Conventional Laboratory Blood Indicators Are Valuable for Early Diagnosis of Colorectal Cancer

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Research Article

Keywords: Colorectal cancer, Early diagnosis, Conventional clinical data, Blood indicator

Posted Date: August 6th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-758680/v1>

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Abstract

Objective: Some conventional laboratory indicators have been found to be of value for the diagnosis of colorectal cancer (CRC). The present study aimed to systematically analyze the diagnostic value of conventional laboratory blood indicators for CRC, especially for early CRC.

Methods: A total of 505 patients with CRC (n=210), colorectal adenoma (CRA) (n=167) or polyp (CRP) (n=128) were retrospectively collected. Clinical, laboratory and imaging data available before treatment were extracted. The diagnostic performances of laboratory blood indicators for discriminating total and early CRCs from CRA and CRP (CRA&P) were evaluated.

Results: Fifty-three of 76 (69.7%) laboratory blood indicators were significant for discriminating CRC from CRA&P with areas under the receiver operating characteristic curve (AUC) ranging within 0.554-0.819, of these indicators, 17 had AUC > 0.7, three had AUC > 0.8, and five had AUCs greater than that for carcinoembryonic antigen (CEA). Fifteen indicators had overall sensitivities comparable to CEA for the diagnosis of CRC (35.7-55.4% vs. 47.7%, all $P > 0.05$) at a specificity of 90%, and they were not or weakly correlated with CEA (absolute $r = 0.058-0.333$). For differentiating early CRC (TNM stage I+II, n=102) from CRA&P, the sensitivities for the 15 indicators ranged within 30.4%-55.5% at a specificity of 90% and similar to stage III+IV CRC.

Conclusion: Conventional laboratory blood indicators are valuable for early CRC diagnosis, and are comparable to or better than CEA.

1 Introduction

Early diagnosis is a key for the survival of patients with colorectal cancer (CRC). The 5-year relative survival rates of CRC patients range from greater than 90% at stage I disease to slightly greater than 10% at stage IV disease, and unfortunately less than 40% of cases are diagnosed at the local cancer stage [1]. Colonoscopy is the gold standard for CRC detection, but this cannot be a regular tool for CRC screening due to its invasive feature, high cost, low adherence of patients, and differences in endoscopic operator skill [2, 3]. Fecal tests for occult blood, including the Guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT), have been widely used for CRC screening in clinic, but these have low sensitivity and specificity [4]. Fecal DNA testing for CRC screening, such as septin 9 [5], multi-objective fecal DNA, and MT-SDNA [6], needs more clinical evaluations for diagnostic value, and more simple and low-cost assay methods [7]. In addition, all fecal tests face low patient compliance due to the reluctant handling of stool samples.

Blood biomarkers are convenient and inexpensive for the diagnosis of diseases. Carcinoembryonic antigen (CEA) is the most widely used biomarker for the detection of CRC, but the sensitivity and specificity are not ideal in clinical practice [8]. In the past decades, tremendous efforts have been made to discover new serum markers for CRC diagnosis. Although a number of new blood-based biomarkers have

been discovered and evaluated, including DNA and its transcription and epigenetics, mRNA and noncoding RNA, proteins and metabolites, these are far from being applied in clinical diagnosis [9].

Daily clinical and healthcare records are useful data for exploiting diagnostic indicators for tumors, including CRC [10]. It has been early observed that there is an association between complete blood count and colon cancer [11]. A recent meta-analysis revealed that the levels of red blood cell (RBC) count, hemoglobin (HGB), mean corpuscular volume (MCV), red blood cell distribution width (RBC-DW), white blood cell (WBC) count, and platelet (PLT) count are valuable for the diagnosis of CRC [12]. Apart from the PLT count, altered mean platelet volume (MPV) and platelet thrombocytocrit (PCT) might be valuable for the diagnosis and prognosis of CRC [13]. The indexes derived from the blood cell count, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been found to be useful in the diagnosis and early detection of CRC, especially in combination [14]. Apart from the metrics in the blood count test, several other laboratory indicators were found to have some diagnostic value for CRC, such as ecto-5'-nucleotidase (5'-NT) [15, 16].

Indeed, some laboratory indicators are valuable for CRC diagnosis, to some extent, indicating that conventional laboratory data may be an alternative approach for CRC screening and detection. However, the value of clinical metrics for the diagnosis of CRC has not been systematically investigated. In the present study, the investigators retrospectively collected hospitalized patients with CRC, colorectal adenoma (CRA) and colorectal polyp (CRP), who underwent surgical or colonoscopic therapy, and systematically evaluated the diagnostic value of conventional blood test indicators for CRC, particularly highlighting the early diagnostic performances.

2 Results

2.1 Demographic and laboratory characteristics of patients

A total of 505 patients were recruited for the present study, which included 210 CRC patients, 167 CRA patients, and 128 CRP patients. The demographic and laboratory blood data of these patients are shown in Table 1. A total of 76 blood indicators were analyzed, including blood cell analysis, biochemistry, tumor markers and coagulation test, and 49 (64.5%) of them significantly differed between CRC and CRA&P.

