cancers

MDPI

Review

The Full Blood Count Blood Test for Colorectal Cancer Detection: A Systematic Review, Meta-Analysis, and Critical Appraisal

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1. Description of the full blood count

Table S1. Description of each component of the full blood count blood test

Full blood count component	Conventional units	Description/purpose
Red blood cell count [1]	10^{12} per litre (10^{12}/L)	The number of red blood cells in the blood. Lower levels can be associated with blood less. Each red blood cell contains levels of haemoglobin.
White blood cell count [1]	10^9 per litre (10^9/L)	The number of white blood cells in the blood. They are of the immune system and involved in protecting the body against disease.
Haemoglobin [1]	Grams per decilitre (g/dL)	Carries oxygen around the body and is found in red blood cells
Haematocrit/packed cell volume [2]	Percentage, i.e. as litres per litre (%)	Proportion of blood that is occupied by the red cells. A possible alternative for detecting anaemia.
Mean corpuscular volume [2]	Femtolitre (f/L)	Average size of red blood cells. Calculated as haematocrit (%) divided by the number of red blood cells (10^{12}/L)
Mean corpuscular haemoglobin [2]	Pictograms (pg)	Average of amount of haemoglobin that is in each red blood cell. Calculated as haemoglobin (g/dL) divided by the red blood cell count (10^{12}/L)
Mean corpuscular haemoglobin concentration [2]	Grams per decilitre (g/dL)	Average of amount of haemoglobin in individual cells based on the volume of red blood cells. Calculated as haemoglobin (g/dL) divided by the haematocrit (%)
Red cell distribution width [2]	A coefficient, as opposed to count	A measure of the amount of variation in the size of red cells; the higher, the more variation.
Platelet count [1]	10^9 per litre (10^9/L)	Not a cell, but instead fragments of cytoplasm. They bind to sites of damaged blood vessels, e.g. cuts, and clump to form a blood clot to help prevent bleeding
Mean platelet volume [2]	Femtolitre (f/L)	Average size of platelets
Basophil count [1]	10^9 per litre (10^9/L)	A type of white blood cell. Controls hypersensitivity reactions, allergic and inflammatory responses and fights parasitic infections

Basophil % [2]	Percentage	Basophil count divided by the number of white blood cells
Eosinophil count [1]	10^9 per litre (10^9/L)	A type of white blood cell. Fights infection, including parasitic; has a role in allergic responses
Eosinophil % [2]	Percentage	Eosinophil count divided by the number of white blood cells
Lymphocyte count [1]	10^9 per litre (10^9/L)	A type of white blood cell. Mediates immune responses
Lymphocyte % [2]	Percentage	Lymphocyte count divided by the number of white blood cells
Monocyte count [1]	10^9 per litre (10^9/L)	A type of white blood cell. Kills micro-organisms including mycobacteria and fungi; presents antigen to cells of the immune system
Monocyte % [2]	Percentage	Monocyte count divided by the number of white blood cells
Neutrophil count [1]	10^9 per litre (10^9/L)	A type of white blood cell. Fights infection
Neutrophil % [2]	Percentage	Neutrophil count divided by the number of white blood cells

[1]This component is measured directly from the blood sample. [2]This component is derived using mathematical formulae programmed into the analyser and describes at least one measured component

2. Final search strategy

Scheme S1. Final search strategy per database

MEDLINE

Database and platform: Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present. Search date: 3 September 2019.

1. Colonic Neoplasms/bl [Blood]
2. Colonic Neoplasms/di [Diagnosis]
3. Colonic Neoplasms/ep [Epidemiology]
4. Colorectal Neoplasms/di [Diagnosis]
5. Colorectal Neoplasms/ep [Epidemiology]
6. Colorectal Neoplasms/bl [Blood]
7. Rectal Neoplasms/bl [Blood]
8. Rectal Neoplasms/di [Diagnosis]
9. Rectal Neoplasms/ep [Epidemiology]
10. Adenomatous Polyposis Coli/
11. Sigmoid Neoplasms/
12. Colorectal Neoplasms, Hereditary Nonpolyposis/
13. ((colorectal or bowel or colon or colonic or rectal or rectum) adj3 (cancer$ or carcinoma$ or adenoma$ or neoplas$ or metasta$ or carcinogen$ or tumour$ or tumor$ or malignan$ or adenocarcinoma$)).ti,ab,kw.
14. or/1-13
15. exp Blood Cell Count/
16. exp Hemoglobins/
17. Blood Platelets/

18. Neutrophils/
19. Basophils/
20. Eosinophils/
21. Lymphocytes/
22. Monocytes/
23. Occult Blood/
24. Thrombocytosis/
25. Leukocytosis/
26. Lymphocytosis/
27. Eosinophilia/
28. Anemia/
29. Leukopenia/
30. Neutropenia/
31. Lymphopenia/
32. Thrombocytopenia/
33. Polycythemia/
34. Erythrocytes/
35. Leukocytes/
36. Pancytopenia/
37. ((blood or platelet) adj2 count$).ti,ab,kw.
38. (CBC or FBC).ti,ab,kw.
39. (blood adj2 exam$).ti,ab,kw.
40. (haematolog$ or hematolog$ or haemoglobin or hemoglobin or haematocrit or hematocrit).ti,ab,kw.
41. ((red or white) adj1 blood adj1 cell$).ti,ab,kw.
42. (mean adj1 (platelet or corpuscular) adj1 volume$).ti,ab,kw.
43. (mean adj1 corpuscular adj1 (haemoglobin or hemoglobin)).ti,ab,kw.
44. (platelet$ or basophil or basophils or eosinophil or eosinophils or lymphocyte$ or monocyte$ or neutrophil or neutrophils or erythrocyte$ or leukocyte$).ti,ab,kw.
45. (blood adj1 (test$ or draw$)).ti,ab,kw.
46. (neutrophili$ or monocytosis or basophili$ or anemi$ or anaemi$ or monocytopenia or eosinopenia or basopenia or basocytopenia or thrombocytopeni$ or leucocytosis or lymphocytosis or eosinophili$ or leucopenia or leukopenia or neutropenia or lymphopenia or lymphocytopenia or pancytopenia or polycythemia or bicytopenia).ti,ab,kw.
47. or/15-46
48. (abnormalit$ or diagnos$ or "pre-diagnos$" or prediagnos$ or change$ or detect$ or elevat$ or distribut$ or deficien$ or identif$ or presence or indicati$ or determin$ or undiagnosed or definition$ or altered or alteration$).ti,ab,kw.
49. 47 and 48
50. (predict$ or prognos$ or suspected).ti,ab,kw.
51. (risk adj1 (predict$ or marker$ or scor$)).ti,ab,kw.
52. Predictive Value of Tests/
53. Probability/
54. Prognosis/
55. Risk Factors/
56. Risk Assessment/
57. Incidence/
58. or/50-57
59. 14 and 49 and 58

EMBASE

Database and platform: Embase 1974 to present. Search date: 3 September 2019.

1. exp Colon Cancer/
2. exp Colon Tumor/
3. exp Rectum Tumor/
4. Colon Polyposis/
5. Hereditary Nonpolyposis Colorectal Cancer/
6. ((colorectal or bowel or colon or colonic or rectal or rectum) adj3 (cancer$ or carcinoma$ or adenoma$ or neoplas$ or metasta$ or carcinogen$ or tumour$ or tumor$ or malignan$ or adenocarcinoma$)).ti,ab,kw.
7. or/1-6
8. exp Blood Cell Count/
9. Hemoglobin/
10. Hemoglobin Blood Level/
11. Thrombocyte/
12. Neutrophil/
13. Basophil/
14. Eosinophil/
15. Lymphocyte/
16. exp Monocyte/
17. Occult Blood/
18. Thrombocytosis/
19. Leukocytosis/
20. Basophilia/
21. exp Lymphocytosis/
22. Eosinophilia/
23. Monocytosis/
24. Neutrophilia/
25. Anemia/
26. Leukopenia/
27. Monocytopenia/
28. exp Neutropenia/
29. Eosinopenia/
30. Lymphocytopenia/
31. Thrombocytopenia/
32. Polycythemia/
33. Erythrocyte/
34. Leukocyte/
35. Pancytopenia/
36. Mean Corpuscular Volume/
37. ((blood or platelet) adj2 count$).ti,ab,kw.
38. (CBC or FBC).ti,ab,kw.
39. (blood adj2 exam$).ti,ab,kw.
40. Hematocrit/
41. (haematolog$ or hematolog$ or haemoglobin or hemoglobin or haematocrit or hematocrit).ti,ab,kw.
42. ((red or white) adj1 blood adj1 cell$).ti,ab,kw.
43. (mean adj1 (platelet or corpuscular) adj1 volume$).ti,ab,kw.
44. (mean adj1 corpuscular adj1 (haemoglobin or hemoglobin)).ti,ab,kw.

45. (platelet$ or basophil or basophils or eosinophil or eosinophils or lymphocyte$ or monocyte$ or neutrophil or neutrophils or erythrocyte$ or leukocyte$).ti,ab,kw.
46. (blood adj1 (test$ or draw$)).ti,ab,kw.
47. (neutrophili$ or monocytosis or basophili$ or anemi$ or anaemi$ or monocytopenia or eosinopenia or basopenia or basocytopenia or thrombocytopeni$ or leucocytosis or lymphocytosis or eosinophili$ or leucopenia or leukopenia or neutropenia or lymphopenia or lymphocytopenia or pancytopenia or polycythemia or bicytopenia).ti,ab,kw.
48. or/8-47
49. (abnormalit$ or diagnos$ or "pre-diagnos$" or prediagnos$ or change$ or detect$ or elevat$ or distribut$ or deficien$ or identif$ or presence or indicati$ or determin$ or undiagnosed or definition$ or altered or alteration$).ti,ab,kw.
50. 48 and 49
51. (predict$ or prognos$ or suspected).ti,ab,kw.
52. (risk adj1 (predict$ or marker$ or scor$)).ti,ab,kw.
53. Predictive Value/
54. exp Prediction/
55. Probability/
56. exp Prognosis/
57. "Sensitivity and Specificity"/
58. Risk Factor/
59. Risk Assessment/
60. or/51-59
61. 7 and 50 and 60

CINAHL

Database and platform: CINAHL (via EBSCOhost). Search date: 3 September 2019.

1. (MH "Colonic Neoplasms")
2. (MH "Colorectal Neoplasms")
3. (MH "Rectal Neoplasms")
4. (MH "Adenomatous Polyposis Coli")
5. (MH "Sigmoid Neoplasms")
6. (MH "Colorectal Neoplasms, Hereditary Nonpolyposis")
7. TI ((colorectal or bowel or colon or colonic or rectal or rectum) N3 (cancer* or carcinoma* or adenoma* or neoplas* or metasta* or carcinogen* or tumour* or tumor* or malignan* or adenocarcinoma*)) OR AB ((colorectal or bowel or colon or colonic or rectal or rectum) N3 (cancer* or carcinoma* or adenoma* or neoplas* or metasta* or carcinogen* or tumour* or tumor* or malignan* or adenocarcinoma*))
8. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
9. (MH "Blood Cells+")
10. (MH "Hemoglobins+")
11. (MH "Occult Blood")
12. (MH "Thrombocytosis")
13. (MH "Eosinophilia")
14. (MH "Anemia")
15. (MH "Leukopenia")
16. (MH "Neutropenia")
17. (MH "Lymphopenia")
18. (MH "Thrombocytopenia")
19. (MH "Polycythemia")

20. (MH "Pancytopenia")
21. TI ((blood or platelet) N2 count*) OR AB ((blood or platelet) N2 count*)
22. TI (CBC or FBC) OR AB (CBC or FBC)
23. TI (blood N2 exam*) OR AB (blood N2 exam*)
24. TI (haematolog* or hematolog* or haemoglobin or hemoglobin or haematocrit or hematocrit) OR AB (haematolog* or hematolog* or haemoglobin or hemoglobin or haematocrit or hematocrit)
25. TI ((red or white) N1 blood N1 cell*) OR AB ((red or white) N1 blood N1 cell*)
26. TI (mean N1 (platelet or corpuscular) N1 volume*) OR AB (mean N1 (platelet or corpuscular) N1 volume*)
27. TI (mean N1 corpuscular N1 (haemoglobin or hemoglobin)) OR AB (mean N1 corpuscular N1 (haemoglobin or hemoglobin))
28. TI (platelet* or basophil or basophils or eosinophil or eosinophils or lymphocyt* or monocyt* or neutrophil or neutrophils or erythrocyt* or leukocyt*) OR AB (platelet* or basophil or basophils or eosinophil or eosinophils or lymphocyt* or monocyt* or neutrophil or neutrophils or erythrocyt* or leukocyt*)
29. TI (blood N1 (test* or draw*)) OR AB (blood N1 (test* or draw*))
30. TI (neutrophili* or monocytosis or basophili* or anemi* or anaemi* or monocytopenia or eosinopenia or basopenia or basocytopenia or thrombocytopeni* or leucocytosis or lymphocytosis or eosinophili* or leucopenia or leukopenia or neutropenia or lymphopenia or lymphocytopenia or pancytopenia or polycythemia or bicytopenia) OR AB (neutrophili* or monocytosis or basophili* or anemi* or anaemi* or monocytopenia or eosinopenia or basopenia or basocytopenia or thrombocytopeni* or leucocytosis or lymphocytosis or eosinophili* or leucopenia or leukopenia or neutropenia or lymphopenia or lymphocytopenia or pancytopenia or polycythemia or bicytopenia)
31. S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30
32. TI (abnormalit* or diagnos* or "pre-diagnos*" or prediagnos* or change* or detect* or elevat* or distribut* or deficien* or identif* or presence or indicati* or determin* or undiagnosed or definition* or altered or alteration*) OR AB (abnormalit* or diagnos* or "pre-diagnos*" or prediagnos* or change* or detect* or elevat* or distribut* or deficien* or identif* or presence or indicati* or determin* or undiagnosed or definition* or altered or alteration*)
33. S31 AND S32
34. TI (predict* or prognos* or suspected) OR AB (predict* or prognos* or suspected)
35. TI (risk N1 (predict* or marker* or scor*)) OR AB (risk N1 (predict* or marker* or scor*))
36. (MH "Predictive Value of Tests")
37. (MH "Probability")
38. (MH "Prognosis")
39. (MH "Risk Factors")
40. (MH "Risk Assessment")
41. (MH "Incidence")
42. S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41
43. S8 and S33 and S42

Web of Science

Database and platform: Web of Science (Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1945-present; Social Sciences Citation Index (SSCI) --1956-present; Conference Proceedings Citation Index- Science (CPCI-S) --1990-present) (via Clarivate). Search date: 3 September 2019.

