Received: 8 August 2024 | Revised: 4 December 2024 | Accepted: 4 December 2024

DOI: 10.1111/trf.18108

REVIEW ARTICLE

TRANSFUSION

Prognostic models for prediction of perioperative allogeneic red blood cell transfusion in adult cardiac surgery: A systematic review and meta-analysis

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Abstract

Objectives: Identifying cardiac surgical patients at risk of requiring red blood cell (RBC) transfusion is crucial for optimizing their outcome. We critically appraised prognostic models preoperatively predicting perioperative exposure to RBC transfusion in adult cardiac surgery and summarized model performance.

Methods: *Design*: Systematic review and meta-analysis. *Study eligibility criteria*: Studies developing and/or externally validating models preoperatively predicting perioperative RBC transfusion in adult cardiac surgery. Information sources MEDLINE, CENTRAL & CDSR, Embase, Transfusion Evidence Library, Web of Science, Scopus, ClinicalTrials.gov, and WHO ICTRP. *Risk of bias and applicability*: Quality of reporting was assessed with the Transparent Reporting of studies on prediction models for Individual Prognosis or Diagnosis adherence form, and risk of bias and applicability with the Prediction model Risk of Bias ASsessment Tool. *Synthesis methods*: Random-effects meta-analyses of concordance-statistics and total observed:expected ratios for models externally validated ≥5 times.

Results: Nine model development, and 27 external validation studies were included. The average TRIPOD adherence score was 66.4% (range 44.1%–85.2%). All studies but 1 were rated high risk of bias. For TRUST and TRACK, the only models externally validated ≥5 times, summary c-statistics were 0.74

(95% CI: 0.65–0.84; 6 contributing studies) and 0.72 (95% CI: 0.68–0.75; 5 contributing studies) respectively, and summary total observed:expected ratios were 0.86 (95% CI: 0.71–1.05; 5 contributing studies) and 0.94 (95% CI: 0.74–1.19; 5 contributing studies), respectively. Considerable heterogeneity was observed in all meta-analyses.

Discussion: Future high quality external validation and model updating studies which strictly adhere to reporting guidelines, are warranted.

KEYWORDS

anesthesia, cardiac surgical procedures, prognosis, risk assessment, transfusion

1 | INTRODUCTION

1.1 | Rationale

Cardiac surgery is the surgical specialty with the highest rate of allogeneic red blood cell (RBC) transfusion.[1] Although RBC transfusion remains an indispensable treatment of severe anemia,[2] it is expensive,[3] potentially harmful,[4,5] and requires availability of voluntarily donated blood products, which is not always guaranteed.[6,7] To avoid unnecessary RBC transfusion, guidelines recommend using blood conservation strategies that can be grouped together under the term "patient blood management".[8,9] Some of these strategies are costly,[10–13] and some are associated with risks.[14] Guidelines therefore recommend identifying patients that will benefit most from them, thus, patients that are most likely to receive blood transfusion during or after their surgery.[9,15] However, there is no guidance on how these patients should best be identified.

The risk of perioperatively receiving RBC transfusion is known to differ significantly between individual cardiac surgical patients. More than 50% of patients require no blood transfusion, but there is a "high-risk" subset (±15%) of patients requiring excessive transfusion and consuming approximately 80% of all blood products that are transfused in this population.[16,17] The risk is known to depend on several patient-, drug-, physician-, and procedure-related predictors.[16,18] However, the predictive value of these individual factors is poor.[19] Therefore, prognostic models mathematically combining multiple predictors have been developed to improve prediction of perioperative RBC transfusion for individual patients.[20,21] However, it is unclear which of these models performs best across a variety of patients undergoing cardiac surgery. Before incorporation of prediction models into guidelines, their quality and predictive performance should be systematically reviewed, so that their predictive ability can be examined across different study populations, and the need for model updating can be evaluated.[22–24] Recommendation of an inaccurate model, or inappropriate use of a model in a population for which its use was not intended, could otherwise lead to inappropriate clinical decision-making and resource allocation.

1.2 | Objectives

Therefore, in this systematic review, we aimed to (1) identify all externally validated prognostic models that for adult patients undergoing cardiac surgery, preoperatively predict the risk of perioperative exposure to RBC transfusion, (2) critically appraise their development and external validation, and (3) summarize their predictive performance.

2 | METHODS

Reporting of this systematic review was guided by the Transparent reporting of multivariable prediction models for individual prognosis or diagnosis: checklist for systematic reviews and meta-analyses (TRIPOD-SRMA),[25] the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, the PRISMA search extension (PRISMA-S),[26] and the Terminology, Application, and Reporting of Citation Searching (TARCiS) statement[27] (Suppporting Information S1).

