Is Interluekin-6 (IL-6) an Appropriate Diagnostic and Prognostic Biomarker for Colorectal Cancers?

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Abstract: Development of colorectal cancer (CRC) is a slow process, where a benign polyp progresses into a malignant stage over a long period of time. The patient may be asymptomatic during this period, thus delayed diagnosis has become a prime obstacle in managing CRC. Improved routine screening for early detection and prognosis will aid in better management of CRCs reducing mortality rates.

Diagnosis of CRCs is primarily based on the invasive colonoscopy and tissue biopsy and fecal occult blood test with alongside evaluation of carcinoembryonic antigen (CEA) levels in blood for prognosis and recurrence. However, CEA as a standalone biomarker for CRCs, fail due to its non-specificity, low sensitivity and high false-positivity highlighting the importance of identification of new biomarkers for CRCs.

In the recent past inflammatory cytokines emerged as key drivers of CRC pathogenesis, particularly as determinants of disease progression. The pleiotropic cytokine, interleukin-6 (IL-6) has been identified as activating oncogenic gene transcription in the colorectal epithelial cells leading to the pathogenesis of CRCs. By activating STAT3 signaling pathway, IL-6 promotes initiation, growth and metastasis of the colorectal cancer cell clone. In this review, we present the prospect of IL-6 in CRCs, describing the emerging evidence for IL-6 as a potential biomarker, the drawbacks of IL-6 and future directions for IL-6 as a diagnostic and prognostic marker for CRC.

The original articles were extracted from the PubMed using the key words: "IL-6/interleukin 6 levels in colorectal cancer/ IL-6/ interleukin 6 concentrations in colorectal cancer/ IL-6 expression/ serum interleukin 6/ IL-6 in colorectal cancer". Full text articles published in English in last 25 years (from 2000 to July 2025) were included and the research carried out in animal models and *in vitro*, reviews, case reports, meta-analyses, editorials and non-relevant articles (post – surgery/treatment, studies on IL-6 in overlapping cancers/conditions etc.) were excluded.

Though IL-6 stands as a potential marker for CRCs with markedly elevated levels, heterogeneity of patient populations with inadequacy of data for defining and distinguishing clinical sub groups, control groups and methodologies have become a barrier for its progression from bench to bed side. Hence, prospective research need to be focused on obtaining data on IL-6 using standardized methodologies to determine stage-specific and population specific cut-off values in well-defined CRC sub groups.

Keywords: Colorectal cancer, IL-6, diagnosis, prognosis.

INTRODUCTION

Colorectal Cancer: Pathogenesis, Diagnosis and Prognosis

Colorectal cancer (CRC) is the third most common form of cancer in the world accounting for 10% of global cancer incidence. The incidence is rising especially in the young with an estimated 3.2 million in 2040 [1,2]. GLOBOCAN 2020 estimates ~63% increase in new CRC cases by 2040 [2]. Thus, CRC has raised public health concerns to implement healthier lifestyles for prevention and to develop enhanced screening strategies to identify CRCs at early stages impeding metastasis and reducing mortality rates [3,4]. Furthermore, appearance of symptoms occurs in the advanced stages of the CRCs delaying its diagnosis and late diagnosis is one of the major challenges faced in the management of CRCs contributing to the large number of deaths [5].

Diagnosis of CRCs is primarily based on the invasive colonoscopy and tissue biopsy and fecal tests such as fecal occult blood test, fecal immunochemical test and multi-target stool DNA test. Additionally,CT colonography, flexible sigmoidoscopy and MRI are useful for structural analyses [6,7]. Evaluation of carcinoembryonic antigen (CEA)levels in blood is performed alongside particularly to determine the prognosis and to predict possibility of recurrence of the disease. Post-surgery recurrence may occur and need early detection for cure by surgical resection [8,9]. Each diagnostic or prognostic test of CRCs has its strengths and weaknesses. Patients tend to avoid invasive and uncomfortable tests like colonoscopy and upsetting tests like stool analyses hindering the timely diagnosis and show preference for blood based diagnostic tests.

CEA is elevated in CRC patients and has long been used as a blood-based marker for CRC [8]. However, CEA's non-specificity, low sensitivity and high false-positivity make it unsuitable as a standalone biomarker for CRCs. High CEA levels have been observed in

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smoking and alcoholism, inflammatory bowel disease (IBD), pancreatitis, and severe hepatitis [10-13]. Therefore, identification of new alternative biomarkers for CRCsis mandatory which can be used alone or together with CEA and carbohydrate antigen 19-9 (CA19-9) to screen for individuals with risk factors, diagnose CRCs at early stage, determine prognosis and prevent metastases or relapse [14]. Expansion of the understanding on the risk factors and pathophysiological mechanisms underlying oncogenesis in CRC will aid developing novel markers for screening, diagnosisandas therapeutic targets.

Inflammation and CRC

Colorectal cancer initiates as a polyp or an adenoma in the intestinal mucosa and can be transformed into a malignant carcinoma in a multi-step sequential process [15]. Origin of the CRC may be heritable (35% of CRCs) and sporadic or inflammation induced [16]. The remaining 65% are known to be sporadic with acquired genetic and epigenetic alterations initiated by unhealthy lifestyles (eg: excessive alcohol and red meat consumption, smoking) and conditions such as IBD and alterations in the gut microbiome [16,17-20]. Alterations in the gut microbiome stimulate macrophages and T-cells to release pro-inflammatory cytokines such as IL-6, IL-17 and TNF-α and the sequence of inflammation-dysplasia-cancer lead to development of CRCs [21,22]. Nevertheless, it is hereditary, sporadic or IBD associated CRC, inflammation is considered as an obligatory driver in the pathogenesis of CRCs with significant roles in its initiation, progression or at least in metastasis [18].

Chronic IBD and colitis may result in dysplasia of the gut mucosa subsequently leading to the development of CRC through activation of NF-κB and IL6/STAT3 signaling pathways by TNF, which is ascribed as a key mediator of inflammation in IBD [23-30]. IBD alters intestinal microbiome paving path to increase pro-inflammatory bacterial residents and secretion of pro-inflammatory and carcinogenic mediators leads to induction of genomic damage and dysplasia [27-30]. Activation of inflammatory signaling by NF-kB, cyclooxygenase-2 (COX-2)/PGE2, IL-23/Th17 and IL-6/STAT3 pathways are known to play crucial roles in driving CRC progression [31, 32].

Disruption of the tissue homeostasis and the interplay of cancer cells with reorganized inflammatorytumor microenvironment (TME) lead to progression of the CRCs [33]. TME's cell components (M1 and M2 macrophages, dendritic cells, T and B lymphocytes, NK cells and regulatory T cells) engage in aberrant cell-cell communications and consequential soluble factors secreted by them and the tumor clone itself disrupt the integrity of the niche. Suppressing the anti-tumor responses, complex networks of pro–inflammatory cytokines and chemokines secreted by aberrant cellular communications among tumor cells, immune cells and CAFs in the TME create a pro-inflammatory tumorigenic environment [34]. Constant inflammatory networks induce epithelial-mesenchymal transition (EMT) of cancer cells and causes development of resistance to therapy leading to metastasis [35].