1. TS = ((colorectal or bowel or colon or colonic or rectal or rectum or sigmoid) NEAR/3 (cancer* or carcinoma* or adenoma* or neoplas* or metasta* or carcinogen* or tumour* or tumor* or malignan* or adenocarcinoma*))
2. SU = Hematology
3. TS = "blood cell count"
4. TS = "occult blood"
5. TS = ((blood or platelet) NEAR/2 count*)
6. TS = (CBC or FBC)
7. TS = (blood NEAR/2 exam*)
8. TS = (haematolog* or hematolog* or haemoglobin or hemoglobin or haematocrit or hematocrit)
9. TS = ((red or white) NEAR/1 blood NEAR/1 cell*)
10. TS = (mean NEAR/1 (platelet or corpuscular) NEAR/1 volume*)
11. TS = (mean NEAR/1 corpuscular NEAR/1 (haemoglobin or hemoglobin))
12. TS = (platelet* or basophil or basophils or eosinophil or eosinophils or lymphocyte* or monocyte* or neutrophil or neutrophils or erythrocyte* or leukocyte*)
13. TS = (blood NEAR/1 (test* or draw*))
14. TS = (neutrophili* or monocytosis or basophili* or anemi* or anaemi* or monocytopenia or eosinopenia or eosinophilia or basopenia or basocytopenia or thrombocytopeni* or thrombocytosis or leucocytosis or lymphocytosis or eosinophili* or leucopenia or leukopenia or neutropenia or lymphopenia or lymphocytopenia or pancytopenia or polycythemia or bicytopenia)
15. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
16. TS = (abnormalit* or diagnos* or "pre-diagnos*" or prediagnos* or change* or detect* or elevat* or distribut* or deficien* or identif* or presence or indicati* or determin* or undiagnosed or definition* or altered or alteration*)
17. #15 and #16
18. TS = (predict* or prognos* or probabilit* or suspected)
19. TS = (risk NEAR/1 (predict* or marker* or scor*))
20. #18 or #19
21. #1 and #17 and #20

3. Association between full blood count and colorectal cancer

Table S2. Full blood count components analysed per study.

Article	RBC	WBC	Hb	Hc	MCV	MCH	MCHC	RDW	Plat	MPV	BasC	BasP	EosC	EosP	LymC	LymP	MonC	MonP	NeuC	NeuP	Total
Acher 2003 [1]			X		X		X														3
Ankus 2018 [2]									X												1
Ay 2015 [3]			X		X			X	X												4
Ayling 2019 [4]	External validation study – does not analyse full blood count, but instead performance of existing prediction models.																				
Bafandeh 2008 [5]			X																		1
Bailey 2017 [6]									X												1
Birks 2017 [7]	External validation study – does not analyse full blood count, but instead performance of existing prediction models.																				
Boursi 2016 [8]	X	X	X	X	X	X			X		X		X		X		X		X		12
Cakmak 2017 [9]			X					X	X												3
Collins 2012 [10]	External validation study – does not analyse full blood count, but instead performance of existing prediction models.																				
Cross 2019 [11]			X																		1
Cubiella 2016 [12]			X		X																2
Fijten 1995 [13]		X	X																		2
Firat 2016 [14]		X	X						X												3

Goldshtein 2010 [15]			X																		1
Goshen 2017 [16]	X	X	X		X			X	X	X	X		X		X		X		X		12
Hamilton 2005 [17]			X																		1
Hamilton 2008 [18]			X		X																2
Hamilton 2009 [19]			X		X																2
Hilsden 2018 [20]	External validation study – does not analyse full blood count, but instead performance of existing prediction models.																				
Hippisley-Cox 2012 [21]			X																		1
Hippisley-Cox 2013 [22]			X																		1
Hippisley-Cox 2013 [23]			X																		1
Hornbrook 2017 [24]	External validation study – does not analyse full blood count, but instead performance of existing prediction models.																				
Huang 2019 [25]		X	X												X						3
Hung 2015 [26]			X																		1
Joosten 2008 [27]			X																		1
Kilincalp 2015 [28]			X						X	X											3
Kinar 2016 [29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	20
Kinar 2017 [30]	External validation study – does not analyse full blood count, but instead performance of existing prediction models.																				

Lawrenson 2006 [31]			X			1
Lee 2006 [32]		X				1
Margolis 2007 [33]		X				1
Marshall 2011 [34]			X	X		2
Mashlab 2018 [35]			X	X		2
Naef 1999 [36]			X			1
Nakama 2000 [37]			X			1
Panagiotopoulou 2014 [38]			X	X		2
Panzuto 2003 [39]			X	X		2
Pilling 2018 [40]			X	X	X	3
Prizment 2011 [41]		X				1
Raje 2007 [42]			X	X		2
Schneider 2018 [43]	X		X	X		3
Shi 2019 [44]					X	1
Song 2018 [45]					X	1
Spell 2004 [46]			X	X	X	3

Stapley 2006 [47]			X																		1
Thompson 2017 [48]			X																		1
van Boxtel-Wilms 2016 [49]			X																		1
Wu 2019 [50]	X	X	X						X	X					X		X		X		8
Yang 2018 [51]			X					X	X						X				X		5
Zhou 2017 [52]		X														X				X	3
Zhu 2018 [53]									X	X											2
Total	5	11	38	2	16	2	2	9	12	5	3	1	3	1	6	2	4	1	5	2	
Proportion of non-validation studies (n = 47)	11 %	23%	81 %	4 %	34%	4%	4%	19%	26 %	11%	6%	2%	6%	2%	13%	4%	9%	2%	11%	4%	

Abbreviations: RBC = red blood cells, WBC = white blood cells, Hb = haemoglobin, Hc = haematocrit, MCV = mean corpuscular volume, MCH = mean corpuscular haemoglobin, MCHC = mean corpuscular haemoglobin concentration, RDW = red blood cell distribution width, Plat = platelet count, MPV = mean platelet volume, BasC = basophil count, BasP = basophil %, EosC = eosinophil count, EosP = eosinophil %, LymC = lymphocyte count, LymP = lymphocyte %, MonC = monocyte count, MonP = monocyte %, NeuC = neutrophil count, NeuP = neutrophil %

Table S3: Red blood cell count for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article (Study outcome window)	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
China	Everyone	Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 No, n = 108		Mean = 4.42 10^{12}/L (SD = 0.63) Mean = 4.73 10^{12}/L (SD = 0.42)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 Polyp, n = 132		Mean = 4.42 10^{12}/L (SD = 0.63) Mean = 4.78 10^{12}/L (SD = 0.72)	<0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes, n = 186 Polyp, n = 132 Healthy, n = 108		Mean = 4.42 10^{12}/L Mean = 4.78 10^{12}/L Mean = 4.73 10^{12}/L	<0.001
Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936 No, n = 28491		Mean = 4.76 10^{12}/L Mean = 4.87 10^{12}/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 1.75 (95% CI = 1.45, 2.24) Reference	
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819 No, n = 26239		Mean = 4.48 10^{12}/L Mean = 4.39 10^{12}/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 1.97 (95% CI = 1.51, 2.61) Reference	
UK	Males	Schneider 2018 [43} (6 months)	Odds ratio	Yes, n = 2266 No, n = 1006	<3.5 10^{12}/L, n = 191, events = 162 3.5–4.2 10^{12}/L, n = 951, events = 721 4.3–4.9 10^{12}/L, n = 1608, events = 1,603	OR = 2.86 (95% CI = 1.90, 4.31) OR = 1.61 (95% CI = 1.34, 1.93) Reference	

					5–5.8 10^{12}/L, n = 516, events = 314	OR = 0.80 (95% CI = 0.65, 0.98)	
					≥5.9 10^{12}/L, n = 6, events = 6	X	
		Schneider 2018 [43] [1] (6 months)	Odds ratio	Yes, n = 2266 No, n = 1006	<3.5 10^{12}/L, n = 191, events = 162	OR = 3.72 (95% CI = 2.36, 5.88)	
					3.5–4.2 10^{12}/L, n = 951, events = 721	OR = 1.93 (95% CI = 1.57, 2.37)	
					4.3–4.9 10^{12}/L, n = 1608, events = 1,603	Reference	
					5–5.8 10^{12}/L, n = 516, events = 314	OR = 0.83 (95% CI = 0.66, 1.04)	
					≥5.9 10^{12}/L, n = 6, events = 6	X	
	Females	Schneider 2018 [43] (6 months)	Odds ratio	Yes, n = 2038 No, n = 857	<3.5 10^{12}/L, n = 352, events = 331	OR = 4.10 (95% CI = 2.72, 6.17)	
					3.5–4.2 10^{12}/L, n = 1302, events = 960	OR = 1.81 (95% CI = 1.53, 2.15)	
					4.3–4.9 10^{12}/L, n = 1119, events = 680	Reference	
					5–5.8 10^{12}/L, n = 122, events = 67	OR = 0.79 (95% CI = 0.21, 1.15)	
					≥5.9 10^{12}/L, n = 6, events = 6	X	
		Schneider 2018 [43] [1] (6 months)	Odds ratio	Yes, n = 2038 No, n = 857	<3.5 10^{12}/L, n = 352, events = 331	OR = 5.68 (95% CI = 3.55, 9.09)	
					3.5–4.2 10^{12}/L, n = 1302, events = 960	OR = 1.94 (95% CI = 1.60, 2.36)	
					4.3–4.9 10^{12}/L, n = 1119, events = 680	Reference	
					5–5.8 10^{12}/L, n = 122, events = 67	OR = 0.75 (95% CI = 0.49, 1.14)	
					≥5.9 10^{12}/L, n = 6, events = 6	X	
6 < outcome time window ≤ 12 months:							
UK	Everyone	Boursi 2016 [8]	Odds ratio	Yes, n = 4929	*Modelled as continuous*	OR = 0.62 (95% CI = 0.57, 0.67)	<0.001

(1 year)	No, n = 11311

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio. [1]Multivariable effect estimate, adjusted for: BMI, smoking status, history of hypertension, diabetes, aspirin or NSAIDS use, vitamin K antagonists, platelet inhibitors

Table S4: White blood cell count for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
China	Everyone	Huang 2019 [25] (At admission)	T-test	Yes, n = 162 No, n = 78		Mean = 6.76 10^9/L (SD = 1.68) Mean = 6.42 10^9/L (SD = 1.60)	≥0.05
		Huang 2019 [25] (At admission)	T-test	Yes, n = 162 Polyp, n = 92		Mean = 6.76 10^9/L (SD = 1.68) Mean = 6.25 10^9/L (SD = 1.5)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 No, n = 108		Mean = 6.77 10^9/L (SD = 1.64) Mean = 6.23 10^9/L (SD = 1.02)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 Polyp, n = 132		Mean = 6.77 10^9/L (SD = 1.64) Mean = 6.32 10^9/L (SD = 1.61)	<0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes = 186 Polyp = 132 Healthy = 108		Mean = 6.77 10^9/L Mean = 6.32 10^9/L Mean = 6.23 10^9/L	0.003
		Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes, n = 242 No, n = 248		Median = 6.62 10^9/L Median = 6.15 10^9/L	<0.001
		Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes, n = 242 Polyp, n = 248		Median = 6.62 10^9/L Median = 6.22 10^9/L	<0.001
		Zhou 2017 [52] (At diagnosis)	Kruskal-Wallis	Yes = 242 Polyp = 248 Healthy = 262		Median = 6.62 10^9/L Median = 6.22 10^9/L Median = 6.15 10^9/L	<0.001
Israel	Males	Goshen 2017 [16]	T-test	Yes, n = 936		Mean = 7.79 10^9/L	<0.0001

