# Preoperative blood management in colorectal cancer surgery: the controversial role of iron

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# Chapter 2 // **Long-term prognostic value of preoperative anemia in patients with colorectal cancer: a systematic review and meta-analysis**

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## ABSTRACT

**Objective**: To evaluate the long-term prognostic factor of preoperative anemia in colorectal cancer patients.

**Background**: Anemia is frequently observed in colorectal cancer patients, with a case incidence of 30 to 67 percent. Besides an indicator of tumor-induced blood loss and inflammation, anemia in cancer is also suggested to be a cause of inferior outcome, possibly via worsening of tumor hypoxia. As surgery is likely to enhance anemia, the long-term prognostic value of preoperative anemia seems most interesting.

**Methods**: Comprehensive searches were carried out in all relevant databases, including MEDLINE, Embase and Web-of-Science. To include studies addressing overall survival, follow-up had to be at least 24 months or till death. For pooling of survival results, a mixed-linear (fixed-effects) model was fit to the reported hazard ratios (HRs) to calculate a pooled estimate and confidence interval.

**Results**: We included 12 studies comprising 3588 patients to estimate the association between preoperative anemia and overall survival (OS) and disease-free survival (DFS). In a fixed-effects meta-analysis of eight studies, including both colon and rectal cancer, preoperative anemia was significantly associated with poor OS (HR 1.56; 95% CI 1.30 to 1.88; $p < 0.001$). A meta-analysis of seven studies also showed that preoperative anemia was significantly associated with poor DFS (HR 1.34; 95% CI 1.11 to 1.61; $p = 0.002$). Restricted to studies exclusively on colon cancer or rectal cancer, HRs for OS were 1.25 (95% CI 1.00 to 1.55; $p = 0.05$) and 2.59 (95% CI 1.68 to 4.01; $p < 0.001$), respectively, while HRs for DFS were 1.21 (95% CI 0.96 to 1.52; $p = 0.11$) and 1.61 (95% CI 1.18 to 2.21; $p = 0.003$).

**Conclusion**: The present meta-analysis reveals the long-term prognostic value of preoperative anemia in colorectal cancer patients, most distinct in in rectal cancer patients. However, this meta-analysis is mainly based on retrospective studies with high heterogeneity. These results justify raised awareness about the impact of preoperative anemia on long-term survival.

## INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer in men and second in women, accounting for more than 1.4 million new cases and 694 000 associated deaths per year worldwide.[1] The primary treatment for patients with colorectal cancer is surgical resection of the primary tumor. Partly because of advances in surgery, coupled with effective (neo)adjuvant therapy, the five- year survival rate of colorectal cancer has increased to 64 percent.[2]

Anemia, defined by the World Health Organization as hemoglobin <13 g/dL in males and <12 g/dL in females, is present in 30 to 67 percent of colorectal cancer patients at some point during the course of their disease.[3] Contributing mechanisms to the development of anemia include tumor-induced blood loss and reduced iron uptake and utilisation due to IL-6 driven overexpression of hepcidin, known as anemia of chronic disease.[4] Myelosuppressive chemotherapy and surgery-induced blood loss further aggravate the severity of the anemia.[5] Besides a marker of more advanced tumor stage and treatment intensity, anemia in cancer is also suggested to be a cause of inferior outcome, possibly via worsening of tumor hypoxia.[6] Hypoxia has been linked to radiotherapy and chemotherapy resistance, as oxygen is essential for the cytotoxic activities of these treatments.[7-9] Furthermore, by inducing proteomic and genomic changes, hypoxia may also increase the proliferative and metastatic potential.[7]

While surgical resection of the tumor, often the primary treatment for patients with colorectal cancer, is likely to abruptly intensify the anemia, we hypothesize that the long-term prognostic value of anemia in colorectal cancer patients is best studied with preoperative hemoglobin values. Several studies in patients undergoing surgery for colorectal cancer have described preoperative anemia to be a prognostic factor for decreased disease-free survival (DFS) and overall survival (OS),[10-13] but no quantitative and comprehensive review examining the correlation between preoperative anemia and long-term survival has been published. The purpose of this systematic review and meta-analysis is to confirm the long-term prognostic value of preoperative anemia in patients with primary colorectal cancer.

## METHODS

All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were followed.[14]

### Literature search strategy

Comprehensive searches were carried out by a medical librarian in MEDLINE, Embase, Web-of-science, Scopus, Cochrane, CINAHL, PubMed publisher, ProQuest, Lilacs, Scielo and Google scholar. The search was performed on articles published through February 2016 relevant to the long-term prognostic value of preoperative anemia in patients with colorectal cancer. No publication year

or publication language restrictions were applied. Our overall search strategies included terms and alternative spellings for anemia (anemia, hemoglobin), preoperative (preoperative, pretreatment, pre surgical, pre therapeutic), recurrence or survival (recurrence, survival, survival analysis, mortality, prognosis, risk factors, risk assessment, follow up, cohort), cancer (cancer, neoplasm, tumor, carcinoma, adenocarcinoma, malignancy), and colorectal (colorectal, large intestine, colon, rectum, bowel).

