees 223843 #15 predictive value 20254 #16 #12 or #13 or #14 or #15 268581 #17 #11 and #16 63	63
4. ClinicalTrials.gov Most recent search: 5 July 2023	transfusion AND prediction AND surgery | Adult (18–64), Older adult (65+) | Observational studies | Study start from 1 January 2000 to 7 May 2023	23
5. ICTRP (WHO Search Portal) Most recent search: 5 July 2023	Transfusion AND risk AND surgery	32
Total before de-duplication		17,538
Total after software de-duplication		14,220
After first assess		**2723**

Appendix 3

TABLE 9 Included studies

Paper	Prediction model(s)	Country	Adults/paediatrics	Surgical site	Outcome	Discrimination
Alghamdi, 2006[27]	TRUST	Canada	Adults	Cardiothoracic	Exposure to blood transfusion	Dev: AUROC: 0.79 (SE: 0.0052) Int. Val.: AUROC: 0.78 (SE: 0.0076) Ext. Val.: AUROC: 0.81 (SE: 0.006)
Biancari, 2017[68]	1. WILL-BLEED 2. CRUSADE 3. PAPWORTH BRS 4. TRUST 5. TRACK 6. ACTION	6 (England, Finland, France, Germany, Italy, Sweden)	N/R	Cardiothoracic	Severe bleeding as defined by the E-CABG bleeding grades 2–3 (transfusion of > 4 units of RBCs and/or resternotomy for excessive bleeding)	WILL-BLEED: Dev: AUROC: 0.738, 95% CI 0.692 to 0.784 Ext. Val.: AUROC: 0.725, 95% CI 0.686 to 0.763 ACTION: AUROC: 0.671, 95% CI 0.631 to 0.710 CRUSADE: AUROC: 0.642, 95% CI 0.602 to 0.681 Papworth BRS: AUROC: 0.605, 95% CI 0.568 to 0.643 TRUST: AUROC: 0.660, 95% CI 0.621 to 0.698 TRACK: AUROC: 0.640, 95% CI 0.600 to 0.681
Booth, 2022[28]	Unnamed points-based model	USA	Not explicitly reported (age signals adults)	General surgery	Transfusion was defined as a binary variable as neither indication for transfusion nor number of units transfused are	Points based model: Dev: *c*-statistic: 0.856 Int. Val.: *c*-statistic: 0.841
Cao, 2022[29]	Unnamed nomogram	China	Adults	General surgery	Transfusion (one or more units of allogeneic RBCs or packed erythrocytes)	Nomogram: Dev: *c*-index: 0.834, 95% CI 0.789 to 0.879 Int. Val.: *c*-index: 0.831, 95% CI 0.766 to 0.896
Carabini, 2014[56]	1. Unnamed model; 2. PMTSS	USA	Adults	Orthopaedic	Transfusion of > 4 units of total RBCs, including allogeneic transfusion and returned cell salvage	Dev: AUC: 0.88 Ext. Val.: AUROC: 0.89, 99% CI 0.80 to 0.90 PMTSS: AUROC: 0.60, 99% CI 0.48 to 0.71

continued

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TABLE 9 Included studies (*continued*)