2.1 | Study eligibility criteria

Studies were included if they reported development and/or external validation of a prognostic model that for adult patients undergoing any type of cardiac surgery, preoperatively predicts perioperative exposure to at least 1 unit of allogeneic RBC transfusion. A prognostic model was defined as a multivariable model (e.g., based on a regression equation or neural network) predicting an individual's risk of an outcome (i.e., exposure to

allogeneic RBC transfusion in the perioperative period) based on his/her characteristics (predictors).[25] External validation was defined as evaluation of the predictive performance of a model in a dataset that was temporally, geographically, or in setting different from that used for model development.[28]

Studies were excluded if (1) they did not describe development or external validation of a prognostic model that incorporated multiple predictors, (2) they used data from patients younger than 18 years, or from patients undergoing other types of surgery than cardiac surgery, (3) they reported development or validation of a prognostic model for prediction of an outcome other than exposure to allogeneic RBC transfusion (e.g., transfusion of other blood products, or massive transfusion, such as exposure to transfusion of ≥2 units of packed RBC), (4) they described development or validation of a model in which predictors included in the final model are not available preoperatively, or (5) they were not written in English. Because this systematic review intended to only summarize externally validated models, studies were also excluded after full text screening if they had reported development of a model for which no external validation study was available before the March 1, 2023.

Eligible external validation studies that had not reported sufficient information to perform certain meta-analyses – thus, studies in which either the sample size, or the observed number of RBC transfusions, or the c-statistic, or the (estimated) total O:E ratio, or standard errors, or 95% confidence intervals for these performance measures were missing – were included in this systematic review, but excluded from these specific meta-analyses.

2.2 | Information sources

Six bibliographic databases were searched on the February 22, 2023: MEDLINE®All/PubMed® (via Ovid), the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL)), Embase (via Embase.com), the Transfusion Evidence Library, Web of Science Core Collection (via webofscience.com) and Scopus (via scopus.com). In addition, 2 clinical trial registries were searched on the February 23, 2023: Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

2.3 | Search strategy

Two clinicians (RV, AV) and 2 librarians (KV, TV) designed the search strategy which is fully described in the Suppporting Information S2. The concepts 'cardiac surgery', 'red blood cell transfusion' and 'prognostic model study' were combined with the Boolean operator AND. Within each concept, index terms (where applicable) were combined with free text words to search in title, abstract and keywords using the Boolean operator OR. For the concept 'prognostic model study', the terms were based on search filters that were recommended by Ingui et al,[29] Haynes et al,[30] and Geersing et al,[31] which were modified to increase the sensitivity and specificity of our search. Two librarians (KV, TV) ran the searches in all databases and registries. The included reports were used for backward (i.e., reference list checking) and forward citation searching to identify additional studies.[32] The Web of Science Core Collection was used for the forward citation searching on June 15, 2023.

2.4 | Study selection process

Records identified by the search strategy were imported into EndNote (version 20)[33] and deduplicated by 2 reviewers (KT, TV) using the method described by Jane Falconer.[34] The unique records were then imported into Rayyan[35] for title and abstract screening by 2 independent reviewers (AV, RF) who then also performed the screening of full texts for eligibility. In case of disagreement, a third reviewer was involved (RV).[31]

2.5 | Quality of reporting assessment

Two reviewers (RV, AV) independently assessed the quality of reporting in each included study by evaluating their adherence to the 'Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis' (TRIPOD) reporting guideline.[36] This evaluation was performed as guided by the TRIPOD adherence form by calculation of an overall TRIPOD adherence score per included study and per TRIPOD item.[37,38] Disagreements in this evaluation were resolved by discussion.

2.6 | Data collection process

Three reviewers (RV, AV, RF) independently performed data extraction in a standardized data extraction form in Microsoft Excel,[39] as guided by the Checklist for critical appraisal and data extraction for systematic reviews of prediction modeling studies (CHARMS).[40] Disagreements in data collection were resolved by discussion.

2.7 | Data items

The items for which data were sought from all eligible studies, included: (1) study information (authors, date of publication, publication journal, and model name), (2) source of data used to develop and/or externally validate a prediction model, (3) study participants (recruitment method, recruitment dates, study setting, study sites, eligibility criteria, baseline characteristics of study participants, concomitant treatments such as the type of surgery, and any use of a transfusion protocol and blood conservation strategies), (4) predicted outcome (definition, for which perioperative period RBC transfusion was predicted), (5) sample size (how it was calculated, number of participants, number of events, i.e., transfusion rate), (6) missing data (number of missing data, how they were handled), and (7) any available measures that described model performance, that is, statistics that quantified the accuracy of a model's predictions. These included:

a. *discrimination* measures including the concordance (c-) statistic (index) and its corresponding 95% confidence interval;
b. *calibration* measures, including the total observed: expected (O:E) ratio and its variance, the calibration plot, calibration intercept and slope, and the Hosmer-Lemeshow goodness-of-fit test chi-square and p-value (for details, see Suppporting Information S3);
c. measures of *overall fit*, including R^2 (i.e., the proportion of the total variance of outcome values that is explained by the model), and the Brier score (mean square error between predicted probabilities and the expected values)[24,25];
d. measures of *classification* (i.e., sensitivity, specificity, positive predictive value, and negative predicted value at the selected optimal cut-off); and,
e. *clinical utility* measures, including net benefit and decision curve analysis.