## Study selection

Studies were evaluated for inclusion by two independent researchers (MvH, MJW) for relevance to the subject. Study selection was accomplished through three levels of study screening. In level 1, the following types of studies were excluded: reviews, case-reports, letters, editorial, poster abstracts editorials, papers studying non-human. In level 2, abstracts were reviewed for relevance and full-text articles were obtained. To be considered relevant, abstracts had to describe (1) preoperative anemia or anemia-related parameters (hemoglobin, hematocrit) in patients with colorectal cancer, and (2) survival-related parameters (disease-free survival, cancer-specific survival, overall survival, mortality). In articles addressing overall survival or mortality, follow-up had to be for at least 24 months or till death. In level 3, full text articles were reviewed for inclusion in qualitative and quantitative synthesis. Any discrepancies in exclusion were resolved by discussion between the reviewers with supervision by MS.

## Critical appraisal and data extraction

The methodological quality of the included studies was assessed according to the 'Newcastle Ottawa Scale (NOS) for Cohort Studies', which score selection, comparability, and outcome.

The following study details were extracted: first author, study type, sample size, definition anemia, therapy anemia, time measurement hemoglobin level, follow up, results survival analysis and hazard ratio (HR) with 95% CI. If HR was not reported, or if HR could not be estimated from reported data, attempts were made to contact the study authors for individual patient data.

## Statistical analysis

The main outcomes were OS and DFS, comparing colorectal cancer patients with preoperative anemia, to those with no preoperative anemia. For pooling of survival results, a mixed-linear (fixed-effects) model was fit to the reported HRs to calculate a pooled estimate and confidence interval. Pooled HRs were calculated for both colon and rectal cancer mixed, and for colon and rectal cancer separated. If the study reported both univariate and multivariate results, the latter was used in the analysis. If these statistical variables were not made available in the article reporting them, HR was estimated from reported or given data using methods reported by Tierney et al.[15] Tests of statistical significant were performed using the Z-test with $\alpha$=0.05. Heterogeneity across

studies was tested using I2 statistics. An I2 value more than 50% is recognized as significant heterogeneity.

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## RESULTS

The identification of eligible studies is shown in fig 1. A total of 803 studies were identified from the literature search and 431 studies remained after excluding duplicate articles. Three additional studies, agreed upon by both reviewers, were included after manually scrutinizing reference lists. Titles and abstracts of all identified studies were reviewed to exclude the clearly irrelevant ones. A total of 33 potentially relevant articles were read in full. Of 33 papers, 13 fell within the scope of the study and were included in the qualitative analysis.[10-13,] 16-24 The main characteristics of the 13 eligible publications are shown in table 1.