Table 1
Demographic and laboratory characteristics of patients

Indicator	Mean ± SD or Percentage						P
	n	CRC	n	CRA	n	CRP	
Age (year)	210	64.3 ± 13.0	167	60.2 ± 11.5**	128	55.6 ± 12.6**	< 0.001 ^a
Gender							
Male	122	58.1%	99	59.3%	78	60.9%	0.875 ^b
Female	88	41.9%	68	40.7%	50	39.1%	
Blood cell analysis							
WBC (×10 ⁹ /L)	210	7.5 ± 3.1	165	6.1 ± 2.0**	128	6.3 ± 2.2**	< 0.001 ^a
NEUT (×10 ⁹ /L)	210	5.5 ± 3.1	165	3.9 ± 1.8**	128	4.0 ± 2.1**	< 0.001 ^a
LYMP (×10 ⁹ /L)	210	1.3 ± 0.6	165	1.7 ± 0.6**	128	1.8 ± 0.6**	< 0.001 ^a
MONO (×10 ⁹ /L)	210	0.6 ± 0.3	165	0.4 ± 0.2**	128	0.4 ± 0.2**	< 0.001 ^a
EO (×10 ⁹ /L)	207	0.1 ± 0.1	165	0.1 ± 0.1	128	0.1 ± 0.1	0.834 ^a
BASO (×10 ⁹ /L)	207	0.0 ± 0.0	165	0.0 ± 0.0	128	0.0 ± 0.0	0.996 ^a
NEUT% (%)	210	70.2 ± 12.0	165	61.9 ± 10.1**	128	61.6 ± 10.7**	< 0.001 ^a
LYMP% (%)	210	19.8 ± 10.0	165	29.3 ± 9.7**	128	25.1 ± 10.6**	< 0.001 ^a
MONO% (%)	210	8.1 ± 3.8	165	7.1 ± 2.4**	128	6.9 ± 2.3**	0.001 ^a
EO% (%)	207	1.8 ± 2.1	165	2.1 ± 2.1	128	2.1 ± 2.3	0.438 ^a
BASO% (%)	207	0.2 ± 0.2	165	0.2 ± 0.2	128	0.2 ± 0.3	0.445 ^a
RBC (×10 ¹² /L)	210	4.0 ± 0.6	165	4.4 ± 0.5**	128	4.4 ± 0.6**	< 0.001 ^a
HGB (g/L)	210	110.0 ± 28.6	165	133.8 ± 15.3**	128	134.4 ± 19.7**	< 0.001 ^a

Indicator	Mean ± SD or Percentage						P
	n	CRC	n	CRA	n	CRP	
HCT (%)	210	33.7 ± 7.3	165	39.2 ± 4.2**	128	40.3 ± 7.1**	< 0.001 _a
MCV (fl)	210	84.1 ± 10.4	165	89.3 ± 5.3**	128	89.4 ± 8.2**	< 0.001 _a
MCH (pg)	210	27.3 ± 4.8	165	30.4 ± 1.9**	128	31.1 ± 6.1**	< 0.001 _a
MCHC (g/L)	210	322.6 ± 23.8	165	340.9 ± 12.9**	128	340.2 ± 14.9**	< 0.001 _a
RDW-CV (%)	207	14.2 ± 2.4	165	12.8 ± 0.9**	128	12.9 ± 1.2**	< 0.001 _a
RDW-SD (fl)	210	42.5 ± 4.5	165	40.9 ± 2.8**	128	41.5 ± 2.9*	< 0.001 _a
PLT (×10 ⁹ /L)	210	251.3 ± 89.3	165	202.6 ± 57.0**	128	200.7 ± 59.0**	< 0.001 _a
PCT (%)	209	0.3 ± 0.6	165	0.2 ± 0.1	128	0.2 ± 0.1	0.066 _a
MPV (fl)	210	10.0 ± 1.9	165	10.4 ± 1.5*	128	10.0 ± 2.5	0.072 _a
PDW (fl)	209	13.5 ± 3.2	165	14.1 ± 3.1	128	13.4 ± 3.9	0.153 _a
Liver function test							
ALT (U/L)	205	17.1 ± 14.6	152	20.6 ± 11.6	115	27.4 ± 42.6**	0.001 _a
AST (U/L)	205	22.1 ± 16.9	152	20.8 ± 6.6	115	24.2 ± 26.0	0.280 _a
TBIL (μmol/L)	205	12.1 ± 6.0	152	15.2 ± 6.6**	115	15.4 ± 5.8**	< 0.001 _a
DBIL (μmol/L)	205	3.3 ± 2.8	152	2.9 ± 1.2	115	2.9 ± 1.1	0.172 _a
IBIL (μmol/L)	205	8.8 ± 4.3	152	12.4 ± 5.6**	115	12.5 ± 5.0**	< 0.001 _a
TP (g/L)	205	64.2 ± 7.4	152	68.2 ± 5.7**	115	69.2 ± 5.9**	< 0.001 _a
PALB (mg/dl)	205	16.9 ± 6.8	152	25.0 ± 6.2**	115	25.1 ± 6.3**	< 0.001 _a