Paper	Prediction model(s)	Country	Adults/paediatrics	Surgical site	Outcome	Discrimination
Chen, 2022[76]	Catboost model	China	Adults	General surgery	Massive transfusion (transfusion of ≥ 18 units of RBC suspension)	Catboost model: Int. Val.: AUROC: 0.81, 95% CI 0.75 to 0.87 Ext. Val.: AUROC: 0.75, 95% CI 0.60 to 0.88
Chin, 2022[26]	1. MSKCC Nomogram 2. Yamamoto model 3. transfusion risk score (TRS)	Singapore	N/R	General surgery	Blood transfusion	MSKCC: AUROC: 0.66, 95% CI 0.62 to 0.69 Yamamoto: AUROC: 0.67, 95% CI 0.63 to 0.70 TRS: AUROC: 0.69, 95% CI 0.66 to 0.73
Covin 2003[30]	Unnamed models	USA	N/R	Cardiothoracic	(1) Transfusion of > 2 units of fresh-frozen plasma, (2) transfusion of platelets, and (3) transfusion of > 2 units of RBCs	Fresh-frozen plasma: Dev: *c*-index: 0.768 Int. Val.: *c*-index: 0.724 Platelet transfusion: Dev: *c*-index: 0.724 Int. Val.: *c*-index: 0.694 RBC model: Dev: *c*-index: 0.775 Int. Val.: *c*-index: 0.752
Cywinski, 2014[66]	Unnamed models	USA	Adults	General surgery	High intraoperative transfusion requirements (> 20 or > 30 units of blood) including blood cell salvage units returned to the patient	> 20 units analysis: Dev: *c*-statistic: 0.70, 95% CI 0.66 to 0.75 > 30 units analysis: Dev: *c*-statistic: 0.67, 95% CI 0.60 to 0.73
Engel, 2021[31]	Unnamed model	Switzerland	N/R	Urology	Perioperative blood transfusions	Dev: AUROC: 0.87
Escoresca Ortega, 2008[59]	McCluskey Index	Spain	N/R	General surgery	Transfusion of > 6 units of RBC concentrates	AUROC: 0.821 (calculated)
Feng, 2021[65]	Unnamed models	China	Aldults + paediatric	N/R	Actual volume of RBC transfusion (total volume of RBCs in units; 1 units of RBC = 150 ml of RBC)	Model 1: Dev: AUROC: 0.908, 95% CI 0.907 to 0.913 Model 2: N/R
Gao, 2020[49]	Unnamed models	China	N/R	Orthopaedic	'Excessive blood loss'	N/R

TABLE 9 Included studies (*continued*)

Paper	Prediction model(s)	Country	Adults/paediatrics	Surgical site	Outcome	Discrimination
Greiff, 2015[47]	1. Local development models 2. Papworth BRS	Norway	N/R	Cardiothoracic	Excessive postoperative blood loss defined as blood loss exceeding 2 ml/kg/hour the first 4 hours postoperatively/Composite bleeding end point defined by Dyke *et al.*	Int. Val.: Model 1: AUROC: 0.688, 95% CI 0.664 to 0.712 Model 2: AUROC: 0.709, 95% CI 0.698 to 0.743 Model 3: AUROC: 0.739, 95% CI 0.722 to 0.755 Model 4: AUROC: 0.761, 95% CI 0.745 to 0.777 Ext. Val.: Papworth BRS > 2 ml/kg/hour: AUROC: 0.729 (calculated)
Guo, 2021[32]	Unnamed nomogram	China	N/R	General surgery/ urology	RBC transfusion	Nomogram: Dev: AUROC: 0.857, 95% CI 0.781 to 0.836 Int. val.: AUROC: 0.831, 95% CI 0.750 to 0.822 Ext. Val.: AUROC: 0.924, 95% CI 0.766 to 1.000
Huang, 2015[77]	Unnamed model	USA	N/R	Cardiothoracic	Blood usage (defined as units of blood products used)	N/R
Huang, 2021[90]	Unnamed model	China	Adults	General surgery	Blood transfusion, defined as the intraoperative transfusion of packed RBCs	Dev: *c*-index: 0.859 Int. Val.: *c*-index: 0.850
Jalali, 2020[78]	Unnamed model	USA + other countries	Paediatric	Paediatric/ orthopaedic	Units of blood product transfused	Dev: AUROC: 0.90 Int. Val.: AUROC: 0.87
Justo, 2021[61]	McCluskey index	Spain	N/R (age range suggests adults + paediatric)	General surgery	Massive blood transfusion (> 6 units of RBC)	AUROC: 0.65, 95% CI 0.614 to 0.685
Karkouti, 2001[34]	Unnamed model	Canada	Not explicitly reported (age signals adults)	Cardiothoracic	Blood transfusion (yes/no)	Dev: AUROC area: 0.86
Karkouti, 2006[79]	Unnamed model	Canada	N/R	Cardiothoracic	Massive blood transfusion (defined as ≥ 5 units of RBC within 1 day of surgery)	Dev: *c*-index: 0.88
Kim, 2017[57]	Unnamed model	Korea	Not explicitly reported (age signals adults)	Obstetric	Massive transfusion (transfusion of ≥ 8 units of packed RBCs)	Dev: AUROC: 0.84, 95% CI 0.75 to 0.92 Ext. Val.: AUROC:0.88, 95% CI 0.81 to 0.94

