## RESEARCH

# Adverse events of iron and/or erythropoiesis-stimulating agent therapy in preoperatively anemic elective surgery patients: a systematic review

Jorien Laermans[1,2*] , Hans Van Remoortel[1,2], Bert Avau[1], Geertruida Bekkering[2,3,4], Jørgen Georgsen[5], Paola Maria Manzini[6], Patrick Meybohm[7], Yves Ozier[8], Emmy De Buck[1,2], Veerle Compernolle[9,10] and Philippe Vandekerckhove[2,11,12]

## Abstract

**Background:** Iron supplementation and erythropoiesis-stimulating agent (ESA) administration represent the hallmark therapies in preoperative anemia treatment, as reflected in a set of evidence-based treatment recommendations made during the 2018 International Consensus Conference on Patient Blood Management. However, little is known about the safety of these therapies. This systematic review investigated the occurrence of adverse events (AEs) during or after treatment with iron and/or ESAs.

**Methods:** Five databases (The Cochrane Library, MEDLINE, Embase, Transfusion Evidence Library, Web of Science) and two trial registries (ClinicalTrials.gov, WHO ICTRP) were searched until 23 May 2022. Randomized controlled trials (RCTs), cohort, and case-control studies investigating any AE during or after iron and/or ESA administration in adult elective surgery patients with preoperative anemia were eligible for inclusion and judged using the Cochrane Risk of Bias tools. The GRADE approach was used to assess the overall certainty of evidence.

**Results:** Data from 26 RCTs and 16 cohort studies involving a total of 6062 patients were extracted, on 6 treatment comparisons: (1) intravenous (IV) versus oral iron, (2) IV iron versus usual care/no iron, (3) IV ferric carboxymaltose versus IV iron sucrose, (4) ESA+iron versus control (placebo and/or iron, no treatment), (5) ESA+IV iron versus ESA+oral iron, and (6) ESA+IV iron versus ESA+IV iron (different ESA dosing regimens). Most AE data concerned mortality/survival ($n=24$ studies), thromboembolic ($n=22$), infectious ($n=20$), cardiovascular ($n=19$) and gastrointestinal ($n=14$) AEs. Very low certainty evidence was assigned to all but one outcome category. This uncertainty results from both the low quantity and quality of AE data due to the high risk of bias caused by limitations in the study design, data collection, and reporting.

**Conclusions:** It remains unclear if ESA and/or iron therapy is associated with AEs in preoperatively anemic elective surgery patients. Future trial investigators should pay more attention to the systematic collection, measurement, documentation, and reporting of AE data.

*Correspondence: jorien.laermans@cebap.org

[1] Centre for Evidence-Based Practice, Belgian Red Cross, Mechelen, Belgium
Full list of author information is available at the end of the article

Laermans *et al. Systematic Reviews* (2022) 11:224

Page 2 of 17

## Introduction

Transfusion of blood components can be a life-saving intervention, but comes with the risks of transfusion reactions and transmission of bloodborne infections. To optimize the care of patients who might need a transfusion and minimize the patient's exposure to allogeneic blood products, a multidisciplinary approach has been developed and termed "Patient Blood Management" (PBM) [1]. PBM encompasses all aspects surrounding the transfusion decision-making process through three pillars: (1) addressing pre-existing preoperative anemia, (2) minimizing intraoperative blood loss, and (3) applying appropriate transfusion triggers to ensure rational allogeneic blood product use. During the 2018 International Consensus Conference on Patient Blood Management (ICC-PBM), the scientific evidence base was assessed and a set of 10 clinical and 12 research recommendations were formulated using the GRADE methodology [2, 3].

Four of the formulated clinical recommendations (Table 1) concerned the treatment of preoperative anemia, which is associated with increased perioperative blood transfusion requirements, increased risk of perioperative infection, mortality, postoperative complications, and extended hospital stay [4–7]. Recommended treatment options included iron supplementation (in case of iron-deficiency anemia) and/or erythropoiesis-stimulating agents (ESAs) [2].

As effectiveness is just one aspect to consider in making a balanced treatment recommendation, the expert panel recommended to investigate the use of short-acting erythropoietins and iron supplementation in adult preoperative patients undergoing elective surgery, with focus on long-term (un)desirable effects, optimal dose, type of surgery (particularly in cancer surgery), copresence of iron deficiency, and cost-effectiveness [2].

Therefore, in a follow-up project, three full-systematic reviews were conducted to gather the best available scientific evidence on the effectiveness (review 1) [8], safety (review 2), and cost-effectiveness (review 3) [9] of iron and/or ESA therapy in adult patients with preoperative anemia undergoing elective surgery. The current systematic review (review 2) focused on the occurrence of adverse events (AEs) during or after treatment with iron and/or ESAs.

## Methods

This systematic review was not prospectively registered, but was carried out in accordance with the pre-defined methodological standards of the Centre for Evidence-Based Practice [10]. Eligibility criteria and data synthesis plans were established a priori by the reviewers (JL and HVR) and approved by a third external methodological expert (GB) and 4 PBM experts (JG, PM, PMM, YO). The reporting of this review adheres to the PRISMA harms checklist [11] (completed checklist in Additional file 1).

### Eligibility criteria

This review's PICO question was "In elective surgery patients with preoperative anemia (P), is the use of iron and/or ESA therapy (I), linked to AEs (O)?".

### Population

Anemic adults (≥18 years) scheduled for elective surgery were eligible for inclusion. Studies were included if the baseline hemoglobin (Hb) levels of the study participants were in line with the World Health Organization (WHO) criteria for anemia, i.e., <13 g/dl for men and <12 g/dl for women. Different criteria for anemia were accepted if the study investigators provided a clear definition of anemia, or if no clear definition was provided but baseline Hb levels were <13 g/dl in all patients (based on the upper

**Table 1** Clinical recommendations formulated during the ICC-PBM as published previously [2]

| Clinical recommendation | Strength of recommendation and certainty of evidence |
| --- | --- |
| 1. Detection and management of preoperative anemia early enough before major elective surgery | Strong recommendation, low-certainty evidence |
| 2. Use of iron supplementation to reduce red blood cell transfusion rate in adult preoperative patients with iron-deficient anemia undergoing elective surgery | Conditional recommendation, moderate-certainty evidence |
| 3. Do not use erythropoiesis-stimulating agents routinely in general for adult preoperative patients with anemia undergoing elective surgery | Conditional recommendation, low-certainty evidence |
| 4. Consider short-acting erythropoietins in addition to iron supplementation to reduce transfusion rates in adult preoperative patients with hemoglobin concentrations < 13 g/dL undergoing elective major orthopedic surgery | Conditional recommendation, low-certainty evidence |

Laermans *et al. Systematic Reviews*    (2022) 11:224

Page 3 of 17

limit of the 99% confidence interval (CI) (mean Hb levels) or the 75th percentile of the interquartile range (IQR) (median Hb levels)). Studies in pregnant women, children, and non-elective surgery patients were excluded.

### Intervention
Studies were eligible if they investigated the administration effect of iron and/or ESAs, regardless of treatment dose, duration, and formulation (enteral or parenteral). Studies were only included if the administration was started, but not necessarily ended, during the preoperative period. If patients received other cointerventions (e.g., vitamins, folic acid, heparin), the study was only included if these cointerventions were identically administered to both (intervention and control) groups.

### Comparison
Studies were included if they compared the intervention(s) of interest to at least one of the following control groups: placebo, no treatment, standard of care (as per each trial protocol), iron monotherapy, other type of iron therapy (e.g., IV versus oral), or other ESA dosing regimen.

### Outcome
AEs were defined as "unfavorable or harmful outcomes that occur during, or after, the use of a drug or other intervention, but are not necessarily caused by it" [12].

Any AE occurring during/after iron and/or ESA administration was eligible for inclusion and classified by the reviewers (JL and HVR), a third external methodological expert (GB) and 4 PBM experts (JG, PM, PMM, YO) in one of 15 categories (listed in Table 2). The classification system of Szebeni [13] served as a starting point and was supplemented with additional categories until consensus with the PBM experts was reached.

AEs were classified into 15 categories (based on the classification system by Szebeni [13]). Examples of individual adverse events listed are non-exhaustive, except for the anemia-associated ischemic and thromboembolic events.

### Study design
Since many AEs are too uncommon or long-term to be observed within randomized trials [12], both controlled experimental studies (e.g., RCTs) as well as an observational cohort and case-control studies were included.

### Publication status
Published and non-published data were included. Study authors of ongoing or prematurely ended registered trials were contacted to obtain the expected completion/publication date or reason for termination (if not specified).

**Table 2** Adverse event categories

| Adverse event category | Examples of individual adverse events |
| --- | --- |
| Gastrointestinal | • Diarrhea |
| | • Constipation |
| | • Dyspepsia |
| | • Nausea |
| Mucocutaneous | • Rash |
| | • Urticaria |
| | • Erythema |
| | • Palor |
| Autonomic | • Fever |
| Neuro-psychosomatic | • Myalgia |
| | • Injection pain |
| | • Headache |
| Neurological | • Postoperative ileus |
| | • Vertigo |
| | • Dysgeusia |
| Wound healing | • Poor wound healing |
| | • Delayed wound healing |
| Bronchopulmonary | • Dyspnea |
| | • Respiratory failure |
| Infectious | • Surgical wound infection |
| | • Urinary tract infection |
| | • Septic shock |
| | • Pneumonia |
| Bleeding | • Upper gastrointestinal bleed |
| Cardiovascular | • Atrial fibrillation |
| | • Cardiac tamponade |
| | • Hypertension |
| | • Tachycardia |
| Renal | • Need for renal replacement therapy |
| Anemia-associated ischemic | • Myocardial infarction |
| | • Myocardial ischemia |
| | • Stroke |
| | • Transient ischemic attack |
| | • Bowel ischemia |
| | • Acute kidney injury |
| | • Acute limb ischemia |
| Thromboembolic | • Deep venous thrombosis |
| | • Pulmonary embolism |
| | • Other thrombotic events |
| Mortality and survival | • Mortality |
| | • Survival |
| Other | • Muscle spasms |
| | • Allergy |
| | • Convulsions |
| | • Need for reoperation |

Laermans *et al. Systematic Reviews* (2022) 11:224

Page 4 of 17

### Other criteria
No date or language restrictions were applied.

### Data sources and searches
The following databases and trial registries were searched from inception up to 23 May 2022 (initial search on 6 November 2020; update search on 23 May 2022): The Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), MEDLINE (using the PubMed interface), Embase (using the Embase.com interface), Transfusion Evidence Library, Web of Science, WHO International Clinical Trials Registry Platform, and Clinicaltrials.Gov. Search strings comprising both index terms and free text words were tailored to each database (Supplementary Table 1 in Additional file 2).