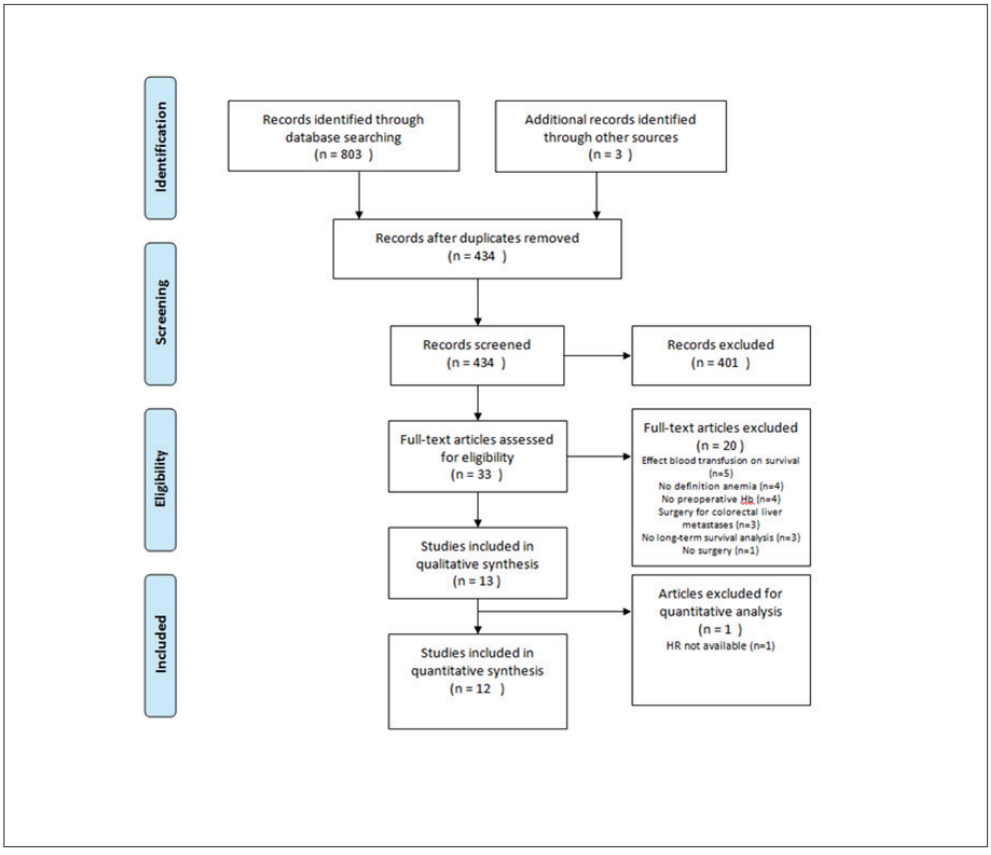


**Figure 1. PRISMA flowchart**

**Table 1: Study characteristics**

| Study | NOS | Study type | Year | Sample size | Tumor type | Definition anemia (g/dL) | Prevalence anemia | Therapy anemia | Follow-up (months) | Survival analysis | HR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| An | 8 | Retro | 2015 | 196 | colon | male<14, female<12 | 59% | NA | mean 61 | OS, DFS | multivariate OS + DFS (R) |
| Berardi | 5 | Pros | 2006 | 317 | rectum | <12 | NA | 1 blood transfusion, 1 ESA | NA | DFS | multivariate DFS (R) |
| Buunen* | 8 | Pros | 2009 | 1076 | colon | male<13, female<12 | 53% | NA | median 53 | OS, DFS | multivariate OS + DFS (E) |
| Box | 5 | Retro | 2005 | 100 | rectum | male<12, female<11.5 | 25% | NA | median 39 | OS, LR, DR | univariate OS (E) |
| Cengiz | 6 | Retro | 2006 | 99 | colon + rectum | male<14.5, female <12.5 | 61% | NA | mean 30 | OS, DFS | univariate OS (E) |
| Fjortoft | 6 | Pros | 2013 | 234 | colon | male<13, female<12 | 54% | blood transfusion 42% | at least 24 | OS | multivariate OS (R) |
| Giessen | 8 | Retro | 2014 | 256 | rectum | <14.2 (median) | 50% | NA | median 101 | DFS, CSS | univariate DFS (E) |
| Giessen-Jung | 8 | Retro | 2015 | 472 | colon | <13.4 (median) | 50% | NA | median 71 | DFS, CSS | univariate DFS (E) |
| Khan** | 3 | Pros | 2012 | 463 | rectum | <12 | NA | NA | median 24 | OS, LR, DR | NA |
| Lee* | 7 | Retro | 2012 | 247 | rectum | male<13.5, female<12 | 36% | blood transfusion 5% | median 44 | OS, DFS, LR, DR | multivariate OS + DFS (E) |
| Peng | 8 | Retro | 2012 | 84 | colon | <11 | 38% | NA | median 45 | DFS | multivariate DFS (R) |
| Qiu | 7 | Retro | 2010 | 363 | colon + rectum | <11 | 21% | blood transfusion excluded | median 26 | OS | multivariate OS (R) |
| van Halteren | 5 | Retro | 2004 | 144 | rectum | <12 | 18% | NA | at least 24 | OS | multivariate OS (R) |

*** = with availability individual patient data**
**** = excluded for meta-analyses**
**Abbreviatons: NOS = Newcastle-Ottawa Score; HR = hazard ratio NA = not available; Pros = prospective; Retro = retrospective; RCT = randomized controlled trial; ESA = erythropoiesis-stimulating agent;**
**DFS = disease-free survival; OS = overall survivall; LR = local recurrence; DR = distant recurrence; CSS = cancer-specific survival; R = reported; E = estimated**

For quantitative analysis, 12 studies were included.[10-13, 16-21, 23, 24] In two studies both colon and rectal cancer patients were included, while five studies reported exclusively on colon cancer, and five studies reported exclusively on rectal cancer. In two studies [16, 23], hazard ratio (HR) could not be estimated from reported data, but patient-level survival data were provided by study authors, making it possible to include the studies in the quantitative analysis. One study was excluded because the HR could not be estimated from reported data and while patient-level data were not