From model development studies, additional details were extracted about: (1) the number and type of candidate predictors, (2) the number of events per predictor (EPP), which is the number of patients that received RBC transfusion divided by the number of candidate predictors,[41] (3) the method for predictor selection, (4) the modeling method, (5) the number of predictors in the final model, and (6) predictor weights with standard errors or confidence intervals. If the number of candidate predictors was not specified in the full text, EPP was estimated by examining the minimum candidate predictors that could be deduced from the full text. Authors were contacted in case of unclear or missing information.

2.8 | Risk of bias and applicability assessment

Three reviewers (RV, AV, RF) independently used the prediction model risk of bias assessment tool (PROBAST)[42–44] to assess the risk of bias in each prognostic model study, and to evaluate if there were concerns regarding applicability. For risk of bias assessment, the included studies were assessed for 4 domains (participants, predictors, outcome, analysis) by answering signaling questions with "yes", "probably yes", "probably no", "no", or "no information", and the rationale for each answer was recorded. Applicability, i.e., the extent to which a study fitted the target population, model, outcome, timing and setting of our review, was judged for the first three domains. Risk of bias and applicability were each graded as "low", "high", or "unclear". Disagreements in these assessments were resolved by discussion.

2.9 | Synthesis methods

Data were summarized with descriptive statistics. All analyses were performed in R version 4.3.2 using the packages metamisc (version 0.4.0)[45] and metafor (version 4.6–0).[46] External validation studies that did not report sufficient information to perform a meta-analysis (i.e., the study's sample size, observed number of RBC transfusions, c-statistic, (estimated) total O:E ratio and either the standard error or the 95% confidence interval) were excluded from the meta-analysis. Meta-analyses of c-statistics and total O:E ratios were performed for prediction models for which at least 5 external validation studies were found.[22,23] Data and code used for meta-analyses are provided in Suppporting Information S9. In summary, after retrieving missing information with metamisc's ccalc and oecalc function, the valmeta function, which by default applies a random effects meta-analysis, was used to yield summary estimates and corresponding 95% confidence intervals for the c-statistics and total O:E ratios. By default, metamisc adopts restricted maximum likelihood estimation and uses the Hartung–Knapp–Sidik–Jonkman method to calculate 95% confidence intervals (CI).[47] C-statistics and total O:E ratios were not transformed to the logit and log scale before meta-analysis. The presence of heterogeneity was assessed with 95% prediction intervals, Cochran's χ^2, τ^2 and I^2.

Publication bias was visually explored with funnel plots in JASP[48] version 0.18.3. *P*-values of Egger's and Debray's funnel plot asymmetry tests <0.05 were considered statistically significant, suggesting funnel plot asymmetry and potential publication bias.

3 | RESULTS

3.1 | Study selection

The study selection process is summarized in Figure 1. The search yielded 8990 unique records of which 8933 were excluded based on title and abstract. For 2 of the resulting 57 records, no full text could be found.[49,50] Full text screening of 55 remaining reports resulted in further exclusion of 39 reports (for details, see Suppporting Information S4). No additional eligible reports were identified by citation searching with the remaining 16 reports. These 16 reports described a total of 12 model development studies, 2 internal validation studies and 27 external validation studies.[20,21,51–64] For 3 of 12 developed models,[57,60,62] no external validation was found at the time of the literature search, and therefore these are not discussed below.

3.2 | Quality of reporting

The average TRIPOD adherence score was 66.4% (range 44.1%–85.2%) (Figure 2). Details of the quality of reporting assessment are provided in Table S1 and Figure S1 in Suppporting Information S5.

3.3 | Study and model characteristics

Nine reports described the development of 9 prognostic models (in chronological order): (1) Bilfinger's model,[51] (2) the Likelihood of Red blood Cell Transfusion (LRCT) score,[53] (3) Magovern's Transfusion Risk Score,[52] (4) the Clinical prediction rule,[55] (5) Litmathe's Transfusion Risk Score (TRS),[56] (6) the Transfusion