Pro-Inflammatory Cytokines in the CRC Niche

Main pro-inflammatory cytokines in the CRC micro-environment (CRC-ME) are interleukins IL-1β, IL-6, and IL-8 and TNF-α [36]. IL-1β in CRCs is less well characterized. Its elevation has been reported in CRCs as well as in other cancer types such as lung and breast cancer. However, the cell types that secrete IL-1β and its role in CRC pathogenesis are largely unknown [36]. It has been demonstrated that secreted IL-1β increases the levels of TNF-α, IL-6, IL-8, IL-17, cyclooxygenase-2 (COX-2), and (prostaglandin E2) PGE2 with roles assigned in proliferation, differentiation, apoptosis and EMT [37,38]. Furthermore, it has been observed that the increase of IL-1β depends on the stage of the CRC, with continuous increase up to metastasis (stage III) and decrease in stage IV [38]. TNF-α, mainly produced by macrophages, monocytes and by cancer cells to defend immune system has been attributed to play roles in the recruitment of leukocytes, inhibition of lymphocytes, tumor angiogenesis and regulation of secretion of other cytokines [38-40]. Elevated concentrations of serum TNF-α and TNF-α mRNA have been reported in CRC patients, correlated to metastasis and poor prognosis [41]. Pro-inflammatory cytokine IL-8 is produced by the epithelial and some immune cells in response to other cytokines such as TNF-α and IL-1β and conditions like hypoxia is elevated in CRCs. It interacts with a membrane receptor on cancer cells and favors tumor angiogenesis, EMT and invasion [42]. The other cytokines contributing to the pro-inflammatory TME in CRCs include IL-17 and IL-12 and pleiotropic cytokines such as interferon γ IFN-γ also promote cancer progression and invasion [40].

IL-6 is a pleiotropic cytokine that has been extensively studied in CRC. Its pro-inflammatory role in

CRC pathogenesis has been linked with increased levels correlating to metastasis and poor prognosis. It initiates IL-6/STAT3 signaling that promote cancer cell proliferation and survival, angiogenesis via activation of CAFs, invasion and metastasis and chemotherapy resistance. In this review, we present the prospect of IL-6 in CRCs, describing the role of IL-6 in CRC initiation and progression with emerging evidence for IL-6 as a potential biomarker for the diagnosis and prognosis of CRC. We also discuss future directions for IL-6 as a diagnostic and prognostic marker for CRC.

IL-6 and its IL-6 Signaling Mechanisms

The IL-6 gene mapped to the chromosome 7p15–p21 encodes a glycoprotein, IL-6 containing 184 amino acids with a varied mass of 21–28 kDa that is determined by the post-translational glycosylations and the cellular source of origin [43,44]. IL-6 is produced by multiple cell types such as macrophages, monocytes, hematopoietic cells, stromal cells, epithelial cells and muscle cells [43-45]. Exerting pleotropic effects, in wider sense IL-6 regulates inflammation, immunity, metabolism, reproduction, bone metabolism, development of hematopoietic and neural systems and angiogenesis [45]. At cellular level, IL-6 signaling influences cell proliferation, survival and death by regulating the transcription of key genes (Bcl2, Bcl-x_L survivin, c-Myc, cyclins B and D1) in cell cycle and apoptosis, thus attributed to play significant roles in cancer pathogenesis [45,46].

IL-6 mediates its signaling action by forming a complex with its receptors: membrane-bound IL-6R (mIL-6R) or its isoform soluble IL6-R (sIL-6R). In classic signaling, which generally has been identified to have anti-inflammatory roles and regenerative functions, IL-6 binds to the IL-6R forming a complex of IL-6-mIL-6R that interacts with the membrane bound form of glycoprotein gp130 (mgp130). In the trans-signaling mechanism, IL-6 interacts with the sIL-6R with a similar affinity and forms IL-6-sIL-6R which can associate with the mgp130 or its soluble isoform sgp130. Trans-signaling mechanism has been characterized as the pro-inflammatory arm of IL-6 and occurs ubiquitously in an array of cell types in contrast to the classic signaling that is restricted to a few cell types such as leukocytes, megakaryocytes, liver hepatocytes and some epithelial cells [45-47]. Interaction of IL-6R with gp130 leads to gp130 dimerization and induces a cascade of phosphorylations of downstream proteins. Auto-phosphorylation and activation of Janus kinases: JAK1, JAK2 and TYK2 initiates JAK-STAT signaling recruits, phosphorylates and activates STATs particularly STAT3 in pro-inflammatory responses [43]. Upon tyrosine residuephosphorylation, STAT3 forms a dimer which translocates into the nucleus to associate with the STAT3-specific DNA response element and activates the gene transcription of downstream target genes that are largely involved in the cell proliferation and survival (Bcl2, Bcl-x_L c-Myc, cyclin D1 and B, and survivin), angiogenesis (HIF-1alpha and VEGF), cell adhesion (ICAM-1), extracellular matrix degradation (metalloproteases 2 and 9), cell adhesion (ICAM-1) and inflammation (IL-6, IL-17, IL-23, and Cox2) [43,47]. Thus, aberrant activation of STAT3 can have dreadful consequences leading to tumorigenesis via uncontrolled cell proliferation and tumor-angiogenesis and invasion. Furthermore, STAT3 activation creates a positive feedback loop for the transcription of IL-6, leading to pro-long inflammatory reactions and immune escape of tumor cells.

IL-6 Signaling in CRCs

IL-6 in CRCs is secreted primarily by cancer associated macrophages which promote migration and invasion of CRC via JAK2/STAT3/miR-506-3p/FoxQ1 signaling [48,49]. Cancer-associated mesenchymal stem cells also produce IL-6 by up-regulation of Notch 1 and CD44 gene expression. IL-6/STAT3 signaling is implicated in CRC propagation by inducing cancer cell proliferation and survival as reported in the DSS–AOM mouse model [50,51]. Furthermore, an association of IL-6/STAT3 signaling with Toll-like receptor 9 (TLR9) signaling in myeloid cells in regressing cancers has been reported [52]. It has also been discovered that IL-6 can induce microsatellite instability (MSI) [53]. Research unveil that IL-6 signaling relocates the mismatch repair (MMR) protein hMSH3 from the nucleus to the cytoplasm leading to MMR deficiencies and subsequent microsatellite alterations via frame shift mutations [53]. Together with TGF-β, IL-6 drives T cell differentiation towards Th17 cells and Th17 derived cytokines such as IL-17A, IL-17F, IL-21, IL-22 drive carcinogenesis. Inflammatory signaling by IL-6 activates CAFs which in turn acts as a source of IL-6 in the TME. Though the mechanisms are unclear yet, CRC cells boost IL-6 secretion from CAFs [54].

Role of IL-6 in tumor progression is characterized by up-regulation of several genes involved in cell cycle regulation. c-Myc, a driver of the cell cycle, is overexpressed in CRC patients specifically in patients with poor prognosis. STAT3 association with the c-Myc

promoter up-regulates the expression of c-Myc, leading to progression of the cancer [55,56]. STAT3 have also been identified as a transcriptional activator for the cell cycle protein D1 (cyclinD1) and mitochondrial single-stranded DNA-binding protein (mtSBB). CyclinD1 facilitates uncontrolled cell proliferation of CRC cells, driving the cell cycle from G1 to S phase [57] and mtSSB through activation of ROS/Akt/mTOR pathway mediate immortalization of CRC cells, stabilizing telomeres via up-regulation of telomerase reverse transcriptase [58].

Inhibition of apoptosis of cancer cells by IL-6/ STAT3 signaling have been demonstrated in CRC mouse models. It has been showed that IL6/STAT3 signaling induces anti-apoptotic proteins Bcl-2, Bcl-xl and survivin [59-61]. Up-regulated survivin enhances vascular infiltration and lymph node metastasis and negatively correlates with overall survival [61, 62].