Indicator	Mean ± SD or Percentage						P
	n	CRC	n	CRA	n	CRP	
ALB (g/L)	205	37.5 ± 5.2	152	41.3 ± 3.5**	115	41.7 ± 3.1**	< 0.001 ^a
GLB (g/L)	205	26.7 ± 4.8	152	27.0 ± 3.9	115	27.4 ± 4.6	0.321 ^a
A/G	205	1.4 ± 0.3	152	1.5 ± 0.3**	115	1.5 ± 0.3**	< 0.001 ^a
5'-NT (U/L)	205	4.9 ± 4.2	152	4.6 ± 2.3	115	4.7 ± 2.1	0.678 ^a
RBP (mg/L)	204	27.1 ± 11.7	152	38.7 ± 9.7**	115	38.8 ± 9.7**	< 0.001 ^a
ALP (U/L)	204	73.6 ± 28.4	152	69.8 ± 18.4	115	69.2 ± 20.1	0.186 ^a
GGT (U/L)	204	33.0 ± 53.7	152	32.0 ± 38.7	115	33.3 ± 28.2	0.968 ^a
CHE (×10 ³ U/L)	204	6.4 ± 2.0	152	8.9 ± 2.1**	115	9.0 ± 2.0**	< 0.001 ^a
ADA (U/L)	204	12.7 ± 15.1	152	9.6 ± 3.2**	115	9.5 ± 3.2**	0.005 ^a
AFU (U/L)	204	23.0 ± 7.9	152	23.5 ± 6.4	115	24.2 ± 7.0	0.370 ^a
BHBA (mmol/L)	155	0.2 ± 0.3	126	0.2 ± 0.2*	96	0.2 ± 0.1*	0.017 ^a
TBA (μmol/L)	204	4.8 ± 7.2	152	4.3 ± 8.6	115	5.3 ± 7.3	0.535 ^a
HCY (μmol/L)	203	16.5 ± 6.5	151	15.3 ± 5.6	112	16.4 ± 10.9**	0.313 ^a
Tumor marker							
AFP (ng/L)	164	2.7 ± 3.3	74	2.9 ± 1.7	64	2.7 ± 1.5	0.850 ^a
CEA (ng/L)	172	38.5 ± 124.5	71	2.6 ± 1.7**	64	8.5 ± 34.0*	0.010 ^a
Ferritin (μg/L)	73	130.4 ± 172.3	33	334.2 ± 254.6**	34	257.4 ± 224.6**	< 0.001 ^a
CA199 (U/ml)	170	60.1 ± 167.8	71	15.4 ± 25.1*	64	12.5 ± 9.8*	0.007 ^a
CA125 (U/ml)	159	24.5 ± 33.4	66	16.3 ± 34.4	63	9.9 ± 5.2**	0.003 ^a
CA153 (U/ml)	75	9.6 ± 4.7	30	10.9 ± 7.4	34	10.0 ± 5.4	0.526 ^a
CA724 (μg/ml)	85	19.2 ± 59.6	32	3.0 ± 3.9	34	2.5 ± 2.5	0.086 ^a

Indicator	Mean ± SD or Percentage						P
	n	CRC	n	CRA	n	CRP	
CY211 (ng/ml)	66	4.3 ± 5.3	30	2.2 ± 0.8*	33	2.5 ± 1.7*	0.022 ^a
NSE (ng/ml)	65	15.2 ± 7.3	31	18.6 ± 8.4	33	23.7 ± 29.0*	0.048 ^a
Renal function							
BUN (mmol/L)	204	5.7 ± 2.9	150	5.1 ± 1.8*	115	5.0 ± 1.4**	0.008 ^a
CRE (μmol/L)	204	79.0 ± 33.3	150	76.7 ± 26.0	115	73.5 ± 17.6**	0.235 ^a
CysC (mg/L)	99	1.0 ± 0.2	57	0.9 ± 0.2	44	0.9 ± 0.2*	0.052 ^a
Urca (μmol/L)	116	287.2 ± 97.4	58	351.0 ± 85.9**	46	356.1 ± 86.3**	< 0.001 ^a
B2MG (mg/L)	116	2.3 ± 0.8	58	1.8 ± 0.5**	46	1.8 ± 0.5**	< 0.001 ^a
HCO3- (mmol/L)	204	24.3 ± 3.1	150	25.0 ± 3.0*	115	24.7 ± 3.2	0.109 ^a
Blood lipid							
CHOL (mmol/L)	126	4.1 ± 0.8	144	4.6 ± 0.9**	111	4.7 ± 0.9**	< 0.001 ^a
TG (mmol/L)	126	1.2 ± 0.7	144	1.7 ± 2.2*	111	1.5 ± 1.1	0.031 ^a
HDL (mmol/L)	126	1.1 ± 0.3	144	1.3 ± 0.3**	111	1.3 ± 0.3**	< 0.001 ^a
LDC (mmol/L)	126	2.7 ± 0.7	144	3.0 ± 0.8**	111	3.1 ± 0.8**	< 0.001 ^a
APOA1 (mg/dl)	126	120.3 ± 37.9	144	137.2 ± 25.3*	111	147.9 ± 113.0**	0.006 ^a
APOB (mg/dl)	126	83.9 ± 22.1	144	86.3 ± 23.6	111	85.9 ± 22.0	0.666 ^a
LP(A) (mg/dl)	126	26.6 ± 24.9	144	17.5 ± 16.9**	111	19.2 ± 22.6**	0.002 ^a
Blood coagulation							
PT (Sec)	199	11.5 ± 2.7	157	10.5 ± 0.9**	121	10.5 ± 0.8**	< 0.001 ^a
PTA%	160	114.1 ± 31.4	155	119.0 ± 25.4	121	117.1 ± 20.9	0.254 ^a

Indicator	Mean ± SD or Percentage						P
	n	CRC	n	CRA	n	CRP	
PT-INR	199	1.0 ± 0.2	157	0.9 ± 0.1**	121	0.9 ± 0.1**	< 0.001 ^a
APTT (Sec)	199	27.8 ± 5.3	156	26.4 ± 4.4**	121	27.1 ± 4.0	0.026 ^a
TT (Sec)	147	18.5 ± 2.9	98	18.2 ± 1.4	81	18.2 ± 1.4	0.626 ^a
FDP (µg/ml)	111	6.4 ± 12.5	32	3.5 ± 2.9	24	2.8 ± 1.2	0.151 ^a
D-Dimer (µg/ml)	110	2.1 ± 4.5	31	0.7 ± 0.9	24	0.7 ± 0.8	0.065 ^a
FIB (g/L)	148	3.0 ± 0.8	97	2.6 ± 0.9**	80	2.4 ± 0.8**	< 0.001 ^a
GLU (mmol/L)	184	5.9 ± 2.2	137	5.6 ± 1.3	105	5.4 ± 1.3*	0.049 ^a
GSP (mmol/L)	155	1.9 ± 0.4	126	2.1 ± 0.4**	96	2.2 ± 0.6**	< 0.001 ^a
C-RP (mg/L)	159	32.6 ± 50.0	152	10.0 ± 25.1**	116	7.1 ± 19.6**	< 0.001 ^a