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TABLE 9 Included studies (*continued*)

Paper	Prediction model(s)	Country	Adults/paediatrics	Surgical site	Outcome	Discrimination
Leff, 2019[35]	TRACK	USA	Adults	Cardiothoracic	Blood transfusion	Any transfusion: AUROC: 0.775, 95% CI 0.775 to 0.794 Transfusion of RBCs: AUROC: 0.817, 95% CI 0.800 to 0.835
Li, 2023[80]	Unnamed model	China	Adults	Orthopaedic	Blood loss	N/R
Liu, 2021[36]	Catboost model	China	N/R	Cardiothoracic	RBC infusion	Catboost model: Dev: AUROC: 0.888, 95% CI 0.845 to 0.909 Int. Val.: AUROC: 0.922, 95% CI 0.883 to 0.956
Lou, 2022[37]	Gradient Boosting Machine	USA	N/R	Multiple (except ophthalmological and gynaecological)	RBC transfusion as binary outcome	Gradient Boosting Machine: Int. Val.: *c*-statistic: 0.924, 95% CI 0.919 to 0.929 Ext. Val.: *c*-statistic: 0.939, 95% CI 0.933 to 0.944
Massicote, 2018[50]	Unnamed model	Canada	Adults	General surgery	Number of RBC units transfused and the total intraoperative blood lost	N/R
Massicotte, 2009[58]	Unnamed model	Canada	Adults	General surgery	Probability of PRBC transfusion	Dev: AUROC: 89.8% Int. Val.: AUROC: 89.8% Ext. Val.: AUROC: 89.8%
Mathai, 2012[51]	Unnamed model	USA	Adults	Orthopaedic	Blood loss	N/R
McCluskey, 2006[62]	Unnamed model	Canada	N/R	General surgery	Massive blood transfusion defined as > 6 units of RBC concentrate	Dev: AUROC: 0.82 Int. Val.: AUROC: 0.79, 95% CI 0.78 to 0.85
Metcalf, 2018[81]	Unnamed model	USA	Adults	General surgery	Packed RBC utilisation	N/R
Nie, 2021[63]	Unnamed models	China	Adults	Orthopaedic	RBC consumption	Lumbar spinal stenosis model: Dev: AUROC curve: 0.73 Femoral fracture surgery: Dev: AUROC curve: 0.76
Paiva, 2021[38]	Unnamed model	Portugal	N/R	Cardiothoracic	Consumption of erythrocyte concentrate	Dev: AUROC: 0.963, 95% CI 0.947 to 0.979 Int. Val.: AUROC: 0.962, 95% CI 0.945 to 0.980

TABLE 9 Included studies (*continued*)

