Author/s:
Roberts, V;Deftereos, I;Mahbub, B;Simons, K;Faragher, I;Chan, STF;Yeung, JM

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Roberts Vanessa (Orcid ID: 0000-0001-6868-1816)



**Title Page**

**Anaemia and its impacts in colorectal cancer patients – how can we better optimize surgical outcomes?**

Running head: Anaemia and colorectal cancer

Key words: anaemia, colorectal cancer, treatment

Vanessa Roberts,[1] BMedSc, MBBS; Irene Deftereos,[2,6] B.NutDietHons, APD; Bilkis Mahbub,[2] PhD, FRACP; Koen Simons,[4,5] PhD; Ian Faragher,[1] FCSSANZ, FRACS; Steven T. F. Chan,[2] PhD (Lond), FRACS; Justin M. Yeung,[1,2,3] DM, FRACS.

Institutional affiliations:

1. Department of Colorectal Surgery, Western Health, Melbourne.

2. Department of Surgery, Western Precinct, University of Melbourne.

3. Chronic Disease Alliance, Western Health, Melbourne.

4. School of Population and Global Health, University of Melbourne

5. Office for Research, Western Health, Melbourne

6. Department of Nutrition and Dietetics, Western Health



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Corresponding Author

Associate Professor Justin Yeung

Head of the Department of Surgery, Western Precinct

University of Melbourne

WCHRE Level 3

176 Furlong Rd, St Albans VIC 3021

Email: justin.yeung@unimelb.edu.au

Ph: 8395 8116

Fax: 8395 8258



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**ABSTRACT**

**Background**

Anaemia is a common manifestation of colorectal cancer (CRC). However, whether appropriate work up prior to surgery and the effect of anaemia on outcomes has not been well-defined. This study aimed to describe preoperative anaemia incidence, investigations performed, treatment and associated complications in a CRC surgical population at a single large tertiary institution in Australia.

**Methods**

Patients who received surgery with curative intent for CRC between 2012 and 2017 were identified from a prospectively maintained database. Demographic and clinical outcome data were analysed.

**Results**

In total, 754 patients with CRC were included. Anaemia was found in 350 (46.4%) patients, of which 124 (35.4%) were microcytic, 20 (5.7%) were macrocytic and 206 (58.9%) were normocytic. Older patients were more likely to have anaemia (mean age 70.28 years, standard deviation (SD) 12.98 vs. 64.74 years, SD 11.74). Only 89 patients (25.4%) were tested for iron deficiency, and of these, 76 (85.4%) were found to be iron deficient and 42 (47.7%) had low ferritin. Preoperative anaemia was associated with a higher incidence of postoperative complications (adjusted odds ratio [OR] 1.46, 95%, CI 1.04 – 2.05; p=0.03) and a longer length of stay [LOS] (average 1.8 days; 95% CI 0.3 – 3.3 days).

**Conclusion**

A significant proportion of CRC patients had anaemia and the majority were normocytic. Only a small number of anaemic patients were tested for iron deficiency. Preoperative anaemia had an

adverse effect on LOS and postoperative complications. The evaluation of anaemic patients is essential in CRC patients undergoing surgery.

## INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in Australia [1], accounting for 11% of all cancers in Victoria. [2] Iron deficiency anaemia is known to be associated with CRC, [3,4] however, other anaemia subtypes are less well-defined.

There is mounting evidence to suggest that anaemia is a strong predictor of poor outcomes within CRC patients.[3-6] A multi-centre study conducted in the United Kingdom (UK) demonstrated that anaemia was associated with advanced tumour stage and greater mortality.[7] Microcytic anaemia was historically linked to CRC presentation. There is emerging evidence that normocytic anaemia is as common as microcytic anaemia in CRC and is associated with poor prognoses. [6,8] However, there is relatively little data on the presentation and variation of anaemia amongst an Australian cohort, nor is there much information on how it is investigated or treated prior to surgery. Recent literature indicates the importance of iron deficiency in preoperative patients, and highlights its association with increased morbidity, mortality, prolonged hospital stay, and reduced disease-free survival.[9,10] As such, new national guidelines recommend routine testing and management of iron deficiency anaemia prior to surgery.[11]

The aim of this study was therefore to explore the incidence and type of preoperative anaemia in patients undergoing surgery for CRC at a large tertiary institution within Australia. Secondary aims were to investigate potential factors associated with anaemia, evaluate preoperative anaemia investigations and management, and the effect of anaemia on surgical complications and LOS.