Reference lists and the 20 first related citations in PubMed of the included records were scanned for additional studies.

### Study selection
Two reviewers (JL and HVR) independently screened the title and abstracts and subsequently the full texts of the identified references guided by the eligibility criteria, using the EPPI-Reviewer Web software [14]. Discrepancies were resolved by discussion. Where necessary, a third reviewer was consulted (BA).

As AE data are notorious for their incomplete/poor reporting, study authors of studies that did not report on AEs but did meet the other eligibility criteria were contacted via email at least twice. If the authors confirmed that no AE data were collected, or did not reply, the study was excluded. If the authors supplied the reviewers with unpublished findings on AEs, the study was included.

### Data extraction
Data extraction was performed independently by two reviewers (JL and HVR). For each individual study, the following data were extracted: source (peer-reviewed publication: author, publication year, and country; trial registration: trial registry number), study design, description of the population, definitions of anemia and iron-deficiency applied by the study investigators, intervention(s), comparison(s), co-interventions, red blood cell transfusion trigger applied, AE outcome(s) of interest (+ method and timing of outcome assessment), and raw event data for each of the reported AEs. If a study presented its data as both composite measures (e.g., "cardiovascular complications") and separate individual AEs (e.g., "atrial fibrillation" and "cardiac tamponade"), only the individual data were extracted.

If a preregistered trial protocol was available, the trial registration webpage was scanned for additional information (e.g., end-of-study reports). In case of missing or insufficiently ambiguous data or composite measure data, study authors were contacted via email at least twice regarding additional or disaggregated data. If a study reported a general statement indicating the absence of an AE (e.g., "no serious AEs were identified in any group," without defining seriousness), this was considered insufficiently ambiguous and the authors were contacted to confirm the absence of events (true "zero events") and to clarify the individual AEs that were studied/recorded. If they did not reply or were not able to specify the events, the study was excluded.

### Quality appraisal: risk of bias and GRADE assessment
The risk of bias and GRADE assessments were performed by two reviewers independently (JL and HVR). Discrepancies were resolved through discussion. The GRADE assessment was verified by a third external methodological expert (GB).

The risk of bias at the study level was assessed using the Cochrane risk-of-bias tool for randomized trials [15] or the GRADE key criteria for observational study limitations ("inappropriate eligibility criteria," "inappropriate methods for exposure variables," "not controlled for confounding," "incomplete or adequate follow-up," "other limitations") for experimental and observational studies, respectively, except for the items regarding "inadequate measurement of the outcomes" and "inadequate selection of the reported results." For these items, domains 4 and 5 of the revised Cochrane risk-of-bias tool (RoB 2) [16] were used, as they cover the important aspects of assessing bias in AE studies more thoroughly. The signaling questions were answered in the Excel RoB 2 implementation tool [17]. Whenever the tool's algorithm proposed "low," the reviewers judged the study at low risk of bias. If the algorithm proposed "some concerns" or "high," they judged it at a high risk of bias.

Next, the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) was used to assess the overall certainty of the evidence. The certainty of the evidence for each outcome (category) was graded as "high," "moderate," "low," or "very low." Experimental and observational studies receive an initial grade of "high" and "low," respectively. Subsequently, these initial levels may be downgraded (based on the risk of bias, imprecision, inconsistency, indirectness, and selective non-reporting bias) or upgraded (based on large effect, dose-response gradient, plausible confounding) [18].

### Data synthesis
If at least 2 studies provided data on the same outcome within the same treatment comparison, and no large heterogeneity in outcome definitions and measurements was

Laermans *et al. Systematic Reviews*    (2022) 11:224

Page 5 of 17

suspected, random effects meta-analysis was performed using the Review Manager 5.3 software [19]. Heterogeneity was assessed through visual inspection of the forest plot and by using the $X^2$ test and the $I^2$ statistic.

To investigate if AEs varied by administration route (i.e., oral versus IV iron), subgroup analyses were performed. Predefined sensitivity analyses were done to explore the influence of (1) different definitions of anemia and (2) different risks of bias judgments concerning "inadequate measurement of the outcomes" and "inadequate selection of the reported results" (see Quality appraisal: risk of bias and GRADE assessment). The statistical significance threshold was set at 5%.

In case a meta-analysis was not possible (i.e., data were only reported by one study) or warranted (i.e., heterogeneity in outcome definitions was observed or suspected), outcome data were presented in a single forest plot per AE categ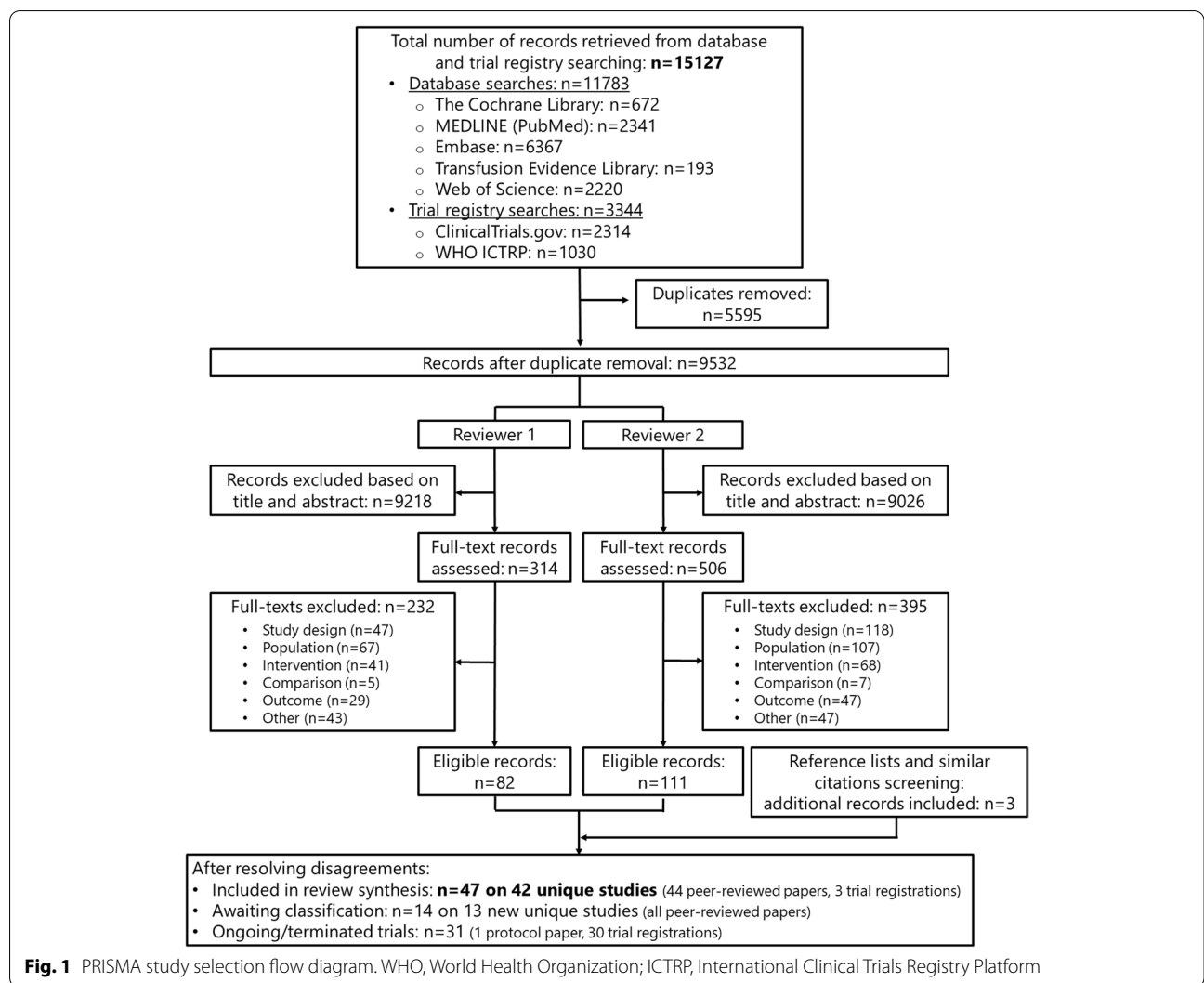ory (without calculating a total effect size) as a visual aid for result interpretation. Statistical synthesis of these results was deemed inappropriate and no statements about the consistency of effects across studies or outcomes were made to avoid unintentional vote counting [20].

To formulate the overall review conclusions as clearly and simply as possible, informative statements were developed in accordance with the set of statements provided by the GRADE Working Group and the Cochrane GRADEing Methods Group [21, 22]. These statements, reflecting both the synthesis of findings and the certainty of the evidence, were used in the Abstract and Discussion sections.

## Results

### Search results

Figure 1 shows the detailed PRISMA study selection flow diagram that summarizes the results of both searches.



**Fig. 1** PRISMA study selection flow diagram. WHO, World Health Organization; ICTRP, International Clinical Trials Registry Platform

The initial search on 6 November 2020 yielded 10142 database records and 3163 trial registry records. After duplicate removal, the title and abstract of the remaining 8221 records were screened. After full-text screening and resolving disagreements, 44 peer-reviewed publications and 3 clinical trial study reports reporting on 42 unique studies were included. The update search on 23 May 2022 rendered an additional 1641 database records and 181 trial registry records. After title and abstract and full-text screening, an additional 14 peer-reviewed publications were identified, reporting on 13 additional studies (one publication provided additional data on the already included RCT of Richards [23]).

A list of studies excluded during full-text screening and the reasons for exclusion is provided in Supplementary Table 2 in Additional file 2. Overall, we identified 21 unique relevant registered ongoing trials (22 trial registrations) and 7 unique prematurely ended or terminated trials (8 registrations), as well as 1 relevant protocol paper (Supplementary Table 3 in Additional file 2).