Paper	Prediction model(s)	Country	Adults/paediatrics	Surgical site	Outcome	Discrimination
Park, 2022[52]	Unnamed model	Korea	Adults	General surgery	Estimated blood loss (EBL; categorised as massive bleeding for EBL ≥ 5000 cc and no massive bleeding for EBL < 5000 cc)	Multivariable logistic regression model Int. Val.: AUROC: 0.840
Pennington, 2020[82]	Unnamed model	USA	Adults	Orthopaedic	Intraoperative blood loss (significant intraoperative blood loss defined as IOBL exceeding 1 l)	Dev: AUROC: 0.939 Int. Val.: AUROC: 0.895
Pennington, 2021[39]	Unnamed models	USA	Adults	Orthopaedic	Intraoperative blood loss/intraoperative blood products transfused	Transfusion model: Int. Val.: AUROC: 0.819
Priem, 2022[53]	Unnamed nomograms	Canada	Adults	General surgery	RBC transfusion/RBC transfusion of > 2 units of RBC/intraoperative bleeding ≥ 900 ml	Nomogram A: AUROC: 0.91 Nomogram B: AUROC: 0.70 Nomogram C: AUROC: 0.70
Pustavoitau, 2017[83]	Unnamed model	USA	Adults	General surgery	Massive transfusion (transfusion > 10 units of packed RBCs)	Int. Val.: *c*-statistic: 0.835, 95% CI 0.781 to 0.888 Ext. Val.: *c*-statistic: 0.895, 95% CI 0.809 to 0.982
Pustavoitau, 2020[64]	ModRI	USA	N/R	General surgery	Massive transfusion (> 10 units of allogeneic RBCs)	Dev: AUROC: 0.72, 95% CI 0.65 to 0.79 Int. Val.: AUROC curve: 0.72, 95% CI 0.65 to 0.79
Saber, 2018[67]	Papworth Bleeding Risk Score	Egypt	Adults	Cardiothoracic	Adverse postoperative bleeding: mean blood loss exceeding 2 ml/kg/hour, measured between arrival in ICU and the earliest of the following events: (1) the elapse of 3 hours; (2) the start of transfusion of any one of fresh-frozen plasma, platelets or cryoprecipitate; (3) return to theatre or (4) death	N/R

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TABLE 9 Included studies (*continued*)

Paper	Prediction model(s)	Country	Adults/paediatrics	Surgical site	Outcome	Discrimination
Salsano, 2020[54]	1. WILL-BLEED 2. CRUSADE 3. PAPWORTH BRS 4. TRUST 5. TRACK 6. ACTION	Italy	Adults	Cardiothoracic	Severe-massive bleeding (UDPB classes 3–4) was defined as chest tube blood loss within 12 hours > 1000 ml and/or reoperation for excessive bleeding and/or transfusion > 4 units of RBC and/or transfusion > 4 units of FFP after closure of the chest	WILL-BLEED: AUROC: 0.658, 95% CI 0.600 to 0.716 CRUSADE: AUROC: 0.489, 95% CI 0.423 to 0.555 Papworth BRS: AUROC: 0.695, 95% CI 0.639 to 0.854 TRUST: AUROC: 0.648, 95% CI 0.589 to 0.707 TRACK: AUROC: 0.605, 95% CI 0.545 to 0.666 ACTION: AUROC: 0.565, 95% CI 0.504 to 0.626
Shah, 2010[40]	Unnamed model	Canada	Adults + paediatric	Oral and Maxillofacial surgery	Perioperative single unit RBC transfusion	Regression model: Dev: AUROC: 0.754
Shen, 2021[44]	Unnamed nomogram	China	Paediatric	Cardiothoracic	Postoperative blood loss was defined as a blood loss in the first 24 hours exceeding cut-off value (20.0 ml/kg)	Nomogram: Dev: AUROC: 0.858, 95% CI 0.758 to 0.958 Int. Val.: AUROC: 0.856, 95% CI 0.754 to 0.958
van Klei, 2001[41]	Unnamed model	The Netherlands	Adults	Multiple	Any allogeneic RBC transfusion (defined as transfusion of one or more units packed cells)	Prediction rule: Dev: AUROC: 0.75, 95% CI 0.71 to 0.78 Int. Val.: AUROC: 0.70, 95% CI 0.63 to 0.77
Vlot, 2022[42]	ACTA-PORT	The Netherlands	Adults	Cardiothoracic	Administration of a perioperative blood transfusion, including allogeneic RBC transfusions, plasma and platelet transfusions	*c*-statistic: 0.78, 95% CI 0.74 to 0.82
Vuylsteke, 2011[48]	Papworth BRS	UK	N/R	Cardiothoracic	Adverse postoperative bleeding (severe and early blood loss) defined as mean blood loss exceeding 2 ml/kg/hour measured between arrival in ICU and the earliest of the following events: the elapse of 3 hours; the start of transfusion of any one of fresh-frozen plasma, platelets or cryoprecipitate; return to theatre or death.	N/R
Wang, 2022[84]	Unnamed model	China	Adults	Obstetric	Blood transfusion defined as at least 2 units of packed RBCs and/or 200 ml plasma and/or 1 unit platelet and/or 4 units cryoprecipitate	Dev: AUROC: 0.819 Ext. Val.: AUROC: 0.786