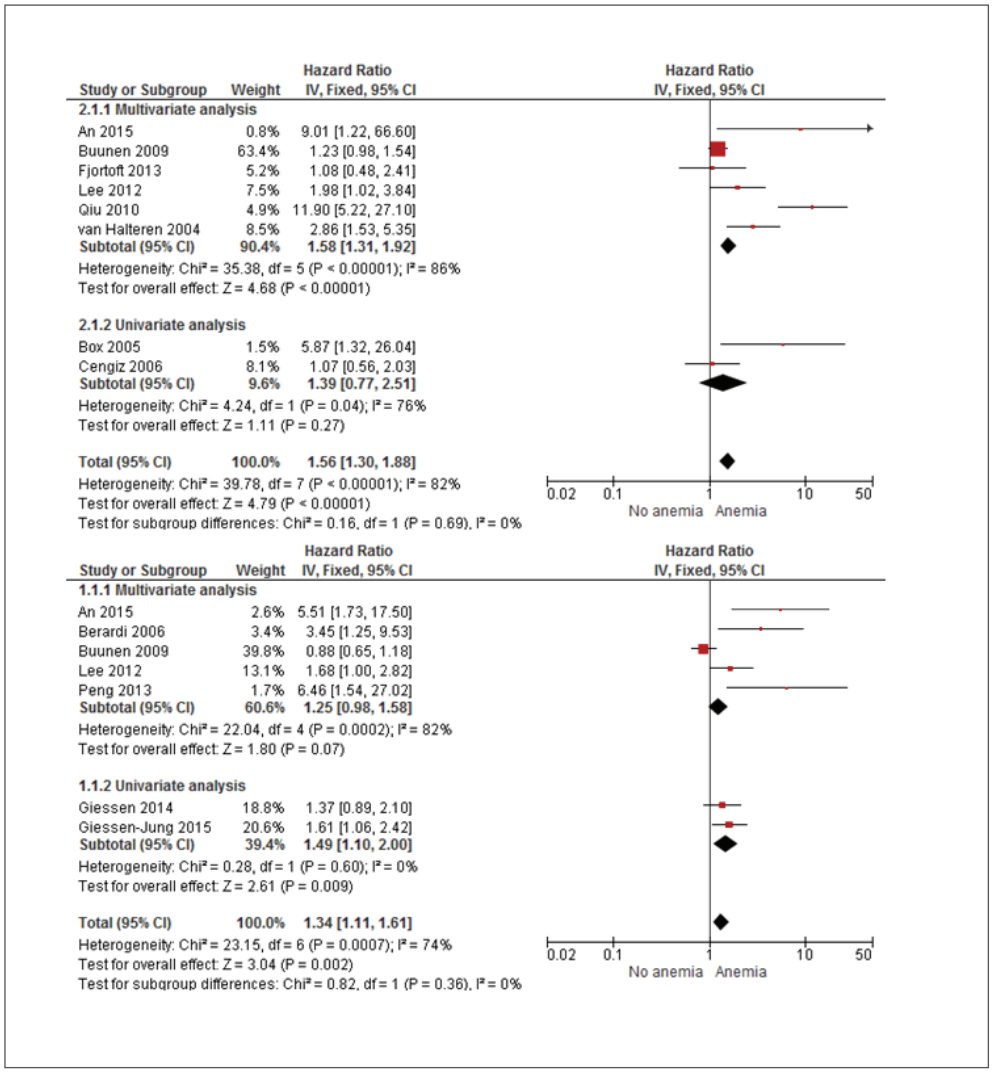


**Figure 2. Forest plot of 8 evaluable studies assessing OS in colorectal cancer according to methods of analysis by a fixed-effects model (above) and forest plot of 7 evaluable studies assessing DFS in colorectal cancer according to methods of analysis by a fixed-effects model (under). HR = hazard ratio, CI = confidence interval, IV = inverse variance (statistical method RevMan)**

shared by the author.[22] In the included studies, the prevalence of anemia varied between 18 and 61%.

In figure 2, meta-analysis of eight studies, including colon and rectal cancer patients, demonstrated that preoperative anemia was significantly associated with poor OS (HR 1.56; 95% CI 1.30 to 1.88; p < 0.001; I2 = 82%). Among studies reporting HRs based on multivariate analysis, preoperative anemia was significantly associated with poor OS as well (HR 1.58; 95% CI 1.31 to 1.92; p < 0.001; I2 = 86%). Two studies reporting HRs based on univariate analysis did not show significance for preoperative anemia (HR 1.39; 95% CI 0.77 to 2.51; p = 0.27; I2 = 76%) (figure 2). Preoperative anemia was also significantly associated with poor DFS (HR 1.34; 95% CI 1.11 to 1.61; p = 0.002; I2 = 74%). When restricted to studies reporting multivariate HR, pooled HR was 1.25 (95% CI 0.98 to 1.58; p = 0.07; I2 = 82%). Pooled HR for studies reporting univariate analysis was 1.49 (95% CI 1.10 to 2.00; p = 0.009; I2 = 0%).