Data charting of the 13 additional studies from the 23 May 2022 update search revealed that the study data were dispersed across study designs (7 cohorts and 6 RCTs), 4 comparisons (comparisons 1, 2, 4, and 6; see description in Study characteristics), all 15 AE outcome categories and 65 different individual AEs. Furthermore, there was again large heterogeneity in the way the adverse event data were measured, collected, and reported (see also Risk of bias and certainty of evidence). As we strongly believed that adding these data to the synthesis would not change the overall conclusions, we decided not to extract or appraise the evidence from these additional studies. Instead, these 13 new studies were presented in a list of studies awaiting classification (Supplementary Table 4 in Additional file 2). Note that the rest of this manuscript only presents and discusses the synthesized evidence provided by the 42 fully extracted included studies.

### Study characteristics

Of the 42 included studies involving a total of 6062 patients, 26 were RCTs [23–50] and 16 were cohort studies [51–66]. Twenty-eight studies were conducted in Europe (Denmark, France, Germany, Greece, Italy, Spain, Sweden, The Netherlands, UK), whereas the other 14 were conducted in Australia (*n*=2) [31, 36], the USA and Canada (*n*=6) [27, 45, 47, 48, 52, 53], and Asia (China and South Korea (*n*=6)) [25, 37, 40, 50, 66].
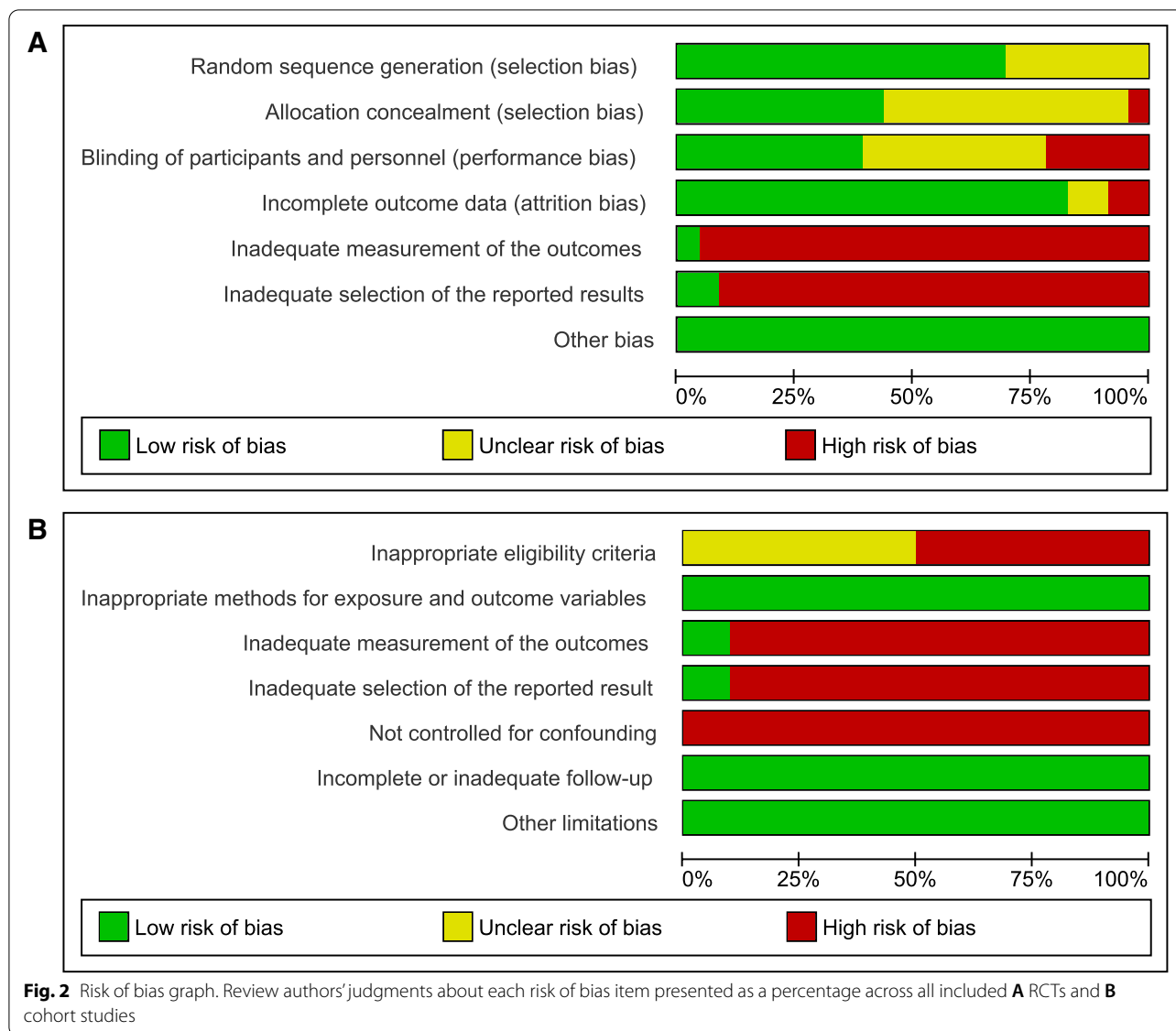
Only 15 studies [23, 28, 31, 33, 34, 42, 46, 48, 50, 51, 54, 57, 59, 61–63] applied the WHO definition of anemia in determining patient study eligibility. Information on the patients' iron-deficiency status was available from just over half the studies (55%) [23–25, 27, 29–32, 35–37, 39–42, 48, 50, 54, 55, 58, 59, 61, 63]. In 8 studies,

the entire study population suffered from iron-deficiency anemia [31, 36, 37, 39, 40, 58, 61, 63]. Patients were scheduled for the following types of elective surgery: colorectal cancer (*n*=12 studies) [26, 28, 32–35, 38, 43, 44, 56, 58, 61, 64, 65], orthopedic (*n*=10) [24, 25, 27, 36, 41, 46, 52, 53, 60, 62], cardiac (*n*=7) [42, 48–51, 55, 57], gynecologic (*n*=6) [29, 30, 37, 39, 40, 66], major head and neck oncologic (*n*=1) [45], abdominal (*n*=2) [23, 31], spinal (*n*=1) [47], vascular (*n*=1) [59] cardiac/ thoracic/orthopaedic/gynecologic/obstetric (*n*=1) [54], or visceral/vascular/gynecologic/maxillofacial/cardiac/ orthopedic/urologic/other major (*n*=1) [63] surgery.

Studies provided data on 6 different treatment comparisons. The majority of the studies (*n*=22; 52%) reported on the comparison of the combined therapy of ESAs and iron versus control (placebo and/or iron, no treatment) [25–27, 29, 30, 32, 35, 38, 39, 41, 43–53, 60, 66]. Seven studies compared IV to oral iron monotherapy [28, 33, 34, 36, 37, 41, 42, 61]. Data on the comparison of IV iron monotherapy versus control (usual care or no iron therapy) were provided by 12 studies [23, 31, 54–59, 63–66]. Two RCTs compared the combined therapy of ESA+IV iron to that of ESA+oral iron [24, 41], whereas one cohort compared different dosing regimens of ESA during the combined therapy with IV iron [62]. Finally, one RCT compared IV ferric carboxymaltose to IV iron sucrose monotherapy [40].

Most commonly, AE data concerned mortality/survival (*n*=24 studies) and the occurrence of thromboembolic (*n*=22), infectious (*n*=20), cardiovascular (*n*=19), gastrointestinal (*n*=14), and anemia-associated ischemic AEs (*n*=10). Autonomic (*n*=8), bronchopulmonary (*n*=8), bleeding (*n*=7), renal (*n*=7), neuro-psychosomatic (*n*=6), mucocutaneous (*n*=6), neurological (*n*=5), AEs related to wound healing (*n*=4), and other types of AEs (*n*=24) were reported by less than 20% of the studies. Supplementary Table 5 in Additional file 2 provides an overview of the AE outcomes for which data were obtained and additionally depicts which RCTs provided data on these outcomes within the 6 treatment comparisons. A similar overview depicting which cohort studies provided data for each of the outcomes within the 6 treatment comparisons is provided in Supplementary Table 6 in Additional file 2. These tables clearly indicate that for any given AE outcome and treatment comparison, data were provided by a very limited number of studies, with the exception of deep venous thrombosis and mortality. In addition, some studies provided data on a multitude of outcomes, whereas others only studied (or at least reported on) a single outcome.