IL-6/STAT3 signaling enhances invasion and metastasis of cancer cells. STAT3 interacts with Fos-related antigen-1 (Fra-1) gene promoter and up-regulates its expression which in-turn causes expression of MMPs and other proteins that favour EMT [63,64]. Promoting cancer invasion and metastasis, IL-6 signaling also up-regulates the transcription of vimentin, FOxQ1, Integrin β6, Twist and hypoxia-inducing factor-1α (HIF-1α) and down-regulates E-cadherin expression [65-67]. HIF-1α associates with upstream regulatory element EP-1 of the CEA gene activating its transcription. Increased CEA level leads to cancer progression with invasion and is considered as an indicator of poor prognosis [68].

microRNA-34a (miR-34a) is known to inhibit the EMT by down-regulating Snail1, a transcription factor with roles attributed in epithelial-mesenchymal transition. Activation of STAT3 by IL-6 signaling down-regulates miR-34a, leading to up-regulation of Snail 1 expression. It also up-regulates IL-6R mRNA levels, becoming a feed-forward loop for IL-6/STAT3 signaling [69,70].

Tumor Angiogenesis is promoted by IL-6/STAT 3 signaling. Vascular endothelial growth factor (VEGF) levels are elevated in CRCs and VEGF facilitates angiogenesis of tumor thus drives its metastasis [71]. STAT3 has been identified as a transcriptional activator for VEGF expression [71, 72]. It has also been identified that VEGF receptor, VEGFR2 is up-regulated in a STAT3 dependent manner in the intestinal epithelium in colitis-associated CRCs [73].

Overall, it is apparent that IL-6/ STAT3 signaling involves in every stage of the CRC development: initiation, propagation, angiogenesis, invasion and metastasis. Furthermore, elevated levels of IL-6 levels have been reported in CRC patients and thus IL-6 and its clinical significance in CRCs drew a central attention over past few decades. Below, we have discussed the evidence for IL-6 as an emerging marker for CRC diagnosis and prognosis.

IL-6 as an Indicator of CRC Development, Progression and Metastasis

In order to evaluate the potency of IL-6 to be used as a marker for colorectal cancer diagnosis and prognosis we reviewed the data published on serum IL-6 concentrations and IL-6 expression in CRCs. The original articles indexed in the PubMed for last 25 years (from 2000 to July 2025) were considered. The key words used for PubMEd search were: IL-6/interleukin 6 levels in colorectal cancer/ IL-6/ interleukin 6 concentrations in colorectal cancer/ IL-6 expression/ serum interleukin 6/ IL-6 in colorectal cancer. Articles written in English with full text available were selected. Research carried in animal models and *in vitro*, reviews, case reports, meta-analyses, editorials and non-relevant articles (post –surgery/treatment, studies on IL-6 in overlapping cancers/conditions etc.) were excluded. Table **1** below summarizes the findings of the research articles that provide evidence for the increased IL-6 in CRCs.

Rising of [IL-6] as a potential indicator of CRC development, progression and metastasis is supplemented by many research as described above (Table **1**). Increased IL-6 levels compared to the controls have been observed: rising to 3 to 4.5 fold in some instances (3-fold: [74, 84, 86, 91], : 4.5 – fold: [99, 103, 105]). This significant rise in blood IL-6 levels clearly indicates its potential to be utilized in the diagnosis and determining the prognosis of CRC. Moreover, IL- 6 levels have been linked to the disease stage [74, 78, 79, 81, 83, 87, 92-94]. A research carried out using archived pre-diagnostic plasma specimens confirms a significant elevation in IL-6 levels at pre-diagnostic stage, emphasizing the role of inflammation in the development of subsequent CRCs [89]. As the diseases progresses, the release of this inflammatory marker elevates facilitating CRC progression and metastasis. Thus, association of IL-6 levels with poor prognosis and metastasis has been reported by many research [82, 88, 90, 91, 94, 95]. Moreover, rise in blood IL-6 concentrations as the disease progresses have been shown to corelate with the short overall

Table 1: Alterations of IL-6 Levels in CRC

Region	Country	Sample Size and Male/female percentage	Assay method	Findings: Association of IL-6 with			Ref.
				Diagnosis (level in pg/mL)	Prognosis (level in pg/mL)	Survival	
Asia	Japan	P-233 M:F -60:40 C-13	Chemilumine scent enzyme immunoassay	Increased, C-2.6 P-6.6	Higher mean [IL-6] for stage II than for stage III	Correlated with CRP and CEA and OS.	[74]
	Japan	P-46 M:F -63:37	ELISA (R&D)	[IL-6] - 4.18	Associated with poor prognosis	Inverse correlation with OS	[75]
	South Korea	P- 132 M:F- 60:40 C-50	ELISA	Increased, C-5.65, P- 14.33	Increase in [IL-6] depending on the stage, lymph node metastasis, degree of differentiation	No significant association with OS	[76]
	South Korea	P-696 M:F – 68:32 C-1835	ELISA (R&D, USA)	Increased C- 1.93, P- 3.64	-	-	[77]
	Taiwan	P-128 M:F -64:36	ELISA (R&D, USA)	Increased P- 12.6	Stage dependent increase S1 - 6.7,S2 - 17.5, S3-45.8, S4- 10.3	-	[78]
	Taiwan	P-164 M:F –66: 34	ELISA (R&D, USA)	Increased, P-14.4	Increased with stage: S1- 6.8, S2-13.3, S3-18.5, S4-18.3	Increased progression-free survival when [IL-6] 6 < 10 pg/mL	[79]
	Taiwan	P- 99 M:F – 57:43 C- 42	ELISA (R&D, USA)	Increased C-3.5, P- 14.5 Increased soluble [IL-6 R]: C-695.2, P- 808.6	No significant association between [IL-6], TNM stage, tumor extent, regional lymph node invasion, histological grade	[IL-6] >10 pg/ml linked to shorter survival	[80]
	China	P-40 M:F -60:40 C-32	ELISA (MultiSciences Biotech Co., Ltd.)	Increased P-32.83 CRC_{young}-5.62, C_{eld}-13.89	Associated with advanced stage (P < 0.05)	-	[81]
	China	P-164 M:F -57:43 C-20	ELISA (Endogen, Inc.)	Increased, Median [IL-6]: C-3.41 P-11.89 49.4% CRC had >12 pg/ml	Serum [IL-6] >12 pg/ml correlated with larger tumor size, CRP and liver metastases and stage.	Decreased OS	[82]
	China	P-88 M:F -51:48	ELISA (CSB-E04638h, CUSABIO, China)	Increased, 57% CRCs had >213.83	Correlated with tumor differentiation, TNM stage and NLR, OS and DFS	High NLR + [IL-6] correlated with worse OS and DFS	[83]
	Kazakhstan	P-216 M:F – 51:49 C-97	Immuno fluorescence, Milliplex Map (Millipor) Human Circulation Biomarker panel	Increased compared to controls.	Increased with grade: G1-6.8, G2-9.05, G3-7.73 No association with the degree of differentiation	-	[84]
	Indonesia	P-46 M:F -63:37	ELISA (Bioassay Tec.Lab. China)	Increased, P- 15.27	Increased with stage	-	[85]
	Sri Lanka	P-35 C-35	ELISA (Elabscience, USA)	Increased, C- 8.35, P-26.67	-	-	[86]

(Table 1). Continued.