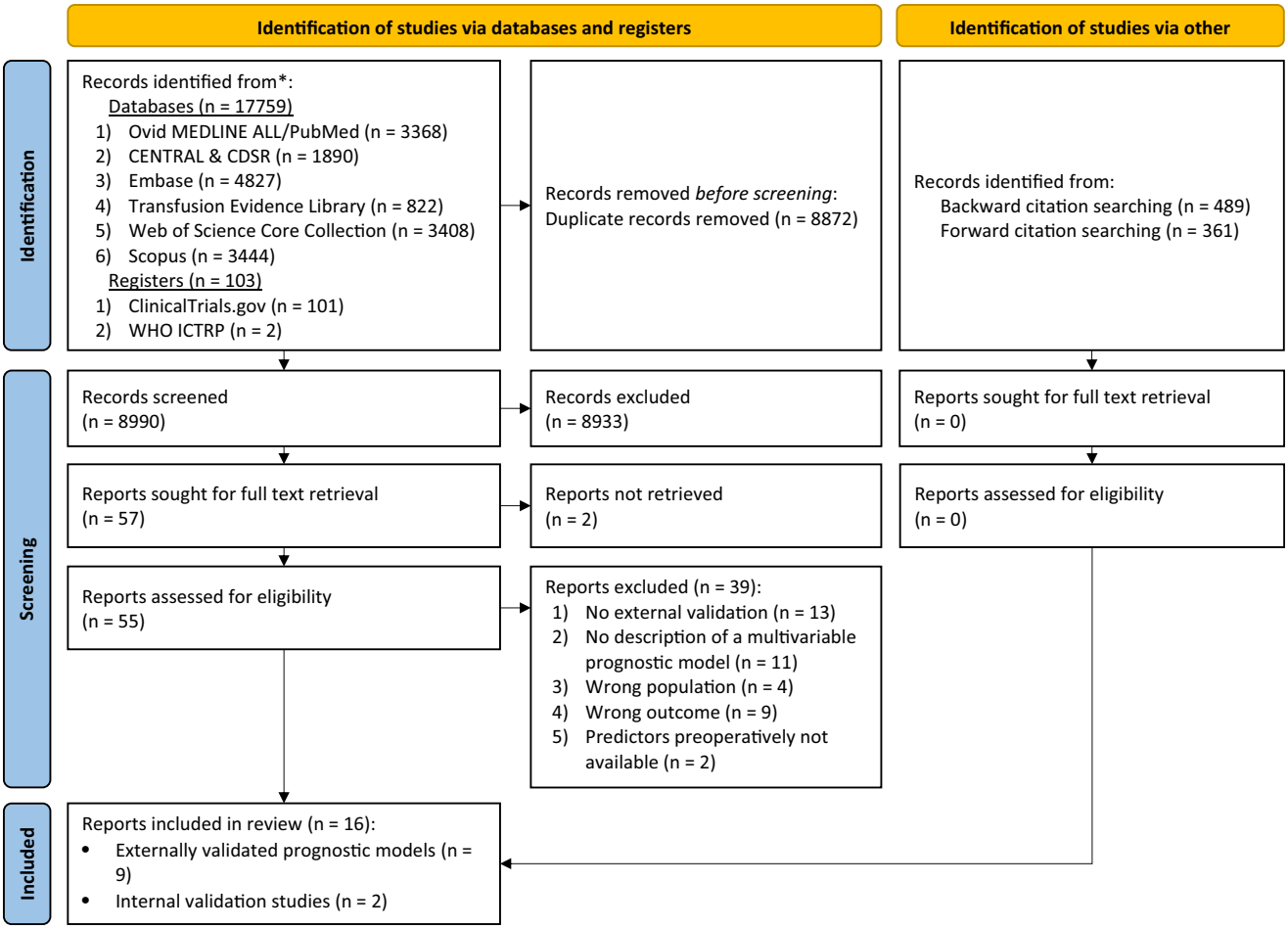


FIGURE 1 PRISMA flow diagram. Modified from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:N71. doi: 10.1136/bmj.n71.

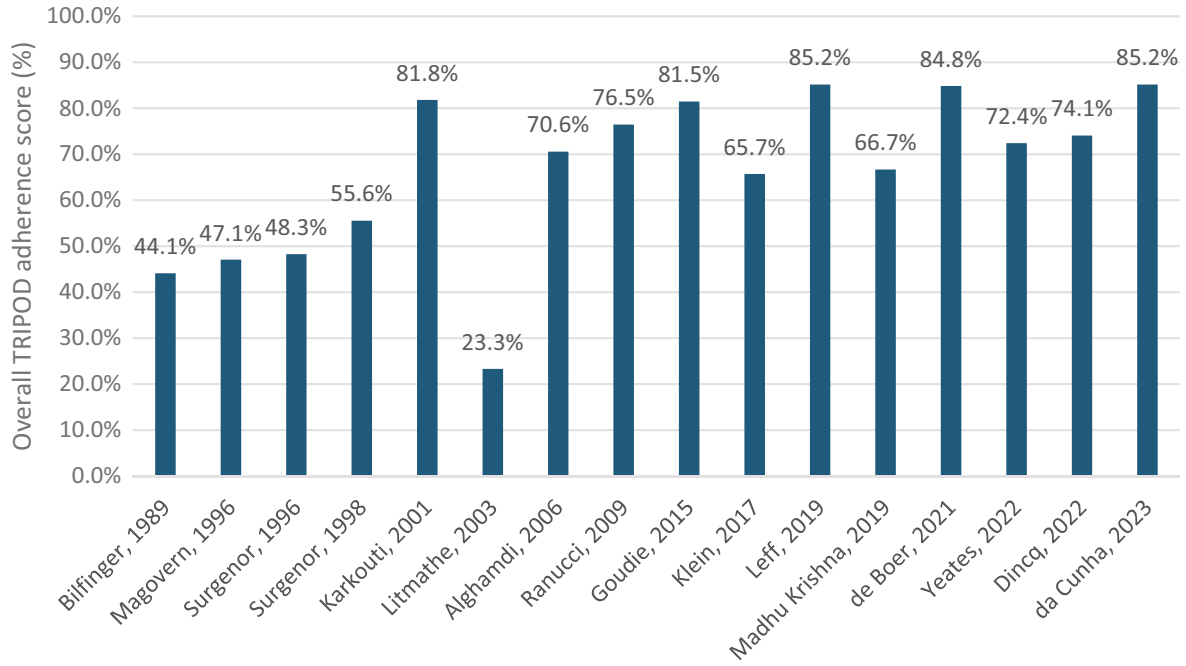


FIGURE 2 Overview of the quality of reporting in the included, chronologically ranked, prognostic model studies as assessed by their adherence to the TRIPOD guideline.[1] Overall TRIPOD adherence score per study was calculated by dividing the sum of the adhered TRIPOD items by the total number of applicable TRIPOD items for that study.