## METHODS

All CRC patients at Western Health (Melbourne, Victoria) were included in a prospectively maintained registry. Patients who underwent curative intent surgical management of CRC between January 2012 and June 2017 were included in this study. Patients were excluded if they were transferred to other facilities for management, underwent a palliative surgical procedure, or had incomplete preoperative blood results (defined as not having a Full Blood Count [FBC] within one week of surgery date).

Data collected included patient demographics, preoperative blood test results (including haemoglobin (Hb), Mean Cell Volume (MCV), and Iron (Fe) studies), treatment of their preoperative anaemia (oral iron, intravenous iron and/or intravenous packed red blood cells (PRBCs), details of neoadjuvant chemotherapy, tumour stage (ACPS) [13], location of tumour, surgical procedure, as well as complication type (medical, surgical) and length of hospital stay (LOS, in days).

### *Ethical Considerations*

This study was conducted in accordance with the principles of the National Statement of Ethical Conduct in Human Research, 2007, published by the National Health & Medical Research Council. Institutional human research ethics committee approval for this study was obtained prior to the commencement of data collection (approval number 2018.12).

### *Statistical analysis*

Descriptive statistics are presented as mean (standard deviation, SD) or count and number (percentage). Univariate analyses were conducted using two sample t-tests for continuous variables, and Chi square and Fisher's exact test for categorical variables. Length of stay was treated as time until discharge-event, and differences in length of stay were assessed with the log-rank test.

Adjusted ORs were obtained from logistic regression for predictors of anaemia diagnosis and predictors of complications post-surgery. Adjusted Hazard Ratios (HR) were obtained from a Cox Proportional Hazards model to assess predictors of length of stay. The HR provides a measure of intensity of discharge, with higher intensity leading to lower length of stay. To translate this back into an average length of stay, we repeated the following bootstrap procedure: the model was fit on a subsample of the data and subsequently predictions were made for all patients with their observed covariates except for anaemia, which was set to false.

## RESULTS

A total of 802 patients surgically treated for CRC were identified. Forty-eight were excluded from the study due to meeting exclusion criteria, leaving 754 patients in the final analysis (Figure 1).

### *Demographics*

Of the 754 patients who were included in this analysis, males constituted the majority (57.8%) with a mean (SD) age of 67.3 (12.6) years (Table 1). Approximately half of patients had never smoked (50.8%), and 31.3% were ex-smokers. Just over seventy three percent of patients were non-diabetic, and 18.5% received neoadjuvant therapy prior to surgery.

*Incidence and Type of Anaemia*

Three hundred and fifty patients (46.4%) were anaemic, and of those, 124 (35.4%) were microcytic, 206 (58.9%) were normocytic and 20 (5.7%) were macrocytic.

*Factors Associated with Anaemia*

Anaemic patients were significantly older (70 vs 65; adjusted OR 1.03, 95% confidence interval (CI) 1.01- 1.04 per year, p<0.001) than non-anaemic patients. Anaemic patients were also more likely to be diagnosed by screening.

Over half of the anaemic patients had right sided tumours (54%, p<0.001), but the most common tumour sites for anaemic patients were the rectum (18.6%), followed by the caecum (16%) and the sigmoid colon (16%) (Table 2).

A logistic regression model found that right sided tumours were more likely to be significantly anaemic compared with left sided tumours (OR 2.33, 95% CI 1.64 – 3.29, p<0.001), but there was no evidence for a relationship between severity of tumour stage with the likelihood of preoperative anaemia.

In both anaemic and non anaemic patients, being symptomatic was the most common way CRC was diagnosed. Three hundred and eight (88.3%) of the 350 anaemic patients, and 315 (78.4%) of non anaemic patients had their cancer detected due to presenting symptomatically (p<0.001). Non anaemic patients were more likely to have their cancer detected through screening compared to anaemic patients (18.7% and 8.6%, respectively, p<0.001).

*Preoperative Investigation of Anaemia*

Of all 754 patients, only 115 (15.3%) had iron studies performed and of the 350 anaemic patients, only 89 (25.4%) had iron studies. Furthermore, of all 124 microcytic anaemia patients, only 45 (36.3%) were tested for iron deficiency. Of these 45, 42 (93%) were found to be iron deficient.