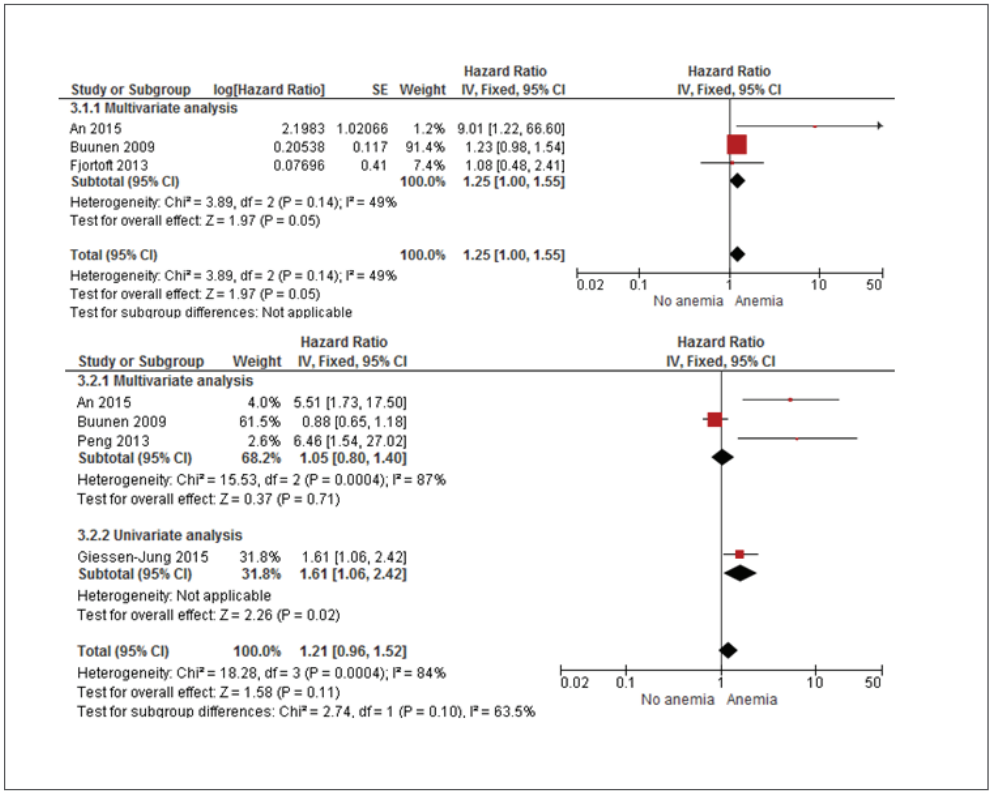


**Figure 3. Forest plot of 3 evaluable studies assessing OS in colon cancer according to methods of analysis by a fixed-effects model (above) and forest plot of 4 evaluable studies assessing DFS in colon cancer according to methods of analysis by a fixed-effects model (under). HR = hazard ratio, CI = confidence interval, IV = inverse variance (statistical method Revman)**

In meta-analysis of three studies including only colon cancer patients, preoperative anemia showed a near significant association with poor OS (HR 1.25; 95% CI 1.00 to 1.55; p = 0.05; I2 = 49%) (figure 3), while in meta-analysis of four studies addressing DFS, significance was clearly lacking (HR 1.21; 95% CI 0.96 to 1.52; p = 0.11; I2 = 84%) (figure 3).

As shown in figure 4, in meta-analysis of four studies including only rectal cancer patients, preoperative anemia was significantly associated with poor OS (HR 2.59; 95% CI 1.68 to 4.01; p <0.001; I2 = 0%). In three studies addressing DFS, pooled HR for preoperative anemia was 1.61 (95% CI 1.18 to 2.21; p = 0.003; I2 = 27%) (figure 4).

As shown in table 2, in subgroup analyses, including both colon and rectal cancer patients and when restricted to studies adjusting for age and tumor stage, pooled HRs for preoperative anemia