Detailed information on the characteristics of the included studies, including the specific AE outcomes and
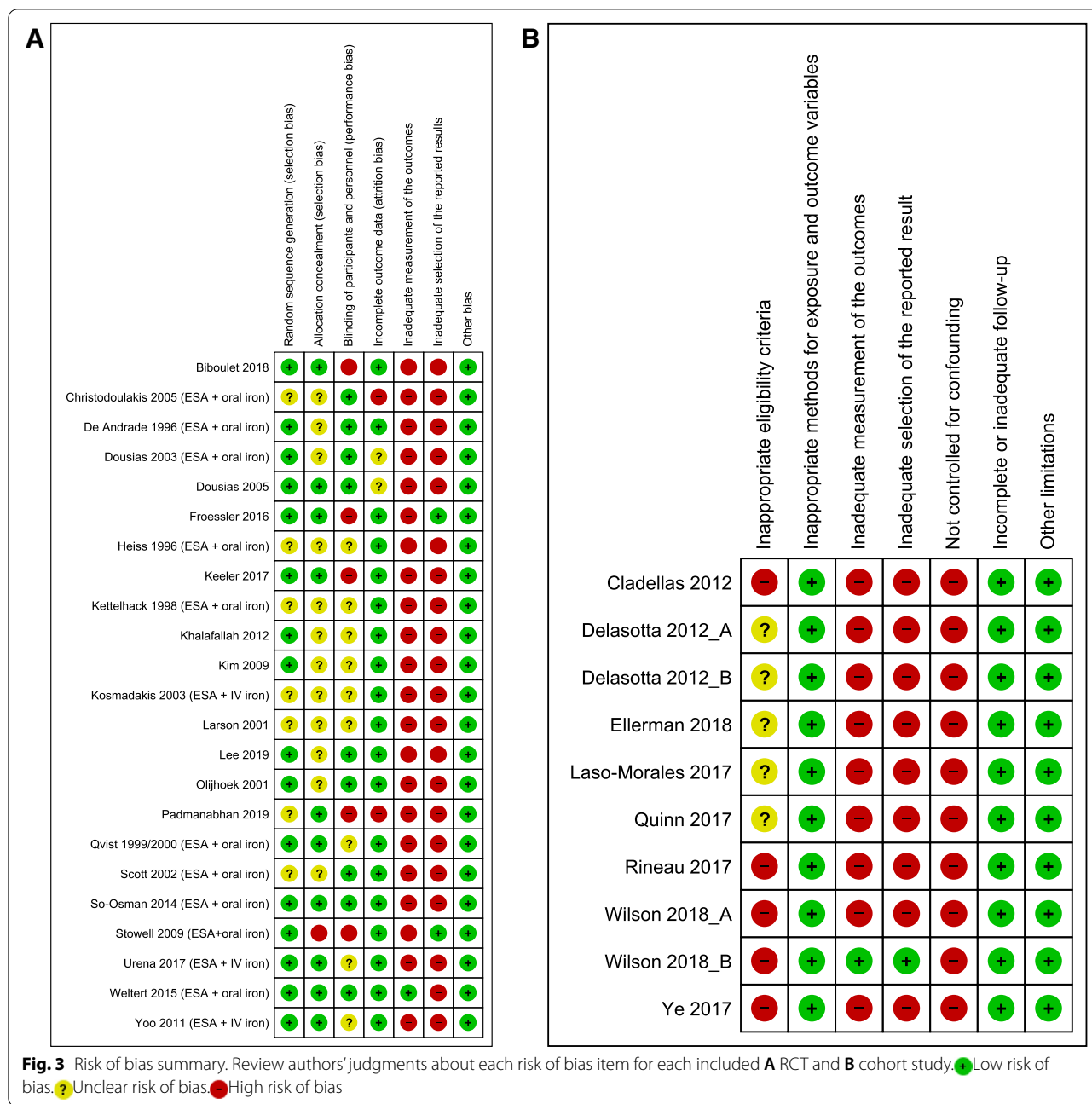
**Fig. 2** Risk of bias graph. Review authors' judgments about each risk of bias item presented as a percentage across all included **A** RCTs and **B** cohort studies

method and timing of their measurement, is presented in Supplementary Table 7 in Additional file 2.

### Risk of bias and certainty of evidence

The risk of bias in the individual studies is presented in Figs. 2 and 3 (details in Supplementary Table 8 in Additional file 2). All but two RCTs [28, 49] and two cohort studies [55, 65] were found to be at high risk of bias in outcome measurement. Often, there was insufficient information available to determine if the measurement of the outcome was a pre-defined part of the study protocol or if data were added post hoc (e.g., by analyzing data on AE that must be reported to regulatory agencies such as the FDA). In addition, many studies failed to clearly mention the methods used for (some of) the actual outcome

measurement, if these methods used were similar across all study participants, and if the outcome assessors were blinded. Only four RCTs [25, 28, 31, 47] and two cohort studies [55, 65] were judged to be at low risk of bias in the selection of reported results. Often, trial protocols or published papers did not describe how (expected or unexpected) adverse outcomes were collected and analyzed. Therefore, the reported AE data may have been selected based on the finding being noteworthy.

Furthermore, 23% of the RCTs were at high risk of performance bias due to lack of blinding of study participants or personnel, whereas only two studies showed high risk of attrition bias. Random sequence generation, allocation concealment, and blinding of study participants or personnel were unclear in 27%, 50%, and 38% of

**Fig. 3** Risk of bias summary. Review authors' judgments about each risk of bias item for each included **A** RCT and **B** cohort study. ➕ Low risk of bias. ❓ Unclear risk of bias. ➖ High risk of bias

the RCTs, respectively. Furthermore, none of the cohort studies adequately controlled for confounding, and 10 of them applied inappropriate eligibility, whereas the other six did not report sufficient information to make an appropriate judgment.

Based on the risk of bias assessment of the individual studies, the overall certainty of the entire body of evidence was downgraded by one level for each outcome (category) of treatment comparisons 2 to 6 (see Synthesis of results). Within the first treatment comparison (IV vs oral iron

monotherapy), most outcomes were also downgraded by one level based on the risk of bias assessment, except for "survival." For this outcome, the reviewers found no reason to downgrade because of the well-designed and -executed RCT of Dickson et al. [28]. Next, for all outcomes within the 6 treatment comparisons, the evidence was further downgraded by two levels due to imprecision because of the very low number of AEs, limited sample sizes and the wide 95% CIs around the effect estimates.

Laermans *et al. Systematic Reviews*      (2022) 11:224

Page 9 of 17

As a result, a very low certainty of evidence was assigned to all AE outcomes within treatment comparisons 2 to 6, indicating that we are uncertain about these effect estimates. Within the first treatment comparison, the overall certainty for "survival" was judged to be low, in contrast to the other outcomes that were assigned a very low certainty of evidence.

## Synthesis of results

Supplementary Table 9 in Additional file 2 contains all AE outcome data extracted from the 42 included studies, classified into the 15 AE categories within the 6 treatment comparisons. Meta-analysis could only be performed for a total of 26 outcomes across 3 treatment comparisons: dyspepsia, postoperative infection, and mortality (Comparison 1: IV versus oral iron monotherapy), nausea, headache, ileus, dyspnea, surgical/superficial wound infection, deep venous thrombosis, mortality, hospital readmission (Comparison 2: IV iron vs usual care/no iron), and 15 outcomes within Comparison 4 on ESA+iron versus control (details listed below). For the vast majority of outcomes, meta-analysis was not warranted or feasible.

Causality assessment [67] was not feasible, as insufficient information was available to judge the relation between the intervention and the AEs reported, i.e., if AEs were related/probably related/possibly related/unlikely to be related/conditionally related to the studied intervention.

Please note that the wording in the narrative synthesis below does not reflect the overall certainty of the evidence, but merely gives an overview of the study findings.

## Comparison 1: IV vs oral iron monotherapy (7 studies, 312 participants)

Neither the meta-analyses on dyspepsia, postoperative infection, and mortality data, nor the other separate analyses on any of the other available AE data (36 outcomes across 13 AE categories, detailed in Supplementary Table 9 in Additional file 2) revealed a statistically significant difference in the occurrence when administering IV compared to oral iron monotherapy.

## Comparison 2: IV iron vs usual care/no iron (12 studies, 2298 participants)

One RCT revealed that IV iron monotherapy was associated with a statistically significantly lower readmission rate for wound infection between discharge and 8 weeks, compared to usual care/no iron therapy [23]. One cohort study showed that IV iron monotherapy was associated with a statistically significantly lower occurrence of dyspepsia, as well as a statistically significantly lower 1-year infection rate and prevalence

of infectious-related codes during the hospital stay, compared to usual care/no iron therapy [54]. Another cohort study showed that IV iron monotherapy was associated with statistically significantly lower 4-year and 5-year disease-free survival rates, as well as 4-year and 5-year overall survival rates, compared to usual care/no iron therapy [65].

Data on the following 8 AE outcomes were meta-analyzed: nausea, headache, ileus, dyspnea, surgical/superficial wound infection, deep venous thrombosis, mortality, and hospital readmission. The meta-analysis of the dyspnea data, provided by two cohort studies [54, 63], showed that IV iron monotherapy was associated with a statistically significantly lower occurrence of dyspnea, compared to usual care/no iron therapy. None of the other meta-analyses, nor the other separate analyses on any of the other available AE data (69 outcomes across 15 categories) revealed a statistically significant difference in the occurrence when administering IV iron monotherapy compared to usual care/no iron therapy.

## Comparison 3: IV ferric carboxymaltose vs IV iron sucrose monotherapy (1 study, 101 participants)

One RCT could not reveal a statistically significant difference in mortality or the occurrence of anaphylactic reactions when administering IV ferric carboxymaltose monotherapy compared to IV iron sucrose monotherapy [40]. Data on AEs in the other 13 AE categories were not available.

## Comparison 4: ESA+iron vs control (placebo and/or iron, no treatment) (22 studies, 3152 participants)

One cohort study revealed that the combined therapy of ESA and IV iron was associated with a statistically significantly lower occurrence of acute renal failure, severe infection (composite measure of sepsis, pneumonia, or mediastinitis), and major adverse cardiovascular events (composite measure), compared to no treatment [51]. In addition, one RCT showed that the combined therapy of ESA and IV iron was associated with a statistically significantly lower postoperative complication rate (composite measure of anastomotic leak abscess/fistula formation, hemorrhage, wound infection, pulmonary complications, complications from blood transfusions), compared to the combination of placebo and IV iron therapy [38].

One RCT showed that the combined therapy of ESA and oral iron was associated with a statistically significant higher occurrence of back pain, compared to the combination of a standard of care and oral iron therapy [47].