Region	Country	Sample Size and Male/female percentage	Assay method	Findings: Association of IL-6 with			Ref.
				Diagnosis (level in pg/mL)	Prognosis (level in pg/mL)	Survival	
Europe and North America	UK	P-118 M:F – 51: 49	ELISA (R&D, UK)	Increased, 2/3 of patients had [IL-6] > 3.4	[IL-6] associated with increased T stage (P<0.05), tumor necrosis (P<0.001), modified Glasgow Prognostic Score (mGPS; P<0.001)	No significant association	[87]
	Norway	P-364 patients in the NORDIC-VII trial M:F-60:40	ELISA (R&D, UK)	50% CRC had [IL-6]> 5.8	Associated with impaired prognosis in metastasis	Median OS was significantly lower at high [IL-6]	[88]
	USA	P-173 M:F- 77:23 C-345 Archived prediagnostic plasma specimens	ELISA (R&D, USA)	Increased, Median C- 1.9 (1.3-3.0), P-2.3 (1.5-3.6) Positive association of [IL-6] and subsequent colon cancer risk	-	-	[89]
	Poland	P-157 M:F -50:50 C-50	ELISA (R&D, USA)	Increased, Median of C-0.8 (0.7-2.4), CRC- 2.8 (0.7-107.0)	Significant association with clinical stage of CRC (p<0.001), tumor grade (p<0.018), and bowel wall invasion (p<0.001).		[90]
	Poland	P-55 M:F -53:47 C-27	ELISA (R&D, UK)	A 2.9-fold increase	1.73 fold higher [IL-6] in metastatic CRC		[91]
	Romania	P- 68 M:F -66:34 C-20	ELISA (Elabscience, USA)	Increased, C-2.0, P- ≥68 yrs -16.29 <68 yrs - 8.03	S1-4.7, S2-12.0, S3-13.5, S4-22.4 Doubled [IL-6] in stage IV than stage III	-	[92]
	Greece	P-74 M:F -53:47 C-25	ELISA (R&D, USA)	Increased in 47.3% of CRCs Median [IL-6] C- 3.52 P- 8.11	Correlated with larger tumor size	Correlated with reduced OS	[93]
Africa	Bosnia	P-75 M:F -53:47 C-20	ELISA (R&D)	Increased, P- 8 C-0	S2-2.5, S3-6.5, S4-28. Correlated with MMP-9 and CRP levels (p <0.001).	-	[94]
	Egypt	P-35 M:F-74: 26 C-30	ELISA (R&D, USA)	Increased, C- 2.7- 2.9 P_{male}- 7.58 P_{female}-7.46	Localized CRC-4.45, metastasis - 8.8 (all P < 0.001)	-	[95]
South America	Brazil	P-20 M:F- 45:55 C-20	Cytometric Bead Array, (BD Biosciences, USA).	Increased, C- 36.1, P-159.3	-	-	[96]

CRC- colorectal cancer, P- Patients, C- Control, S- stage of CRC, G1 -highly differentiated, G2 - moderately differentiated, G3- low differentiated, OS- overall survival, PFS- Progression-Free Survival.

survival and recurrence (Prognosis and OS- [74, 75, 79, 80, 82, 88, 90, 93]. Eldesoky A. *et al*., has reported a high diagnostic accuracy of IL-6 for CRCs (66%) with a cut off value = 6.7 pg/ml and sensitivity and specificity of 74% and 59% respectively.

Is IL-6 an Appropriate Marker for CRC Diagnosis and Prognosis?

The overall picture of IL-6 in CRCs comprise its significant elevation compared to the healthy. Its association with disease progression and short overall survival provides clear insights to consider IL-6 as a potential marker for diagnosis, prognosis and predictor of survival. Furthermore, the correlation of rising IL-6 levels with CRP and CEA levels demonstrates the possibility of using IL-6 along with these markers in assessing the disease progression and disease related quality of life [88].

However, usefulness of IL-6 as a standalone biomarker is doubtful. To be used as a standalone diagnostic or prognostic marker, a molecule has to be highly specific, sensitive and show a distinct elevation compared to healthy. In this regard, the data reported from past research are ambiguous, specifically on the level of elevation of IL-6. Though majority of the research have reported elevated levels of IL-6, the cut-off level of significance is questionable. The reported levels of IL-6 in CRC patients are highly variable and sometimes contradictive, which may not be fully attributed to the disease stage or severity. The variability in [IL-6] can be attributed to many factors: differences in sample processing and assay methods, assay environments, heterogeneous characteristics of the patient cohorts including individual physical and psychological differences, underlying conditions other than CRC and the differences in control group characteristics. While majority of the research had used ELISA to quantify IL-6, some had used other assay methods like chemiluminescent enzyme immunoassay [74], immunofluorescence [84] and cytometric bead array [96]. The differences in assay methods used by different research and even if the same assay method performed under different laboratory conditions may give results differently. Furthermore, sample handing from collection to storage to analysis can largely affect the quantity of IL-6 present in serum. This heterogeneity in analysis makes it difficult to set a cut-off value for IL-6 as a diagnostic marker for CRC.

One of the main challenges that interpreters of IL-6 analyses face is the heterogeneous nature of the patient characteristics. Being a disease at elderly onset, many patients present with an array of underlying conditions apart from the individual physical and behavioural variations like obesity, smoking, exercise etc. [89]. Most of the studies draw general conclusions reporting mean/median values of the entire study population and analysis based on grouping of matching variables is sparse. Setting cut-off values for IL-6 for CRC diagnosis is also hampered by lack or inadequacy of characteristics of the control groups. Studies report male:female ratios with only a few studies reporting the mean or median IL-6 values separately for males and females. A study from Egypt reports that both male and female CRC patients show comparable levels of IL-6. Normalization of factors like age and gender dependency is required to set cut-off values for IL-6 in diagnosis of CRC. Furthermore, population-based and age-related variations of IL-6 values have been reported [97,98]. Apart from the two papers from Japan [74,75], the other Asian studies show comparable elevation of IL-6 in CRC patients (>10 pg/mL), whereas the selected studies from Europe and North America demonstrate IL-6 values ranging 5-10 pg/mL. This highlights the importance of establishment of population-specific cut-off values for IL-6 if to be used as diagnostic marker for CRCs. Given that IL-6 is a general inflammatory marker, presence of a cancer or/and other underlying conditions such as stress or other infectious/inflammatory disease can induce IL-6 signaling [99-101]. Therefore, the observed variations of IL-6, specifically when it is not significant, is difficult to consider as a sole indicator of CRC.

In contrast to the majority of studies, a minor portion of studies also reports comparable IL-6 levels in both CRC patients and healthy at the point of initial diagnosis [102,103]. Most of the studies on IL-6 in CRCs, report merely the levels of IL-6, with no evaluation as a diagnostic or prognostic marker, thus, data on specificity and the sensitivity is limited.

Many research demonstrate a strong association of IL-6 with clinical features such as tumor size, location, stage, degree of differentiation and stage of metastasis [74, 78, 81, 84, 88, 90, 92]. However, compilation and analysis of the associations are challenging due to the non-specific nature of IL-6, differences in the study group characteristics and methods of analysis. A study reported high IL-6 values in CRCs but with no co-relation to clinical features [91].

The current diagnostic markers of CRC, CEA and CA19-9 are in the forefront of the CRC diagnosis, with huge amount of research conducted on different populations with stage-specific, behavioural-specific and age-specific manner [104-106]. CEA and CA 19-9 have pre-operative cut-off values set to 5.00 ng/ml and 37 U/m respectively [107]. However, both markers possess certain degree of variability and non-specificity with some patients demonstrating no elevation to cut-

off levels at least at the early stages of the disease. These markers are also elevated in other carcinomas such as lung, breast, gastrointestinal, and gynecologic cancers [108]. Furthermore, as seen in IL-6, CEA shows sensitivity to behavioral factors like smoking which elevates CEA levels up to 10 ng/ml [109-111]. Thus, the cut-off values of CEA have been set for patients with different comorbid factors which necessarily need to be done prior to setting IL-6 as a diagnostic marker for CRCs. In spite of large amount of data, CEA and CA 19-9 still face challenges in the CRC diagnosis with due to variabilities in assay methods and settings and lack of specificity with some contradictive findings reported in some cases [112, 113]. Thus, with markedly elevated levels reported in CRCs, IL-6 could be a potential marker to augment CEA and CA 19-9, but needs large scale characterization and validation on stage and population and other variable specific manner. In this regard, studies done on multiple populations with well-defined patient and control cohorts are essential.