Risk Understanding Scoring Tool (TRUST),[21] (7) the Transfusion Risk and Clinical Knowledge (TRACK) score,[20] (8) the Association of Cardiothoracic Anesthetists (ACTA) PeriOperative Risk of blood Transfusion (ACTA-PORT) score,[58] and (9) de Boer's model.[61] Fourteen reports reported 27 external validation studies in which the performance of these prognostic models was evaluated.[20,21,51,52,54,55,57–64]

The characteristics of these studies and models are summarized in Suppporting Information S6.

3.4 | Risk of bias and applicability

Results of the risk of bias and applicability assessment are summarized in Figure 3.

All prognostic model studies, except 1 study externally validating the ACTA-PORT score,[62] were judged to be at high risk of bias. Seventy-eight percent of studies received a rating of high concern for applicability. Details of the risk of bias and applicability assessment are provided in the Suppporting Information S7.

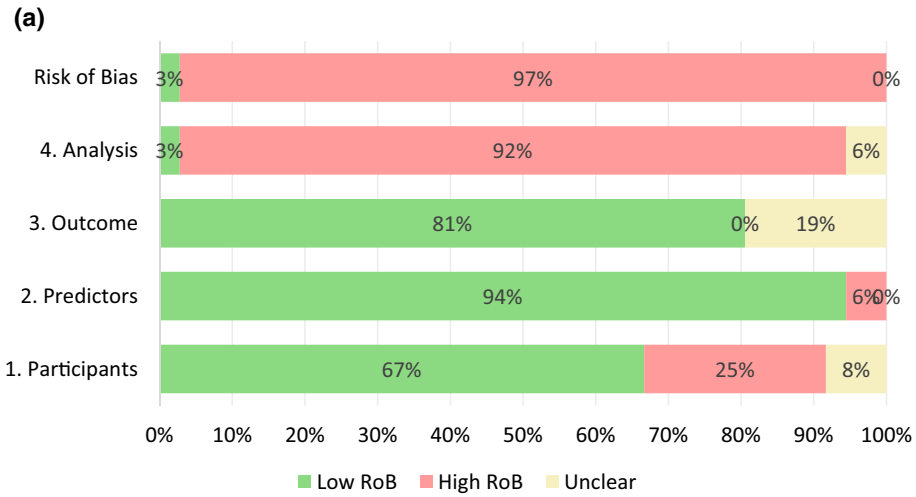
3.5 | Results of model performance in individual studies

The performance estimates reported in individual studies are summarized in the Suppporting Information S8.

3.6 | Results of syntheses

Only the TRUST[21] and TRACK score[20] were externally validated ≥5 times. The meta-analyses of c-statistics and total O:E ratios retrieved from these external validation studies are depicted in Figures 4–7. The summary c-statistic from 6 studies externally validating the TRUST score was 0.74 (95% confidence interval 0.65–0.81, 95% prediction interval 0.47–0.90) (Figure 4), whereas that of the 5 studies externally validating the TRACK score was 0.72 (95% confidence interval 0.68–0.75, 95% prediction interval 0.64–0.78) (Figure 5). The summary total O:E ratio from 5 studies externally validating the TRUST score (exclusion of 1 external validation study[21] because the expected probability could not be estimated as mean patient characteristics had not been reported) was 0.86 (95% confidence interval 0.71–1.05, 95% prediction interval 0.50–1.49) (Figure 6), whereas that of the 5 studies externally validating the TRACK score was 0.94 (95% confidence interval 0.74–1.19, 95% prediction interval 0.49–1.81) (Figure 7).

In all meta-analyses of c-statistics and total O:E ratios of both the TRUST and TRACK score, the between-study heterogeneity was considerable. The proportion of total variability reflecting variability in true effects rather than sampling error (I^2) was ≥75% in all meta-analyses. The variance of the true effects (τ^2) was 0.14 and 0.01 in the meta-analyses of the c-statistics of the TRUST and TRACK score respectively, and 0.02 and 0.04 in the meta-