Data on the following 15 AE outcomes were meta-analyzed: 3 gastrointestinal AEs (nausea, vomiting, and

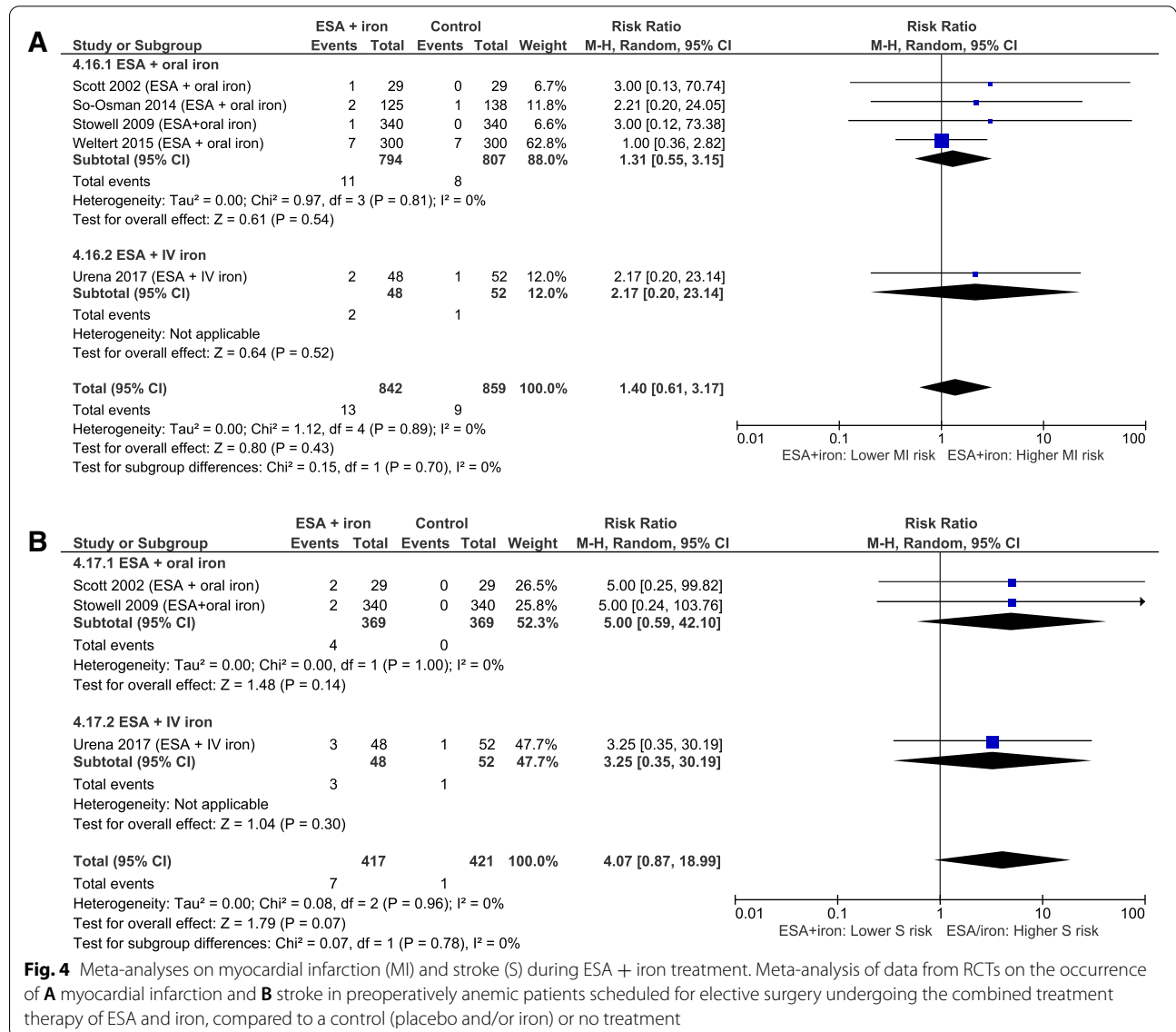Laermans *et al. Systematic Reviews*     (2022) 11:224

Page 10 of 17

obstipation), 2 infectious AEs (surgical/superficial wound infection and urinary tract infection), 4 cardiovascular AEs (atrial fibrillation, heart failure, hypertension, and cardiac tamponade), 3 anemia-associated ischemic AEs (acute kidney injury, myocardial infarction, and stroke; see Fig. 4), 2 thromboembolic AEs (pulmonary embolism and deep venous thrombosis; see Fig. 5), and mortality. Interestingly, the meta-analysis of the mortality data provided by two small cohort studies [51, 60] showed that the combined therapy of ESA and IV iron was associated with a statistically significantly lower mortality rate compared to the control (risk ratio (RR) 0.39, 95%CI [0.17; 0.91], $p=0.03$), while this could not be demonstrated by the meta-analysis of the mortality data provided by two RCTs [38, 41] (RR 0.48, 95%CI [0.21; 1.09], $p=0.08$).
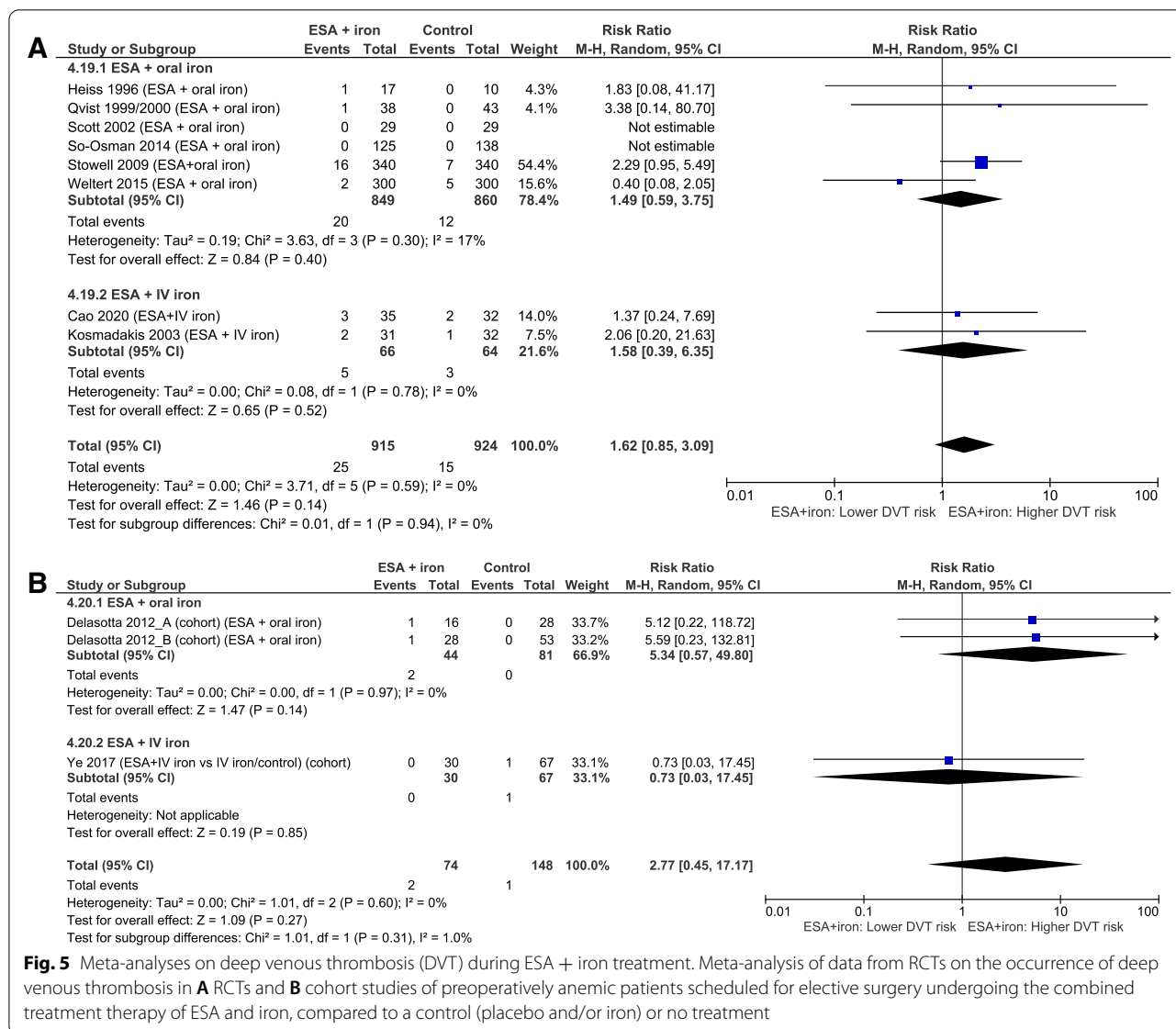
When combining all RCTs [26, 32, 35, 38, 41, 45, 49, 53] comparing the combined therapy of ESA and iron (both oral and IV) to control in one meta-analysis, a statistically significant difference in mortality could not be demonstrated.

None of the other meta-analyses, nor the other separate analyses on any of the other available AE data (90 outcomes across 14 categories) revealed a statistically significant difference in the occurrence when administering ESA+iron compared to control.

The findings related to atrial fibrillation and myocardial infarction were not influenced by excluding studies that were not in line with the WHO definition of anemia.

To investigate if AEs differentially occurred during treatment with ESA+IV iron and ESA+oral iron,



**Fig. 4** Meta-analyses on myocardial infarction (MI) and stroke (S) during ESA + iron treatment. Meta-analysis of data from RCTs on the occurrence of **A** myocardial infarction and **B** stroke in preoperatively anemic patients scheduled for elective surgery undergoing the combined treatment therapy of ESA and iron, compared to a control (placebo and/or iron) or no treatment

**Fig. 5** Meta-analyses on deep venous thrombosis (DVT) during ESA + iron treatment. Meta-analysis of data from RCTs on the occurrence of deep venous thrombosis in **A** RCTs and **B** cohort studies of preoperatively anemic patients scheduled for elective surgery undergoing the combined treatment therapy of ESA and iron, compared to a control (placebo and/or iron) or no treatment

subgroups were created if possible. Subgroup analyses were performed for 3 cardiovascular AEs (atrial fibrillation, heart failure, hypertension), 2 anemia-associated ischemic AEs (myocardial infarction, stroke), deep venous thrombosis, and mortality. The only statistically significant difference was detected for the outcome of mortality reported by the RCTs, but there was considerable heterogeneity (*p* value $X^2$ test = 0.03, $I^2$=78.8%). Two small RCTs (117 participants) that used ESA+IV iron as a treatment [38, 41] reported a lower mortality in the intervention group compared to the control group (risk ratio (RR): 0.48, 95%CI [0.21;1.09], *p*=0.08), whereas the 6 RCTs (1054 participants) that used ESA+oral iron [26, 32, 35, 41, 45, 49] demonstrated non-significantly higher mortality rates in the intervention group (RR 1.75, 95%CI [0.76;4.02], *p*=0.18). This between-subgroup heterogeneity may result from the difference in a sample size and the follow-up period applied by the studies.

