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COMPARISON OF SERUM CONCENTRATIONS OF INTERLEUKIN-8 AND CARCINOEMBRYONIC ANTIGEN IN A SOUTH ASIAN COHORT OF PATIENTS WITH COLORECTAL CANCER

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Abstract – *Objective:* *Colorectal cancer (CRC) is the third most common cancer type in the world. Carcinoembryonic antigen (CEA) is widely used as a marker for CRCs. Interleukin-8 (IL-8) is a pro-inflammatory cytokine noticeably up-regulated in CRCs. Research have been conducted in different populations to investigate the CEA and IL-8 levels in CRCs and to elucidate their correlation with clinical findings. However, data on Sri Lankan CRC patients are sparse; none reports the CEA or IL-8 levels or their correlations with clinical findings. The objective of this study was to compare the CEA and IL-8 levels in a cohort of CRC patients.*

Patients and Methods: *Blood samples from forty patients with CRCs and thirty-five healthy volunteers were obtained after informed consent. Their clinical findings and CEA values were recorded. The concentrations of IL-8 were measured using enzyme-linked immunosorbent assay (ELISA). The mean values of IL-8 levels in patients and the control group were compared and the data were analysed to evaluate if there is a correlation between CEA and IL8 levels.*

Results: *At the time of diagnosis, most of the tumors were moderately differentiated (83%) and the average tumor length was 4.4 cm. The tumor location was mostly left-sided (88.7%). Mean CEA level was 21.3 ng/dl at the diagnosis. Mean [IL-8] in patients was 38.16 pg/ml and was higher than that of controls (33.67 pg/ml). However, the difference was not statistically significant ($p > 0.05$). Additionaly, a strong positive correlation between [CEA] and [IL8] was not observed ($r=0.19$).*

Conclusions: *This study shows that most of the CRCs are diagnosed at moderately differentiated stage with high CEA values. The results of this study are in favor of using CEA as a diagnostic marker. It provided no evidence of a correlation between high CEA and IL-8. Even though not significantly different from that of controls, elevated IL-8 could be a potential marker for CRCs which needs further validation by higher sample numbers.*

KEYWORDS: *Carcinoembryonic antigen, Colorectal cancer, Diagnostic marker, Interleukin-8.*

INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer, affecting 1.80 million people in the world per year[1]. It has been identified as the fourth most common cause of cancer-related deaths[1]. The age-standardized global incidence rate of CRC is higher in men (20.6 per 100,000 individuals) than in women (14.3 per 100,000)[2]. The prevalence of CRCs is reported to be higher in Caucasian populations; however, this burden is currently shifting towards low-income and mid-

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dle-income populations in Asian countries due to fast urbanization and lack of healthy life style[3]. Furthermore, the incidence of CRC is rising at younger ages (< 50 years)[4].

Diagnosis of CRCs at early stage is crucial for treatment outcome and survival[5]. It has been observed that more than one-third of patients are diagnosed when CRCs have already spread to the lymph nodes. One out of five patients is diagnosed with metastatic CRCs. The present clinical examinations such as colonoscopy and fecal occult blood test are widely used for CRC screening[5,6]. However, these tests have an array of limitations. Colonoscopy is an invasive and fecal occult blood test screening suffers for its low sensitivity for polyps and depends on the size of the polyp[7]. Therefore, development of non-invasive diagnostic and prognostic biomarkers is vital for early identification of CRCs which can significantly reduce the morbidity and mortality of CRCs.

Tumour markers secreted into the circulation by tumour cells have been used as markers for the diagnosis of different cancers. Currently, the glycoprotein, carcinoembryonic antigen (CEA) is used as a non-invasive blood-based molecular marker for the diagnosis of CRCs[8]. In addition to tumor markers, abnormal levels of cytokines produced due to the aberrations in the signaling pathways of cancer cells are known to be inflammatory mediators that determine both pro-tumorigenic and anti-tumorigenic signals within the tumour environment[9,10]. Both systemic and local changes in cytokine profiles have been observed in CRCs[11]. Interleukins are types of cytokines, which have been identified to play a role in tumorigenesis, angiogenesis, cancer cell invasion and metastasis of CRCs [12].