IL-6 may be used as an alongside marker with CEA, when CRC clinical symptoms are presented and may be used as a general indicator suggestive of subsequent CT scan and other investigations when the patients present with non-CRC specific features such as fatigue, weight loss but with no infections or inflammatory disease. Moreover, approximately 30% of CRC patients do show high CEA values at least at the early stage of the disease [114] and in such cases IL-6 can be utilized as an indicator to determine the further management. As evidenced by some research [89], prolong higher IL-6 levels in a healthy adult, specifically when there is a family history of CRCs or other malignancies may be an indicator of subsequent CRC development, thus measuring IL-6 for such individuals may be beneficial for future.

CONCLUSIONS

Early diagnosis and prognostication of CRC is still challenging due to lack of a reliable early diagnostic marker, with a significant number of patients detected at the advanced stages of the disease hampering early interventions. Thus, identification of a reliable, non-invasive marker is a timely need. Evidence generated from recent past, highlights the potency of IL-6 as a marker for CRC. However, the inconclusive nature of the findings resulted from controversial elevation levels, irregularities in the cut-off values, heterogeneity of IL-6 level and clinical features have become a barrier for its progression from bench to bed side. Hence, research need to be focused on validation of the past findings, evaluation of the diagnostic value of IL-6 in defined CRC populations, setting up cut-off values at distinct CRC stages and definite co-relations of IL-with CRC clinical features.

Prospective multicenter studies on different but defined CRC sub groups need to be carried out along with other inflammatory markers and standard assay protocols to acquire more data and to improve diagnostic and prognostic accuracy.

CONSENT FOR PUBLICATION

All authors agreed to the publication.

DECLARATION OF COMPETING INTEREST

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WMMS Bandara: Conceptualization, literature search, data extraction, writing the review and finalizing the manuscript.

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REFERENCES

[1] Roshandel G, Ghasemi-Kebria F, Malekzadeh R. Colorectal Cancer: Epidemiology, Risk Factors, and Prevention. Cancers 2024; 16: 1530. https://doi.org/10.3390/cancers16081530

[2] Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Trans Oncol 2021; 14(10): 101174. https://doi.org/10.1016/j.tranon.2021.101174

[3] Ferlay J, Ervik M, Lam F, *et al.* Global Cancer Observatory. International Agency for Research on Cancer 2024. https://gco.iarc.who.int/media/globocan/factsheets/populations/591-panama-fact-sheet.pdf

[4] Ionescu VA, Gheorghe G, Bacalbasa N, *et al.* Colorectal Cancer: From Risk Factors to Oncogenesis. Medicina 2023; 59(9): 1646. https://doi.org/10.3390/medicina59091646

[5] Skalitzky MK, Zhou PP, Goffredo P, *et al.* Characteristics and symptomatology of colorectal cancer in the young. Surgery 2023; 173(5): 1137-1143. https://doi.org/10.1016/j.surg.2023.01.018

[6] Beniwal SS, Lamo P, Kaushik A. *et al.* Current Status and Emerging Trends in Colorectal Cancer Screening and Diagnostics. Biosensors (Basel) 2023; 13(10): 926. https://doi.org/10.3390/bios13100926

[7] Gude SS, Veeravalli RS, Vejandla B, *et al.* Colorectal Cancer Diagnostic Methods: The Present and Future. Cureus 2023; 15: 4. https://doi.org/10.7759/cureus.37622

[8] Hall C, Clarke L. Pal A. *et al.* A Review of the Role of Carcinoembryonic Antigen in Clinical Practice. Ann Coloproctol 2019; 35(6): 294-305 https://doi.org/10.3393/ac.2019.11.13

[9] Kawai K, Nozawa H, Hata K. *et al.* Nomogram predicting survival after recurrence in patients with stagei to III colon cancer a nationwide multicenter study. Dis Colon Rectum 2018; 61(9): 1053-1062. https://doi.org/10.1097/DCR.0000000000001167

[10] Stockley RA, Shaw J, Whitfield AG, *et al.* Effects of cigarette smoking, pulmonary inflammation, and lung disease on concentrations of carcinoembryonic antigen in serum and secretions. Thorax 1986; 41(1): 17-24. https://doi.org/10.1136/thx.41.1.17

[11] Moore TL, Kantrowitz PA, Zamcheck N. Carcinoembryonic Antigen (CEA) in Inflammatory Bowel Disease. JAMA 1972; 222 (8): 944-947. https://doi.org/10.1001/jama.1972.03210080028007

[12] Imaoka H, Mizuno N, Hara K, *et al.* Prognostic impact of carcinoembryonic antigen (CEA) on patients with metastatic pancreatic cancer: A retrospective cohort study. Pancreatology 2016; 16: 859-64. https://doi.org/10.1016/j.pan.2016.05.007

[13] Kaur A, Azeez GA, Thirunagari M, *et al.* Association of Chronic Hepatitis B With Colorectal Cancer and Its Dual Impact on Colorectal Liver Metastasis: A Narrative Review. Cureus 2024; 16(12). https://doi.org/10.7759/cureus.76079

[14] Gramkow MH, Mosgaard CS, Schou JV, *et al.* The prognostic role of circulating CA19-9 and CEA in patients with colorectal cancer. Cancer Treat Res Commun 2025; 43: 100907. https://doi.org/10.1016/j.ctarc.2025.100907

[15] Testa U, Pelosi E, Castelli G, *et al.* Colorectal Cancer: Genetic Abnormalities, Tumor Progression, Tumor Heterogeneity, Clonal Evolution and Tumor-Initiating Cells. Medical Sciences 2018; 6(2): 31. https://doi.org/10.3390/medsci6020031

[16] Burt R. Inheritance of Colorectal Cancer. Drug Discov Today Dis Mech 2007; 4(4): 293-300. https://doi.org/10.1016/j.ddmec.2008.05.004

[17] Nadeem M S, Kumar V, Al-Abbasi FA, *et al.* Risk of colorectal cancer in inflammatory bowel diseases. Semin Cancer Biol 2020; 64: 51-60. https://doi.org/10.1016/j.semcancer.2019.05.001

[18] Ahmad A, Mahmood N, Raza MA, *et al.* Gut microbiota and their derivatives in the progression of colorectal cancer: Mechanisms of Action Genome and Epigenome Contributions 2024; 10: 8. https://doi.org/10.1016/j.heliyon.2024.e29495

[19] Kumar R, Herold JL, Schady D, Davis J, *et al.* Streptococcus gallolyticus subsp. gallolyticus promotes colorectal tumor development. PLoS Pathog 2017; 13(7): e1006440. https://doi.org/10.1371/journal.ppat.1006440

[20] Quaglio AEV, Grillo TG, De Oliveira ECS, *et al.* Gut microbiota, inflammatory bowel disease and colorectal cancer. World J Gastroenterol 2022; 28(30): 4053-4060. https://doi.org/10.3748/wjg.v28.i30.4053

[21] Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol 2014; 5: 491. https://doi.org/10.3389/fimmu.2014.00491

[22] Khalyfa AA, Punatar S, Aslam R, *et al.* Exploring the Inflammatory Pathogenesis of Colorectal Cancer. Diseases 2021; 9(4): 79. https://doi.org/10.3390/diseases9040079

[23] Schmitt M, Greten FR. The inflammatory pathogenesis of colorectal cancer. Nat Rev Immunol 2021; 21(10): 653-667. https://doi.org/10.1038/s41577-021-00534-x

[24] Luo C, Zhang H. The Role of Proinflammatory Pathways in the Pathogenesis of Colitis-Associated Colorectal Cancer. Mediat Inflamm 2017; 2017: 5126048. https://doi.org/10.1155/2017/5126048

[25] Stidham RW, Higgins PDR. Colorectal Cancer in Inflammatory Bowel Disease. Clin Colon Rectal Surg 2018; 31(3): 168-178. https://doi.org/10.1055/s-0037-1602237