a: ANOVA test. b: Pearson's Chi-squared test. *P < 0.05, **P < 0.01, compared with the colorectal cancer group. Abbreviations: CRC, colorectal cancer; CRA, colorectal adenoma; CRP, colorectal polyp; WBC, white blood cells; NEUT, neutrophils; LYMP, lymphocytes; MONO, monocytes; EO, eosinophils; BASO, basophilic granulocytes; RBC, red blood cells; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean hemoglobin content; MCHC, mean corpuscular hemoglobin concentration; RDW-CV, red blood cell distribution width-coefficient of variation; RDW-SD, red blood cell distribution width-standard deviation; PLT, platelet; PCT, platelet thrombocytocrit; MPV, mean platelet volume; PDW, platelet distributing width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; TP, total protein; PALB, prealbumin; ALB, albumin; GLB, globulin; A/G, albumin/globulin; 5'-NT, 5'-nucleotidase; RBP, retinol binding protein; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; CHE, cholinesterase; ADA, adenosine deaminase; AFU, alpha-L-fucosidase; TBA, total bile acid; HCY, homocysteine; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CY211, cytokeratin 19; NSE, neuron specific enolase; BUN, blood ureanitrogen; CRE, creatinine; CysC, cystatin C; Urca, uric acid; B2MG, β-2 microglobulin; CHOL, cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDC, low density lipoprotein; APOA1, apolipoprotein A1; APOB, apolipoprotein B; LP(A), lipoprotein(A); PT, prothrombin time; PTA, prothrombin activity; PT-INR, prothrombin time international normalized ratio; APTT, activated partial thromboplastin time; TT, thrombin time; FDP, fibrinogen degradation products; FIB, fibrinogen; GLU, glucose; GSP, glycated serum protein; BHBA, β-hydroxybutyric acid; C-RP, C-reactive protein.

2.2 Pathological characteristics and clinical stages of colorectal cancer patients

The pathological characteristics and TNM stage of these CRC patients are presented in Table 2. Only 190 surgical patients had the TNM classification data available. The colorectal lesions were dominantly located in the colon (91.0%). Most of CRC were at TNM stage II or III (77.9%), with the size of 3-5cm (54.3%), histological type of adenocarcinoma (90%), and middle or poor differentiation (94.3%).

Table 2
The pathological characteristics and TNM stages of colorectal cancer

Pathological indicator	n (%)	TNM classification*	n (%)
Location		T category	
Right-sided colon	90 (42.9)	T1	6 (3.2)
Left-sided colon	101 (48.1)	T2	26 (13.7)
Rectum	19 (9.0)	T3	14 (7.4)
Size (the largest diameter, cm)		T4	144 (75.8)
<3	18 (8.6)	N category	
3 ~ 5	114 (54.3)	N0	111 (58.4)
>5	61 (29.0)	N1	55 (28.9)
Unknown	17 (8.1)	N2	24 (12.6)
Histological type		M category	
Adenocarcinoma	189 (90.0)	M0	173 (91.1)
Mucinous adenocarcinoma	14 (6.7)	M1	17 (8.9)
Signet ring cell carcinoma	5 (2.4)	TNM stage	
Carcinoma in situ	2 (1.0)	I	25 (13.2)
Differentiation grade		II	77 (40.5)
Well-differentiated	2 (1.0)	III	71 (37.4)
Middle-differentiated	118 (56.2)	IV	17 (8.9)
Poor-differentiated	80 (38.1)		
Unknown	10 (4.8)		
* The TNM stage data available only in 190 cases of CRC patients who received surgical therapy.			

2.3 The diagnostic value of laboratory blood indicators for CRC

The diagnostic value of each indicator for discriminating CRC from CRA + CRP (CRA&P) was evaluated using the ROC curve and 54 indicators with significant AUCs (all $P < 0.05$) are shown in Table 3. Among these indicators, 19 indicators had an AUC of > 0.7 , three indicators had an AUC of > 0.8 , and five indicators had an AUC of greater than that for CEA.

Table 3
Laboratory blood indicators with a significant AUC for discriminating colorectal cancer from colorectal adenoma and polyp

Indicator	AUC (95%CI)	Indicator	AUC (95%CI)
Blood cell analysis		Liver function test	
WBC	0.638 (0.588–0.688)	ALT	0.666(0.617–0.716)
NEUT	0.682 (0.634–0.730)	AST	0.579(0.525–0.633)
LYMP	0.676 (0.629–0.724)	TBIL	0.675(0.626–0.724)
MONO	0.656(0.607–0.704)	IBIL	0.720(0.674–0.767)
NEUT%	0.703(0.656–0.750)	TP	0.676(0.627–0.725)
LYMP%	0.749(0.705–0.792)	PALB	0.815(0.776–0.854)
MONO%	0.589(0.538–0.640)	ALB	0.742(0.696–0.789)
EO%	0.579(0.526–0.631)	GLB	0.537(0.484–0.590)
RBC	0.705(0.659–0.751)	A/G	0.619(0.567–0.671)
HGB	0.770(0.727–0.813)	GGT	0.568(0.515–0.621)
HCT	0.748(0.703–0.792)	RBP	0.807(0.767–0.847)
MCV	0.652(0.602–0.702)	CHE	0.819(0.780–0.857)
MCH	0.730(0.682–0.777)	ADA	0.666(0.616–0.716)
MCHC	0.738(0.693–0.783)	Blood lipid	
RDW-CV	0.696(0.647–0.744)	CHOL	0.660(0.603–0.718)
RDW-SD	0.583(0.531–0.636)	TG	0.620(0.561–0.679)
PLT	0.665(0.616–0.713)	HDL	0.651(0.591–0.711)
PCT	0.663(0.614–0.712)	LDL	0.610(0.550–0.670)
Tumor marker		APOA1	0.684(0.621–0.747)
CEA	0.758(0.704–0.811)	LP(A)	0.634(0.576–0.692)
CA199	0.662(0.600–0.724)	Blood coagulation	
CA125	0.654(0.596–0.712)	PT	0.686(0.636–0.735)
CA724	0.598(0.507–0.688)	PT-INR	0.675(0.625–0.725)
CY211	0.689(0.596–0.781)	APTT	0.554(0.501–0.607)

AUC: area under the receiver operating characteristic curve. For other abbreviations, refer to the notes in Table 1.