		(1–6 months)		No, n = 28491		Mean = 7.20 10^9/L	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 2.31 (95% CI = 1.87, 3.05)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
	Females	Goshen 2017 [16]	T-test	Yes, n = 819		Mean = 7.46 10^9/L	<0.0001
		(1–6 months)		No, n = 26239		Mean = 6.65 10^9/L	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 2.17 (95% CI = 1.66, 3.02)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
Turkey	Everyone	Firat 2016 [14]	Chi-squared	Yes			0.463
		(At diagnosis)		No			
6 < outcome time window ≤ 12 months:							
UK	Everyone	Boursi 2016 [8]	Odds ratio	Yes, n = 4929	*Modelled as continuous*	OR = 1.11 (95% CI = 1.09, 1.13)	<0.001
		(1 year)		No, n = 11311			
		Boursi 2016 [8] [1]	Odds ratio	Yes, n = 3375	*Modelled as fractional polynomials (powers: 1, 1)*	OR = 5.25*WBC^1	
		(1 year)		No, n = 8560		OR = 0.30*WBC^1 × ln(WBC)	
Outcome time window ≥ 36 months:							
Korea	Males	Lee 2006 [32]	Odds ratio	Yes, n = 1122	≤5000 µL, n = 18611, events = 183	Reference	
		(10 years)		No, n = 107785	5501–6500 µL, n = 24567, events = 228	OR = 0.94 (95% CI = 0.78, 1.15)	
					6501–7600 µL, n = 28018, events = 276	OR = 1.00 (95% CI = 0.83, 1.21)	
					>7600 µL, n = 37711, events = 435	OR = 1.18 (95% CI = 0.99, 1.4)	
	Males	Lee 2006 [32] [2]	Hazard ratio	Yes, n = 1122	≤5000 µL, n = 18611, events = 183	Reference	
		(10 years)		No, n = 107785	5501–6500 µL, n = 24567, events = 228	HR = 0.95 (95% CI = 0.78, 1.15)	

					6501–7600 μL, n = 28018, events = 276	HR = 1.02 (95% CI = 0.84, 1.23)
					>7600 μL, n = 37711, events = 435	HR = 1.23 (95% CI = 1.03, 1.47)
	Females	Lee 2006 [32] (10 years)	Odds ratio	Yes, n = 1529 No, n = 313983	≤5000, n = 90790, events = 405	Reference
					5501–6500 μL, n = 84260, events = 400	OR = 1.06 (95% CI = 0.93, 1.22)
					6501–7600 μL, n = 73364, events = 353	OR = 1.08 (95% CI = 0.94, 1.24)
					>7600 μL, n = 67098, events = 371	OR = 1.24 (95% CI = 1.08, 1.43)
	Females	Lee 2006 [32] [2] (10 years)	Hazard ratio	Yes, n = 1529 No, n = 313983	≤5000, n = 90790, events = 405	Reference
					5501–6500 μL, n = 84260, events = 400	HR = 1.03 (95% CI = 0.90, 1.19)
					6501–7600 μL, n = 73364, events = 353	HR = 1.03 (95% CI = 0.89, 1.19)
					>7600 μL, n = 67098, events = 371	HR = 1.15 (95% CI = 0.99, 1.33)
UK	Everyone	Margolis 2007 [33] [3] (11 years)	Hazard ratio	Yes, n = 1341 No, n = 142407	*Modelled as continuous*	HR = 1.08 (95% CI = 1.04, 1.12)
USA	Everyone	Prizment 2011 [41] (19 years)	Odds ratio	Yes, n = 308 No, n = 13106	≤4.8 10^9/L, n = 3554, events = 79	Reference
					4.9–5.8 10^9/L, n = 3413, events = 65	OR = 0.80 (95% CI = 0.58, 1.12)
					5.9–7.0 10^9/L, n = 3155, events = 86	OR = 1.18 (95% CI = 0.86, 1.60)
					≥7.1 10^9/L, n = 3292, events = 78	OR = 1.01 (95% CI = 0.73, 1.38)
		Prizment 2011 [41] [4] (19 years)	Hazard ratio	Yes, n = 308 No, n = 13106	≤4.8 10^9/L, n = 3554, events = 79	Reference
					4.9–5.8 10^9/L, n = 3413, events = 65	HR = 0.86 (95% CI = 0.61, 1.21)

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					5.9–7.0 10^9/L, n = 3155, events = 86	HR = 1.26 (95% CI = 0.91, 1.74)	
					≥7.1 10^9/L, n = 3292, events = 78	HR = 1.13 (95% CI = 0.79, 1.60)	
OUTCOME WINDOW NOT CATEGORISABLE: > 12-month risk of CRC diagnosis:							
Netherlands	Everyone	Fijten 1995 [13] (>12 months)	Chi-squared	Yes, n = 4 No, n = 215	Low, n = 194, events = 1 High, n = 25, events = 3		<0.01
		Fijten 1995 [13] (>12 months)	Odds ratio	Yes, n = 4 No, n = 215	Low, n = 194, events = 1 High, n = 25, events = 3	Reference OR = 26.3 (95% CI = 2.6, 264.0)	

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio, HR = hazard ratio, WBC = white blood cell count. [1]Multivariable effect estimate, adjusted for: haemoglobin, mean corpuscular volume, neutrophil-lymphocyte ratio, platelet count, sex, previous metformin prescriptions, previous prescriptions for oral hypoglycemic drugs other than metformin. [2]Multivariable effect estimate, adjusted for: age, BMI, total cholesterol, smoking status, regular exercise, alcohol consumption per day, frequency of meat intake per week, hypertension, diabetes. [3]Multivariable effect estimate, adjusted for: age, ethnicity, smoking, alcohol use, physical activity, aspirin/nonsteroidal anti-inflammatory drug use, hormone therapy use, BMI, history of diabetes, family history of colorectal cancer. [4]Multivariable effect estimate, adjusted for: age, race, center, education, BMI, aspirin use, smoking status, pack-years of smoking, gender–HRT, diabetes.

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Table S5: Haemoglobin levels for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
China	Everyone	Huang 2019 [25] (At admission)	T-test	Yes, n = 162 No, n = 78		Mean = 119.62 g/dL (SD = 23.8) Mean = 146.25 g/dL (SD = 15.1)	<0.05
		Huang 2019 [25] (At admission)	T-test	Yes, n = 162 Polyp, n = 92		Mean = 119.62 g/dL (SD = 23.8) Mean = 134.1 g/dL (SD = 16.1)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 No, n = 108		Mean = 121.27 g/L (SD = 23.07) Mean = 142.47 g/L (SD = 11.80)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 Polyp, n = 132		Mean = 121.27 g/L (SD = 23.07) Mean = 132.12 g/L (SD = 20.03)	<0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes = 186 Polyp = 132 Healthy = 108		Mean = 121.27 g/L Mean = 132.12 g/L Mean = 142.47 g/L	<0.001
		Yang 2018 [51] (At admission)	Mann-Whitney U	Yes, n = 85 Polyp, n = 54		Median = 122 g/L Median = 131.5 g/L	0.004
Belgium	Everyone	Joosten 2008 [27]	Chi-squared	Yes, n = 55	Men<13 g/dL, Women<12 g/dL, n = 251, events = 42		0.26

		(8 weeks)		No, n = 304	Men≥13 g/dL, Women≥12 g/dL, n = 108, events = 13		
		Joosten 2008 [27]	T-test	Yes, n = 55		Mean = 10.2 g/dL (SD = 2.9)	0.14
		(8 weeks)		No, n = 304		Mean = 10.8 g/dL (SD = 2.7)	
		Joosten 2008 [27]	Odds ratio	Yes, n = 55	Men<13 g/dL, Women<12 g/dL, n = 251, events = 42	OR = 1.47 (95% CI = 0.75, 2.86)	
		(8 weeks)		No, n = 304	Men≥13 g/dL, Women≥12 g/dL, n = 108, events = 13	Reference	
		Joosten 2008 [27] [1] (8 weeks)	Odds ratio	Yes, n = 55 No, n = 304			≥0.05
Israel	Males	Goshen 2017 [16]	T-test	Yes, n = 936		Mean = 13.30 g/dL	<0.0001
		(1–6 months)		No, n = 28491		Mean = 14.43 g/dL	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 3.06 (95% CI = 2.76, 3.52)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
		Goshen 2017 [16] [2]	Risk ratio	Yes, n = 936	Highest-risk quintile	RR = 3.83 (95% CI = 3.38, 4.46)	
		(1–6 months)		No, n = 28491	Lowest-risk quintile	Reference	
	Females	Goshen 2017 [16]	T-test	Yes, n = 819		Mean = 11.80 g/dL	<0.0001
		(1–6 months)		No, n = 26239		Mean = 13.02 g/dL	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 5.69 (95% CI = 4.31, 7.97)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
		Goshen 2017 [16] [3]	Risk ratio	Yes, n = 819	Highest-risk quintile	RR = 5.69 (95% CI = 4.31, 7.97)	
		(1–6 months)		No, n = 26239	Lowest-risk quintile	Reference	

Netherlands	Everyone	van Boxtel-Wilms 2016 [49] (3 months)	Descriptive	Yes No	Anaemia, n = 5, events = 5 No anaemia, n = 545, events = 0		
Spain	Everyone	Cubiella 2016 [12] [4] (1 week)	Odds ratio	Yes, n = 214 No, n = 1358	<10 g/dL 10–12 g/dL >12 g/dL	OR = 4.8 (95% CI = 2.2, 10.3) OR = 1.8 (95% CI = 1.1, 3.0) Reference	
Turkey	Everyone	Ay 2015 [3] (1 week)	T-test	Yes, n = 30 Polyp, n = 110		Mean = 13.5 g/dL (SD = 1.1) Mean = 13.9 g/dL (SD = 1.1)	≥0.05
		Cakmak 2017 [9] (6 months)	T-test	Yes, n = 59 No, n = 59		Mean = 11.9 g/dL (SD = 2.2) Mean = 14.4 g/dL (SD = 1.1)	<0.001
		Firat 2016 [14] (At diagnosis)	Chi-squared	Yes No			0.002
		Kilincalp 2015 [28] (At diagnosis)	T-test	Yes, n = 144 No, n = 143		Mean = 11.6 g/dL (SD = 2.20) Mean = 14.2 g/dL (SD = 1.17)	<0.001
UK	Everyone	Acher 2003 [1] [5] (6 months)	Descriptive	Yes No	<10.1 g/dl, n>5000, events = 112 ≥10.1 g/dL, events = 274		
		Mashlab 2018 [35] (2 weeks)	Chi-squared	Yes, n = 60 No, n = 955	Men<130 g/L, Women<120 g/L, n = 388, events = 39 Men≥130 g/L, Women≥120 g/L, n = 627, events = 21		0.001
		Mashlab 2018 [35]	Odds ratio	Yes, n = 60	Men<130 g/L, Women<120 g/L, n = 388, events = 39	OR = 3.22 (95% CI = 1.87, 5.57)	

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	(2 weeks)		No, n = 955	Men≥130 g/L, Women≥120 g/L, n = 627, events = 21	Reference	
	Mashlab 2018 [35] [6]	Odds ratio	Yes, n = 60	Men<130 g/L, Women<120 g/L, n = 388, events = 39	OR = 2.77 (95% CI = 1.55, 4.95)	
	(2 weeks)		No, n = 955	Men≥130 g/L, Women≥120 g/L, n = 627, events = 21	Reference	
	Raje 2007 [42] [7]	Descriptive	Yes	Men<11 g/dL, Women <10 g/dL, n = 142, events = 9		
	(1–2 months)		No			
Centre A	Panagiotopoulou 2014 [38]	Chi-squared	Yes, n = 30	Anaemia, n = 105, events = 16		0.434
	(3 months)		No, n = 199	No anaemia, n = 124, events = 14		
	Panagiotopoulou 2014 [38]	Odds ratio	Yes, n = 30	Anaemia, n = 105, events = 16	OR = 1.4 (95% CI = 0.7, 3.1)	
	(3 months)		No, n = 199	No anaemia, n = 124, events = 14	Reference	
Centre B	Panagiotopoulou 2014 [38]	Chi-squared	Yes, n = 76	Anaemia, n = 257, events = 35		0.103
	(3 months)		No, n = 613	No anaemia, n = 432, events = 41		
	Panagiotopoulou 2014 [38]	Odds ratio	Yes, n = 76	Anaemia, n = 257, events = 35	OR = 1.5 (95% CI = 0.9, 2.4)	
	(3 months)		No, n = 613	No anaemia, n = 432, events = 41	Reference	
	Panagiotopoulou 2014 [38] [8] (3 months)	Odds ratio	Yes, n = 76	Anaemia, n = 257, events = 35	OR = 1.5 (95% CI = 0.9, 2.5)	
			No, n = 613	No anaemia, n = 432, events = 41	Reference	
Males	Schneider 2018 [43}	Odds ratio	Yes, n = 2551	≤9 g/dL, n = 243, events = 243	X	
	(6 months)		No, n = 1113	9–9.9 g/dL, n = 207, events = 193	OR = 10.3 (95% CI = 5.9, 17.8)	