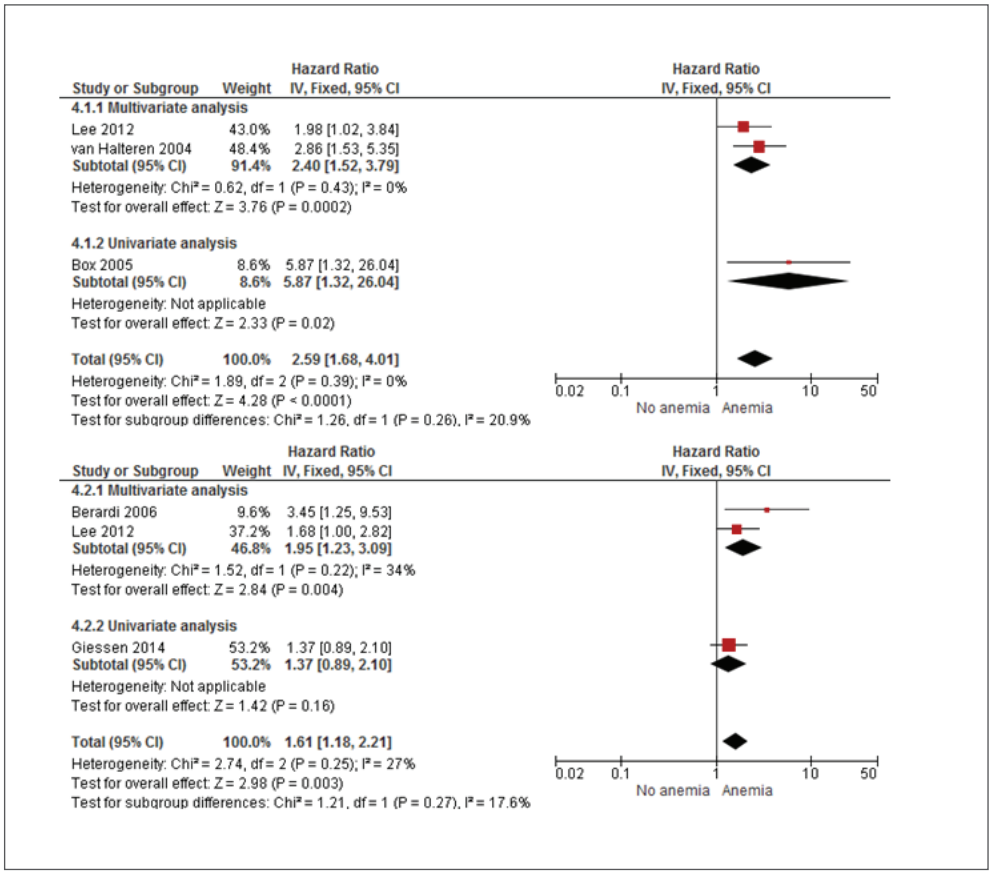


**Figure 4. Forest plot of 3 evaluable studies assessing OS in rectal cancer according to methods of analysis by a fixed-effects model (above) and forest plot of 3 studies assessing DFS in rectal cancer according to methods of analysis by a fixed-effects model (under). HR = hazard ratio, CI = confidence interval, IV = inverse variance (statistical method Revman)**

in OS were 1.28 (95% CI 1.04 to 1.57; I2 = 0%) and 1.25 (95% CI 1.00 to 1.55; I2 = 49%). In DFS, pooled HRs for studies adjusting for age and tumor stage were 1.11 (95% CI 0.86 to 1.42; I2 = 79%) and 1.98 (95% CI 0.82 to 1.42; I2 = 86), respectively. In subgroup analyses based on the various definitions of anemia used by included studies, pooled HRs in OS and DFS were 1.56 (95% CI 1.28 to 1.91; I2 = 89%) and 1.05 (95% CI 0.79 to 1.38; I2 = 84%) respectively, for studies using a restricted cut off defining anemia (<12 g/dL in female and <13 g/dL in male), as compared to pooled HRs of 1.58 (95% CI 1.01 to 2.47; I2 = 58%) and 1.63 (95% CI 1.27 to 2.10; I2 = 39%) respectively, for studies using a more liberal cut off (>12 g/dL in female or >13 in male).

In the quantitative analysis of specifically rectal cancer patients, two studies did report data on hemoglobin levels prior to or during neoadjuvant therapy, in contrast to 3 studies reporting data on directly preoperative hemoglobin level. On average, neoadjuvant therapy was 5 weeks prior to surgery. In a sensitivity analysis in which the pooled HR was calculated for all studies, excluding the two studies reporting data on hemoglobin level prior to or during neoadjuvant therapy, pooled HR for preoperative anemia remained significant for OS (p = 0.0002; HR 2.40; 95% CI 1.52 to 3.79) and DFS (p = 0.02; HR 1.49; 95% CI 1.07 to 2.07) and was almost equal in both OS and DFS compared to HR in main meta-analysis (OS; HR 2.59, DFS; HR 1.61).

| Analysis | Number of studies | Fixed effects HR (95% CI) | I2 statistics (%) |
|---|---|---|---|
| **Colorectal cancer** | | | |
| *Overall survival* | | | |
| Adjustment | | | |
| Age | 3 (Buunen Fjortoft, Lee) | 1.28 (1.04-1.57) | 0 |
| Stage | 3 (An, Buunen, Fjortoft) | 1.25 (1.00-1.55) | 49 |
| Definition anemia (g/dL) | | | |
| <12 female and <13 male | 5 (Box, Buunen, Fjortoft, Qiu, Halteren) | 1.56 (1.28-1.91) | 89 |
| >12 female or >13 male | 3 (An, Cengiz, Lee) | 1.58 (1.01-2.47) | 58 |
| *Disease-free survival* | | | |
| Adjustment | | | |
| Age | 3 (Berardi, Buunen, Lee) | 1.11 (0.86-1.42) | 79 |
| Stage | 3 (An, Berardi, Buunen) | 1.98 (0.82-1.42) | 86 |
| Definition anemia (g/dL) | | | |
| <12 female and <13 male | 3 (Berardi, Buunen, Peng) | 1.05 (0.79-1.38) | 84 |
| >12 female or >13 male | 4 (An, Lee, Giessen, Giessen-Jung) | 1.63 (1.27-2.10) | 39 |

**Table 2: Main meta-analysis results**

## DISCUSSION

This meta-analysis shows that preoperative anemia is significantly associated with decreased long-term OS and DFS in patients with colorectal cancer. For colorectal cancer patients, separate subgroup analyses of studies with adjustment for important prognostic factors, such as age and tumor stage, showed that preoperative anemia is particularly associated with decreased long-term OS. However, since the effect of all confounding factors could not be assessed, a causal relationship cannot definitely be claimed.