## Comparison 5: ESA+IV iron vs ESA+oral iron (2 studies, 158 participants)

One RCT revealed that the combined therapy of ESA and IV iron was associated with statistically significantly less digestive complications, compared to the combined therapy of ESA and oral iron [24]. Statistically significant differences in the occurrence of preoperative prostatitis, cardiac or respiratory failure, deep venous thrombosis or preoperative femoral vein thrombosis, thrombotic and/or vascular events, study mortality, or mortality during hospitalization, when using the combined therapy of ESA

Laermans *et al. Systematic Reviews*     (2022) 11:224

Page 12 of 17

and IV iron compared to ESA and oral iron, could not be demonstrated [24, 41]. For 10 AE categories, data were not available.

### Comparison 6: ESA+ IV iron vs ESA+IV iron (different ESA dosing regimens) (1 study, 127 participants)

The only included cohort study [62] could not reveal a statistically significant increase in the occurrence of intestinal obstruction, 3 bronchopulmonary AEs (pulmonary edema, the need for re-intubation, the need for prolonged ventilation), 3 infectious AEs (pneumonia, wound infection, urinary tract infection), 2 bleeding AEs (hemorrhagic shock, postoperative hematoma), 4 cardiovascular AEs (atrial fibrillation, acute coronary syndrome, arrhythmia, cardiac arrest), 3 anemia-associated ischemic AEs (acute limb ischemia, stroke, acute kidney injury), 2 thromboembolic AEs (deep venous thrombosis, pulmonary embolism), epileptic seizures, or allergy when comparing different ESA dosing regimens during the combined treatment of ESA and IV iron. Data on AEs in the other 7 AE categories were not available.

### Discussion

This systematic review synthesised data from 42 studies containing data on AEs occurring during/after the treatment with iron and/or ESAs, classified into 15 AE categories within 6 treatment comparisons. In addition, we identified 13 recent studies and 21 relevant registered ongoing trials that should be included in the update of this review.

From the 42 included studies, regarding iron monotherapy, we can conclude the following:

- IV iron monotherapy may not be associated with changes in survival compared to oral iron monotherapy (low-certainty evidence).
- We are uncertain (all very low-certainty evidence) whether:

  ° IV iron monotherapy is associated with an increased occurrence of AEs compared to oral iron monotherapy or compared to usual care/no iron therapy.
  ° IV ferric carboxymaltose monotherapy is associated with an increased occurrence of AEs compared to IV iron sucrose monotherapy.

Regarding the combination treatment with ESAs and iron, we are uncertain (all very-low certainty evidence) whether:

- The combined administration of ESAs and iron is associated with an increased occurrence of AEs compared to placebo and/or iron or no treatment.
- The combined administration of ESAs and IV iron is associated with an increased occurrence of AEs compared to treatment with ESAs and oral iron.
- The use of different ESA dosing regimens during the combination treatment with ESAs and IV iron is associated with differences in the occurrence of AEs.

The majority of the overall certainty of the evidence was judged to be very low due to three main reasons. Firstly, the incidence of many of the studied AEs is low, thereby hindering the precision of the results. Similar to transfusion reactions (e.g., 8.1 per 100,000 transfused blood components for transfusion-related acute lung injury [68]), experiencing AE after iron, and/or ESA administration is rare. For example, incidence rates of anaphylactic reactions after IV iron administration are reported to lie around 0.1–1% [69, 70]. Hence, several hundreds of patients would have been required to detect a difference between IV ferric carboxymaltose and IV iron sucrose patients in the study by Lee [40]. The issue of low incidence is also illustrated in Fig. 5 on deep vein thrombosis. In 4 of the 10 studies [32, 43, 52, 53], deep venous thrombosis was detected in just one treatment participant. Two other studies [45, 46] did not detect deep venous thrombosis in any of the treatment or control group participants. Although this highlights the successful use of thromboprophylaxis, the small number of events decreases the precision of the estimate and therefore renders the results fragile [71]. A closer look at the entire dataset of treatment comparison 4 reveals that 17 of the 22 studies did not observe any event in the treatment group for at least one of their studied AEs (45 in total).

The issue is further complicated by the fact that in 20% and 36% of the included peer-reviewed publications on iron monotherapy and the combination treatment with ESAs and iron, respectively, the study authors failed to properly report on study duration and patient follow-up time. Only 36% of the studies on the combination treatment with ESAs and iron certainly employed a follow-up period of at least 30 postoperative days. As a result, some longer-term AEs of these therapies (e.g., thromboembolic, cardiac AEs) may only have become apparent after a follow-up of these patients had ended.

A second independent important reason for the very low certainty of the evidence is the lack of systematic surveillance of pre-defined AE outcomes: just 5 studies [28, 47, 49, 55, 65] explicitly indicated that patients were systematically assessed for AEs or that AE recording was part of the study protocol, whereas the others probably

Laermans *et al. Systematic Reviews*      (2022) 11:224

Page 13 of 17

used spontaneous report monitoring and/or reporting. Moreover, there is heterogeneity in definitions and data collection methods used, as well as a lack of reporting on the exact methods used to ascertain the events.

Thirdly, selective non-reporting bias is likely to have occurred, for example, due to conflicts of interest: entire study reports may be unpublished due to the unexpected findings of harms, or alternatively, particular study results may be selectively unavailable (e.g., because of the magnitude, direction, or *p* value were considered unfavorable by the investigators). This may put the results of this review at risk, as these missing results may differ from the available results. Therefore, the results of these analyses should be interpreted with caution. Nevertheless, the maximal effort has been put in to ensure minimal bias occurring at the review level by including both published and unpublished study data retrieved from an extensive array of databases and trial registries relevant to the topic of PBM and by contacting study authors to request missing information.

This systematic review has several other strengths. By adopting comprehensive selection criteria, the review has captured any possible AE that may (have) occur(red) during or after the administration of iron and/or ESA therapy in preoperatively anemic elective surgery patients. In contrast to most systematic reviews of RCTs only, observational studies were eligible as well. No effort was spared in contacting study authors to obtain additional data or clarification. Special attention was paid to inadequate monitoring and incomplete reporting, both pivotal issues in assessing the risk of bias for AE data. Finally, the GRADE assessment was checked by a third independent methodological expert.

To the best of our knowledge, this is the first systematic review to summarize the available direct evidence on potential AEs of iron and/or ESA therapy in preoperatively anemic patients scheduled for any type of elective surgery.

A previous systematic review on the use of ESAs (whether or not augmented with preoperative autologous blood donation) in anemic patients undergoing elective hip, knee, and spine orthopedic surgery demonstrated that recombinant human erythropoietin was associated with an increased risk of deep vein thrombosis (Peto odds ratio 1.66, 95%CI [1.10; 2.48]), but was inconclusive regarding the risk of mortality, myocardial infarction, and cerebrovascular accidents [72]. In contrast, in a more recent systematic review that only included RCTs that investigated preoperative erythropoietin administration in adult surgical patients and contained data on allogeneic transfusions as their primary outcomes, an association between preoperative erythropoietin and an increased risk of

thromboembolic events could not be demonstrated (RR 1.02, 95%CI [0.78; 1.33], *p*=0.68) [73]. In a third systematic review of RCTs investigating the combination therapy of ESAs and iron compared to iron monotherapy in adult surgical patients, an association could not be demonstrated between the combination therapy and an increased risk of deep vein thrombosis (RR 1.48, 95%CI [0.95; 2.31], *p*=0.09), pulmonary embolism, mortality, stroke, myocardial infarction, or renal dysfunction [74]. A recent Cochrane systematic review of RCTs comparing preoperative recombinant human erythropoietin plus iron therapy to control (placebo, no treatment, or standard of care with or without iron) in preoperatively anemic adults undergoing non-cardiac surgery found moderate-certainty evidence indicating little or no difference in the risk of mortality within 30 days of surgery or of experiencing any adverse event (including local rash, fever, constipation, or transient hypertension) [75]. Other prior systematic reviews on ESA safety have focused on other patient populations such as rheumatoid arthritis [76], chronic heart failure [77, 78], predialysis [79], chronic kidney disease [80], and critically ill [81] patients. Similar to our review, these reviews concluded that the question of whether ESAs affect the risk of AEs in these patient populations remains unanswered. The very narrow scope of the population of interest (in our case preoperatively anemic elective surgery patients) has certainly played a role in this, since it resulted in a limited number of included studies covering a wide range of AEs.

A recent systematic review has shed light on the safety of perioperative iron administration. Gómez-Ramírez et al. synthetized the evidence on the efficacy and safety of short-term perioperative intravenous iron, with or without erythropoietin, in both elective and non-elective major orthopedic surgery [82]. In 10 of the 14 studies identified, only 25 adverse drug effects were reported in patients treated with intravenous iron, which consisted mainly of gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or constipation) and hypotension. There was no difference in the incidence of clinically relevant adverse drug effects in patients receiving iron, with or without EPO, compared to those assigned to control (1.13 vs. 0.85%; RR 1.34, 95% CI [0.63; 2.86], *p*=0.56). When focusing on elective surgery patients, one RCT and 3 observational studies were identified, of which 2 observational studies reported on 30-day mortality and infection rates. No statistically significant differences in postoperative infection rates were found. Mortality rates were 0 in both studies, hindering further statistical analysis. Similar to our review, a recent Cochrane systematic review of RCTs evaluating the effect of preoperative iron therapy (compared to placebo, no treatment, standard of

care, or another form of iron therapy) in anemic patients undergoing surgery concluded that the effects on short-term mortality or postoperative morbidity (including infection and adverse events within 30 days) remain uncertain and that the inclusion of new research in the future is therefore very likely to change the results [83].

Other previous systematic reviews investigating the safety and tolerability of iron therapy [84–86] have generally employed broader selection criteria at the population level, in combination with narrow criteria at the intervention (e.g., comparing IV iron supplements to each other) and/or outcome level (i.e., limiting the number of AEs of interest). For example, a systematic review and meta-analysis by Tolkien revealed that oral ferrous sulfate therapy in patients with iron-deficiency anemia is associated with significantly more gastrointestinal-specific side-effects, compared to IV iron or placebo [87]. By including patients with iron-deficiency anemia of any cause (e.g., chronic kidney disease, pregnancy, blood donation), the reviewers were able to meta-analyze data from 43 RCTs comprising 6831 adults.

Therefore, future systematic review teams may benefit from employing broad selection criteria at the population level in combination with narrow intervention criteria. Expanding the population scope will facilitate the retrieval of AE data of regulated iron and ESA products published in regulatory agency databases (e.g., Food and Drug Administration AE Reporting System). If sufficient numbers of studies/data sources are included and significant heterogeneity is detected, the reviewers should consider performing subgroup analyses at the population level.