				10–10.9 g/dL, n = 284, events = 255	OR = 6.5 (95% CI = 4.4, 9.7)
				11–11.9 g/dL, n = 379, events = 296	OR = 2.7 (95% CI = 2.0, 3.4)
				12–12.9 g/dL, n = 497, events = 384	OR = 2.5 (95% CI = 2.0, 3.2)
				13–15.9 g/dL, n = 1834, events = 1052	Reference
				≥16 g/dL, n = 180, events = 88	OR = 0.71 (95% CI = 0.52, 0.97)
	Schneider 2018 [43} [9] (6 months)	Odds ratio	Yes, n = 2551 No, n = 1113	≤9 g/dL, n = 243, events = 243	OR = 95.9 (95% CI = 23.5, 391.8)
				9–9.9 g/dL, n = 207, events = 193	OR = 12.2 (95% CI = 6.8, 21.8)
				10–10.9 g/dL, n = 284, events = 255	OR = 8.6 (95% CI = 5.3, 13.8)
				11–11.9 g/dL, n = 379, events = 296	OR = 3.1 (95% CI = 2.3, 4.2)
				12–12.9 g/dL, n = 497, events = 384	OR = 2.9 (95% CI = 2.2, 3.8)
				13–15.9 g/dL, n = 1834, events = 1052	Reference
				≥16 g/dL, n = 180, events = 88	OR = 0.7 (95% CI = 0.5, 1.04)
Females	Schneider 2018 [43} (6 months)	Odds ratio	Yes, n = 2089 No, n = 1086	≤9 g/dL, n = 341, events = 336	OR = 70.6 (95% CI = 29, 172.2)
				9–9.99 g/dL, n = 368, events = 252	OR = 16.5 (95% CI = 9.8, 27.8)
				10–10.9 g/dL, n = 379, events = 333	OR = 7.6 (95% CI = 5.5, 10.6)
				11–11.9 g/dL, n = 442, events = 326	OR = 3.0 (95% CI = 2.3, 3.8)

					12–12.9 g/dL, n = 667, events = 365	OR = 1.5 (95% CI = 1.2, 1.8)	
					13–15.9 g/dL, n = 978, events = 477	Reference	
					≥16 g/dL, n = 0	X	
		Schneider 2018 [43] [9] (6 months)	Odds ratio	Yes, n = 2089	≤9 g/dL, n = 341, events = 336	OR = 84.6 (95% CI = 30.4, 235.2)	
				No, n = 1086	9–9.99 g/dL, n = 368, events = 252	OR = 23.3 (95% CI = 12.4, 43.5)	
					10–10.9 g/dL, n = 379, events = 333	OR = 10.6 (95% CI = 6.9, 16.1)	
					11–11.9 g/dL, n = 442, events = 326	OR = 3.7 (95% CI = 2.7, 5.1)	
					12–12.9 g/dL, n = 667, events = 365	OR = 1.5 (95% CI = 1.2, 1.9)	
					13–15.9 g/dL, n = 978, events = 477	Reference	
					≥16 g/dL, n = 0	X	
USA	Everyone	Spell 2004 [46] (6 months)	Chi-squared	Yes, n = 225	Men<13 g/dL, Women<11 g/dL, n = 160, events = 130		<0.001
				No, n = 487	Men≥13 g/dL, Women≥11 g/dL, n = 552, events = 95		
		Spell 2004 [46] (6 months)	Odds ratio	Yes, n = 225	Men<13 g/dL, Women<11 g/dL, n = 160, events = 130	OR = 20.8 (95% CI = 13.2, 32.8)	
				No, n = 487	Men≥13 g/dL, Women≥11 g/dL, n = 552, events = 95	Reference	
6 < outcome time window ≤ 12 months:							
UK	Everyone	Acher 2003 [1] [5] (6–12 months)	Descriptive	Yes	<10.1 g/dl, n>5000, events = 28		
				No	≥10.1 g/dL, events = 274		
		Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929	*Modelled as continuous*	OR = 0.67 (95% CI = 0.66, 0.69)	<0.001
				No, n = 11491			

Boursi 2016 [8] [10] (1 year)	Odds ratio	Yes, n = 3375 No, n = 8560	*Modelled as fractional polynomials (powers: 2, 2)*	OR = 0.02*Hb² OR = 32.17*Hb² × ln(Hb)
Hamilton 2009 [19] (2 years)	Odds ratio	Yes, n = 5477 No, n = 38314	<12 g/dL, n = 3227, events = 1424 ≥12 g/dL,n = 40564, events = 4053	OR = 7.11 (95% CI = 6.59, 7.68) Reference
Hamilton 2009 [19] [11] (2 years)	Odds ratio	Yes No	<9 g/dL 9–9.9 g/dl 10–10.9 g/dl 11–11.9 g/dl 12–12.9 g/dl ≥12 g/dL	OR = 18 (95% CI = 14, 25) OR = 9.3 (95% CI = 7.1, 12) OR = 5.9 (95% CI = 4.8, 7.2) OR = 2.8 (95% CI = 2.4, 3.2) OR = 1.7 (95% CI = 1.5, 1.9) Reference
Lawrenson 2006 [31] (1 year)	Rate ratios	Yes No	Anaemia No anaemia	
Marshall 2011 [34] (2 years)	Odds ratio	Yes, n = 5477 No, n = 38314	<9 g/dL, n = 487, events = 385 9–9.999 g/dL, n = 421, events = 268 10–10.999 g/dL, n = 771, events = 354 11–11.999 g/dL, n = 1548, events = 417 12–12.999 g/dL, n = 3001, events = 517 13–13.999 g/dL, n = 4284, events = 573	OR = 50.9 (95% CI = 40.2, 64.5) OR = 23.5 (95% CI = 18.9, 29.1) OR = 12.3 (95% CI = 10.5, 14.4) OR = 5.4 (95% CI = 4.7, 6.1) OR = 3.0 (95% CI = 2.7, 3.3) OR = 2.0 (95% CI = 1.8, 2.2)

				≥14 g/dL, n = 33279, events = 2963	Reference	
	Marshall 2011 [34]	Odds ratio	Yes, n = 5477	Men<12 g/dL, Women<11, n = 2211, events = 1181	OR = 11.4 (95% CI = 10.3, 12.6)	
	(2 years)		No, n = 38314	Men≥12 g/dL, Women≥11, n = 41580, events = 4296	Reference	
	Marshall 2011 [34] [12]	Odds ratio	Yes, n = 5477	<9 g/dL, n = 487, events = 385	OR = 15.9 (95% CI = 11.8, 21.6)	
	(2 years)		No, n = 38314	9–9.999 g/dL, n = 421, events = 268	OR = 8.08 (95% CI = 6.13, 10.65)	
				10–10.999 g/dL, n = 771, events = 354	OR = 5.18 (95% CI = 4.19, 6.39)	
				11–11.999 g/dL, n = 1548, events = 417	OR = 2.54 (95% CI = 2.16, 2.99)	
				12–12.999 g/dL, n = 3001, events = 517	OR = 1.63 (95% CI = 1.42, 1.87)	
				13–13.999 g/dL, n = 4284, events = 573	OR = 1.33 (95% CI = 1.18, 1.50)	
				≥14 g/dL, n = 33279, events = 2963	Reference	
	Stapley 2006 [47]	Odds ratio	Yes	<9 g/dL, n = 73, events = 39		0.73
	(1 year)		No	≥9 g/dL, n = 276	Reference	
Males	Hamilton 2008 [18]	Odds ratio	Yes, n = 1604	<9 g/dL, n = 225, events = 178	OR = 19.4 (95% CI = 14.0, 27.0)	
	(1 year)		No, n = 5226	9–9.9 g/dL, n = 167, events = 118	OR = 12.4 (95% CI = 8.8, 17.4)	
				10–10.9 g/dL, n = 260, events = 129	OR = 5.1 (95% CI = 3.9, 6.5)	
				11–11.9 g/dL, n = 464, events = 171	OR = 3.0 (95% CI = 2.4, 3.7)	
				12–12.9 g/dL, n = 775, events = 203	OR = 1.8 (95% CI = 1.5, 2.2)	

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				>12.9 g/dL, n = 4939, events = 805	Reference	
	Hippisley-Cox 2012 [21] [13] (2 years)	Hazard ratio	Yes	<11 g/dL	HR = 3.33 (95% CI = 2.86, 3.87)	
			No	≥11 g/dL	Reference	
	Hippisley-Cox 2013 [22] [14, 15] (2 years)	Odds ratio	Yes, n = 3250	<11 g/dL	OR = 4.08 (95% CI = 3.65, 4.57)	
			No, n = 1240550	≥11 g/dL	Reference	
	Stapley 2006 [47] (1 year)	Odds ratio	A	10–12.9 g/dL, n = 80, Stage A = 3, B = 3, C = 11, D = 10	OR = 2.2 (95% CI = 1.2, 4.3)	0.021
			B	≥12.9 g/dL, n = 269	Reference	
			C			
			D			
Females	Hamilton 2008 [18] (1 year)	Odds ratio	Yes, n = 1579	<9 g/dL, n = 257, events = 221	OR = 40.0 (95% CI = 27.8, 57.7)	
			No, n = 5226	9–9.9 g/dL, n = 231, events = 146	OR = 14.0 (95% CI = 3.3, 59.3)	
				10–10.9 g/dL, n = 451, events = 226	OR = 6.6 (95% CI = 5.3, 8.1)	
				11–11.9 g/dL, n = 854, events = 238	OR = 2.5 (95% CI = 2.1, 3.0)	
				12–12.9 g/dL, n = 1626, events = 289	OR = 1.4 (95% CI = 1.2, 1.7)	
				>12.9 g/dL, n = 3451, events = 459	Reference	
	Hippisley-Cox 2012 [21] [16] (2 years)	Hazard ratio	Yes	<11 g/dL	HR = 3.26 (95% CI = 2.84, 3.74)	
			No	≥11 g/dL	Reference	
	Hippisley-Cox 2013 [23] [14, 15] (2 years)	Odds ratio	Yes, n = 2607	<11 g/dL	OR = 4.37 (95% CI = 3.94, 4.86)	
			No, n = 1217648	≥11 g/dL	Reference	

12 < outcome time window ≤ 36 months:

UK	Everyone	Cross 2019 [11]	Odds ratio	Yes, n = 337	Men<13 g/dL, Women<12 g/dL, n = 1660, events = 184	OR = 2.39 (95% CI = 1.91, 2.98)
		(3 years)		No, n = 4405	Men≥13 g/dL, Women≥12 g/dL , n = 3082, events = 153	Reference
		Cross 2019 [11]	Yield	Yes	Anaemia with distal cancer	Yield = 6.4%
		(3 years)		No	Anaemia with proximal cancer	Yield = 4.7%
					No anaemia with distal cancer	Yield = 4.3%
					No anaemia with proximal cancer	Yield = 0.6%
		Hamilton 2005 [17]	Odds ratio	Yes, n = 349	<10 g/dl, n = 61, events = 40	OR = 12.4 (95% CI = 7.2, 21.38)
		(2 years)		No, n = 1744	10–11.9 g/dl, n = 87, events = 38	OR = 5.05 (95% CI = 3.24, 7.87)
					12–12.9 g/dl, n = 37, events = 17	OR = 5.5 (95% CI = 2.7, 10.7)
					≥13 g/dL, n = 1908, events = 254	Reference
		Hamilton 2005 [17] [17]	Odds ratio	Yes, n = 349	<10 g/dl, n = 61, events = 40	OR = 13.0 (95% CI = 6.2, 28.0)
		(2 years)		No, n = 1744	10–11.9 g/dl, n = 87, events = 38	OR = 4.3 (95% CI = 2.1, 9.0)
					12–12.9 g/dl, n = 37, events = 17	OR = 2.5 (95% CI = 0.95, 6.8)
					≥13 g/dL, n = 1908, events = 254	Reference
		Thompson 2017 [48]	Odds ratio	Yes	IDA	OR = 6.09 (95% CI = 5.04, 7.35)
		(3 years)		No	No IDA	Reference
		Thompson 2017 [48] [18]	Odds ratio	Yes, n = 990	IDA	OR = 8.38 (95% CI = 5.10, 16.05)
		(3 years)		No, n = 16413	No IDA	Reference

Outcome time window > 36 months:							
Taiwan	Everyone	Hung 2015 [26]	Incidence ratio	Yes	IDA, n = 32390, events = 171	SIR = 1.48 (95% CI = 1.27, 1.72)	
		(1–10 years)		No	No IDA		
		Hung 2015 [26]	Incidence ratio	Yes	IDA, n = 32390, CRC = 54	SIR = 1.14 (95% CI = 0.85, 1.48)	
		(1–10 years)		No	No IDA		
UK	Everyone	Pilling 2018 [40] [19]	Hazard ratio	Yes, n = 914	*Modelled as continuous*	sHR = 0.97 (95% CI = 0.87, 1.08)	
		(4.5 years)		No, n = 237,302			
		Pilling 2018 [40] [19]	Hazard ratio	Yes, n = 413	*Modelled as continuous*	sHR = 1.01 (95% CI = 0.87, 1.18)	
		(4.5–9 years)		No, n = 237,451			
OUTCOME WINDOW NOT CATEGORISABLE: > 3-month risk of CRC diagnosis:							
Iran	Everyone	Bafandeh 2008 [5]	Odds ratio	Yes	Unexplained anaemia, n = 35		0.004
		(>3 months)		Polyp	No unexplained anaemia, n = 445	Reference	
		Bafandeh 2008 [5] [20]	Odds ratio	Yes	Unexplained anaemia, n = 35, events = 5		0.006
		(>3 months)		Polyp	No unexplained anaemia, n = 445	Reference	
OUTCOME WINDOW NOT CATEGORISABLE: > 12-month risk of CRC diagnosis:							
Netherlands	Everyone	Fijten 1995 [13]	Chi-squared	Yes, n = 6	Men<8.5 mmol/L, Women<7.5 mmol/L, n = 14, events = 2		<0.01
		(> 1 year)		No, n = 219	Men≥8.5 mmol/L, Women≥7.5 mmol/L, n = 211, events = 4		
		Fijten 1995 [13]	Odds ratio	Yes, n = 6	Low, n = 14, events = 2	OR = 8.6 (95% CI = 1.4, 51.9)	
		(> 1 year)		No, n = 219	High, n = 211, events = 4	Reference	
UK	Everyone	Acher 2003 [1] [5]	Descriptive	Yes	<10.1 g/dl, n>5000, events = 26		
		(> 1 year)		No	≥10.1 g/dL, events = 274		
Unspecified outcome time window:							