TABLE 9 Included studies (*continued*)

Paper	Prediction model(s)	Country	Adults/paediatrics	Surgical site	Outcome	Discrimination
Yamamoto, 2011[55]	Unnamed model	Japan	N/R	General surgery	Intraoperative blood loss of > 1500 ml during hepatectomy	Score: Dev: AUROC: 0.814, 95% CI 0.731 to 0.898 Ext. Val.: AUROC: 0.839, 95% CI 0.710 to 0.969
Yamamoto, 2014[43]	Unnamed model	Japan	Adults	General surgery	Blood transfusion (blood transfusion understood as transfusion of packed RBCs)	Score: Dev: AUROC: 0.758
Yin, 2021[46]	Unnamed models	China	N/R	Orthopaedic	Massive blood loss: > 3000 ml	Clinical-RN1 based on CTE features: Dev: AUROC: 0.83, 95% CI 0.78 to 0.88 Int. Val.: AUROC: 0.83, 95% CI 0.75 to 0.90 Clinical-RN2 based on CTE features: Dev: AUROC: 0.84, 95% CI 0.77 to 0.91 Int. Val.: AUROC: 0.83, 95% CI 0.76 to 0.89 Clinical-RN1 based on CT features: Dev: AUROC: 0.84, 95% CI 0.79 to 0.88 Int. Val.: AUROC: 0.80, 95% CI 0.72 to 0.87 Clinical-RN2 based on CT features: Dev: AUROC: 0.82, 95% CI 0.75 to 0.88 Int. Val.: AUROC: 0.82, 95% CI 0.76 to 0.88

AUROC, area under curve; Dev., development model; Ext. Val., external validation; FFP, fresh frozen plasma; Int. Val., internal validation; IOBL, intraoperative blood loss; MSKCC, Memorial Sloan–Kettering Cancer Center; N/R, not reported; RBC, red blood cells.

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Appendix 4

TABLE 10 Included variables in paper

Prediction model name (or study name where model is unnamed)	Model version	Anatomical	Antithrombotic related	Blood chemistry	Body mass metrics	Haemostasis related	Comorbidities	Demographics	Full blood count	Interventions to prevent blood loss	Medication related variables	Perioperative complications	Surgery related	Surgical service related	Time to surgery related	Tumour related	Vital signs	Other
ACTION[68]			X	X	X		2X	2X	X			X					3X	
CRUSADE[68]				X			3X	X	X								2X	
McCluskey[62]				2X		X		X	2X				X					
Papworth Bleeding Risk Score[68]					X		X	X					2X					
TRACK[68]					X			2X	X				X					
TRUST[68]				X	X		X	2X	X				2X					
WILL-BLEED[68]			2X	X			X	X	X			X						
Alghamdi, 2006[27]				X	X			2X	X				3X					
Booth, 2022[28]				X			4X	X	X				X					
Cao, 2022[29]				X		X	3X		X							2X		
Carabini, 2014[56]								X	X				3X					
	PMTSS							X	X				2X					
Chen, 2022[76]				7X	X	3X		X	3X									
Chin, 2022[26]	MSKCC							2X					2X			X		
	TRS								X				X			X		
Covin, 2003[30]	Fresh-frozen plasma transfusion model		X				2X		X								X	

TABLE 10 Included variables in paper (*continued*)