However, in order to be able to perform systematic reviews and meta-analyses that provide higher-certainty evidence that can influence decision-making in healthcare, further transparent post-marketing safety surveillance of iron and ESA products is warranted. In addition, the authors of experimental studies on iron and/or ESA therapy should spend time thinking about expected AEs, how to measure and analyze them, and document this in an a priori (ideally published) protocol. They should keep track of expected and unexpected AEs and may want to consider providing all AE data online (e.g., in an End of Trial report, open-access) if reporting in a peer-reviewed publication is impeded by word limitations. Finally, publishers and funders should stress the importance of the collection, documentation, and reporting of AEs and adopt rigorous conflict of interest policies.

## Conclusions

In conclusion, it remains unclear if ESA and/or iron therapy is associated with the occurrence of AEs in preoperatively anemic elective surgery patients. This uncertainty results from both low quantity and quality of AE data due to limitations in study design, data collection, and reporting.

## Abbreviations

AE: Adverse event; CI: Confidence interval; ESA: Erythropoiesis-stimulating agent; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; ICC-PBM: International Consensus Conference – Patient Blood Management; IV: Intravenous; IQR: Interquartile range; PBM: Patient blood management; PICO: Population Intervention Comparison Outcome; RCT: Randomized controlled trial; RoB: Risk of bias; RR: Risk ratio; WHO: World Health Organization.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-022-02081-5.

---

**Additional file 1.** Completed PRISMA harms checklist.

**Additional file 2.** Supplementary tables.

---

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

Laermans *et al. Systematic Reviews*     (2022) 11:224

Page 15 of 17

## Competing interests

## Author details

[1]Centre for Evidence-Based Practice, Belgian Red Cross, Mechelen, Belgium. [2]Department of Public Health and Primary Care, Leuven Institute for Healthcare Policy, KU Leuven, Leuven, Belgium. [3]Center for Evidence-Based Medicine, Leuven, Belgium. [4]Cochrane Belgium, Leuven, Belgium. [5]South Danish Transfusion Service, Odense University Hospital, Odense C, Denmark. [6]SC Banca del Sangue Servizio di Immunoematologia, University Hospital Città della Salute e della Scienza di Torino, Torino, Italy. [7]Department of Anesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Wuerzburg, Germany. [8]University Hospital of Brest, Brest, France. [9]Blood Services, Belgian Red Cross, Mechelen, Belgium. [10]Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium. [11]Belgian Red Cross, Mechelen, Belgium. [12]Centre for Evidence-Based Health Care, Stellenbosch University, Cape Town, South Africa.

## References

1.  (WHO) WHO. WHO global forum for blood safety: patient blood management. 2011. Available from: https://www.who.int/bloodsafety/events/gfbs_01_pbm/en/. Accessed 5 June 2020.
2.  Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, et al. Patient blood management: recommendations from the 2018 Frankfurt consensus conference. JAMA. 2019;321(10):983–97.
3.  Van Remoortel H, Aranko K, Mueller MM, De Buck E, Devine D, Follea G, et al. The systematic use of evidence-based methodologies and technologies enhances shared decision-making in the 2018 International Consensus Conference on Patient Blood Management. Vox Sang. 2020;115(1):60–71.
4.  Benoist S, Panis Y, Pannegeon V, Alves A, Valleur P. Predictive factors for perioperative blood transfusions in rectal resection for cancer: a multivariate analysis of a group of 212 patients. Surgery. 2001;129(4):433–9.
5.  Dunne JR, Malone D, Tracy JK, Gannon C, Napolitano LM. Perioperative anemia: an independent risk factor for infection, mortality, and resource utilization in surgery. J Surg Res. 2002;102(2):237–44.
6.  Leichtle SW, Mouawad NJ, Lampman R, Singal B, Cleary RK. Does preoperative anemia adversely affect colon and rectal surgery outcomes? J Am Coll Surg. 2011;212(2):187–94.
7.  Padmanabhan H, Siau K, Curtis J, Ng A, Menon S, Luckraz H, et al. Preoperative anemia and outcomes in cardiovascular surgery: systematic review and meta-analysis. Ann Thorac Surg. 2019;108(6):1840–8.
8.  Van Remoortel H, Laermans J, Avau B, Bekkering G, Georgsen J, Manzini PM, et al. Effectiveness of iron supplementation with or without erythropoiesis-stimulating agents on red blood cell utilization in patients with preoperative anaemia undergoing elective surgery: a systematic review and meta-analysis. Transfus Med Rev. 2021;35(2):103–24.
9.  Avau B, Van Remoortel H, Laermans J, Bekkering G, Fergusson D, Georgsen J, et al. Lack of cost-effectiveness of preoperative erythropoiesis-stimulating agents and/or iron therapy in anaemic, elective surgery patients: a systematic review and updated analysis. PharmacoEconomics. 2021;39(10):1123–39.
10.  CEBaP. Development of evidence-based guidelines and systematic reviews: methodological charter. 2020. Available from: https://www.cebap.org/storage/cebap/inf-methodology-charter-cebap.pdf. Accessed 5 June 2020.
11.  Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ. 2016;352:i157.
12.  Peryer G, Golder S, Junqueira D, Vohra S, Loke YK. Chapter 19: adverse effects. In:  Cochrane handbook for systematic reviews of interventions version 60 (updated July 2019): Cochrane; 2019. Available from: www.training.cochrane.org/handbook.
13.  Szebeni J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, Patni S, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. Br J Pharmacol. 2015;172(21):5025–36.
14.  Thomas J, Brunton J, Graziosi S. EPPI-Reviewer 4: software for research synthesis. In:  EPPI-centre software. London: Social Science Research Unit, UCL Institute of Education; 2010.
15.  Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011. Available from: http://handbook-5-1.cochrane.org/.
16.  Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
17.  Available from: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2. Accessed 29 July 2020.
18.  Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.
19.  Centre CTNC. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Cochrane Collaboration; 2014.
20.  McKenzie JE, Brennan SE. Chapter 12: synthesizing and presenting findings using other methods. In:  Cochrane handbook for systematic reviews of interventions version 60 (updated July 2019): Cochrane; 2019. Available from www.training.cochrane.org/handbook.
21.  Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: interpreting results and drawing conclusions. In: Cochrane handbook for systematic reviews of interventions version 60 (updated July 2019): Cochrane; 2019. Available from: www.training.cochrane.org/handbook.
22.  Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020;119:126–35.
23.  Richards T, Baikady RR, Clevenger B, Butcher A, Abeysiri S, Chau M, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet. 2020;396(10259):1353–61.
24.  Biboulet P, Bringuier S, Smilevitch P, Loupec T, Thuile C, Pencole M, et al. Preoperative epoetin-alpha with intravenous or oral iron for major orthopedic surgery: a randomized controlled trial. Anesthesiology. 2018;129(4):710–20.
25.  Cao SL, Ren Y, Li Z, Lin J, Weng XS, Feng B. Clinical effectiveness of 3 days preoperative treatment with recombinant human erythropoietin in total knee arthroplasty surgery: a clinical trial. QJM. 2020;113(4):245–52.
26.  Christodoulakis M, Tsiftsis DD, Hellenic Surgical Oncology P, Group EPOS. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. Ann Surg Oncol. 2005;12(9):718–25.
27.  de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. Baseline hemoglobin as a predictor of risk of transfusion and response to Epoetin alfa in orthopedic surgery patients. Am J Orthop. 1996;25(8):533–42.
28.  Dickson EA, Keeler BD, Ng O, Kumar A, Brookes MJ, Acheson AG, et al. Preoperative intravenous iron therapy and survival after colorectal cancer

Laermans *et al. Systematic Reviews*    (2022) 11:224

Page 16 of 17

surgery: long-term results from the IVICA randomised controlled trial. Colorectal Dis. 2020;22(12):2018–27.

29. Dousias V, Paraskevaidis E, Dalkalitsis N, Tsanadis G, Navrozoglou I, Lolis D. Recombinant human erythropoietin in mildly anemic women before total hysterectomy. Clin Exp Obstet Gynecol. 2003;30(4):235–8.

30. Dousias V, Stefos T, Navrozoglou I, Staikos I, Ditto A, Paraskevaidis E. Administration of recombinant human erythropoietin in patients with gynecological cancer before radical surgery. Clin Exp Obstet Gynecol. 2005;32(2):129–31.

31. Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial. Ann Surg. 2016;264(1):41–6.

32. Heiss MM, Tarabichi A, Delanoff C, Allgayer H, Jauch KW, Hernandez R, et al. Perisurgical erythropoietin application in anemic patients with colorectal cancer: a double-blind randomized study. Surgery. 1996;119(5):523–7.

33. Keeler BD, Dickson EA, Simpson JA, Ng O, Padmanabhan H, Brookes MJ, et al. The impact of pre-operative intravenous iron on quality of life after colorectal cancer surgery: outcomes from the intravenous iron in colorectal cancer-associated anaemia (IVICA) trial. Anaesthesia. 2019;74(6):714–25.

34. Keeler BD, Simpson JA, Ng O, Padmanabhan H, Brookes MJ, Acheson AG. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. Br J Surg. 2017;104(3):214–21.

35. Kettelhack C, Hones C, Messinger D, Schlag PM. Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma. Br J Surg. 1998;85(1):63–7.

36. Khalafallah A, Al-Barzan AM, Chan J, Sung MF, Bates G, Ahuja KDK, et al. A prospective randomized controlled trial to assess the effect of intravenous versus oral iron therapy in the treatment of orthopaedic preoperative anaemia. J Blood Disord Transf. 2012;3(4):1000127.

37. Kim YH, Chung HH, Kang SB, Kim SC, Kim YT. Safety and usefulness of intravenous iron sucrose in the management of preoperative anemia in patients with menorrhagia: a phase IV, open-label, prospective, randomized study. Acta Haematol. 2009;121(1):37–41.

38. Kosmadakis N, Messaris E, Maris A, Katsaragakis S, Leandros E, Konstadoulakis MM, et al. Perioperative erythropoietin administration in patients with gastrointestinal tract cancer: prospective randomized double-blind study. Ann Surg. 2003;237(3):417–21.