Italy	Everyone	Panzuto 2003 [39] [21]	Odds ratio	Yes, n = 41	Men<14 g/dL, Women<12 g/dL, n = 69, events = 28	OR = 10.4 (95% CI = 4.9, 21.7)	
				No, n = 239	Men≥14 g/dL, Women≥12 g/dL, n = 211, events = 13	Reference	
		Panzuto 2003 [39] [22, 23]	Odds ratio	Yes, n = 41	Men<14 g/dL, Women<12 g/dL, n = 69, events = 28	OR = 8.8 (95% CI = 3.9–19.8)	
				No, n = 239	Men≥14 g/dL, Women≥12 g/dL, n = 211, events = 13	Reference	
Japan	Everyone	Nakama 2000 [37] [24]	Chi-squared	Yes, n = 96	Men<12.5 g/dL, Women<11.5 g/dL, n = 1132, events = 31		<0.05
				No, n = 17568	Men≥12.5 g/dL, Women≥11.5 g/dL, n = 16532, events = 65		
		Nakama 2000 [37] [24]	Odds ratio	Yes, n = 96	Men<12.5 g/dL, Women<11.5 g/dL, n = 1132, events = 31	OR = 7.1 (95% CI = 4.6, 11.0)	
				No, n = 17568	Men≥12.5 g/dL, Women≥11.5 g/dL, n = 16532, events = 65	Reference	
Switzerland	Everyone	Naef 1999 [36]	Descriptive	Yes Polyp	Anaemic, n = 23, events = 16 Non-anaemic, n = 31		

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio, SIR = standardised incidence ratios. [1]Multivariable effect estimate, adjusted for: age, sex, serum iron, transferrin, saturation index, and ferritin. [2]Multivariable effect estimate, adjusted for: mean corpuscular volume, neutrophil count, platelets, red blood cell distribution width, alanine aminotransferase, protein, iron, ferritin. 3Multivariable effect estimate, adjusted for: mean corpuscular volume, monocyte count, platelets, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, iron, ferritin. [4]Multivariable effect estimate, adjusted for: change in bowl habit, rectal bleeding, benign anorrectal lesion, rectal mass, serum CEA, Faecal haemoglobin, previous colonoscopy, aspirin use, sex, age. [5]In the presence of serum ferritin<12 ng/ml and mean corpuscular volume<78 fL. [6]Multivariable effect estimate, adjusted for: age, sex. [7]In the presence of serum ferritin<12 ng/ml and mean corpuscular volume<78 fL. [8]Multivariable effect estimate, adjusted for: sex, age, change in bowel habit, weight loss, bleeding per rectum, mucus per rectum, abdominal mass, abdominal fullness, lesion on digital rectal examination, anal lesion, abdominal distension, abdominal pain, family history, previous polyps, FOBt. [9]Multivariable effect estimate, adjusted for: BMI, smoking status, history of hypertension, diabetes, aspirin or NSAIDS use, vitamin K antagonists, platelet inhibitors. [10]In the presence of mean corpuscular volume<78 fL and/or mean corpuscular haemoglobin concentration<32 g/dL. [11]Multivariable effect estimate, adjusted for: mean corpuscular volume, white blood cell count, neutrophil-lymphocyte ratio, platelets, sex, previous metformin prescriptions, previous prescriptions for oral hypoglycemic drugs other than metformin. [12]Multivariable effect estimate, adjusted for: rectal bleeding, change in bowel habit, abdominal pain, diarrhoea, constipation, weight loss, mean corpuscular volume. [13]Multivariable effect estimate, adjusted for: constipation, diarrhoea, change in bowel habit, flatulence, Irritable bowel syndrome, abdominal pain/antispasmodic, rectal bleeding, mean corpuscular volume, weight loss, deep venous thrombosis/pulmonary embolism, diabetes, obesity. [14]Multivariable effect estimate, adjusted for: alcohol status, family history of gastrointestinal cancer, current rectal bleeding, current abdominal pain, current appetite loss, current weight loss, change in bowel habit in previous year. [15]Effect estimates are from multinomial logistic regression model, where the outcomes are different types of cancer. The estimates for the colorectal cancer vs no cancer are reported here. [16]Multivariable effect estimate, adjusted for: family history gastrointestinal cancer, alcohol status, abdominal distension, abdominal pain, appetite loss, rectal bleeding, weight loss, change in bowel habit, constipation. [17]Multivariable effect estimate, adjusted for: family history of gastrointestinal cancer, current rectal bleeding, current abdominal pain, current appetite loss, current weight loss. [18]Multivariable effect estimate, adjusted for: rectal bleeding, weight loss, number of episodes of abdominal pain, constipation, number of episodes of diarrhoea, rectal disease on rectal examination, tenderness on palpation of abdomen, positive faecal occult blood, blood sugar. [19]Multivariable effect estimate, adjusted for: age, sex, symptom combinations, physical signs, characteristics of rectal bleeding, characteristics of change in bowel habit, other characteristics of bowel cancer. [20]Multivariable effect estimate, adjusted for: age, sex, smoking status, highest education level attained, mean corpuscular volume, red blood cell distribution width. [21]Multivariable effect estimate, adjusted for: age, gender, duration of symptoms. [22]In the presence of ferritin<30 and mean corpuscular volume<80 fL. [23]Multivariable effect estimate, adjusted for: age, weight loss. [24]In the presence of serum ferritin<45.5 μg/L and serum iron<40 μg/L

Table S6: Haematocrit (or packed cell volume) for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
6 < outcome time window ≤ 12 months:							
UK	Everyone	Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929 No, n = 11311	*Modelled as continuous*	OR = 0.97 (95% CI = 0.95, 0.98)	<0.001
		Boursi 2016 [8] [1] (1 year)	Odds ratio	Yes, n = 4929 No, n = 11311	*Modelled as fractional polynomials (powers: -1, -1)*	OR = 0.681*Hc^{-1} OR = 0.894*Hc^{-1} × ln(Hc)	<0.001

Abbreviations: CRC = colorectal cancer, OR = odds ratio, Hc = haematocrit. [1]Multivariable effect estimate, adjusted for: mean corpuscular volume, lymphocyte count, neutrophil-lymphocyte ratio.

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Table S7: Mean corpuscular volume for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	P-value
				0 < outcome time window ≤ 6 months:			
Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936 No, n = 28491		Mean = 85.7 fL Mean = 88.9 fL	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 3.44 (95% CI = 2.7, 4.87) Reference	
		Goshen 2017 [16] [1] (1–6 months)	Risk ratio	Yes, n = 936 No, n = 28491	Highest-risk quintile Lowest-risk quintile	RR = 2.98 (95% CI = 2.58, 3.42) Reference	<0.001
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819 No, n = 26239		Mean = 84.5 fL Mean = 88.6 fL	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 3.52 (95% CI = 2.84, 4.39) Reference	
		Goshen 2017 [16] [2] (1–6 months)	Risk ratio	Yes, n = 819 No, n = 26239	Highest-risk quintile Lowest-risk quintile	RR = 3.04 (95% CI = 2.7, 3.54) Reference	<0.001
Spain	Everyone	Cubiella 2016 [12] (1 week)	Mann-Whitney U	Yes, n = 214 No, n = 1358		Median = 89.1 fL Median = 90.8 fL	<0.001
Turkey	Everyone	Ay 2015 [3] (1 week)	T-test	Yes, n = 30 Polyp, n = 110		Mean = 85.2 fL (SD = 4.8) Mean = 86.7 fL (SD = 4.9)	≥0.05
UK	Everyone	Raje 2007 [42] [3] (1–2 months)	Descriptive	Yes No	<78 fL, n = 142, events = 9 ≥78 fL		
		Acher 2003 [1] [4] (6 months)	Descriptive	Yes No	<78 fL, n>5000, events-112 ≥78 fL, events-274		
	Males	Schneider 2018 [43}	Odds ratio	Yes, n = 544	≤80 fL, n = 561, events = 544	OR = 18.7 (95% CI = 11.5, 30.6)	

	(6 months)		No, n = 3000	81–85 fL, n = 440, events = 364	OR = 2.80 (95% CI = 2.15, 3.65)
				86–95 fL, n = 1944, events = 1226	Reference
				96–100 fL, n = 475, events = 260	OR = 0.7 (95% CI = 0.6, 0.9)
				>100 fL, n = 124, events = 63	OR = 0.6 (95% CI = 0.4, 0.9)
	Schneider 2018 [43} [5] (6 months)	Odds ratio	Yes, n = 2457 No, n = 1087	≤80 fL, n = 561, events = 544	OR = 25.5 (95% CI = 13.9, 46.8)
				81–85 fL, n = 440, events = 364	OR = 2.8 (95% CI = 2.1, 3.8)
				86–95 fL, n = 1944, events = 1226	Reference
				96–100 fL, n = 475, events = 260	OR = 0.7 (95% CI = 0.5, 0.8)
				>100 fL, n = 124, events = 63	OR = 0.6 (95% CI = 0.4, 0.9)
Females	Schneider 2018 [43} (6 months)	Odds ratio	Yes, n = 2089 No, n = 1086	≤80 fL, n = 616, events = 585	OR = 12.8 (95% CI = 8.8, 18.7)
				81–85 fL, n = 512, events = 409	OR = 2.7 (95% CI = 2.1, 3.4)
				86–95 fL, n = 1499, events = 893	Reference
				96–100 fL, n = 280, events = 127	OR = 0.6 (95% CI = 0.4, 0.7)
				>100 fL, n = 82, events = 42	OR = 0.7 (95% CI = 0.5, 1.1)
	Schneider 2018 [43} [6] (6 months)	Odds ratio	Yes, n = 2056 No, n = 933	≤80 fL, n = 616, events = 585	OR = 11.4 (95% CI = 7.6, 17.1)
				81–85 fL, n = 512, events = 409	OR = 2.8 (95% CI = 2.1, 3.6)

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					86–95 fL, n = 1499, events = 893	Reference	
					96–100 fL, n = 280, events = 127	OR = 0.5 (95% CI = 0.4, 0.6)	
					>100 fL, n = 82, events = 42	OR = 0.7 (95% CI = 0.4, 1.1)	
	Centre B	Panagiotopoulou 2014 [38] (3 months)	Odds ratio	Yes, n = 17	<80 fL, n = 106, events = 17	OR = 1.73 (95% CI = 0.96, 3.1)	
				No, n = 672	≥80 fL	Reference	
		Panagiotopoulou 2014 [38] [2] (3 months)	Odds ratio	Yes, n = 76	<80 fL, n = 106, events = 17	OR = 2.2 (95% CI = 1.2, 4.1)	
				No, n = 613	≥80 fL	Reference	
USA	Everyone	Spell 2004 [46] (6 months)	Chi-squared	Yes, n = 225	<80 fL, n = 108, events = 92		<0.001
				No, n = 487	≥80 fL, n = 604, events = 133		
		Spell 2004 [46] (6 months)	Odds ratio	Yes, n = 92	<80 fL, n = 108, events = 92	OR = 20.4 (95% CI = 11.6, 35.8)	
				No, n = 620	≥80 fL, n = 604, events = 133	Reference	
6 < outcome time window ≤ 12 months:							
UK	Everyone	Acher 2003 [1] [4] (6–12 months)	Descriptive	Yes	<78 fL, n>5000, events = 28		
				No	≥78 fL, events-274		
		Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929	*Modelled as continuous*	OR = 0.90 (95% CI = 0.89, 0.91)	<0.001
				No, n = 11311			
		Boursi 2016 [8] [7] (1 year)	Odds ratio	Yes, n = 4929	*Modelled as fractional polynomials (powers: 3, 3)*	OR = 0.933*MCV^3	
				No, n = 11311		OR = 1.026*MCV^3 × ln(MCV)	
		Boursi 2016 [8] [8] (1 year)	Odds ratio	Yes, n = 3375	*Modelled as fractional polynomials (powers: 3, 3)*	OR = 0.971*MCV^3	
				No, n = 8560		OR = 1.010*MCV^3 × ln(MCV)	