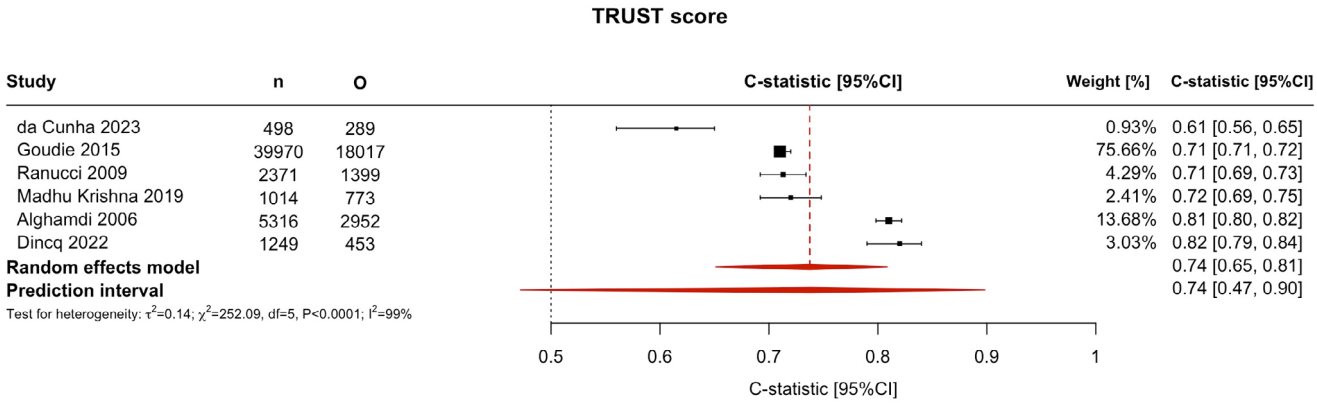


FIGURE 3 Summary of risk of bias (a) and applicability (b) assessment.

FIGURE 4 Meta-analysis of c-statistics retrieved from studies externally validating the TRUST score. Studies were arranged in order of increasing effect size. *N* = sample size; O = observed number of patients who perioperatively received allogeneic red blood cell transfusion.

analysis of the total O:E ratios of the TRUST and TRACK score respectively. The 95% prediction intervals in which the true c-statistics were expected to fall were 0.47–0.90 and 0.64–0.78 for TRUST and TRACK respectively. The 95% prediction intervals in which the true total O:E ratios were expected to fall were 0.50–1.49 and 0.49–1.81 for TRUST and TRACK respectively.

Unweighted Egger and Debray funnel plot asymmetry tests yielded $p \geq 0.05$ (Supporting Information S10), suggesting no evidence for the presence of publication bias.

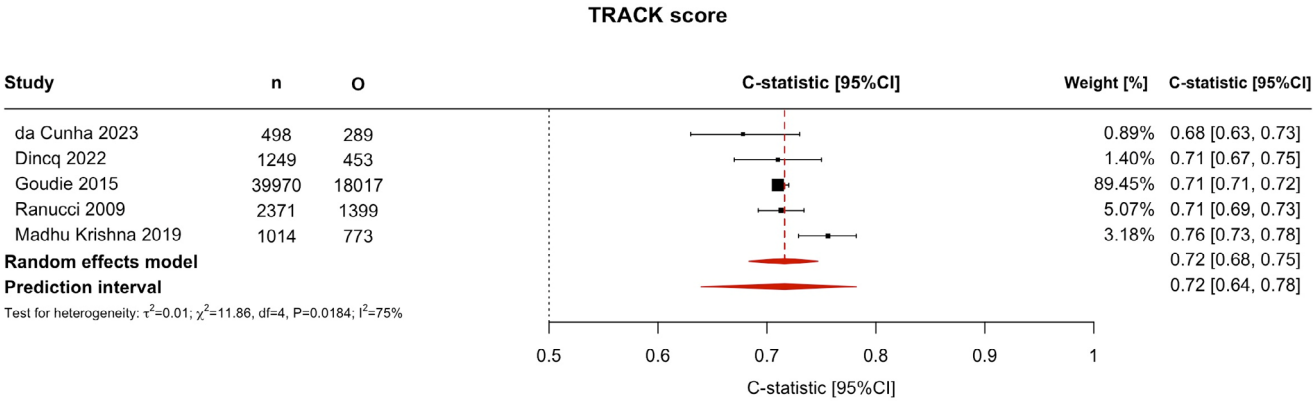


FIGURE 5 Meta-analysis of c-statistics retrieved from studies externally validating the TRACK score. Studies were arranged in order of increasing effect size. *N* = sample size; O = observed number of patients who perioperatively received allogeneic red blood cell transfusion.