Indicator	AUC (95%CI)	Indicator	AUC (95%CI)
NSE	0.657(0.563–0.750)	FDP	0.635(0.550–0.721)
Ferritin	0.754(0.675–0.834)	D-Dimer	0.778(0.699–0.856)
Renal function		FIB	0.704(0.647–0.760)
Urca	0.678(0.607–0.748)	GSP	0.728(0.674–0.781)
B2MG	0.720(0.653–0.787)	C-RP	0.754(0.706–0.802)
AUC: area under the receiver operating characteristic curve. For other abbreviations, refer to the notes in Table 1.			

2.4 The sensitivities of laboratory blood indicators for diagnosing various stages of CRC

The optimal cut-off value for each blood indicator for discriminating CRC from CRA&P was determined according to the ROC curve. Setting the specificity at 90%, the sensitivities of 16 clinical indicators with an AUC of ≥ 0.7 (ferritin and D-Dimer were excluded due to the small sample size) were calculated for the diagnosis of CRC, and compared with CEA and among the CRC stages. The overall sensitivity for the 16 indicators, except FIB, were comparable with CEA at a specificity of 90% for the diagnosis of CRC (Fig. 2A, Table 4), and five indicators presented higher overall sensitivities than that for CEA at 90% specificity, although the differences in sensitivity were not significant. The bivariate correlation analysis showed that there were no or weak correlations between these indicators and CEA ($P < 0.001$ –0.274) (Fig. 2B).

Table 4

The sensitivities of laboratory blood indicators with AUC ≥ 0.7 for discriminating colorectal cancer from adenoma and polyp at 90% specificity

Indicator (Cut-off value)	n (CRC/A&P)	TNM stage of CRC (n, Sensitivity %)	P
CEA (≥ 4.94 ng/mL)	172/135	Overall (172, 47.7)	-
		I (20, 15.0), II (60, 55.0), III (63, 47.6), IV (13, 61.5), Unknown (16, 50.0)	0.022 b [#]
		I + II (80, 45.0), III + IV (76, 50.0)	0.532 c
NEUT% ($\geq 74.8\%$)	210/293	Overall (210, 35.7)	0.057 ^a
		I (25, 20.0), II (77, 33.8), III (71, 35.2), IV (17, 41.2), Unknown (20, 60.0)	0.085 b
		I + II (102, 30.4), III + IV (88, 36.4)	0.383 c
LYMP% ($\leq 17.3\%$)	210/293	Overall (210, 43.8)	0.442 a
		I (25, 24.0), II (77, 44.2), III (71, 40.8), IV (17, 58.8), Unknown (20, 65.0)	0.051 b
		I + II (102, 39.2), III + IV (88, 44.3)	0.477 c
RBC ($\leq 3.835 \times 10^{12}/L$)	210/293	Overall (210, 37.1)	0.111 a
		I (25, 36.0), II (77, 41.6), III (71, 32.4), IV (17, 35.2), Unknown (20, 40.0)	0.838 b
		I + II (102, 40.2), III + IV (88, 33)	0.302 c
HGB (≤ 117.5 g/L)	210/293	Overall (210, 51.4)	0.448 a
		I (25, 40.0), II (77, 51.9), III (71, 45.1), IV (17, 70.6), Unknown (20, 70.0)	0.102 b

a: compared with CEA by the McNemar test. b: compared among TNM stages by the Pearson's Chi-squared test or the Fisher's exact test (marked with [#]). c: compared between stage I + II and III + IV by Pearson's Chi-squared test. The cut-off point for each indicator is the threshold value at 90% specificity. AUC: area under the receiver operating characteristic curve. CRC: colorectal cancer. A&P: adenoma and polyp. For the other abbreviations, see the notes in Table 1.

Indicator (Cut-off value)	n (CRC/A&P)	TNM stage of CRC (n, Sensitivity %)	P
		I + II (102,49.0), III + IV (88,50.0)	0.893 c
HCT ($\leq 34.65\%$)	210/293	Overall (210, 47.6)	0.921 a
		I (25, 36.0), II (77, 46.8), III (71, 46.5), IV (17, 64.7), Unknown (20, 55.0)	0.428 b
		I + II (102, 44.1), III + IV (88, 50.0)	0.418 c
MCH (≤ 28.65 pg)	210/293	Overall (210, 49.5)	0.505 a
		I (25, 44.0), II (77, 48.1), III (71, 43.7), IV (17, 64.7), Unknown (20, 70.0)	0.180 b
		I + II (102, 47.1), III + IV (88, 47.7)	0.927 c
MCHC (≤ 325.5 g/L)	210/293	Overall (210, 44.8)	0.291 a
		I (25, 48.0), II (77, 40.3), III (71, 42.3), IV (17, 41.2), Unknown (20, 70.0)	0.188 b
		I + II (102, 42.2), III + IV (88, 42.0)	0.988 c
C-RP (≥ 17.55 mg/L)	159/268	Overall (159, 40.3)	0.434 a
		I (17, 17.6), II (55, 43.6), III (60, 38.3), IV (12, 50.0), Unknown (15, 53.3)	0.228 b#
		I + II (72, 37.5), III + IV (72, 40.3)	0.864 c
IBIL (≤ 6.75 μ mol/L)	205/267	Overall (205, 39.5)	0.403 a

a: compared with CEA by the McNemar test. b: compared among TNM stages by the Pearson's Chi-squared test or the Fisher's exact test (marked with #). c: compared between stage I + II and III + IV by Pearson's Chi-squared test. The cut-off point for each indicator is the threshold value at 90% specificity. AUC: area under the receiver operating characteristic curve. CRC: colorectal cancer. A&P: adenoma and polyp. For the other abbreviations, see the notes in Table 1.