		Hamilton 2008 [18] (1 year)	Odds ratio	Yes, n = 2951	<80, n = 974	OR = 15.7 (95% CI = 13.4, 18.4)
				No, n = 9648	> = 80, n = 11625	Reference
12 < outcome time window ≤ 36 months:						
UK	Everyone	Marshall 2011 [34] (2 years)	Odds ratio	Yes, n = 5477	<80, n = 1045, events = 761	OR = 26.1 (95% CI = 22.4, 30.4)
				No, n = 38314	80–84.999 fL, n = 1306, events = 444	OR = 4.95 (95% CI = 4.37, 5.61)
					≥85 fL, n = 41440, events = 4272	Reference
		Marshall 2011 [34] (2 years)	Odds ratio	Yes, n = 5477	<80 fL, n = 1045, events = 761	OR = 23.3 (95% CI = 20.0, 27.1)
				No, n = 38314	≥80 fL, n = 42746, events = 4716	Reference
		Marshall 2011 [34] [9] (2 years)	Odds ratio	Yes, n = 5477	<80, n = 1045, events = 761	OR = 7.67 (95% CI = 6.23, 9.44)
				No, n = 38314	80–84.999 fL, n = 1306, events = 444	OR = 2.71 (95% CI = 2.30, 3.19)
					≥85 fL, n = 41440, events = 4272	Reference
		Hamilton 2009 [19] (2 years)	Odds ratio	Yes, n = 363	<80, n = 1286, events = 363	OR = 2.86 (95% CI = 2.52, 3.24)
				No, n = 43428	≥80 fL, n = 42505, events = 5114	Reference
		Hamilton 2009 [19] [10] (2 years)	Odds ratio	Yes	<80 fL	OR = 6.5 (95% CI = 5.3, 7.9)
				No	≥80 fL	Reference
Outcome time window > 36 months:						
UK	Everyone	Pilling 2018 [40] [11] (4.5 years)	Hazard ratio	Yes, n = 914	*Modelled as continuous*	sHR = 0.98 (95% CI = 0.96, 1.00)
				No, n = 237,302		
		Pilling 2018 [40] [11]	Hazard ratio	Yes, n = 413	*Modelled as continuous*	sHR = 1.00 (95% CI = 0.97, 1.04)

		(4.5–9 years)		No, n = 237,451			
OUTCOME WINDOW NOT CATEGORISABLE: > 12-month risk of CRC diagnosis:							
UK	Everyone	Acher 2003 [1] [4] (> 1 year)	Descriptive	Yes	<78 fL, n>5000, events = 26		
				No	≥78 fL, events = 274		
Unspecified outcome time window:							
Italy	Everyone	Panzuto 2003 [39] [12,13]	Odds ratio	Yes, n = 41	<80 fL, n = 69, events = 28	OR = 8.8 (95% CI = 3.9–19.8)	<0.001
				No, n = 170	≥80 fL, n = 211, events = 13	Reference	

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio, SIR = standardised incidence ratios, sHR = sub-distribution hazard ratio. [1]Multivariable effect estimate, adjusted for: haemoglobin, neutrophil count, platelets, red blood cell distribution width, alanine aminotransferase, protein, iron, ferritin. [2]Multivariable effect estimate, adjusted for: haemoglobin, monocyte count, platelets, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, iron, ferritin. [3]In the presence of serum ferritin<12 ng/ml and haemoglobion<11 g/dL for males and <10 g/dL for females. [4]In the presence of haemoglobin<10.1 g/dL and/or mean corpuscular haemoglobin concentration<32 g/dL. [5]Multivariable effect estimate, adjusted for: BMI, smoking status, history of hypertension, diabetes, aspirin or NSAIDS use, vitamin K antagonists, platelet inhibitors. [6]Multivariable effect estimate, adjusted for: sex, age, change in bowel habit, weight loss, bleeding per rectum, mucus per rectum, abdominal mass, abdominal fullness, lesion on digital rectal examination, anal lesion, abdominal distension, abdominal pain, family history, previous polyps, FOBt. [7]Multivariable effect estimate, adjusted for: haematocrit, lymphocyte count, neutrophil-lymphocyte ratio. [8]Multivariable effect estimate, adjusted for: haemoglobin, white blood cell count, neutrophil-lymphocyte ratio, platelets, sex, previous metformin prescriptions, previous prescriptions for oral hypoglycemic drugs other than metformin. [9]Multivariable effect estimate, adjusted for: constipation, diarrhoea, change in bowel habit, flatulence, irritable bowel syndrome, abdominal pain/antispasmodic, rectal bleeding, haemoglobin, weight loss, deep venous thrombosis/pulmonary embolism, diabetes, obesity. [10]Multivariable effect estimate, adjusted for: rectal bleeding, change in bowel habit, abdominal pain, diarrhoea, constipation, weight loss, haemoglobin. [11]Multivariable effect estimate, adjusted for: age, sex, smoking status, highest education level attained, haemoglobin, red blood cell distribution width. [12]In the presence of ferritin<30 and haemoglobion<14 g/dL for males and <12 g/dL for females. [13]Multivariable effect estimate, adjusted for: age, weight loss.

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Table S8: Red blood cell distribution width for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
				0 < outcome time window ≤ 6 months:			
China	Everyone	Yang 2018 [51] (At admission)	Mann-Whitney U	Yes, n = 85 Polyp, n = 54		Median = 13.2% Median = 12.6%	0.004
		Yang 2018 [51] (At admission)	ROC	Yes, n = 30 Polyp, n = 110	13.25% (derived using Youden's index)	AUC = 0.72 (95% CI = 0.61, 0.83) Sensitivity = 65.9% Specificity = 75.6% PPV = 81.2% NPV = 58.6%	
		Shi 2019 [44] (2 weeks)	T-test	Yes, n = 211 Polyp, n = 103		Median = 14.3% (SD = 2.7) Median = 12.7% (SD = 1.1)	<0.001
		Shi 2019 [44] (2 weeks)	ROC	Yes, n = 30 Polyp, n = 110	13.2% (derived using Youden's index)	AUC = 0.72 Sensitivity = 53.1% Specificity = 77.7% PPV = 58.3% NPV = 18.9%	
		Song 2018 [45] (At diagnosis)	Mann-Whitney U	Yes, n = 783 No, n = 331		Median = 13.3% Median = 12.9%	<0.001
		Song 2018 [45] (At diagnosis)	Mann-Whitney U	Yes, n = 783 Polyp, n = 463		Median = 13.3% Median = 13.0%	<0.05
		Song 2018 [45] (At diagnosis)	ROC	Yes, n = 783 No, n = 331	13.95% (derived using Youden's index)	AUC = 0.64 (95% CI = 0.61, 0.67) Sensitivity = 41% Specificity = 94% PPV = 94% NPV = 40%	

		Song 2018 [45] (At diagnosis)	ROC	Yes, n = 30 Polyp, n = 110	14.05% (derived using Youden's index)	AUC = 0.50 (95% CI = 0.47, 0.53) Sensitivity = 29% Specificity = 82% PPV = 73% NPV = 41%	
Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936 No, n = 28491		Mean = 14.26% Mean = 13.61%	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 2.87 (95% CI = 2.23, 3.78) Reference	
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819 No, n = 26239		Mean = 14.81% Mean = 13.71%	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 4.54 (95% CI = 3.58, 6.26) Reference	
		Goshen 2017 [16] [1] (1–6 months)	Risk ratio	Yes, n = 819 No, n = 26239	Highest-risk quintile Lowest-risk quintile	RR = 3.14 (95% CI = 2.81, 3.66) Reference	<0.0001
Turkey	Everyone	Ay 2015 [3] (1 week)	T-test	Yes, n = 30 Polyp, n = 110		Mean = 17.7% (SD = 2.7) Mean = 15.5% (SD = 1.9)	0.02
		Ay 2015 [3] (1 week)	ROC	Yes, n = 30 Polyp, n = 110	17.5% (derived using unknown methods)	AUC = 0.747 Sensitivity = 53.3% Specificity = 91.4%	
		Cakmak 2017 [9] (6 months)	T-test	Yes, n = 59 No, n = 59		Mean = 16.1% (SD = 3.4) Mean = 13.6% (SD = 0.6)	<0.001

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		Cakmak 2017 [9] (6 months)	ROC	Yes, n = 59 No, n = 59	14% (derived using unknown methods)	AUC = 0.774 Sensitivity = 68% Specificity = 73%	
USA	Everyone	Spell 2004 [46] (6 months)	Chi-squared	Yes, n = 255 No, n = 487	≥14.2%, n = 213, events = 156 <14.2%, n = 499, events = 69		<0.001
		Spell 2004 [46] (6 months)	Odds ratio	Yes, n = 156 No, n = 556	≥14.2%, n = 213, events = 156 <14.2%, n = 499, events = 69	OR = 17.1 (95% CI = 11.5, 25.3) Reference	
Outcome time window > 36 months:							
UK	Everyone	Pilling 2018 [40] [2] (4.5 years)	Hazard ratio	Yes No	<12%	Reference	
					≥12.5–12.9%	sHR = 1.25 (95% CI = 0.90, 1.72)	
					≥13–13.4%	sHR = 1.28 (95% CI = 0.94, 1.75)	
					≥13.5–13.9%	sHR = 1.55 (95% CI = 1.33, 2.12)	
					≥14–14.4%	sHR = 1.39 (95% CI = 0.99, 1.97)	
					≥14–14.9%	sHR = 1.88 (95% CI = 1.26, 2.80)	
					≥15%	sHR = 2.24 (95% CI = 1.47, 3.40)	
		Pilling 2018 [40] [2] (4.5–9 years)	Hazard ratio	Yes No	<12%	Reference	
					≥12.5–12.9%	sHR = 1.04 (95% CI = 0.68, 1.59)	
					≥13–13.4%	sHR = 1.23 (95% CI = 0.82, 1.84)	
					≥13.5–13.9%	sHR = 0.91 (95% CI = 0.59, 1.40)	

≥14–14.4%	sHR = 1.13 (95% CI = 0.70, 1.81)
≥14–14.9%	sHR = 1.25 (95% CI = 0.69, 2.24)
≥15%	sHR = 1.46 (95% CI = 0.76, 2.79)

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio, sHR = sub-distribution hazard ratio (from Fine-Gray model), ROC = receiver operating characteristic, AUC = area under the curve, PPV = positive predictive value, NPV = negative predictive value. [1]Multivariable effect estimate, adjusted for: haemoglobin, monocyte count, platelets, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, iron, ferritin. [2]Multivariable effect estimate, adjusted for: age, sex, smoking status, highest education level attained, haemoglobin, red blood cell distribution width.

Table S9: Platelet levels for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
				0 < outcome time window ≤ 6 months:			
China	Everyone	Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 No, n = 108		Mean = 279.8 10^9/L (SD = 80.56) Mean = 207.83 10^9/L (SD = 37.4)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 Polyp, n = 132		Mean = 279.8 10^9/L (SD = 80.56) Mean = 223.9 10^9/L (SD = 42.59)	<0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes = 186 Polyp = 132 Healthy = 108		Mean = 279.8 10^9/L (SD = 80.56) Mean = 223.9 10^9/L (SD = 42.59) Mean = 207.83 10^9/L (SD = 37.4)	<0.001
		Yang 2018 [51] (At admission)	Mann-Whitney U	Yes, n = 85 Polyp, n = 54		Median = 219 10^9/L Median = 201 10^9/L	0.021
		Zhu 2018 [53] [1] (At diagnosis)	T-test	Yes, n = 783 No, n = 689		Mean = 272.4 10^9/L (SD = 86.86) Mean = 220 10^9/L	<0.01
		Zhu 2018 [53] [1] (At diagnosis)	T-test	Yes, n = 783 Polyp, n = 463		Mean = 272.4 10^9/L (SD = 86.86) Mean = 216.67 10^9/L	<0.01
		Zhu 2018 [53] (At diagnosis)	ROC	Yes, n = 783 Polyp, n = 689	242.5 10^9/L (derived using Youden's index)	AUC = 0.71 (95% CI = 0.68, 0.74) Sensitivity = 62% Specificity = 72% PPV = 78.9% NPV = 52.8%	

Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936 No, n = 28491		Mean = 261 10^9/L Mean = 222 10^9/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 3.78 (95% CI = 2.95, 4.88) Reference	
		Goshen 2017 [16] [2] (1–6 months)	Risk ratio	Yes, n = 936 No, n = 28491	Highest-risk quintile Lowest-risk quintile	RR = 2.84 (95% CI = 2.5, 3.27) Reference	
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819 No, n = 26239		Mean = 305 10^9/L Mean = 254 10^9/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 3.87 (95% CI = 3.09, 5.21) Reference	
		Goshen 2017 [16] [3] (1–6 months)	Risk ratio	Yes, n = 819 No, n = 26239	Highest-risk quintile Lowest-risk quintile	RR = 2.95 (95% CI = 2.56, 3.35) Reference	
Turkey	Everyone	Ay 2015 [3] (1 week)	T-test	Yes, n = 30 Polyp, n = 110		Mean = 287.7 /μL (SD = 78.4) Mean = 278.9 /μL (SD = 59.6)	≥0.05
		Cakmak 2017 [9] (6 months)	T-test	Yes, n = 59 No, n = 59		Mean = 308.9 10^9/L (SD = 99.1) Mean = 243 10^9/L (SD = 46.2)	<0.001
		Firat 2016 [14] (At diagnosis)	Chi-squared	Yes No			0.001
		Kilincalp 2015 [28] (At diagnosis)	T-test	Yes, n = 144 No, n = 143		Mean = 280.8 10^9/L (SD = 106) Mean = 239.7 10^9/L (SD = 50.7)	<0.001

6 < outcome time window ≤ 12 months:

UK	Everyone	Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929 No, n = 11491	*Modelled as continuous*	OR = 1.01 (95% CI = 1.005, 1.01)	<0.001
		Boursi 2016 [8] [4] (1 year)	Odds ratio	Yes, n = 3375 No, n = 8560	*Modelled as fractional polynomials (powers: 2, 3)*	OR = 605076.39*Plat^2 OR = 0.00001*Plat^3	
		Ankus 2018 [2] (1 year)	Odds ratio	Yes, n = 22 No, n = 2697	325–349 10^9/L, n = 1439, events = 7 350–374 10^9/L, n = 779, events = 8 375–399, n = 486, events = 7	Reference OR = 2.39 (95% CI = 0.89, 6.45) OR = 2.99 (95% CI = 1.04, 8.57)	
12 < outcome time window ≤ 36 months:							
UK	Everyone	Bailey 2017 [6] (2 years)	Descriptive	Yes No	≤400 10^9/L, n = 7969, events = 627 >400 10^9/L, n = 31261		

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio, ROC = receiver operating characteristic, AUC = area under the curve, PPV = positive predictive value, NPV = negative predictive value. [1]Mean measured from graphs. [2]Multivariable effect estimate, adjusted for: haemoglobin, mean corpuscular volume, neutrophil count, red blood cell distribution width, alanine aminotransferase, protein, iron, ferritin. [3]Multivariable effect estimate, adjusted for: haemoglobin, mean corpuscular volume, monocyte count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, iron, ferritin. [4]Multivariable effect estimate, adjusted for: haemoglobin, mean corpuscular volume, white blood cell count, neutrophil-lymphocyte ratio, sex, previous metformin prescriptions, previous prescriptions for oral hypoglycemic drugs other than metformin.