A difference was found in the prognostic value of preoperative anemia between colon and rectal cancer patients. Namely after subdividing colorectal cancer patients into colon and rectal cancer patients, our findings only apply to rectal cancer patients. In colon cancer patients, statistical significance is no longer present, however, a similar clear trend for preoperative anemia as a negative long-term prognostic factor is observed. As a whole, survival rates are known to be different for colon and rectal cancer patients, and different treatment strategies are required. In rectal cancer, particularly in stage 2 and 3, neoadjuvant chemoradiation therapy plays a pivotal role in treatment, whilst in colon cancer this is not the case. Furthermore, despite the lack of good quality comparative studies, in general, rectal cancer surgery is associated with longer operation time and more blood loss as compared to surgery for colon cancer.[16, 25] Hence, in rectal cancer, more extensive blood loss in these patients likely aggravates anemia even further. This condition therefore will increase the chance on hypoxia and hypoxia driven survival of remnant tumor mass and might explain a stronger association of preoperative anemia with long-term OS and DFS in rectal cancer patients than in colon cancer patients. In these respects, a separate analysis for colon and rectal cancer patients seems to be justified.

In studying the prognostic value of preoperative anemia, gender should be preferably considered. In defining anemia distinction is made between male and female, and moreover, in colorectal cancer patients, sex differences in long-term survival are demonstrated. This is best known for the survival advantage of young and middle-aged female colorectal cancer patients with localized disease.[26] Unfortunately, despite this known variation, in defining anemia only half of included studies used gender based anemia criteria, and the vast majority of studies failed to include gender in the analyses. As a result, gender could not be included in our subgroup analyses.

Meta-analysis in patients with other cancer types similarly showed that anemia, at any point during course of the disease, is associated with shorter survival. This was the case for patients with lung cancer, cervicouterine cancer, head and neck cancer, prostate cancer, lymphoma and multiple myeloma.[27] Anemia in this respect may be a common cause for treatment resistance, progression or even recurrence of cancer by several mechanisms, of which tumor hypoxia leading to an imbalance between oxygen supply and consumption receives most attention. Experimental studies indeed showed that the oxygen supply to tumors is greatly reduced and hypoxia is

intensified at hemoglobin levels below 10–12 g/dl. Tumor hypoxia in its turn is known to reduce the effectiveness of both chemotherapy and radiotherapy, and can also negatively impact therapeutic outcome by causing a broad variety of proteomic and genetic changes, leading to increased metastatic potential.[28] Moreover, under hypoxic conditions, the concentration of transcription factor hypoxia-inducible factor 1 is increased and may stimulate hypoxia-inducible gene transcription resulting in metabolic, invasive and apoptotic changes; up regulation of vascular endothelial growth factor; and tumor angiogenesis.[6, 29]

Results from experimental studies, showing that tumor hypoxia is intensified below hemoglobin levels 10-12 g/dl, may suggest that not every anemic condition will result in tumor hypoxia. However, when anemia is abruptly intensified by surgery, hypoxia driven survival of remnant tumor mass is likely important for eventual outcome. Our results from subgroup analyses based on the definition of anemia do not support the finding from experimental studies showing that tumor hypoxia, suggested to be the cause of inferior outcome, is intensified at decreasing hemoglobin levels. No trend was observed suggesting that lower hemoglobin levels are associated with worse long-term prognosis, however, high statistical heterogeneity was found in the various analyses.

The reported association between anemia and survival might suggest that correcting the preoperative anemia might positively influence long-term survival of colorectal cancer patients. However, treatment modalities for correcting anemia may also negatively influence outcome. Three principal options for treatment of anemia are to be considered, namely red blood cell transfusions, erythropoiesis-stimulating agents (ESAs) and iron, but so far there is no solid evidence that correction of anemia would improve long-term tumor prognosis.

Blood transfusions are implicated to have immunomodulatory effects that could compromise wound-healing and pathogen control, and also the immune-surveillance against cancer.30 Especially in patients with colorectal cancer, blood transfusions have been reported to be associated with worse prognosis.[31, 32] Interestingly, and refuting the immunomodulation of allogeneic blood transfusion, autologous blood transfusion showed no benefit as compared to standard allogeneic blood transfusion. From these studies, it was concluded that blood transfusion was not likely to modulate prognosis.[33, 34] Hence, a restrictive transfusion policy was implemented in favour for iron and erythropoiesis-stimulating agents (ESAs) therapy as transfusion sparing alternative. However, both these alternatives might not be indifferent for the prognosis of colorectal cancer either.