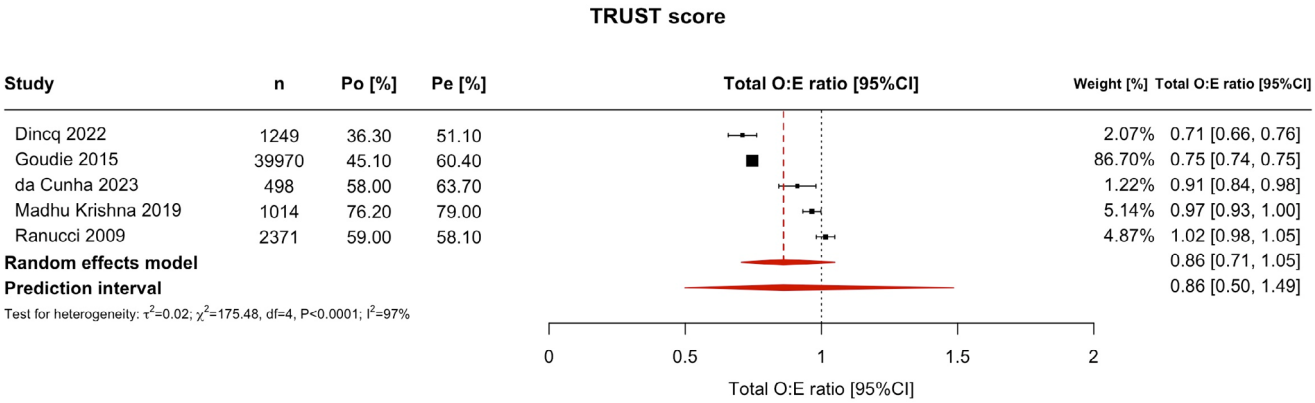


FIGURE 6 Meta-analyis of total observed:Expected (O:E) ratios retrieved from studies externally validating the TRUST score. Studies were arranged in order of increasing effect size. *N* = sample size; Po = observed probability of perioperative exposure to allogeneic red blood cell transfusion, calculated as the observed number of patients who perioperatively received allogeneic red blood cell transfusion divided by the sample size; Pe = predicted probability of perioperative exposure to allogeneic red blood cell transfusion, estimated from incorporation of the mean values of the subject characteristics in the prediction model.

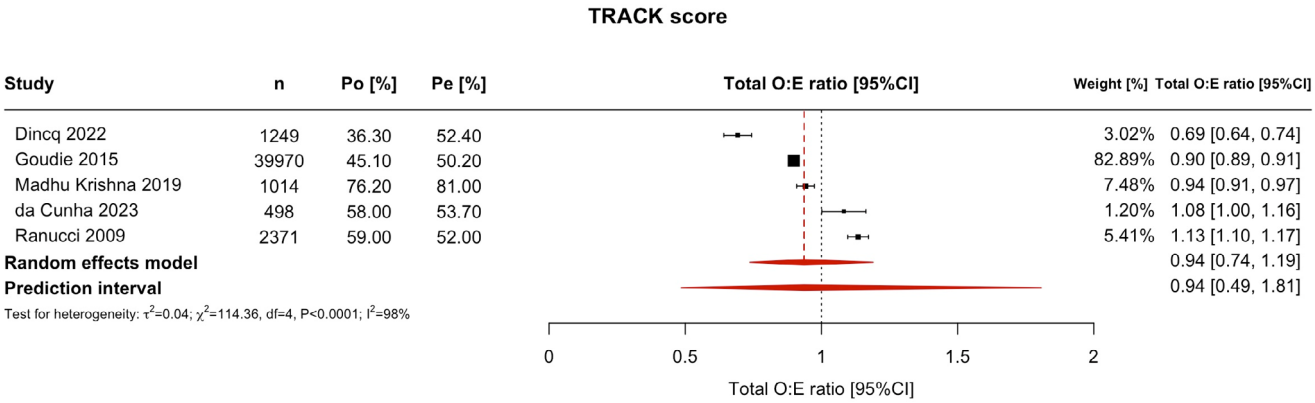


FIGURE 7 Meta-analyis of total observed:Expected (O:E) ratios retrieved from studies externally validating the TRACK score. Studies were arranged in order of increasing effect size. *N* = sample size; Po = observed probability of perioperative exposure to allogeneic red blood cell transfusion, calculated as the observed number of patients who perioperatively received allogeneic red blood cell transfusion divided by the sample size; Pe = predicted probability of perioperative exposure to allogeneic red blood cell transfusion, estimated from incorporation of the mean values of the subject characteristics in the prediction model.

4 | DISCUSSION

4.1 | Summary of evidence

This systematic review and meta-analysis of prognostic models for preoperative prediction of perioperative exposure to RBC transfusion in adult cardiac surgery, identified 9 externally validated prognostic models and a total of 27 external validation studies. Reporting was incomplete in all studies developing or externally validating these models, and most studies were judged to be at high risk of bias and received a high concern of applicability. Because only few external validation studies were found for each prognostic model, meta-analyses of model discrimination and calibration were only possible for the TRACK and TRUST score. Our results suggest that these 2 models may only have moderate ability to differentiate between patients who would and would not perioperatively receive RBC transfusion, with summary estimates of the c-statistic of 0.74 (95% CI: 0.65–0.81) and 0.72 (95% CI: 0.68–0.75) for the TRUST and TRACK score respectively. Both models may also mildly overpredict the exposure to RBC transfusion since summary estimates of the total O:E ratio of 0.86 (95% CI: 0.71–1.05) and 0.94 (0.74–1.19) were <1. As expected,[65] considerable between-study heterogeneity was found in all meta-analyses. Funnel plot asymmetry tests did not seem to find evidence for the presence of publication bias, but these results should be interpreted with caution because only few external validation studies were included.

4.2 | Strenghts and limitations

Strengths of our systematic review include an extensive literature search conducted in collaboration with librarians, and a thorough appraisal of risk of bias and quality of reporting with recommended checklists.