Table S10: Mean platelet volume for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
				0 < outcome time window ≤ 6 months:			
China	Everyone	Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 No, n = 108		Mean = 8.48 fL (SD = 1.10) Mean = 8.98 fL (SD = 0.77)	<0.001
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 Polyp, n = 132		Mean = 8.48 fL (SD = 1.10) Mean = 8.83 fL (SD = 0.90)	<0.05
		Wu 2019 [50] (At diagnosis)	ROC	Yes, n = 186 Healthy, n = 108		AUC = 0.66 (95% CI = 0.60, 0.71) Sensitivity = 92.6% Specificity = 44.6% PPV = 49.3% NPV = 91.2%	
		Zhu 2018 [53] [1] (At diagnosis)	T-test	Yes, n = 783 No, n = 689		Mean = 10 fL (SD = 5.82) Mean = 9.13 fL	<0.01
		Zhu 2018 [53] [1] (At diagnosis)	T-test	Yes, n = 783 Polyp, n = 463		Mean = 10 fL (SD = 5.82) Mean = 9.2 fL	<0.01
		Zhu 2018 [53] (At diagnosis)	ROC	Yes, n = 783 Polyp, n = 463	<9.25 fL optimal (calculated using Youden's index)	AUC = 0.66 (95% CI = 0.66, 0.69) Sensitivity = 69% Specificity = 59% PPV = 74% NPV = 52.9%	
Israel	Males	Goshen 2017 [16]	T-test	Yes, n = 936		Mean = 10.08 fL	<0.0001

		(1–6 months)		No, n = 28491		Mean = 11.07 fL	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 2.33 (95% CI = 1.8, 2.93)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
	Females	Goshen 2017 [16]	T-test	Yes, n = 819		Mean = 10.78 fL	<0.0001
		(1–6 months)		No, n = 26239		Mean = 11.06 fL	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 2.33 (95% CI = 1.72, 3.26)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
Turkey	Everyone	Kilincalp 2015 [28]	T-test	Yes, n = 144		Mean = 8.41 fL (SD = 0.98)	<0.001
		(At diagnosis)		No, n = 143		Mean = 7.87 fL (SD = 0.49)	
		Kilincalp 2015 [28]	ROC	Yes, n = 144	<8.25 fL optimal (calculated using unknown method)	AUC = 0.717	
		(At diagnosis)		No, n = 143		Sensitivity = 54% Specificity = 76%	

Abbreviations: CRC = colorectal cancer, RR = risk ratio, ROC = receiver operating characteristic, AUC = area under the curve, PPV = positive predictive value, NPV = negative predictive value. [1]Mean measured from graphs.

Study	Diagnosis, Mean (SD), n	No diagnosis, Mean (SD), n	T-test p-value	Mean difference (95% CI)	% Weight
Goshen 2017 males	10.78, n=936	11.07, n=28491	p<0.0001	-0.29 (-0.44, -0.14)	21.58
Goshen 2017 females	10.78, n=819	11.06, n=26239	p<0.0001	-0.28 (-0.42, -0.14)	21.62
Kilincalp 2015	8.41 (0.98), n=144	7.82 (0.49), n=143		0.59 (0.41, 0.77)	21.30
Wu 2019	8.48 (1.10), n=186	8.98 (0.77), n=108		-0.50 (-0.71, -0.29)	20.95
Zhu 2018	10.25 (5.82), n=783	9.13, n=689	p<0.01	1.12 (0.47, 1.77)	14.56
Overall (I-squared = 95.9%, p = 0.000)				0.06 (-0.36, 0.49)	100.00

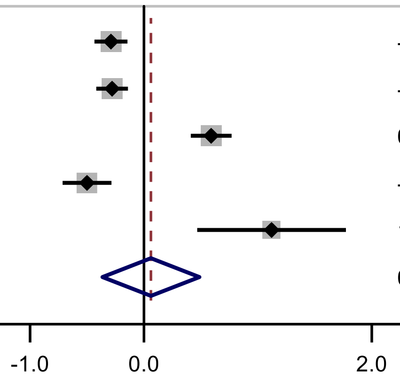

Figure S1: Forest plot of mean difference in mean platelet volume between those with and without a diagnosis of colorectal cancer 0-6 months later. Abbreviations: SD = standard deviation, CI = confidence interval. Mean platelet volume measurements are in fL.

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Table S11: Basophil count for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936		Mean = 0.03 10^9/L	0.0017
				No, n = 28491		Mean = 0.03 10^9/L	
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes	Highest-risk quintile	RR = 1.4 (95% CI = 1.14, 1.75)	
				No	Lowest-risk quintile	Reference	
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819		Mean = 0.03 10^9/L	0.0003
				No, n = 26239		Mean = 0.03 10^9/L	
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes	Highest-risk quintile	RR = 1.19 (95% CI = 1.02, 1.48)	
				No	Lowest-risk quintile	Reference	
6 < outcome time window ≤ 12 months:							
UK	Everyone	Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929	*Modelled as continuous*	OR = 1.34 (95% CI = 0.93, 1.95)	0.12
				No, n = 11311			

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio

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Table S12: Eosinophil count for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936 No, n = 28491		Mean = 0.25 10^9/L Mean = 0.22 10^9/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 1.62 (95% CI = 1.29, 2.04) Reference	
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819 No, n = 26239		Mean = 0.21 10^9/L Mean = 0.18 10^9/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 2.03 (95% CI = 1.58, 2.79) Reference	
6 < outcome time window ≤ 12 months:							
UK	Everyone	Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929 No, n = 11311	*Modelled as continuous*	OR = 1.09 (95% CI = 0.98, 1.2)	0.1

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio

Table S23: Lymphocyte count for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
China	Everyone	Huang 2019 [25] (At admission)	T-test	Yes, n = 162 No, n = 78		Mean = 1.97 10^9/L (SD = 0.57) Mean = 2.03 10^9/L (SD = 0.57)	≥0.05
		Huang 2019 [25] (At admission)	T-test	Yes, n = 162 Polyp, n = 92		Mean = 1.97 10^9/L (SD = 0.57) Mean = 1.98 10^9/L (SD = 0.61)	≥0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 No, n = 108		Mean = 1.99 10^9/L (SD = 0.58) Mean = 2.18 10^9/L (SD = 0.51)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 Polyp, n = 132		Mean = 1.99 10^9/L (SD = 0.58) Mean = 1.99 10^9/L (SD = 0.60)	≥0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes = 186 Polyp = 132 Healthy = 108		Mean = 1.99 10^9/L (SD = 0.58) Mean = 1.99 10^9/L (SD = 0.60) Mean = 2.18 10^9/L (SD = 0.51)	0.01
		Yang 2018 [51] (At admission)	Mann-Whitney U	Yes, n = 85 Polyp, n = 54		Median = 1.6 10^9/L Median = 1.7 10^9/L	0.526
Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936 No, n = 28491		Mean = 2.13 10^9/L Mean = 2.21 10^9/L	0.026

		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes	Highest-risk quintile	RR = 1.17 (95% CI = 1.01, 1.53)	
				No	Lowest-risk quintile	Reference	
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819		Mean = 2.25 10^9/L	0.43
				No, n = 26239		Mean = 2.21 10^9/L	
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes	Highest-risk quintile	RR = 1.37 (95% CI = 1.06, 1.78)	
				No	Lowest-risk quintile	Reference	
6 < outcome time window ≤ 12 months:							
UK	Everyone	Boursi 2016 [8] [1] (1 year)	Odds ratio	Yes, n = 4929	*Modelled as fractional polynomial (powers: 0, 0.5)*	OR = 1.16*Lym^0	
				No, n = 11311		OR = 12.23*$Lym^{0.5}$	

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio. [1]Multivariable effect estimate, adjusted for: haematocrit, mean corpuscular volume, neutrophil-lymphocyte ratio.

Table S34: Lymphocyte proportion for colorectal cancer

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Median per outcome group	*p*-value
0 < outcome time window ≤ 6 months:						
China	Everyone	Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes, n = 242	Median = 23.95%	<0.001
				No, n = 262	Median = 35.15%	
		Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes, n = 242	Median = 23.95%	<0.001
				Polyp, n = 248	Median = 31.50%	
		Zhou 2017 [52] (At diagnosis)	Kruskal-Wallis	Yes, n = 242	Median = 23.95%	<0.001
				Polyp, n = 248	Median = 31.50%	
				No, n = 262	Median = 35.15%	

Abbreviations: CRC = colorectal cancer

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Table S45: Monocyte count for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
China	Everyone	Wu 2019 [50]	T-test	Yes, n = 186		Mean = 0.53 10^9/L (SD = 0.19)	<0.05
		(At diagnosis)		No, n = 108		Mean = 0.45 10^9/L (SD = 0.15)	
		Wu 2019 [50]	T-test	Yes, n = 186		Mean = 0.53 10^9/L (SD = 0.19)	≥0.05
		(At diagnosis)		Polyp, n = 132		Mean = 0.50 10^9/L (SD = 0.17)	
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes = 186 Polyp = 132 Healthy = 108		Mean = 0.53 10^9/L Mean = 0.50 10^9/L Mean = 0.45 10^9/L	0.001
Israel	Males	Goshen 2017 [16]	T-test	Yes, n = 936		Mean = 0.68 10^9/L	<0.0001
		(1–6 months)		No, n = 28491		Mean = 0.61 10^9/L	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 2.11 (95% CI = 1.74, 2.8)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
		Goshen 2017 [16] [1]	Risk ratio	Yes, n = 936	Highest-risk quintile	RR = 1.85 (95% CI = 1.6, 2.12)	
		(1–6 months)		No, n = 28491	Lowest-risk quintile	Reference	
	Females	Goshen 2017 [16]	T-test	Yes, n = 819		Mean = 0.56 10^9/L	<0.0001
		(1–6 months)		No, n = 26239		Mean = 0.51 10^9/L	
		Goshen 2017 [16]	Risk ratio	Yes	Highest-risk quintile	RR = 1.99 (95% CI = 1.63, 2.65)	
		(1–6 months)		No	Lowest-risk quintile	Reference	
6 < outcome time window ≤ 12 months:							

UK	Everyone	Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929 No, n = 11311	*Modelled as continuous*	OR = 1.08 (95% CI = 1.03, 1.14)

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio. [1]Multivariable effect estimate, adjusted for: haemoglobin, mean corpuscular volume, platelets, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, iron, ferritin

Table S56: Neutrophil count for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:							
China	Everyone	Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 No, n = 108		Mean = 3.92 10^9/L (SD = 1.26) Mean = 3.40 10^9/L (SD = 0.79)	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes, n = 186 Polyp, n = 132		Mean = 3.92 10^9/L (SD = 1.26) Mean = 3.57 10^9/L (SD = 1.26)	<0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes = 186 Polyp = 132 Healthy = 108		Mean = 3.92 10^9/L Mean = 3.57 10^9/L Mean = 3.40 10^9/L	<0.001
		Yang 2018 [51] (At admission)	Mann-Whitney U	Yes, n = 85 Polyp, n = 54		Median = 3.6 10^9/L Median = 3.2 10^9/L	0.136
Israel	Males	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 936 No, n = 28491		Mean = 4.69 10^9/L Mean = 4.13 10^9/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 2.29 (95% CI = 1.73, 2.96) Reference	
		Goshen 2017 [16] [1] (1–6 months)	Risk ratio	Yes, n = 936 No, n = 28491	Highest-risk quintile Lowest-risk quintile	RR = 2.03 (95% CI = 1.82, 2.35) Reference	<0.0001
	Females	Goshen 2017 [16] (1–6 months)	T-test	Yes, n = 819 No, n = 26239		Mean = 4.33 10^9/L Mean = 3.7 10^9/L	<0.0001
		Goshen 2017 [16] (1–6 months)	Risk ratio	Yes No	Highest-risk quintile Lowest-risk quintile	RR = 1.99 (95% CI = 1.63, 2.65) Reference	

6 < outcome time window ≤ 12 months:						
UK	Everyone	Boursi 2016 [8] (1 year)	Odds ratio	Yes, n = 4929 No, n = 11311	*Modelled as continuous*	OR = 1.24 (95% CI = 1.21, 1.27)