Indicator (Cut-off value)	n (CRC/A&P)	TNM stage of CRC (n, Sensitivity %)	P
		I (25, 36.0), II (75, 40.0), III (70, 34.3), IV (17, 58.8), Unknown (18, 44.4)	0.446 b
		I + II (100, 39.0), III + IV (87, 39.1)	1.000 c
PALB (≤ 17.45 mg/dl)	205/267	Overall (205, 52.7)	0.232 a
		I (25, 40.0), II (75, 50.7), III (70, 51.4), IV (17, 70.6), Unknown (18, 66.7)	0.254 b
		I + II (100, 48.0), III + IV (87, 55.2)	0.328 c
ALB (≤ 37.05 g/L)	205/267	Overall (205, 44.9)	1.000 a
		I (25, 44.0), II (75, 41.3), III (70, 40.0), IV (17, 58.8), Unknown (18, 66.7)	0.212 b
		I + II (100, 42.0), III + IV (87, 43.7)	0.883 c
RBP (≤ 25.95 mg/L)	204/267	Overall (204, 50.0)	0.839 a
		I (25, 52.0), II (74, 43.2), III (70, 45.7), IV (17, 82.4), Unknown (18, 61.1)	0.042 b
		I + II (99, 45.5), III + IV (87, 52.9)	0.313 c
CHE (≤ 6646.5 U/L)	204/267	Overall (204, 55.4)	0.064 a
		I (25, 48.0), II (74, 58.1), III (70, 47.1), IV (17, 76.5), Unknown (18, 66.7)	0.154 b
		I + II (99, 55.6), III + IV (87, 52.9)	0.714 c

a: compared with CEA by the McNemar test. b: compared among TNM stages by the Pearson's Chi-squared test or the Fisher's exact test (marked with #). c: compared between stage I + II and III + IV by Pearson's Chi-squared test. The cut-off point for each indicator is the threshold value at 90% specificity. AUC: area under the receiver operating characteristic curve. CRC: colorectal cancer. A&P: adenoma and polyp. For the other abbreviations, see the notes in Table 1.

Indicator (Cut-off value)	n (CRC/A&P)	TNM stage of CRC (n, Sensitivity %)	P
B2MG (≥ 2.425 mg/L)	116/104	Overall (116, 44.8)	0.065 ^a
		I (15, 20.0), II (44, 54.5), III (37, 35.2), IV (11, 54.5), Unknown (9, 66.7)	0.059 ^{b#}
		I + II (59, 45.8), III + IV (48, 39.6)	0.521 ^c
GSP (≤ 1.785 mmol/L)	155/222	Overall (155, 40.6)	0.918 ^a
		I (20, 45.0), II (52, 32.7), III (55, 45.5), IV (14, 50.0), Unknown (14, 35.7)	0.610 ^b
		I + II (72, 36.1), III + IV (69, 46.4)	0.216 ^c
FIB (≥ 3.355 g/L)	148/177	Overall (148, 31.1)	0.002 ^a
		I (19, 10.5), II (47, 40.4), III (54, 27.8), IV (16, 37.5), Unknown (12, 33,3)	0.160 ^{b#}
		I + II (66,31.8), III + IV (70,30.0)	0.819 ^c
a: compared with CEA by the McNemar test. b: compared among TNM stages by the Pearson's Chi-squared test or the Fisher's exact test (marked with [#]). c: compared between stage I + II and III + IV by Pearson's Chi-squared test. The cut-off point for each indicator is the threshold value at 90% specificity. AUC: area under the receiver operating characteristic curve. CRC: colorectal cancer. A&P: adenoma and polyp. For the other abbreviations, see the notes in Table 1.			

2.5 The diagnostic value of laboratory blood indicators for early CRC

ROC curve analyses were performed to evaluate the early diagnostic value of conventional blood indicators, and eight indicators had AUCs greater than that for CEA, in terms of differentiating early CRC (stage I + II) from CRA&P (Fig. 3).

3 Discussion

The present study retrospectively analyzed the difference in conventional laboratory blood metrics among CRC, CRA and CRP. It was found that 49 of 76 (64.5%) indicators significantly differed between

CRC and CRA&P. Furthermore, 54 indicators were significant for discriminating CRC from CRA&P, with AUCs ranging within 0.537–0.815. In addition, 19 indicators had AUCs > 0.7, three indicators had AUCs > 0.8, and five indicators had AUCs greater than that for CEA. Moreover, 15 of 16 indicators had overall sensitivities comparable with CEA at a specificity of 90% for the diagnosis of CRC (35.7–55.4% vs. 47.7%, all $P > 0.05$). For differentiating early CRC (TNM stage I + II) from CRA&P, the sensitivities of 15 indicators ranged within 30.4%–55.5% at a specificity of 90%, but there were no significant differences from CRCs at stage III + IV. Eight clinical indicators had AUCs greater than that for CEA in differentiating early CRC (stage I + II) from CRA&P (0.757–0.847 vs. 0.742). In addition, the 15 indicators were not or weakly correlated with CEA (absolute $r = 0.058$ –0.333). These results indicate that many conventional laboratory indicators are valuable for diagnosing CRC, including early CRC, and are comparable to CEA.