*Preoperative Management of Anaemia*

Of 350 anaemic patients, only 117 (33.4%) received preoperative corrective management. Twelve percent (12) received oral iron replacement, 10.6% (37) received intravenous iron replacement, and 20.9% (73) received at least one unit of PRBCs (Table 3*)*.

*Anaemia and Clinical Outcomes*

A large proportion of patients developed postoperative complications (n=324; 43.7%). (Table 4). Anaemic patients were more likely to experience medical complications than non-anaemic patients (55.6% vs. 44.4%, p 0.046), and were also more likely to experience both medical *and* surgical complications (51.5% vs. 48.5%, p 0.046).

On multivariate analysis, preoperative anaemia was associated with a higher incidence of postoperative complications (adjusted OR 1.46, 95%, CI 1.04 – 2.05; p=0.03). In addition, anaemic patients also had a lower hazard of discharge (HR 0.8, 95% CI 0.68 – 0.95, p=0.009) and had a longer LOS of 1.8 days (95% CI 0.3 – 3.3).

**DISCUSSION**

International studies have demonstrated that CRC is associated with an increased prevalence of anaemia,[5,8,14,15] and that anaemia in this cohort is largely microcytic due to iron deficiency.[15,16,17] Many studies within the literature have also found that the preoperative presence of microcytic anaemia is mainly associated with right sided tumours.[3] However, the results from our study demonstrate that over half of patients with CRC presented with normocytic anaemia, with just over one third having microcytic anaemia. This is a significant finding for clinical practice, as microcytic iron deficiency anaemia has been traditionally taught as the "representative" haematological finding in CRC. [17] This is a paradigm shift and will broaden our differential when faced with a patient with unexplained anaemia.

Within Australia, the Cancer Council recommend the routine testing of iron studies in those with preoperative anaemia.[19,20] Despite these recommendations, only a quarter of anaemic patients in our study had iron tests conducted. The reasons for this can be complex. The greatest barrier we believe is that patients generally have blood tests performed just prior to surgery, and in many cases, only within a few days; reducing the time available to treat any iron deficiency effectively and therefore reducing the "perceived need" to do this test. Furthermore, to our knowledge, no institutional or cross-institutional protocols exist to guide junior medical staff to perform such tests, or to treat iron deficiency when found, when preparing patients for surgery.

Within our cohort for example, we found that only a third of anaemic patients received any preoperative treatment with the intention to correct this. Twenty percent of these patients received intravenous blood transfusions, while only approximately ten percent received intravenous iron. There is evidence to support the use of intravenous iron therapy for the management of perioperative iron deficiency in CRC as it may reduce the need for transfusions and has also been shown to reduce hospital LOS.[21,22,23] The reasons for a reduced utilisation of iron transfusions for treatment in our institution could be multifactorial. As mentioned earlier, patient preoperative blood tests within our institution were often performed only a few days prior to surgery, limiting the ability to access this therapy in the correct timeframe. In addition, iron transfusion therapy was more routinely performed during the latter half of our study period. Our results have also been based on a retrospective review of medical records, where we acknowledge that community information about treatment can be difficult to ascertain and confirm.

We also found that anaemic patients were associated with a higher incidence of postoperative complications (both medical and surgical) and were also significantly linked to a longer LOS (1.8 days). This adds to the current data from a recent Australian cohort study, which found that non-anaemic iron deficiency was associated with several adverse postoperative outcomes, such as increased readmission rates and higher all-cause infection rates.[24] It should be noted that the apparent high complication rates in our study was due to a thorough prospective capture of all events within the registry, including urinary tract infections, PR bleeding, pressure sores, and acute confusion. Unfortunately, there was an inability to draw concrete conclusions from our study regarding the impact of preoperative iron deficiency anaemia due to a lack of meaningful data, with only 89 tests performed for anaemic patients.

Finally with an aging population, factors including frailty which are associated with anaemia and surgical outcomes, is an important parameter that should be considered as part of the pre-surgery assessment. [12] Future studies on anaemia should ideally include information about these patient characteristics, including the Charlson Comorbidity Index or the Frailty Index. [25]

The results of our study highlight the inconsistencies with which we investigate and treat preoperative anaemia in patients undergoing surgery for CRC within our institution. Although patients have haematological investigations after diagnosis, these have been traditionally performed in the preassessment clinic. The appointments for these clinics are often only several days prior to surgery, therefore restricting the ability to detect and adequately treat these patients.