[26] Paradisi A, Maisse C, Coissieux M-M, *et al.* Netrin-1 up-regulation in inflammatory bowel diseases is required for colorectal cancer progression. Proc Natl AcadSci USA 2009; 106 (40): 17146-17151. https://doi.org/10.1073/pnas.0901767106

[27] Becker C, Fantini MC, Schramm C, *et al.* TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. Immunity 2004; 21(04): 491-501. https://doi.org/10.1016/j.immuni.2004.07.020

[28] Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol 2012; 10(6): 639-645. https://doi.org/10.1016/j.cgh.2012.01.010

[29] Nadeem MS, Kumar V, Al-Abbasi FA, *et al.* Risk of colorectal cancer in inflammatory bowel diseases. Semin. Cancer Biol 2020; 64: 51-60. https://doi.org/10.1016/j.semcancer.2019.05.001

[30] Lin Y, He Z, Ye J, *et al.* Progress in Understanding the IL-6/STAT3 Pathway in Colorectal Cancer. Onco Targets Ther. 2020; 13: 13023-13032. https://doi.org/10.2147/OTT.S278013

[31] Jana A, Krett NL, Guzman G, *et al.* NFkB is essential for activin-induced colorectal cancer migration via upregulation of PI3K-MDM2 pathway. Oncotarget 2017; 8(23): 37377-37393. https://doi.org/10.18632/oncotarget.16343

[32] Li J, Yang J, Xing R, Wang Y. A novel inflammation-related signature for predicting prognosis and characterizing the tumor microenvironment in colorectal cancer. Aging (Albany NY) 2023; 15(7): 2554-2581. https://doi.org/10.18632/aging.204630

[33] Pieniądz P, Pięt M, Paduch R. Characteristics of the Colorectal Cancer Microenvironment—Role in Cancer Progression and Therapeutic Possibilities. Applied Sciences 14(7): 2930. https://doi.org/10.3390/app14072930

[34] Li S, Zhang J, Qian S, *et al.* S100A8 promotes epithelial-mesenchymal transition and metastasis under TGF-β/USF2 axis in colorectal cancer. Cancer Commun (Lond) 2021; (2): 154-170. https://doi.org/10.1002/cac2.12130

[35] Fryczkowski M, Hejmo T, Bułdak M, *et al.* Impact of selected pro-inflammatory cytokines and oxidative stress on carcinogenesis and progression of prostate and colorectal adenocarcinomas. Ann Acad Med Siles 2019; 73: 182-193. https://doi.org/10.18794/aams/110503

[36] Li Y, Wang L, Pappan L, *et al.* IL-1β Promotes Stemness and Invasiveness of Colon Cancer Cells through Zeb1 Activation. Mol Cancer 2012; 23; 11: 87. https://doi.org/10.1186/1476-4598-11-87

[37] Park JW, Chang HJ, Yeo HY, *et al.* The relationships between systemic cytokine profiles and inflammatory markers in colorectal cancer and the prognostic significance of these parameters. Br J Cancer 2020; 123: 610-618. https://doi.org/10.1038/s41416-020-0924-5

[38] Stanilov N, Miteva L, Dobreva Z, *et al.* Colorectal Cancer Severity and Survival in Correlation with Tumour Necrosis

Factor-Alpha. Biotechnol Biotechnol Equip 2014; 28(5): 911-917.
https://doi.org/10.1080/13102818.2014.965047

[39] Warsinggih Limanu F, Labeda I, Lusikooy RE, *et al.* The Relationship of Tumor Necrosis Factor Alpha Levels in Plasma toward the Stage and Differentiation Degree in Colorectal Cancer. Med Clínica Práctica 2021; 4: 100224.
https://doi.org/10.1016/j.mcpsp.2021.100224

[40] West NR, McCuaig S, Franchini F. Emerging cytokine networks in colorectal cancer. Nat Rev Immunol 2015; 15(10): 615-29.
https://doi.org/10.1038/nri3896

[41] Conciatori F, Bazzichetto C, Falcone I. Colorectal Cancer Stem Cells Properties and Features: Evidence of Interleukin-8 Involvement. Cancer Drug Resist 2019; 2(4): 968-979.
https://doi.org/10.20517/cdr.2019.56

[42] Huang B, Lang X, Li X. The role of IL-6/JAK2/STAT3 signaling pathway in cancers. Front Oncol 2022; 16: 12.
https://doi.org/10.3389/fonc.2022.1023177

[43] Ataie-Kachoie P, Pourgholami MH, Richardson DR, *et al.* Gene of the month: Interleukin 6 (IL-6). J Clin Pathol 2014; 67(11): 932-7.
https://doi.org/10.1136/jclinpath-2014-202493

[44] Scheller J, Chalaris A, Schmidt-Arras D, *et al.* The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011; 1813(5): 878-88.
https://doi.org/10.1016/j.bbamcr.2011.01.034

[45] Heinrich PC, Behrmann I, Haan S, *et al.* Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J 2003; 374(Pt 1): 1-20.
https://doi.org/10.1042/BJ20030407

[46] Hirano T. IL-6 in inflammation, autoimmunity and cancer. IntImmunol 2021; 33(3): 127-148.
https://doi.org/10.1093/intimm/dxaa078

[47] Lin Y, He Z, Ye J, Progress in Understanding the IL-6/STAT3 Pathway in Colorectal Cancer. Onco Targets Ther 2020; 13: 13023-13032.
https://doi.org/10.2147/OTT.S278013

[48] Wei C, Yang C, Wang S, *et al.* Crosstalk between cancer cells and tumor associated macrophages is required for mesenchymal circulating tumor cell-mediated colorectal cancer metastasis. Mol Cancer 2019; 18: 64.
https://doi.org/10.1186/s12943-019-0976-4

[49] Bollrath J, Phesse TJ, von Burstin VA, *et al.* gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell 2009; 3: 91-102.
https://doi.org/10.1016/j.ccr.2009.01.002

[50] Grivennikov S, Karin E, Terzic J, *et al.* IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 2009; 3: 103-13.
https://doi.org/10.1016/j.ccr.2009.01.001

[51] Gao C, Kozlowska A, Nechaev S, *et al.* TLR9 signaling in the tumor microenvironment initiates cancer recurrence after radiotherapy. Cancer Res 2013; 15: 7211-21.
https://doi.org/10.1158/0008-5472.CAN-13-1314

[52] Tseng-Rogenski SS, Hamaya Y, Choi DY, *et al.* Interleukin 6 alters localization of hMSH3, leading to DNA mismatch repair defects in colorectal cancer cells. Gastroenterology 2015; 148: 579-89.
https://doi.org/10.1053/j.gastro.2014.11.027

[53] Dang CV. MYC on the path to cancer. Cell 2012; 149: 22-35.
https://doi.org/10.1016/j.cell.2012.03.003

[54] Rochlitz CF, Herrmann R, de Kant E. Overexpression and amplification of c-myc during progression of human colorectal cancer. Oncology 1996; 53: 448-454.
https://doi.org/10.1159/000227619

[55] Kiuchi N, Nakajima K, Ichiba M, *et al.* STAT3 is required for the gp130-mediated full activation of the c-myc gene. J Exp Med 1999; 189: 63-73.
https://doi.org/10.1084/jem.189.1.63

[56] Alt JR, Cleveland JL, Hannink M, *et al.* Phosphorylation-dependent regulation of cyclin D1 nuclear export and cyclin D1-dependent cellular transformation. Genes Dev 2000; 14: 3102-3114.
https://doi.org/10.1101/gad.854900

[57] Wang G, Wang Q, Huang Q, *et al.* Upregulation of mtSSB by interleukin-6 promotes cell growth through mitochondrial biogenesis-mediated telomerase activation in colorectal cancer. Int J Cancer 2019; 144: 2516-2528.
https://doi.org/10.1002/ijc.31978