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio. [1]Multivariable effect estimate, adjusted for: haemoglobin, mean corpuscular volume, platelets, red blood cell distribution width, alanine aminotransferase, protein, iron, ferritin

Table S67: Neutrophil proportion for colorectal cancer

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Median per outcome group	*p*-value
0 < outcome time window ≤ 6 months:						
China	Everyone	Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes, n = 242	Median = 66.50%	<0.001
				No, n = 262	Median = 56.75%	
		Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes, n = 242	Median = 66.50%	<0.001
				Polyp, n = 248	Median = 58.15%	
		Zhou 2017 [52] (At diagnosis)	Kruskal-Wallis	Yes, n = 242	Median = 66.50%	<0.001
				Polyp, n = 248	Median = 58.15%	
				No, n = 262	Median = 56.75%	

Abbreviations: CRC = colorectal cancer

Table S78: Combined components for colorectal cancer, with analyses sorted by outcome time window, country, and strata

Country	Strata	Article	Analysis type	CRC outcome groups and no. per group	Combined component	Blood level categories and no. per group	Analysis estimates	*p*-value
0 < outcome time window ≤ 6 months:								
China	Everyone	Huang 2019 [25] (At admission)	T-test	Yes No	Red blood cell distribution width-lymphocyte ratio		Mean = 8.21 Mean = 7.2	<0.05
		Huang 2019 [25] (At admission)	T-test	Yes Polyp	Red blood cell distribution width-lymphocyte ratio		Mean = 8.21 Mean = 7.59	≥0.05
		Huang 2019 [25] (At admission)	ROC	Yes No	Red blood cell distribution width-lymphocyte ratio	8.91 cut-off	AUC = 0.57 (95% CI = 0.73, 0.83) Sensitivity = 41% Specificity = 72%	
		Wu 2019 [50] (At diagnosis)	T-test	Yes No	Mean platelet volume-platelet ratio		Mean = 0.0330 Mean = 0.0447	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes Polyp	Mean platelet volume-platelet ratio		Mean = 0.0330 Mean = 0.0411	<0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes Polyp Healthy	Mean platelet volume-platelet ratio		Mean = 0.0330 Mean = 0.0411 Mean = 0.0447	<0.001
		Wu 2019 [50] (At diagnosis)	ROC	Yes No	Mean platelet volume-platelet ratio		AUC = 0.81 (95% CI = 0.76, 0.86)	
		Wu 2019 [50] (At diagnosis)	T-test	Yes No	Neutrophil-lymphocyte ratio		Mean = 1.98 Mean = 1.57	<0.05
		Wu 2019 [50] (At diagnosis)	T-test	Yes Polyp	Neutrophil-lymphocyte ratio		Mean = 1.98 Mean = 1.67	<0.05
		Wu 2019 [50] (At diagnosis)	ANOVA	Yes Polyp Healthy	Neutrophil-lymphocyte ratio		Mean = 1.98 Mean = 1.67 Mean = 1.57	<0.001
		Wu 2019 [50] (At diagnosis)	ROC	Yes No	Neutrophil-lymphocyte ratio		AUC = 0.67 (95% CI = 0.62, 0.73)	
		Wu 2019 [50] (At diagnosis)	T-test	Yes No	Platelet-lymphocyte ratio		Mean = 140.26 Mean = 94.55	<0.05

Wu 2019 [50] (At diagnosis)	T-test	Yes Polyp	Platelet-lymphocyte ratio		Mean = 140.26 Mean = 113.03	<0.05
Wu 2019 [50] (At diagnosis)	ANOVA	Yes Polyp Healthy	Platelet-lymphocyte ratio		Mean = 140.26 Mean = 113.03 Mean = 94.55	<0.001
Wu 2019 [50] (At diagnosis)	ROC	Yes No	Platelet-lymphocyte ratio		AUC = 0.78 (95% CI = 0.73, 0.82)	
Yang 2018 [51] (At admission)	Mann-Whitney U	Yes Polyp	Neutrophil-lymphocyte ratio		Median = 2.08 Median = 1.87	0.091
Yang 2018 [51] (At admission)	Mann-Whitney U	Yes Polyp	Platelet-lymphocyte ratio		Median = 124.48 Median = 113.19	0.059
Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes No	Neutrophil-white blood cell count ratio		Median = 66.50 Median = 58.15	<0.001
Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes Polyp	Neutrophil-white blood cell count ratio		Median = 66.50 Median = 58.15	<0.001
Zhou 2017 [52] (At diagnosis)	Kruskal-Wallis	Yes Polyp Healthy	Neutrophil-white blood cell count ratio		Median = 66.50 Median = 58.15 Median = 58.15	<0.001
Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes Polyp	Neutrophil-white blood cell count ratio		Median = 23.95 Median = 31.50	<0.001
Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes Healthy	Neutrophil-white blood cell count ratio		Median = 23.95 Median = 35.15	<0.001
Zhou 2017 [52] (At diagnosis)	Kruskal-Wallis	Yes Polyp Healthy	Neutrophil-white blood cell count ratio		Median = 23.95 Median = 31.50 Median = 35.15	<0.001
Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes No	Neutrophil-lymphocyte ratio		Median = 2.76 Median = 1.60	<0.001
Zhou 2017 [52] (At diagnosis)	Mann-Whitney U	Yes Polyp	Neutrophil-lymphocyte ratio		Median = 2.76 Median = 1.875	<0.001
Zhou 2017 [52] (At diagnosis)	Kruskal-Wallis	Yes Polyp Healthy	Neutrophil-lymphocyte ratio		Median = 2.76 Median = 1.875 Median = 1.60	<0.001
Zhou 2017 [52] (At diagnosis)	ROC	Yes No	Neutrophil-lymphocyte ratio	2.33 cut-off	Sensitivity = 66.9% Specificity = 77.6%	

Turkey	Everyone	Cakmak 2017 [9] (6 months)	T-test	Yes No	Neutrophil-lymphocyte ratio		Mean = 2.9 Mean = 2.0	<0.001
		Cakmak 2017 [9] (6 months)	ROC	Yes No	Neutrophil-lymphocyte ratio	2.05 cut-off	AUC = 0.740 Sensitivity = 78% Specificity = 66%	
		Cakmak 2017 [9] (6 months)	T-test	Yes No	Platelet-lymphocyte ratio		Mean = 163.6 Mean = 118.5	<0.001
		Cakmak 2017 [9] (6 months)	ROC	Yes No	Platelet-lymphocyte ratio	130 cut-off	AUC = 0.702 Sensitivity = 65% Specificity = 72%	
		Kilincalp 2015 [28] (At diagnosis)	T-test	Yes No	Neutrophil-lymphocyte ratio		Mean = 6.1 Mean = 1.5	<0.001
		Kilincalp 2015 [28] (At diagnosis)	ROC	Yes No	Neutrophil-lymphocyte ratio	2.02 cut-off	AUC = 0.921 Sensitivity = 86% Specificity = 84%	
		Kilincalp 2015 [28] (At diagnosis)	T-test	Yes No	Platelet-lymphocyte ratio		Mean = 230.5 Mean = 106.3	<0.001
		Kilincalp 2015 [28] (At diagnosis)	ROC	Yes No	Platelet-lymphocyte ratio	135 cut-off	AUC = 0.854 Sensitivity = 70% Specificity = 90%	
UK	Everyone	Boursi 2016 [8] (1 year)	Odds ratio	Yes No	Neutrophil-lymphocyte ratio	*Modelled as continuous*	OR = 1.21 (95% CI = 1.18, 1.24)	<0.001
		Boursi 2016 [8] [1] (1 year)	Odds ratio	Yes No	Neutrophil-lymphocyte ratio	*Modelled as fractional polynomials (powers: -0.5, -0.5)*	OR = 0.11*NLR$^{-0.5}$ OR = 0.70*NLR$^{-0.5}$ × ln(NLR)	
		Boursi 2016 [8] [2] (1 year)	Odds ratio	Yes No	Neutrophil-lymphocyte ratio	*Modelled as fractional polynomials (powers: -0.5, -0.5)*	OR = 0.31*NLR$^{-0.5}$ OR = 0.77*NLR$^{-0.5}$ × ln(NLR)	

6 < outcome time window ≤ 12 months:

UK	Centre A	Panagiotopoulou 2014 [38] (3 months)	Chi-squared	Yes No	Mean platelet volume & haemoglobin	MCV <80 fL & anaemia MCV ≥80 fL & no anaemia		0.285
		Panagiotopoulou 2014 [38] (3 months)	Chi-squared	Yes No	Mean platelet volume & haemoglobin	MCV <80 fL & anaemia MCV ≥80 fL & anaemia		0.781
		Panagiotopoulou 2014 [38] (3 months)	Odds ratio	Yes No	Mean platelet volume & haemoglobin	MCV <80 fL & anaemia MCV ≥80 fL & anaemia	OR = 1.3 (95% CI = 0.5, 3.9)	
	Centre B	Panagiotopoulou 2014 [38] (3 months)	Chi-squared	Yes No	Mean platelet volume & haemoglobin	MCV <80 fL & anaemia MCV ≥80 fL & no anaemia		0.285 0.019
		Panagiotopoulou 2014 [38] (3 months)	Chi-squared	Yes No	Mean platelet volume & haemoglobin	MCV <80 fL & anaemia MCV ≥80 fL & anaemia		0.196
		Panagiotopoulou 2014 [38] (3 months)	Odds ratio	Yes No	Mean platelet volume & haemoglobin	MCV <80 fL & anaemia MCV ≥80 fL & anaemia	OR = 1.6 (95% CI = 0.8, 3.3)	

Abbreviations: CRC = colorectal cancer, OR = odds ratio, RR = risk ratio, NLR = Neutrophil-lymphocyte ratio, ROC = receiver operating characteristic, AUC = area under the curve, MPV = mean platelet volume. [1]Multivariable effect estimate, adjusted for: haematocrit, mean corpuscular volume, lymphocyte count. [2]Multivariable effect estimate, adjusted for: haemoglobin, mean corpuscular volume, white blood cell count, platelets, sex, previous metformin prescriptions, previous prescriptions for oral hypoglycemic drugs other than metformin.

cancers

4. Performance statistics from model validation studies

Table S89: Performance statistics from internal (n = 9) and external (n = 11) validation models.

Article	Model name/description	Primary outcome window	No. cases	No. controls	Discrimination: AUC (95% CI)	Calibration
		Internal validation:				
Boursi 2016 [8]	Laboratory model	1 year			0.77 (0.75, 0.78)	
Boursi 2016 [8]	Combined model	1 year	1702	3324	0.73 (0.71, 0.74)	Calibration plot
Firat 2016 [14]		At diagnosis			0.81	
Hippisley-Cox 2012 [21]	QCancer Colorectal males	2 years			0.91 (0.90, 0.91)	Calibration plot
Hippisley-Cox 2012 [21]	QCancer Colorectal females	2 years			0.89 (0.88, 0.90)	Calibration plot
Hippisley-Cox 2013 [22]	QCancer males	2 years	125	667261	0.90 (0.90, 0.91)	Calibration plot
Hippisley-Cox 2013 [23]	QCancer females	2 years	1356	655311	0.89 (0.88, 0.90)	Calibration plot
Kinar 2016 [29]	ColonFlag	0–1 month			0.84 (0.81, 0.86)	
		3–6 months	698		0.82 (0.79, 0.84)	Hosmer-Lemeshow: p = 0.47
		22–24 months			0.72 (0.69, 0.75)	
Thompson 2017 [48]		3 years	636	10966	0.86 (0.84, 0.87)	Calibration plot
		External validation:				
Ayling 2019 [4]	ColonFlag		21	571		
Birks 2017 [7]	ColonFlag	3–6 months	5935	2478764	0.84 (0.84, 0.85)	
		6–12 months	6821	2429503	0.81 (0.81, 0.82)	
		12–24 months	5744	2328636	0.79 (0.79, 0.80)	
		18–24 months	5141	2220108	0.78 (0.78, 0.78)	
		24–36 months	7360	2102947	0.75 (0.75, 0.76)	
Collins 2012 [10]	QCancer Colorectal males	2 years	2036	1057729	0.92 (0.91, 0.92)	Calibration plot
Collins 2012 [10]	QCancer Colorectal females	2 years	1676	1074099	0.91 (0.90, 0.92)	Calibration plot

Cubiella 2016 [12]	COLONPREDICT	1 week	136	1345	0.92 (0.90, 0.94)	
Hilsden 2018 [20]	ColonFlag	1 year	60	8704		
Hornbrook 2017 [24]	ColonFlag	6 months	900	16195	0.80 (0.79, 0.82)	
Kinar 2016 [29]	ColonFlag	0–1 month			0.84 (0.82, 0.86)	
		3–6 months	5061	20552	0.81 (0.80, 0.83)	Hosmer-Lemeshow: $p < 0.001$
Kinar 2017 [30]	ColonFlag	18 months	133	112451		
Marshall 2011 [34]	Bristol-Birmingham	2 years	349	1744	0.92 (0.91, 0.94)	
Marshall 2011 [34]	CAPER [1]	2 years	5477	38314	0.79 (0.77, 0.80)	

[1]The CAPER model was developed study by Hamilton and includes haemoglobin level as a predictor, but was not included in this review because it was never published, instead only a conference abstract was available [54].

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