In the present study, 16 of 23 indicators of blood cell analysis in CRC were significantly different from CRA&P, which is consistent with the meta-analysis of the full blood count test for CRC detection [18]. All eight RBC-related indicators had significant differences between CRC and CRA&P, and the hemoglobin-related indicators (HCT, MCH and MCHC) had larger AUCs for CRC diagnosis compared to the volume-related indicators (MCV, RDW-CV and RDW-SD). HGB exhibited the highest value for the diagnosis of CRC, and there were no differences between early-stage and late-stage CRCs. Anemia is a frequent sign in CRC patients due to tumor hemorrhage, which induces iron deficiency, especially with tumors in the proximal colon and at the advanced stage [19]. The iron deficiency-related indicator, ferritin, also significantly decreased in CRC and this is consistent to a previous report [20], which further confirms the above anemia-related results. In addition, these present results exhibited that the levels of hemoglobin-related indicators (HCT, MCH, MCHC) were significantly reduced in the CRC of stage I compared with the CRA&P (data not shown), but there were no significant differences among the various stages (Table 4). These are similar to the results of a recent study, in which the levels of HGB, MCV and serum ferritin (SF) decreased shortly before the CRC diagnosis [21].

Apart from the RBC-related indicators, most of the WBC- and PLT-related indicators were valuable for the CRC diagnosis, but these were not as good as the RBC-related indicators, and only two indicators (NEUT% and LYMP%) had an AUC of > 0.7. WBC-related indicators indicate the inflammatory condition of body. Inflammation has been well-known to be closely associated with the onset and progression of cancer, including CRC. The inflammatory cells and cytokines in tumors have been considered to more likely contribute to tumor growth, progression, and immunosuppression, when compared to mounting an effective host anti-tumor response [22]. In addition to the lower circulation lymphocyte number and percentage, and higher circulation neutrophil number and percentage in CRC, when compared to CRA&P, significantly higher levels of C-reactive protein (C-RP) and fibrinogen (FIB) were also found in the present study, and both of these presented AUCs greater than 0.7 for the diagnosis of CRC. These results are consistent with the reports, in which low tumor CD4 + T-lymphocyte infiltration is associated with elevated C-RP concentration and poor cancer-specific survival in CRC patients [23] and FIB is epidemiologically and mechanistically linked with diseases with an inflammatory component [24].

Furthermore, 10 of 20 liver function indicators with AUCs > 0.6 for discriminating CRC from CRA&P, PALB, RBP and CHE presented the greatest AUCs (0.807–0.819) in all indicators, with the diagnostic performance at the “good” level. This was superior to CEA, and but was not different between early- and late-stage CRC patients. Although it has been early found that blood levels of PALB and RBP are correlated to the nutrition and prognosis of CRC [25], the diagnostic value of PALB has just been recently reported. Sun et al. [26] used the ratio of circulating FIB to PALB levels to diagnose CRC, and obtained an AUC of 0.845. In the present study, PALB and RBP had a similar diagnostic performance for CRC, but PALB had a higher sensitivity than ALB. This may be because PALB has a much shorter half-life than ALB (2 vs. 20 days), as well as a smaller body pool and a more rapid synthesis rate. Therefore, PALB was considered the most sensitive and stable indicator, when compared to ALB, in terms of nutritional evaluation [27, 28]. Malnutrition in CRC is more frequent, when compared to other common cancers [29], and early-stage CRC can present apparent sarcopenia, and correlate to survival [30]. These features make PALB valuable in the early diagnosis of CRC. RBP strongly interacts with PALB, and circulates in plasma in a 1:1 molar RBP-PALB complex [31]. Thus, a similar diagnostic performance was observed in the present study.

Among all indicators, serum cholinesterase (CHE) exhibited the highest AUC for the diagnosis of CRC, including early CRC. The reduced serum CHE activity has been early reported in cancer, when compared to normal control [32], and in CRC, when compared to non-cancer patients [33]. Furthermore, this has been considered to be a prognostic factor for CRC patients [34], but this has not been evaluated for the diagnosis of CRC. The diagnosis value of CHE for CRC is probably correlated to its association with inflammation and malnutrition. It was found that serum CHE activity inversely correlates with subclinical inflammation [35] and severe systemic inflammation [36]. In the present study, negative correlations were observed between serum CHE activity and C-reactive protein ($r = -0.278$) and NEUT% ($r = -0.275$). CHE activity reduction in inflammation is correlated to the cholinergic anti-inflammatory pathway, in which acetylcholine, the substrate of CHE, plays an anti-inflammatory function and regulates the CHE activity in a negative-feedback manner [36]. Low CHE activity is also a serum marker of nutritional status in patients with CRC [37], and an increase of CHE activity was found after nutritional support therapy [38]. In addition, it was found that CHE is downregulated in CRC tissues, when compared to paired normal tissues, and it was presumed that the over-stimulating muscarinic receptors via increasing acetylcholine is correlated to the gut carcinogenesis [39]. These above findings provide the rationale for serum CHE as a valuable biomarker for CRC diagnosis.

