Potential of Pre-Operative Serum Interleukin-6 as a Biomarker for Colorectal Cancers

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Abstract: The diagnosis of colorectal cancers (CRC) at its early stage is challenging due to lack of early markers. Current diagnostic tests are either invasive or show low sensitivity. Interleukins are known to elevate and play important roles in the development and progression of the CRC. The studies on interleukin profiles of CRC patients are mainly confined to Caucasian populations while South Asian data are sparse. Therefore, the aim of this study was to investigate the serum IL-6 and IL-10 levels in a cohort of Sri Lankan CRC patients and explore their potential to be used as markers for early diagnosis/prognosis of CRC. Blood samples from 35 CRC patients and 35 healthy volunteers were obtained after informed consent. Their clinical findings and carcinoembryonic antigen (CEA) levels were recorded. Concentrations of IL-6 and IL-10 were measured using ELISA according to manufacturer's protocols.

Mean serum [IL-6] was found to be significantly higher in CRC patients than controls ($p<0.05$). The mean [IL-10]showed no difference to that of controls. ($p>0.05$). Interestingly, the [IL-6] in CRC patients were correlated with the disease stage (Stage I-0.16pg/ml; stage II-7.01pg/ml; stage III-15.8pg/ml and stage IV-35.48pg/ml). CEA levels were not correlated with the disease stage or withIL-6 levels. This study provided preliminary evidence to use IL-6 as a potential biochemical marker for the diagnosis of CRC inaddition to CEA. Furthermore, IL-6 could be a marker for prognosis of CRC. Further studies with higher patient samples are needed to validate the results of this study.

Keywords: Colorectal cancer, Interleukin-6, Interleukin-10, Carcinoembryonic antigen, Biomarker, Diagnosis.

INTRODUCTION

Colorectal cancer (CRC) is a significant global health concern, ranking as the third most prevalent type of cancer and the fourth leading cause of cancer-related deaths. Its incidence is increasing, particularly among Asian and South Asian populations [1]. In 2020, there were 1.93 million new CRC cases reported worldwide, with 935,173 deaths attributed to CRC. Asia had the highest CRC incidence rate, accounting for 10.6% of all cases with cancers [2,3].

Colonoscopy and fecal occult blood test are widely used for CRC screening [4,5]. However, colonoscopy is invasive, and fecal occult blood test possess low sensitivity for polyps, especially for smaller ones [6]. Therefore, development of non-invasive diagnostic and prognostic biomarkers is critical for the early detection of CRC as well as in predicting prognosis and determining treatment interventions.

Currently, the glycoprotein carcinoembryonic antigen (CEA) is the mostly used non-invasive blood-based molecular marker for CRC [7-9]. Despite the widespread use in monitoring CRC, CEA has various limitations, including its negative expression in approximately 20% of CRC tumors [10,11]. CEA levels may also be elevated in various non-malignant conditions and other malignancies [12-14]. Additionally, some patients with CRC do not give higher values of CEA and for the CEA negative cohort there is no serological test available to assess the disease status. These lackings highlight the need for new biomarkers which may be used concurrently with CAE in diagnosis /prognosis of CRC.

Interleukin-6 is an inflammatory cytokine that plays a pivotal role in the pathogenesis of CRC [15]. Overexpression of IL-6 within CRC tissues has been observed and its pathological role in CRC has been suggested by many researchers [16-18].It facilitates cancer cell proliferation, angiogenesis and progression [19-22]. Interleukin 10 (IL-10) is an anti-inflammatory cytokine which increases over time during CRC progression [23,24]. High preoperative serum levels of IL-10 have shown correlation with poor survival of CRC patients [25].

The above literature highlights the importance of these molecules in the development and progression of the CRC. However, the concentrations of these cytokines in blood have been investigated in a few studies confined to Caucasian populations and are not being used in clinical practice. None of the studies up to date have investigated the serum levels of these cytokines in South Asian populations. Therefore, the aim of this study was to fill the gap in the current

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literature by investigating the serum levels of IL-6 and IL-10 in a cohort of Sri Lankan patients. This may help in exploring their potential as markers for early diagnosis/prognosis of CRCs.

MATERIALS AND METHODS

Patient Recruitment

A total of thirty five colorectal cancer patients were recruited from the University Hospital of General Sir John Kotelawala Defence University (UHKDU) and National Cancer Institute (NCI), Sri Lanka between January 2021 and February 2022. Patients under 18 years of age, patients who had received any treatment for colorectal cancer or had other cancers, patients with chronic diseases (such as diabetes), immune diseases, cardiovascular diseases or cerebrovascular diseases were excluded. The control group consisted of thirty five healthy volunteers with no comorbidities or family history of malignancy who were registered at the Blood Bank of UHKDU. Informed written consent of patients and controls was obtained prior to their participation in the study. This study was conducted in adherence to the principles outlined in the 2014 Helsinki Declaration [26], and ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, General Sir John Kotelawala Defence University. Patients and volunteers were recruited only after obtaining written informed consent.