[58] Lin Y, He Z, Ye J, *et al.* Progress in Understanding the IL-6/STAT3 Pathway in Colorectal Cancer. Onco Targets Ther 2020; 13: 13023-13032
https://doi.org/10.2147/OTT.S278013

[59] Tian Y, Ye Y, Gao W, *et al.* Aspirin promotes apoptosis in a murine model of colorectal cancer by mechanisms involving downregulation of IL-6-STAT3 signaling pathway. Int J Colorectal Dis 2011; 26: 13-22.
https://doi.org/10.1007/s00384-010-1060-0

[60] Ryan BM, O'Donovan N, Duffy MJ. Survivin: a new target for anti-cancer therapy. Cancer Treat Rev 2009; 35: 553-562.
https://doi.org/10.1016/j.ctrv.2009.05.003

[61] Krieg A, Werner TA, Verde PE, *et al.* Prognostic and clinicopathological significance of survivin in colorectal cancer: a meta-analysis. PLoS One 2013; 8.
https://doi.org/10.1371/journal.pone.0065338

[62] Iskit S, Schlicker A, Wessels L, *et al.* Fra-1 is a key driver of colon cancer metastasis and a Fra-1 classifier predicts disease-free survival. Oncotarget 2015; 6: 43146-43161.
https://doi.org/10.18632/oncotarget.6454

[63] Liu H, Ren G, Wang T, *et al.* Aberrantly expressed Fra-1 by IL-6/STAT3 transactivation promotes colorectal cancer aggressiveness through epithelial-mesenchymal transition. Carcinogenesis 2015; 36: 459-468.
https://doi.org/10.1093/carcin/bgv017

[64] Han C, Sun B, Zhao X, *et al.* Phosphorylation of STAT3 promotes vasculogenic mimicry by inducing epithelial-to-mesenchymal transition in colorectal cancer. Technol Cancer Res Treat 2017; 16: 1209-1219.
https://doi.org/10.1177/1533034617742312

[65] Wei C, Yang C, Wang S, *et al.* Crosstalk between cancer cells and tumor associated macrophages is required for mesenchymal circulating tumor cell-mediated colorectal cancer metastasis. Mol Cancer 2019; 18: 64.
https://doi.org/10.1186/s12943-019-0976-4

[66] Sun Q, Shang Y, Sun F, *et al.* Interleukin-6 promotes epithelial-mesenchymal transition and cell invasion through integrin β6 upregulation in colorectal cancer. Oxid Med Cell Longev 2020; 8032187.
https://doi.org/10.1155/2020/8032187

[67] Blumenthal RD, Hansen HJ, Goldenberg DM. Inhibition of adhesion, invasion, and metastasis by antibodies targeting CEACAM6 (NCA-90) and CEACAM5 (carcinoembryonic antigen). Cancer Res 2005; 65: 8809-8817.
https://doi.org/10.1158/0008-5472.CAN-05-0420

[68] Rokavec M, Öner MG, Li H, *et al.* Corrigendum. IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. J Clin Invest 2015; 125: 1362.
https://doi.org/10.1172/JCI81340

[69] Li H, Rokavec M, Hermeking H. Soluble IL6R represents a miR-34a target: potential implications for the recently identified IL-6R/STAT3/miR-34a feed-back loop. Oncotarget 2015; 6: 14026-14032.
https://doi.org/10.18632/oncotarget.4334

[70] Xiong H, Zhang ZG, Tian XQ, *et al.* Inhibition of JAK1, 2/STAT3 signaling induces apoptosis, cell cycle arrest, and reduces tumor cell invasion in colorectal cancer cells. Neoplasia 2008; 10: 287-297. https://doi.org/10.1593/neo.07971

[71] Martins SF, Reis RM, Rodrigues AM, *et al.* Role of endoglin and VEGF family expression in colorectal cancer prognosis and anti-angiogenic therapies. World J ClinOncol 2011; 2: 272-280. https://doi.org/10.5306/wjco.v2.i6.272

[72] Waldner MJ, Wirtz S, Jefremow A, *et al.* VEGF receptor signaling links inflammation and tumorigenesis in colitis-associated cancer. J Exp Med 2010; 207: 2855-2868. https://doi.org/10.1084/jem.20100438

[73] Han J, Theiss AL. Stat3: friend or foe in colitis and colitis-associated cancer? Inflamm Bowel Dis 2014; 20(12): 2405-11. https://doi.org/10.1097/MIB.0000000000000180

[74] Shiga K, Hara M, Nagasaki T, *et al.* Preoperative Serum Interleukin-6 Is a Potential Prognostic Factor for Colorectal Cancer, including Stage II Patients. Gastroenterol Res Pract 2016: 9701574. https://doi.org/10.1155/2016/9701574

[75] Shimazaki J, Goto Y, Nishida K, *et al.* In patients with colorectal cancer, preoperative serum interleukin-6 level and granulocyte/lymphocyte ratio are clinically relevant biomarkers of long-term cancer progression. Oncology 2013; 84: 356-61. https://doi.org/10.1159/000350836

[76] Kwon KA, Kim SH, Oh SY, *et al.* Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer. BMC Cancer 2010; 14: 203. https://doi.org/10.1186/1471-2407-10-203

[77] Kim J, Lee J, Oh JH, Chang HJ, *et al.* Circulating Interleukin-6 Level, Dietary Antioxidant Capacity, and Risk of Colorectal Cancer. Antioxidants (Basel) 2019; 28: 595. https://doi.org/10.3390/antiox8120595

[78] Yu YL, Fan CW, Tseng WK, *et al.* Correlation Between the Glasgow Prognostic Score and the Serum Cytokine Profile in Taiwanese Patients with Colorectal Cancer. Int J Biol Markers 2021; 36: 40-49. https://doi.org/10.1177/17246008211022769

[79] Chang PH, Pan YP, Fan CW, *et al.* Pretreatment serum interleukin-1β, interleukin-6, and tumor necrosis factor-α levels predict the progression of colorectal cancer. Cancer Med 2016; 5: 426-33. https://doi.org/10.1002/cam4.602

[80] Yeh KY, Li YY, Hsieh LL, *et al.* Analysis of the effect of serum interleukin-6 (IL-6) and soluble IL-6 receptor levels on survival of patients with colorectal cancer. Jpn J Clin Oncol 2010; 40: 580-7. https://doi.org/10.1093/jjco/hyq010

[81] Li X, Wang Y, Han C, Li P, Zhang H. Colorectal cancer progression is associated with accumulation of Th17 lymphocytes in tumor tissues and increased serum levels of interleukin-6. Tohoku J Exp Med 2014; 233: 175-82. https://doi.org/10.1620/tjem.233.175

[82] Chung YC, Chang YF. Serum interleukin-6 levels reflect the disease status of colorectal cancer. J Surg Oncol 2003; 83: 222-6. https://doi.org/10.1002/jso.10269

[83] Yang Z, Li Y, Zhang K, *et al.* Combined detection of preoperative neutrophil to lymphocyte ratio and interleukin-6 as an independent prognostic factor for patients with non-metastatic colorectal cancer. J Gastrointest Oncol 2021; 12: 2838-2845. https://doi.org/10.21037/jgo-21-763

[84] Akhmaltdinova L, Sirota V, Zhumaliyeva V, *et al.* Inflammatory Serum Biomarkers in Colorectal Cancer in Kazakhstan Population. Int J Inflam 2020; 8: 9476326. https://doi.org/10.1155/2020/9476326

[85] Hidayat F, Labeda I, Sampetoding S, *et al.* Correlation of interleukin-6 and C-reactive protein levels in plasma with the stage and differentiation of colorectal cancer: A cross-sectional study in East Indonesia. Ann Med Surg (Lond) 2021; 23: 334-340. https://doi.org/10.1016/j.amsu.2021.01.013