CEA, a classical biomarker of CRC, presented fair and similar diagnostic performances for overall CRC and early CRC (AUC = 0.758 and 0.742) in the present study. CEA has been recommended to be used in CRC relapse monitoring [40]. However, its low sensitivity limits its application in early diagnosis. In the present study, eight indicators (HGB, HCT, PALB, ALB, RBP, CHE, Ferritin and B2MG) had greater AUCs, when compared to CEA, for the diagnosis of early CRC. Furthermore, these had null or weak correlations with CEA, indicating that these indicators are superior or at least equal to CEA for the early diagnosis of CRC, in terms of diagnostic performance. In the eight indicators, beta-2-microglobulin (B2MG) is a biomarker for kidney filtration and cell turnover. This has been found to be elevated in some cancers,

including CRC [41], and negatively correlated to the prognosis of recurrent CRC [42]. In a population-based cohort study followed-up for a maximum of 17 years, participants with the highest quartile of serum B2MG concentration had a 121% higher risk of CRC incidence, when compared to those with the lowest quartile, and furthermore, this was much higher than the risk of total cancer incidence (25%) and independence of conventional clinical factors [43], indicating that B2MG is strongly associated with CRC incidence risk. The mechanism for the association of serum B2MG concentrations with CRC carcinogenesis remains unclear. This is probably correlated to the pro-angiogenic, pro-tumorigenic, driving innate pro-inflammatory cytokines and growth promoting factors, epithelial-mesenchymal transition, and cell turnover [43]. For ferritin, which is a well-known iron binding protein, the reduction in serum ferritin level could be prior to anemia [20]. This is more remarkable in eastern countries, when compared to western countries, according to a meta-analysis [44].

Although the diagnostic value of conventional laboratory blood indicators for CRC was systematically and comprehensively analyzed in the present study, there were several limitations. First, we did not perform a multivariate analysis on these indicators due to the missing values in some indicators. Therefore, the independent indicators for CRC diagnosis need to be clarified in future studies. Second, since systematical blood tests could not be performed in outpatients and normal controls, merely inpatients with CRC, CRA and CRP were enrolled in the present study, which may cause the results to be inconsistent with the situation in the real world. Third, as a monocenter and retrospective study, further studies with a prospective and multicenter design and multivariate analysis are warranted to elucidate and validate the diagnostic significance of conventional laboratory blood tests in patients with CRC.

In summary, the investigators retrospectively and systematically analyzed the diagnostic performance of conventional laboratory blood indicators in differentiating CRC and CRA&P. It was found that most of the indicators have certain value for the diagnosis of CRC, including early CRC. Indicators correlated to anemia, nutrition status, and inflammation had greater value, when compared to the other indicators, and some of these were superior to that of CEA. Prospective studies with a more rigid design should be performed to validate these present results.

4 Patients And Methods

4.1 Patients

Patients with CRC, CRA, or CRP, who were hospitalized for surgical or colonoscopic therapy in the Three Affiliated Hospital of Nanchang University from March 2014 to July 2019, were collected. The medical records of these patients were reviewed, and the clinical data available were extracted, including the demographics, medical history, laboratory blood tests (blood cell analysis, biochemistry, coagulation function, tumor markers, etc.), pathological diagnostic data, medical image examination (ultrasonography, and CT and/or MRI), and therapy data (surgery, colonoscopy and other treatments). The laboratory data collected were the results of the first test after admission prior to therapy, which was close to the time of diagnosis.

Age at the laboratory test was recorded. All colorectal lesions were pathologically confirmed. These CRC patients were staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system [17]. This study was approved by the Ethical Committee of the First Affiliated Hospital of Nanchang University, which also waived the need for informed consent for the retrospective study. All methods were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki.

Patients with one of following conditions were excluded: (1) patients with no definite pathological diagnosis; (2) patients with recurrent or secondary colorectal cancer; (3) patients with other concurrent cancers; (4) patients suffering from liver diseases, hematological diseases, or other diseases that can affect the results of the laboratory blood tests; (5) patients who received anti-tumor therapies before surgery; (6) patients who received special therapies that affect the results of the laboratory blood tests, such as iron agent, anticoagulant, anti-lipemic agent, nonsteroidal anti-inflammatory drugs, and blood transfusion; (7) patients with incomplete data for the TNM staging of CRC or the definite diagnosis.

Figure 1 shows the enrollment of patients.

4.2 Statistical analysis

The patient demographics, laboratory tests, and clinical and pathological characteristics were descriptively summarized. Continuous data were expressed as mean $\pm$ standard deviation (SD), and enumeration data were expressed in frequency and percentage. The difference of each indicator among the three groups was compared using ANOVA or Pearson's Chi-squared test, according to the type of variable. The difference of indicators between TNM stages was compared using Pearson's Chi-squared test or the Fisher's exact test. The area under the receiver operating characteristic (ROC) curve (AUC) was utilized to evaluate the diagnostic performance of each indicator. The McNemar test was used to compare the diagnostic sensitivity between CEA and other laboratory indicators. The Pearson's correlation was used to analyze the bivariate correlation between the blood indicators. A two-sided P-value of < 0.05 was considered statistically significant. The statistical analyses were carried out using the SPSS version 24.0 software (IBM, NY, USA).

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Figures

Figure 1

The flowchart of patient enrollment.

Figure 2

The diagnostic performances and correlations with CEA of 16 laboratory blood indicators valuable for discriminating colorectal cancer from adenoma and polyp. (A): the sensitivities of the 16 laboratory blood indicators at 90% specificity. (B): the bivariate coefficients between the 16 indicators and CEA. Refer to the notes in Table 1 for the abbreviations.

Figure 3

The receiver operating characteristic curves of laboratory blood indicators with areas under the curve greater than that for CEA in discriminating early colorectal cancer from colorectal adenoma and polyp. AUC: area under the receiver operating characteristic curve; CEA: carcinoembryonic antigen; ECRC: early colorectal cancer; A&P: adenoma and polyp; HGB: hemoglobin; HCT: hematocrit; PALB: prealbumin; ALB: albumin; RBP: retinol binding protein; CHE: cholinesterase; B2MG: β -2 microglobulin