39. Larson B, Bremme K, Clyne N, Nordstrom L. Preoperative treatment of anemic women with epoetin beta. Acta Obstet Gynecol Scand. 2001;80(6):559–62.

40. Lee SH, Shim JK, Soh S, Song JW, Chang BC, Lee S, et al. The effect of perioperative intravenously administered iron isomaltoside 1000 (Monofer(R)) on transfusion requirements for patients undergoing complex valvular heart surgery: study protocol for a randomized controlled trial. Trials. 2018;19(1):350.

41. Olijhoek G, Megens JGN, Musto P, Nogarin L, Gassmann-Mayer C, Vercammen E, et al. Role of oral versus IV iron supplementation in the erythropoietic response to rHuEPO: a randomized, placebo-controlled trial. Transfusion. 2001;41(7):957–63.

42. Padmanabhan H, Siau K, Nevill AM, Morgan I, Cotton J, Ng A, et al. Intravenous iron does not effectively correct preoperative anaemia in cardiac surgery: a pilot randomized controlled trial. Interact Cardiovasc Thorac Surg. 2018;28(3):447–54.

43. Qvist N, Boesby S, Wolff B, Hansen CP. Recombinant human erythropoietin and hemoglobin concentration at operation and during the postoperative period: reduced need for blood transfusions in patients undergoing colorectal surgery–prospective double-blind placebo-controlled study. World J Surg. 1999;23(1):30–5.

44. Qvist N, Boesby S, Wolff B, Hansen CP. Perioperative administration of recombinant human erythropoietin in colorectal cancer surgery. A prospective, randomized, double-blind placebo controlled study. Ugeskr Laeger. 2000;162(3):355–8.

45. Scott SN, Boeve TJ, McCulloch TM, Fitzpatrick KA, Karnell LH. The effects of epoetin alfa on transfusion requirements in head and neck cancer patients: a prospective, randomized, placebo-controlled study. Laryngoscope. 2002;112(7 Pt 1):1221–9.

46. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Poll RG, Onstenk R, et al. Patient blood management in elective total hip- and knee-replacement surgery (Part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. Anesthesiology. 2014;120(4):839–51.

47. Stowell CP, Jones SC, Enny C, Langholff W, Leitz G. An open-label, randomized, parallel-group study of perioperative epoetin alfa versus standard of care for blood conservation in major elective spinal surgery: safety analysis. Spine. 2009;34(23):2479–85.

48. Urena M, Del T, Altisent OA, Campelo-Prada F, Regueiro A, DeLarochellière R, et al. Combined erythropoietin and iron therapy for anaemic patients undergoing transcatheter aortic valve implantation: the EPICURE randomised clinical trial. EuroIntervention. 2017;13(1):44–52.

49. Weltert L, Rondinelli B, Bello R, Falco M, Bellisario A, Maselli D, et al. A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: results of a prospective single-blind randomized controlled trial. Transfusion. 2015;55(7):1644–54.

50. Yoo YC, Shim JK, Kim JC, Jo YY, Lee JH, Kwak YL. Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. Anesthesiology. 2011;115(5):929–37.

51. Cladellas M, Farré N, Comín-Colet J, Gómez M, Meroño O, Bosch MA, et al. Effects of preoperative intravenous erythropoietin plus iron on outcome in anemic patients after cardiac valve replacement. Am J Cardiol. 2012;110(7):1021–6.

52. Delasotta LA, Rangavajjula A, Frank ML, Blair J, Orozco F, Ong A. The use of preoperative epoetin-alpha in revision hip arthroplasty. Open Orthop J. 2012;6:179–83.

53. Delasotta LA, Rangavajjula AV, Frank ML, Blair JL, Orozco FR, Ong AC. The use of epoetin-alpha in revision knee arthroplasty. Adv Orthop. 2012;2012:595027.

54. Ellermann I, Bueckmann A, Eveslage M, Buddendick H, Latal T, Niehoff D, et al. Treating anemia in the preanesthesia assessment clinic: results of a retrospective evaluation. Anesth Analg. 2018;127(5):1202–10.

55. Evans CR, Jones R, Phillips G, Greene G, Phillips M, Morris-Clarke R. Observational study of pre-operative intravenous iron given to anaemic patients before elective cardiac surgery. Anaesthesia. 2021;76(5):639–46.

56. Kam PM, Chu CW, Chan EM, Liu OL, Kwok KH. Use of intravenous iron therapy in colorectal cancer patient with iron deficiency anemia: a propensity-score matched study. Int J Colorectal Dis. 2020;35(3):521–7.

57. Klein AA, Chau M, Yeates JA, Collier T, Evans C, Agarwal S, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. Br J Anaesth. 2020;124(3):243–50.

58. Laso-Morales M, Jericó C, Gómez-Ramírez S, Castellví J, Viso L, Roig-Martínez I, et al. Preoperative management of colorectal cancer–induced iron deficiency anemia in clinical practice: data from a large observational cohort. Transfusion. 2017;57(12):3040–8.

59. Nandhra S, Chau M, Klein AA, Yeates JA, Collier T, Evans C, et al. Preoperative anaemia management in patients undergoing vascular surgery. Br J Surg. 2020;107(12):1558–61.

60. Pinilla-Gracia C, Mateo-Agudo J, Herrera A, Munoz M. On the relevance of preoperative haemoglobin optimisation within a Patient Blood Management programme for elective hip arthroplasty surgery. Blood Transfus. 2020;18(3):182–90.

61. Quinn EM, Meland E, McGinn S, Anderson JH. Correction of iron-deficiency anaemia in colorectal surgery reduces perioperative transfusion rates: a before and after study. Int J Surg. 2017;38:1–8.

62. Rineau E, Stoyanov A, Samson E, Hubert L, Lasocki S. Patient blood management in major orthopedic surgery: less erythropoietin and more iron? Anesth Analg. 2017;125(5):1597–9.

63. Triphaus C, Judd L, Glaser P, Goehring MH, Schmitt E, Westphal S, et al. Effectiveness of preoperative iron supplementation in major surgical patients with iron deficiency: a prospective observational study. Ann Surg. 2021;274(3):e212–e219.

64. Wilson MJ, Dekker JW, Bruns E, Borstlap W, Jeekel J, Zwaginga JJ, et al. Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study. Transfusion. 2018;58(3):795–803.

65. Wilson MJ, Dekker JWT, Buettner S, Harlaar JJ, Jeekel J, Schipperus M, et al. The effect of intravenous iron therapy on long-term survival in anaemic

Laermans *et al. Systematic Reviews*      (2022) 11:224

Page 17 of 17

colorectal cancer patients: results from a matched cohort study. Surg Oncol. 2018;27(2):192–9.

66. Ye Z, Wu J, Wang Q, Wang Q, Han L, Ulain Q, et al. Perioperative administration of erythropoietin combined with iron sucrose in gynecological tumor patients: a retrospective study. Int J Clin Exp Med. 2017;10(4):7111–6.

67. UMC. The use of the WHO-UMC system for standardised case causality assessment: The World Health Organization Uppsala Monitoring Centre; 2015. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf. Accessed 27 July 2020

68. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. Ann Intern Med. 2012;157(1):49–58.

69. Gomez-Ramirez S, Shander A, Spahn DR, Auerbach M, Liumbruno GM, Vaglio S, et al. Prevention and management of acute reactions to intravenous iron in surgical patients. Blood Transfus. 2019;17(2):137–45.

70. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA. 2015;314(19):2062–8.

71. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011;64(12):1283–93.

72. Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth. 2011;106(1):13–22.

73. Cho BC, Serini J, Zorrilla-Vaca A, Scott MJ, Gehrie EA, Frank SM, et al. Impact of preoperative erythropoietin on allogeneic blood transfusions in surgical patients: results from a systematic review and meta-analysis. Anesth Analg. 2019;128(5):981–92.

74. Kei T, Mistry N, Curley G, Pavenski K, Shehata N, Tanzini RM, et al. Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: a systematic review and meta-analysis. Can J Anaesth. 2019;66(6):716–31.

75. Kaufner L, von Heymann C, Henkelmann A, Pace NL, Weibel S, Kranke P, et al. Erythropoietin plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery. Cochrane Database Syst Rev. 2020;8:CD012451.

76. Marti-Carvajal AJ, Agreda-Perez LH, Sola I, Simancas-Racines D. Erythropoiesis-stimulating agents for anemia in rheumatoid arthritis. Cochrane Database Syst Rev. 2013;2:CD000332.

77. Mesgarpour B, Heidinger BH, Roth D, Schmitz S, Walsh CD, Herkner H. Harms of off-label erythropoiesis-stimulating agents for critically ill people. Cochrane Database Syst Rev. 2017;8:CD010969.

78. Ngo K, Kotecha D, Walters JA, Manzano L, Palazzuoli A, van Veldhuisen DJ, et al. Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients. Cochrane Database Syst Rev. 2010;1:CD007613.

79. Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM. Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients. Cochrane Database Syst Rev. 2017;1:CD011690.

80. Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database Syst Rev. 2014;12:CD010590.

81. Litton E, Latham P, Inman J, Luo J, Allan P. Safety and efficacy of erythropoiesis-stimulating agents in critically ill patients admitted to the intensive care unit: a systematic review and meta-analysis. Intensive Care Med. 2019;45(9):1190–9.

82. Gomez-Ramirez S, Maldonado-Ruiz MA, Campos-Garrigues A, Herrera A, Munoz M. Short-term perioperative iron in major orthopedic surgery: state of the art. Vox Sang. 2019;114(1):3–16.

83. Ng O, Keeler BD, Mishra A, Simpson JA, Neal K, Al-Hassi HO, et al. Iron therapy for preoperative anaemia. Cochrane Database Syst Rev. 2019;12:CD011588.

84. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015;90(1):12–23.

85. Cancelo-Hidalgo MJ, Castelo-Branco C, Palacios S, Haya-Palazuelos J, Ciria-Recasens M, Manasanch J, et al. Tolerability of different oral iron supplements: a systematic review. Curr Med Res Opin. 2013;29(4):291–303.

86. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ. 2013;347:f4822.

87. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015;10(2):e0117383.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.