[86] Bandara WMMS, Muhinudeen FT, Malaviarachchi S, *et al.* Potential of Pre-Operative Serum Interleukin-6 as a Biomarker for Colorectal Cancers. J Can Res Updates 2024; 13: 31-36. https://doi.org/10.30683/1929-2279.2024.13.05

[87] Guthrie GJ, Roxburgh CS, Richards CH, *et al.* Circulating IL-6 concentrations link tumour necrosis and systemic and local inflammatory responses in patients undergoing resection for colorectal cancer. Br J Cancer 2013; 9: 131-7. https://doi.org/10.1038/bjc.2013.291

[88] Thomsen M, Kersten C, Sorbye H, *et al.* Interleukin-6 and C-reactive protein as prognostic biomarkers in metastatic colorectal cancer. Oncotarget 2016; 7: 75013-75022. https://doi.org/10.18632/oncotarget.12601

[89] Kakourou A, Koutsioumpa C, Lopez DS, *et al.* Interleukin-6 and risk of colorectal cancer: results from the CLUE II cohort and a meta-analysis of prospective studies. Cancer Causes Control 2015; 26: 1449-60. https://doi.org/10.1007/s10552-015-0641-1

[90] Kaminska J, Nowacki MP, Kowalska M, *et al.* Clinical significance of serum cytokine measurements in untreated colorectal cancer patients: soluble tumor necrosis factor receptor type I--an independent prognostic factor. Tumour Biol 2005; 26: 186-94. https://doi.org/10.1159/000086951

[91] Koper-Lenkiewicz OM, Dymicka-Piekarska V, *et al.* The Relationship between Inflammation Markers (CRP, IL-6, sCD40L) and Colorectal Cancer Stage, Grade, Size and Location. Diagnostics (Basel) 2021; 31: 1382. https://doi.org/10.3390/diagnostics11081382

[92] Florescu DN, Boldeanu MV, Şerban RE, *et al.* Correlation of the Pro-Inflammatory Cytokines IL-1β, IL-6, and TNF-α, Inflammatory Markers, and Tumor Markers with the Diagnosis and Prognosis of Colorectal Cancer. Life (Basel) 2023; 27: 2261. https://doi.org/10.3390/life13122261

[93] Nikiteas NI, Tzanakis N, Gazouli M, *et al.* Serum IL-6, TNF-alpha and CRP levels in Greek colorectal cancer patients: prognostic implications. World J Gastroenterol 2005; 21: 1639-43. https://doi.org/10.3748/wjg.v11.i11.1639

[94] Rasic I, Rebic V, Rasic A, *et al.* The Association of Simultaneous Increase in Interleukin-6, C Reactive Protein, and Matrix Metalloproteinase-9 Serum Levels with Increasing Stages of Colorectal Cancer. J Oncol 2018; 30: 2830503. https://doi.org/10.1155/2018/2830503

[95] Eldesoky A, Shouma A, Mosaad Y, *et al.* Clinical relevance of serum vascular endothelial growth factor and interleukin-6 in patients with colorectal cancer. Saudi J Gastroenterol 2011; 17: 170-3. https://doi.org/10.4103/1319-3767.80378

[96] Oliveira Miranda D, Soares de Lima TA, Ribeiro Azevedo L, *et al.* Proinflammatory cytokines correlate with depression and anxiety in colorectal cancer patients. Biomed Res Int 2014; 739650. https://doi.org/10.1155/2014/739650

[97] Ognjanovic S, Yamamoto J, Saltzman B, *et al.* Serum CRP and IL-6, genetic variants and risk of colorectal adenoma in a multiethnic population. Cancer Causes Control 2010; 21: 1131-8. https://doi.org/10.1007/s10552-010-9540-7

[98] Li X, Wang Y, Han C, *et al.* Colorectal cancer progression is associated with accumulation of Th17 lymphocytes in tumor tissues and increased serum levels of interleukin-6. Tohoku J Exp Med 2014; 233: 175-82. https://doi.org/10.1620/tjem.233.175

[99] Popko K, Gorska E, Demkow U. Influence of interleukin-6 and G174C polymorphism in IL-6 gene on obesity and energy balance. Eur J Med Res 2010; 2(Suppl 2): 123-127. https://doi.org/10.1186/2047-783X-15-S2-123

[100] Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 2018; 15: 234-248. https://doi.org/10.1038/nrclinonc.2018.8

[101] McCollum SE, Shah YM. Stressing Out Cancer: chronic Stress Induces Dysbiosis and Enhances Colon Cancer Growth. Cancer Res 2024; 84: 645-647. https://doi.org/10.1158/0008-5472.CAN-23-3871

[102] Yamaguchi M, Okamura S, Yamaji T, *et al.* Plasma cytokine levels and the presence of colorectal cancer. PLoS One 2019; 18: 14: e0213602. https://doi.org/10.1371/journal.pone.0213602

[103] Chan AT, Ogino S, Giovannucci EL, *et al.* Inflammatory markers are associated with risk of colorectal cancer and chemopreventive response to anti-inflammatory drugs. Gastroenterology 2011; 140: 799-808, quiz e11. https://doi.org/10.1053/j.gastro.2010.11.041

[104] Wang WS, Lin JK, Chiou TJ, *et al.* CA19-9 as the most significant prognostic indicator of metastatic colorectal cancer. Hepatogastroenterology 2002; 49(43): 160-4.

[105] Gao Y, Wang J, Zhou Y, *et al.* Evaluation of Serum CEA, CA19-9, CA72-4, CA125 and Ferritin as Diagnostic Markers and Factors of Clinical Parameters for Colorectal Cancer. Sci Rep 2018; 8: 2732. https://doi.org/10.1038/s41598-018-21048-y

[106] Vukobrat-Bijedic Z, Husic-Selimovic A, Sofic A, *et al.* Cancer Antigens (CEA and CA 19-9) as Markers of Advanced Stage of Colorectal Carcinoma. Med Arch 2013; 67(6): 397-401. https://doi.org/10.5455/medarh.2013.67.397-401

[107] Lakemeyer L, Sander S, Wittau M, Henne-Bruns D, Kornmann M, Lemke J. Diagnostic and Prognostic Value of CEA and CA19-9 in Colorectal Cancer. Diseases. 2021; 9(1): 21. https://doi.org/10.3390/diseases9010021

[108] Chevinsky AH. CEA in tumors of other than colorectal origin. Semin Surg Oncol 1991; 7: 162-166.

[109] Stockley RA, Shaw J, Whitfield AG, *et al.* Effect of cigarette smoking, pulmonary inflammation, and lung disease on concentrations of carcinoembryonic antigen in serum and secretions. Thorax 1986; 41: 17-24.

[110] Go VL. Carcinoembryonic antigen: clinical application. Cancer 1976; 37(1 suppl): 562-566.

[111] Loewenstein MS, Zamcheck N. Carcinoembryonic antigen (CEA) levels in benign gastrointestinal disease states. Cancer 1978; 42(3 suppl): 1412-1418.

[112] Thomas D, Fourkala EO, Apostolidou S, *et al.* Evaluation of serum CEA, CYFRA21-1 and CA125 for the early detection of colorectal cancer using longitudinal preclinical samples. Br J Cancer 2015; 113: 268-274. https://doi.org/10.1038/bjc.2015.202

[113] Bormer OP: Standardization, specificity, and diagnostic sensitivity of four immunoassays for carcinoembryonic antigen. Clin Chem 1991; 37: 231-236.

[114] Tan E, Gouvas N, Nicholls RJ, *et al.* Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. Surg Oncol 2008; 18: 15-24. https://doi.org/10.1016/j.suronc.2008.05.008

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