Indeed, ESAs reduce anemia and transfusion requirements in cancer patients. However, ESAs have also been reported to worsen cancer prognosis.[35-37] Possible mechanisms by which ESAs enhance tumor growth in general, and tumor recurrence in particular, is by increasing the production of pro-angiogenic factors, such as VEGF and by anti-apoptotic action.38 Increased serum VEGF is

associated with decreased disease-free and overall survival in patients with advanced colorectal cancer. In current clinical practice, treatment with ESAs should only be considered in patients with symptomatic chemotherapy-induced anemia and hemoglobin levels <10 g/dL. Moreover in patients treated with curative intent, ESAs should be used with caution. However, available analyses of data from RCTs have not stratified results on the basis of treatment intent (i.e. palliative versus curative), and therefore, future research on this topic is warranted [39, 40]

Similarly, iron therapy is reported to increase hemoglobin levels and with it reduction in allogeneic blood transfusion in patients with colorectal cancer.[41, 42] However, iron is also known to be an essential nutrient for proliferating tumor cells, and anemia of chronic disease, characterized by adequate iron stage but insufficient iron supply for erythroblasts and other iron dependent tissues, is believed to be a potentially effective defense strategy of the human body to inhibit growth of tumor cells.[4] Numerous studies support the hypothesis that both dietary iron and elevated iron levels increase the risk of colorectal cancer,[43-45] and a relationship between levels of iron stores and cancer risk is suggested by studies showing that blood donation, which reduces body iron stores, is associated with lower cancer risk.[46] This notion that iron therapy and high iron levels could pose a risk, is further enforced by the reversed, namely that systemic iron reduction by phlebotomy decreased the incidence of visceral malignancies and mortality in patients with peripheral arterial disease.[47] Finally, several animal experiment studies show iron as a risk factor for developing colorectal cancer and tumor growth.[48, 49] Clearly, while preoperative anemia is a risk factor for OS and DFS, to our knowledge, no study has addressed the long-term hazards of iron therapy in patients with colorectal cancer.

## LIMITATIONS

In this meta-analysis, next to 12 observational studies, one RCT was included. This RCT was not designed primarily to examine the effect of anemia, but HR of preoperative anemia could be computed from shared individual patient data. However, this was limited by the lack of information on anemia related factors, for example blood transfusion rates.

Anemia is associated with important prognostic factors as disease severity, and with treatment strategies, and thus with outcome itself. In this meta-analysis, to adjust for important prognostic factors, subgroup analyses of studies adjusting for age and tumor stage were performed. However, since the vast majority of the included studies were observational and of retrospective nature, many factors significantly associated with DFS and OS could not be corrected for. For example, blood management strategies themselves, like preoperative blood transfusion, ESAs and iron therapy, all reduce anemia and should ideally be known and corrected for. Only in one study, the patients receiving blood transfusion were excluded, while in two studies, blood transfusion was adjusted for in the multivariate analysis. In these studies, the HRs for preoperative anemia differed greatly.

Additionally, a principal limitation to this study was the high level of statistical and clinical heterogeneity in the findings, likely due to the variety of populations studied and the different definitions of anemia used by included studies. Before including studies in the meta-analysis, a quality assessment was performed, which showed that the evidence of each individual study varied from high to very low. However, the study with the lowest quality assessment score did not provide sufficient data to include in the quantitative analysis. As the larger studies tended to be those conducted with more methodological rigour, a fixed-effects analysis was used. In this fixed-effects meta-analysis relatively more weight is rewarded to larger studies. This seems to be justified as results of the study with the most patients, addressing colon cancer, differed considerably from results of the other studies, particularly in the DFS. In general, the studies addressing rectal cancer were of less quality.

## CONCLUSION

The present systematic review and meta-analysis reveals the long-term prognostic value of preoperative anemia in colorectal cancer patients This finding is particularly the case for rectal cancer patients and is supported by subgroup analyses of studies adjusting for important prognostic factors, such as age and tumor stage. However, since the effect of all confounding factors could not be assessed, a causal relationship can still not be claimed. The results should be interpreted with care given the retrospective observational nature of the vast majority of included studies, with high levels of heterogeneity. This meta-analysis does not answer the intriguing question if, and to what extent, correction of anemia by blood transfusion, ESAs or iron, will also modulate the outcome. Instead of improving survival, circumstantial evidence seems to indicate that these treatment modalities may even negatively influence long-term outcome. Future well designed RCTs therefore have to prove the observed associations of our meta-analysis and have to provide evidence if the present preoperative blood management strategy for colorectal cancer patients is optimal and safe as regards to long-term outcome.

## CONTRIBUTORS

Study concept and design: MW, MvH. JH, JJ, JJZ, MS. Literature search and figures: MW, MvH. Data acquisition: MW, JB, HCP. Data analysis and interpretation: MW, JH, JJ, JJZ, MS. Writing manuscript: MW, JH, JJZ, MS. Reviewing manuscript: MvH, JH, JB, HCP JJ, JJZ, MS.

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