Sample Collection and Serum Separation

Demographics and relevant clinical data were recorded. Peripheral venous blood samples (3-5 mL) were collected from patients (n=35) and controls (n=35) and transported in plain tubes containing no anticoagulants,to the laboratory at 4^0C. Samples were collected from patients prior to any form of treatment at the time of diagnostic blood sampling. Blood samples from healthy blood donors were obtained for the control group. Blood samples were centrifuged within 30-60 minutes at 1000 g for 15 minutes in a refrigerated centrifuge to separate serum. Serum samples were collected and stored in pyrogen-free plastic microcentrifuge tubes at – 80^0C until the diagnosis of CRC is confirmed to proceed with analysis. Samples were stored with a code instead of the participant's name.

Enzyme-Linked Immunosorbent Assays for IL-6 and IL-10

Serum IL-6 and IL-10 cytokine levels of patients and controls were analyzed using a commercial Enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, USA). The assay was performed according to the manufacturer's protocols. The standard and all samples were assayed in duplicate. Readings were taken at a wavelength of 450 nm using an ELISA microplate reader. Analyses of some samples were not possible due to the lack of adequate sample volumes. The serum concentrations of CEA were obtained from the patient's laboratory reports.

Statistical Analysis

t-test was used to investigate if there is a significant difference between serum CEA IL-6 and IL-10 levels of patient and control groups. P values <0.05 were considered statistically significant.The correlation was calculated to understand the relationships between CEA and IL-6 levels, CEA and the stage of the disease and IL-6 and the stage of the disease. All statistical analyses were performed using IBM SPSS Statistics for Windows (Armonk, NY, USA) version 28.

RESULTS

Demographic and Clinical Characteristics

Patient characteristics, tumor characteristics and pre-operative blood test findings are summarized in Table **1**. Four patient samples and seven control samples were excluded from analysis due to inadequate serum volume. The mean age of patients (n=31) was 65 years, and majority of them were males (61.29%).The mean age of the control group (n=28) was 31 years. Tumors have beenclassified according to the 8^{th} edition of the American Joint Committee on Cancer (AJCC) staging system with the aid of radiological images. Mean tumor size was 4.89 cm (1.40 -9.00 cm) and majority of tumors were left sided (77.42%), moderately differentiated (64.52%), stage III (48.39%) and were adenocarcinomas (90.32%).

Serum IL-6 and IL-10 Levels

Mean IL-6 concentration of the patient group(26.67 pg/ml)was significantly higher than that of controls (8.35 pg/ml) ($p < 0.05$). There was no significant difference between the [IL-10] serum levels of CRC patients and the control group ($p > 0.05$). No significant difference was observed in the IL-6 or IL10 serum levels of smokers and non-smokers ($p > 0.05$).

Relationship between Serum IL-6 and CEA Levels

The mean concentration of CEA was 41.6 ng/mL in this patient cohort. When data was analysed to see if

Table 1: Demographic and Clinical Characteristics of Subjects

Variables		Patients (P) (n=31)	Controls (C) (n=28)
Age		65 (41-89 yrs)	31 (22-50 yrs)
Gender	Male	19 (61.29%)	20 (71.43%)
	Female	12 (38.71%)	8 (28.57%)
Histology	Adenocarcinoma	28 (90.32%)	
	Signet ring cell carcinoma	1 (3.23%)	
	Not available	2 (6.45%)	
Stage	I	0 (0.00%)	
	II	3 (9.68%)	
	III	15 (48.39%)	
	IV	4 (12.90%)	
	Not available	9 (29.03%)	
Grade	Well-differentiated	1 (3.23%)	
	Well to moderately differentiated	1 (3.23%)	
	Moderately differentiated	20 (64.52%)	
	Poorly differentiated	1 (3.23%)	
	Not available	8 (25.81%)	
Tumor Location	Right sided	3 (9.68%)	
	Left sided	24 (77.42%)	
	Transverse colon	2 (6.45%)	
	Not available	2 (6.45%)	
Tumor size (cm)		4.89	
Mean IL-6 (pg/mL)		26.67	8.35
Mean IL-10 (pg/mL)		2.46	2.45
Mean CEA (ng/mL)		41.6	
Selected Blood Parameters	Mean Hb (g/dL)	10.31	
	Mean Platelet ($X10^9$/L)	348.80	
	Mean RBC ($X10^{12}$/L)	4.23	
	Mean WBC ($X10^9$/L)	9.57	
Liver Function Tests	Mean ALT (U/L)	21.24	
	Mean AST (U/L)	24.04	
	Mean ALP (U/L)	137.70	
	Mean GGT (U/L)	36.10	

there is a correlation between [CEA] and [IL6], it was found that the correlation was not significant (r^2=0.10). Any correlation between CEA and IL10 levels was also not observed.