## STRENGTHS & LIMITATIONS

The strengths of this study include having a large sample size, all from a single institution, with information obtained from a prospectively maintained registry. Our study has also provided “real world” data.

The limitations of this study include the way in which details regarding blood test results were obtained. While the registry holding patient information is prospectively maintained, blood test results were retrospectively obtained by manually checking though electronic patient medical records.

It is worth noting that intravenous iron replacement has become standard treatment only in the past five years, and as such, may partially explain the relatively low numbers of iron infusions in this cohort. [21,22] Although the preassessment clinic within our institution routinely recorded information on whether any treatment for anaemia had been provided outside the hospital setting, some patients may have had treatment through general practitioners prior to presentation to hospital. However, it was outside the scope of this study to obtain patient records from general practice clinics.

## CONCLUSION

Anaemia in this Australian CRC cohort is common and presents in several variants. Normocytic anaemia is a more common finding in CRC patients, and patients are rarely tested for iron deficiency. Anaemic patients are more likely to have both medical and surgical postoperative complications as well as a longer LOS. Clinicians need to be aware of the importance of routine testing and active anaemia management, which may help reduce these complications.

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**Conflicts of interest:** None declared

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**Figure legend:**

Figure 1: Flow chart of participants

**Table 1** Patient demographics, comparing pre-operative anaemic and non-anaemic patients (n=754)

| Demographic | Anaemic (n = 350) | Not Anaemic (n = 404) | Total (n = 754) | p value |
|---|---|---|---|---|
| Age | | | | <0.001 |
| Mean (SD) | 70.28 (13.0) | 64.74 (11.7) | 67.32 (12.6) | |
| Range | 25.36 - 95.7 | 26.78 - 88.2 | 25.36 - 95.7 | |
| Sex | | | | 0.46 |
| Female | 153 (43.7%) | 165 (40.8%) | 318 (42.2%) | |
| Male | 197 (56.3%) | 239 (59.2%) | 436 (57.8%) | |
| Smoking | | | | 0.004 |
| No data | 4 (1.1%) | 4 (1.0%) | 8 (1.1%) | |
| Current smoker | 44 (12.6%) | 83 (20.5%) | 127 (16.8%) | |
| Ex-smoker | 105 (30.0%) | 131 (32.4%) | 236 (31.3%) | |
| Never smoked | 197 (56.3%) | 186 (46.1%) | 383 (50.8%) | |
| Diabetes | | | | 0.004 |
| No data | 2 (0.6%) | 2 (0.5%) | 4 (0.5%) | |
| No | 239 (68.3%) | 314 (77.7%) | 553 (73.3%) | |
| Yes | 109 (31.1%) | 88 (21.8%) | 197 (26.2%) | |
| Neoadjuvant Therapy | | | | <0.001 |
| No data | 24 (6.9%) | 20 (5.0%) | 44 (5.8%) | |
| No | 282 (80.6%) | 289 (71.5%) | 571 (75.7%) | |
| Yes | 44 (12.5%) | 95 (23.5%) | 139 (18.5%) | |
| Presentation | | | | <0.001 |
| No data | 1 (0.3%) | 2 (0.5%) | 3 (0.4%) | |
| Incidental | 9 (2.6%) | 6 (1.5%) | 15 (2%) | |
| Screen detected | 30 (8.5%) | 75 (18.6%) | 105 (14%) | |
| Symptomatic | 308 (88.0%) | 315 (77.9%) | 623 (82.6%) | |
| Unknown | 2 (0.6%) | 6 (1.5%) | 8 (1.0%) | |