However, this systematic review and meta-analysis also suffers from several limitations. First, while the aim of this review was to only appraise and summarize models that had already been externally validated, this approach may have excluded potentially valuable, but not yet validated, prediction models. Second, total O:E ratios were estimated from reported group characteristics, also in three studies reporting calibration plots, because the number of patients per risk stratum could not be extracted. Third, sources of heterogeneity were not explored. We decided to not explore these with for example subgroup analysis or meta-regression, because these analyses were not pre-specified in the protocol and post-hoc analyses are at risk of finding apparent, but false, explanations for heterogeneity.[66] Furthermore, only few external validation studies could be included in the meta-analyses, and participant data were insufficiently reported, making any post-hoc analysis difficult. Last, the certainty of the evidence was also not assessed because guidance for transparent reporting of the assessment of the certainty of the evidence regarding prognostic studies is not yet available. Recently, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group published concepts which may help to develop such assessment in the future.[67]

4.3 | Comparison with other studies

In this systematic review, we confirm the findings of a previous systematic review which found poor reporting, high risk of bias and pooled c-statistics ranging between 0.67 and 0.78 in studies developing or externally validating models for prediction of any type of blood transfusion in patients undergoing any type of elective surgery.[68] This systematic review provides the additional insight that prognostic model studies published before 2000, and those including patients undergoing urgent cardiac surgery, also suffered from poor reporting and high risk of bias. Furthermore, this systematic review adds that considerable between-study variability may be present between external validation studies. Although sources of heterogeneity were not explored, it appears that the use of different patient blood management strategies may have contributed to differences in observed and predicted RBC transfusion rates in these external validation studies.

4.4 | Implications

Accurate prediction of perioperative blood transfusion is important, because it helps ensuring sufficient availability of compatible blood products, and effective and cost-effective use of patient blood management strategies, especially in cardiac surgery, the surgical specialty with the highest rate of allogeneic RBC transfusion.[69]

However, the results of this review strengthen the results of another systematic review and meta-analysis[68] that the currently available models seem to be insufficiently externally validated, at high risk of bias, and/or insufficiently performant. This review therefore underlines the need for future external validation and model updating studies of high methodological quality and adequate reporting as guided by the TRIPOD statement.[36] Researchers may find insight in this systematic review

which models are suitable for external validation.[28] Guidance on how to undertake high quality external validation studies was recently published.[70–72] Still, clinicians may be discouraged in undertaking external validation or model updating studies because prediction formulas were not clearly reported. Currently, for only 1 model, an online application is available to easily estimate the predicted probability of RBC transfusion.[58,73,74] Therefore, to support clinicians in externally validating the prognostic models included in this review, an OpenDocument Spreadsheet named "Expected probability calculator.ods" was provided in the Supporting Information, with which the expected probability of RBC transfusion can be estimated for each included model.

This review also highlights that model performance is heterogeneous across external validation studies. This heterogeneity may be explained by variable transfusion practices between physicians, potentially caused by inconsistent adherence to patient blood management guidelines[75,76] or the existence of gray areas in these guidelines where transfusion seems to be optional based on clinical judgment. To improve the generalizability of models, while also capturing variability in transfusion practices between physicians, researchers may consider using (1) large, multicenter data, preferentially from hospitals where patient blood management guidelines have been well implemented, (2) hierarchical modeling that considers physician-level predictors (e.g., physician's experience, frequency of past transfusions, specialty) and hospital-level predictors (e.g., transfusion protocol, available resources, overall hospital case volume), and (3) stepwise internal-external cross-validation.[77] Incorporation of granular patient data, hierarchical data (e.g., provider-level variability), and advanced machine learning techniques, may further enhance the discrimination, calibration, and clinical utility of future prognostic models.

5 | CONCLUSION

This systematic review and meta-analysis investigating prognostic models to predict perioperative exposure to RBC transfusion in adult patients undergoing any type of cardiac surgery, found poor reporting, and high risk of bias in most studies. In addition, the performance of the only 2 models that were sufficiently externally validated to conduct a meta-analysis, seemed only moderate. Furthermore, interpretation of these summary performance estimates was complicated by the presence of between-study variability. These findings highlight the need for future external validation and model updating studies which strictly adhere to reporting guidelines and minimize the risk of bias.

AUTHOR CONTRIBUTIONS

Concept and design: Van den Eynde. Acquisition, analysis, or interpretation of data: Van den Eynde, Vrancken, Foubert, Tuand, Vandendriessche. Drafting the manuscript: Van den Eynde, Vrancken, Rex. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis: Van den Eynde. Supervision: Rex.

CONFLICT OF INTEREST STATEMENT

Raf Van den Eynde received financial support from CSL Vifor for lectures during the conduct of this study, but this did not influence the study's conduct or interpretation.

DATA AVAILABILITY STATEMENT

Template and completed data collection forms are available on request. All other data, including data used for all analyses and the analytic code, are available in the manuscript or Supporting Information.

REGISTRATION AND PROTOCOL

The protocol of this systematic review was registered at the International Prospective register of systematic reviews (PROSPERO CRD42023457374) on the 4th of September 2023.

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How to cite this article: Van den Eynde R, Vrancken A, Foubert R, Tuand K, Vandendriessche T, Schrijvers A, et al. Prognostic models for prediction of perioperative allogeneic red blood cell transfusion in adult cardiac surgery: A systematic review and meta-analysis. Transfusion. 2025;65(2):397–409. https://doi.org/10.1111/trf.18108