Correlation between Serum IL-6 / IL-10 Levels and Clinical Findings

The serum [IL-6] concentrations observed in different CRC stages were: stage I: 0.16pg/ ml; stage II: 7.01pg/ ml; stage III: 15.8pg/ ml, and stage IV: 35.48pg/ml. Interestingly, the serum IL-6 level was significantly correlated with the disease stage (r = 0.52, p = 0.0136) and degree of metastasis (r = 0.43, p = 0.0379). However, the analyses revealed that the serum IL-6 levels are not significanly associated with other clinical findings such as hemoglobin, liver enzyme concentrations or the tumor size. Furthermore, there was no correlation between IL-10 levels with the disease satge or any other clinical finding.

Correlation Between Serum CEA Levels and Clinical Findings

CEA levels were not significantly associated with any of the following; disease stage, hemoglobin, liver enzyme levels or thetumor size.

DISCUSSION

Most CRC are diagnosed at later stages of the disease due to the lack of precise molecular marker. Therefore, identification of early molecular markers of CRC is vital for early treatments to reduce the mortality rates. This study was conducted to investigate the IL-6 and IL-10levels in a cohort of South Asian patients with CRC and to evaluate their potential to be used as diagnostic and prognostic markers for CRC.

Interleukins are emerging as novel molecular drivers in CRC development and progression [15-18, 23-24]. Thus, they could be used as markers in diagnosing and predicting prognosis of CRC. Research data on interleukin profiles of CRC patient populations are mainly confined to the Caucasian populations. Therefore, more and more data from different populations are needed to substantiate the current findings which will enable ILs to be used as molecular markers for CRC.

In this study, we demonstrate that IL-6 could be a useful diagnostic and prognostic marker for CRC to be used along with CEA. The observed mean IL-6 level of CRC patients in this cohort was significantly higher than that of control group. Similar observations have been reported by Shigaet *et al*. with significantly increased expression of IL-6 in patients with CRC. Elevated IL-6 levels in both serum and tumour tissue itself have been reported by many other groups [27-30].

Our data shows a strong correlation between the mean [IL-6] and the stage of the disease (stage I vs IV: 0.16pg/ ml vs 35.48pg/ml stage). Consistent findings have been reported previously. High levels of IL-6 have shown to be correlated with advanced stages of CRC [31]. In line, Kaminska *et al*., has reported a significant increase in serum IL-6 levels in advanced tumor stage of CRC and the levels have shown reduction on the 10^{th} day following surgery [32]. Moreover, Belluco *et al.* reports that patients with stage III and stage IV CRC had a significantly higher IL-6 serum concentrations than those with stage I and stage II disease [33].

CEA is currently in clinical practice in the routine diagnosis of CRC. Significantly elevated CEA levels were observed in our patient group compared to the control group ($p<0.05$). However, in contrast to the previous findings, the CEA levels in our study showed no correlation with the disease stage or other clinical findings [34]. Some studies have shown that serum CEA level is higher in advanced stages of CRC [34,35]. Hence, our data is in favor of assessing IL-6 levels in CRC patients along with CEA in routine diagnostic work up particularly when predicting the prognosis.

Some studies show a positive correlation between serum IL-6 and CEA levels [33,36]. However, we did not find a correlation between IL-6 and CEA levels in this patient cohort. Consistent observations have been reported by Goydos *et al*. [37].

In our study no significant difference was found in IL-10 serum levels between patients and controls. Previous studies report higher serum levels of IL-10 in advanced stages of CRC [38, 39], while others do not report such association [40]. Abtahi *et al.* have reported that higher IL-10 levels are associated with poor prognosis [39].Though our data does not demonstrate a significance of IL-10 in CRC diagnosis or prognosis, the potential of IL-10 as a marker in CRC needs more investigation.

CONCLUSIONS

Overall, our results shed light on IL-6 as a potential candidate interleukin marker for CRC which needs validation with higher sample numbers. Herein we suggest IL-6 could be used along with CEA in the diagnosis and prognosis of CRC.

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CONFLICT OF INTEREST

The authors have no financial or non-financial competing interests to declare.

AUTHOR CONTRIBUTIONS

W M M S Bandara: concept, design, definition of intellectual content, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. F T Muhinudeen: literature search, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation. S L Malaviarachchi: concept,

clinical studies, manuscript editing and manuscript review**.** A J I S Rathnayake: concept, design, definition of intellectual content, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review

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