**Table 2** Tumour location and staging characteristics on patient presentation (n=754)

| Demographic | Anaemic (n = 350) | Not Anaemic (n = 404) | Total (n = 754) | p value |
|---|---|---|---|---|
| Tumour Site | | | | <0.001 |
| No data | 0 | 3 (0.7%) | 3 (0.4%) | |
| Appendix | 1 (0.3%) | 1 (0.2%) | 2 (0.3%) | |
| Caecum | 56 (16%) | 35 (8.7%) | 91 (12.1%) | |
| Ascending Colon | 53 (15.1%) | 32 (9.0%) | 85 (11.3%) | |
| Hepatic Flexure | 26 (7.4%) | 17 (4.2%) | 43 (5.7%) | |
| Transverse Colon | 35 (10.0%) | 22 (5.4%) | 57 (7.6%) | |
| Splenic Flexure | 18 (5.1%) | 15 (3.7%) | 33 (4.4%) | |
| Descending Colon | 16 (4.6%) | 16 (4%) | 32 (4.2%) | |
| Sigmoid Colon | 56 (16.0%) | 110 (27.2%) | 166 (21.9%) | |
| Rectosigmoid | 24 (6.9%) | 34 (8.4%) | 58 (7.7%) | |
| Rectum | 65 (18.6%) | 119 (29.5%) | 184 (24.4%) | |
| Tumour Location | | | | <0.001 |
| No data | 0 | 2 (0.5%) | 2 (0.3%) | |
| Left | 161 (46%) | 279 (69.1%) | 440 (58.3%) | |
| Right | 189 (54%) | 123 (30.4%) | 312 (41.4%) | |
| ACPS Staging † | | | | <0.001 |
| No data | 3 (0.9%) | 3 (0.7%) | 6 (0.8%) | |
| 1 | 51 (14.6%) | 111 (27.5%) | 162 (21.5%) | |
| 2 | 131 (37.4%) | 115 (28.5%) | 246 (32.6%) | |
| 3 | 101 (28.8%) | 106 (26.2%) | 207 (27.5%) | |
| 4 | 52 (14.8%) | 41 (10.2%) | 93 (12.3%) | |
| 0 | 0 (0.0%) | 1 (0.2%) | 1 (0.1%) | |
| X | 3 (0.9%) | 0 (0.0%) | 3 (0.4%) | |
| Y | 9 (2.6%) | 27 (6.7%) | 36 (4.8%) | |

†**ACPS (Australian Clinicopathological Staging System) (9)**

1 = T1 or T2, N0M0. 2 = T3 or T4, N0M0. 3 = any T, N1/2 M0. 4 = Any T, Any N, M1. ACPS X is used where a local excision or other local procedure such as fulguration is done, without lymphadenopathy. ACPS Y is used when the pathological details are not known or are incomplete.

**Table 3** Summary of the treatment received by preoperative anaemic patients (n=350)

| Treatment Received | Iron-deficient (76) | Non-iron deficient anaemia (13) | Not tested (261) | Total (350) | p value |
|---|---|---|---|---|---|
| Oral Iron Supplementation | | | | | <0.001 |
| Yes | 21 (27.6%) | 0 (0.0%) | 21 (8%) | 42 (12%) | |
| No | 55 (72.4%) | 13 (100%) | 240 (92%) | 308 (88%) | |
| IV Iron Infusion † | | | | | <0.001 |
| Yes | 25 (32.9%) | 2 (15.4%) | 10 (3.8%) | 37 (10.6%) | |
| No | 51 (67.1%) | 11 (84.6%) | 251 (96.2%) | 313 (89.4%) | |
| IV Blood Transfusion | | | | | <0.001 |
| Yes | 42 (55.3%) | 3 (23.1%) | 28 (10.7%) | 73 (20.9%) | |
| No | 34 (44.7%) | 10 (76.9%) | 233 (89.3%) | 277 (79.1%) | |
| Oral + IV Iron | | | | | 0.002 |
| Yes | 7 (9.2%) | 0 (0.0%) | 1 (0.4%) | 8 (2.3%) | |
| No | 69 (90.8%) | 13 (100%) | 260 (99.6%) | 342 (97.7%) | |
| IV Blood Transfusion + Oral or IV Iron | | | | | <0.001 |
| Yes | 60 (78.9%) | 5 (38.5%) | 52 (19.9%) | 117 (33.4%) | |
| No | 16 (21.1%) | 8 (61.5%) | 209 (80.1%) | 233 (66.6%) | |

**† IV: intravenous.**

**Table 4** Summary of the postoperative complications experienced by patients in the study

| Complication | Anaemic (n = 350) | Not Anaemic (n = 404) | Total (n = 754) |
|---|---|---|---|
| Surgical | 51 (14.6%) | 59 (14.6%) | 110 (14.6%) |
| Medical | 65 (18.5%) | 52 (12.9%) | 117 (15.5%) |
| Both | 50 (14.3%) | 47 (11.6%) | 97 (12.9%) |
| None | 176 (50.3%) | 242 (59.9%) | 418 (55.4%) |
| Missing data | 8 (2.3%) | 4 (1.0%) | 12 (1.6%) |

***Figure 1.*** *Flow chart demonstrating sequence of data collection.*