Prediction model name (or study name where model is unnamed)	Model version	Anatomical	Antithrombotic related	Blood chemistry	Body mass metrics	Haemostasis related	Comorbidities	Demographics	Full blood count	Interventions to prevent blood loss	Medication related variables	Perioperative complications	Surgery related	Surgical service related	Time to surgery related	Tumour related	Vital signs	Other
	Platelet transfusion model			2X			X	X	X		X						X	
	RBC transfusion model			X	X		4X	2X	X								X	X
Cywinski, 2014[66]	> 20 units CART analysis			3X	4X	X	2X	2X	2X						X			
	> 20 units			X		X	X		2X					X				
	> 30 units CART analysis			2X	4X	X	X	2X	3X					X	X			
	> 30 units						X		X					X				
Engel, 2021[31]			X					X	X	X				X		4X		2X
Feng, 2021[65]	Model 1			2X		X		X	4X	X			6X	4X				X
	Model 2			4X	X	2X	X	X	3X				3X	3X				2X
Gao, 2020[49]													3X			2X		
Greiff, 2015[47]	Model 1		X		X								2X					
	Model 2		X		X						X		3X					
	Model 3		2X				2X						X					
	Model 4		2X				X				X		2X					
Guo, 2021[32]											2X		X			X	X	
Huang, 2015[77]						4X			X									
Huang, 2021[33]							2X		X							2X		
Jalali, 2020[78]			X		X		4X	5X	4X	X		X	4X	X				

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TABLE 10 Included variables in paper (*continued*)

Prediction model name (or study name where model is unnamed)	Model version	Anatomical	Antithrombotic related	Blood chemistry	Body mass metrics	Haemostasis related	Comorbidities	Demographics	Full blood count	Interventions to prevent blood loss	Medication related variables	Perioperative complications	Surgery related	Surgical service related	Time to surgery related	Tumour related	Vital signs	Other
Karkouti, 2001[34]								3X	X									
Karkouti, 2006[79]					X			X	3X			2X	4X	X				
Kim, 2017[57]		3X					X	X										
Li, 2023[80]					X								5X			X		
Liu, 2021[36]				3X	3X	2X	X	2X	5X				3X	X				
Lou, 2022[37]				4X	2X	2X	5X	2X	2X				2X					X
Massicote, 2018[50]				X	X				X				X				X	
Massicotte, 2009[58]									X	X			X					
Mathai, 2012[51]													2X	X				X
Metcalf, 2018[81]						X	2X		X									
Nie, 2021[63]	Lumbar spinal stenosis model	X			X	X		X	X				X					
	Femoral fracture model	X	X		X	X		X	X						X			
Paiva, 2021[38]				X	X		2X	X	X									
Park, 2022[52]				X		X	X						X			X	2X	X
Pennington, 2020[82]					X					X			2X					
Pennington, 2021[39]	Intraoperative blood loss model			X									2X					
	Transfusion model								3X				2X					

TABLE 10 Included variables in paper (*continued*)

Prediction model name (or study name where model is unnamed)	Model version	Anatomical	Antithrombotic related	Blood chemistry	Body mass metrics	Haemostasis related	Comorbidities	Demographics	Full blood count	Interventions to prevent blood loss	Medication related variables	Peri-opertive complications	Surgery related	Surgical service related	Time to surgery related	Tumour related	Vital signs	Other
Priem, 2022[53]	Nomogram A								X	X			X					
	Nomogram B			X	X				X				X				X	
	Nomogram C						X		X				X					
Pustavoitau, 2017[83]						2X	2X		2X				X					
Pustavoitau, 2020[64]	ModRI					2X	2X		2X				2X					
Shah, 2010[40]					X			X	X				X			X		
Shen, 2021[44]						X			2X									
van Klei, 2001[41]								2X					X					
Vlot, 2022[42]				X	X			X	X				X					X
Wang, 2022[84]		X				X		X	X			X						
Yamamoto, 2011[55]					X	X							X			2X		
Yamamoto, 2014[43]				X					X				X			X		
Yin, 2021[46]	CT-based clinical-RN1							X					X			4X		
	CT-based clinical-RN2							X								2X		
	CTE-based clinical-RN1												X			4X		
	CTE-based clinical-RN2															3X		

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