Interleukin-8 (IL-8) is an inflammatory cytokine that is mainly produced by macrophages, T cells, B cells and plays a vital role in the inflammatory response of cells[13]. Up-regulation of IL-8 expression has been observed in CRC patients[14]. *In vitro* experiments conducted on CRC cell lines have shown that IL-8 promotes tumour growth, cell proliferation, angiogenesis, metastasis and chemoresistance[15]. IL-8 influences the growth and invasion of CRC cells through various mechanisms.

IL-8 signifies a strong prognostic factor in CRC and has the potential to be used in prognostic assessment of CRCs as well as in determining therapeutic strategies in CRC patients [16].

Studies on tumor markers in CRCs have been confined to Caucasian populations and data on South Asian populations are sparse. Therefore, it is worth to assess the potential biomarkers for CRCs which have not been evaluated adequately in South Asian populations. The aim of this study was to evaluate and compare the concentrations of serum IL-8 and CEA levels in a cohort of Sri Lankan CRC patients and to understand the potential of IL-8 as a non-invasive biomarker for CRCs.

PATIENTS AND METHODS

Patient selection

Forty patients with CRCs reported to the University Hospital of General Sir John Kotelawala Defence University (UHKDU) and National Cancer Institute (NCI), Sri Lanka during the period of January 2021 to December 2021 were recruited for the study. This study was conducted in accordance with the Declaration of Helsinki and the ethical clearance was obtained from the Ethics Review Committee of the Faculty of Medicine, General Sir John Kotelawala Defence University. Permission was obtained from oncologists and oncological surgeons of respective hospitals to recruit their patients. Patients and volunteers were recruited only after written informed consent. Patients who were not able to provide written informed consent, patients under 18 years of age, patients who have undergone treatment for colorectal cancer (surgery/chemotherapy/radiotherapy) and patients with other cancers, chronic infections, HIV, chronic diseases, diabetes, immune disease, cardiovascular and cerebrovascular disease were excluded. The control group consisted of thirty-five healthy volunteers with no comorbidities and family history of malignancy, who visited the Blood Bank of UHKDU.

Samples

Demographic and relevant clinical data were recorded. Whole blood samples (3–5 mL) were collected form 40 patients and 35 controls in plain tubes containing no anticoagulant and transported to the laboratory at 4°C. Samples were obtained at the time of diagnostic/follow up blood sampling and from the blood donation campaign in the control group. Serum was separated by centrifugation at 1000xg for 15 minutes in a refrigerated centrifuge and stored at -80°C until use. Serum was analyzed after histology was confirmed. The samples were stored with a code assigned to it instead of the participant's name.

Enzyme-linked immunosorbent assays

All serum samples were removed from –80°C and left to thaw on ice at room temperature before analysis. Serum IL-8 of patients and controls were analyzed using commercial enzyme-linked immunosorbent assay (ELISA) kits (Elabscience,

USA). The assays were performed according to the manufacturer's instructions. All samples were tested in duplicates. The serum concentrations values 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 the serum [IL-8] in patients and the control group. *p*-values less than 0.05 were considered to be statistically significant. The correlation was calculated to understand the relationship between CEA and IL8 levels. A correlation of CEA levels with degree of differentiation was also analyzed. To investigate if the CEA levels are influenced by smoking/tobacco use, the mean CEA levels of smokers (n=9) and non-smokers (n=31) were compared. All statistical analyses were performed using IBM SPSS Statistics for Windows (Armonk, NY, USA) version 28.

RESULTS

Demographic characteristics

The mean age of the patients recruited to this study was 64 years (41-82 years) and that of controls was 32 years (24-50 years). Majority of the patients were males (68%). Demographic and clincal data are shown in Table 1. The tumors were mostly left sided (85.7%), moderately differentiated (71.4%) and were adenocarcinomas (91.4%). Most of the tumors were at stage III (51.4%), while 17.1% were advanced stage IV tumors.

Serum CEA and IL8 Concentrations

Mean CEA cencentration of this patient cohort showed high [CEA] with in 21.3 ng/dl. The mean concentration for IL-8 was 38.16 pg/ml (n=40) and it was higher than that of controls: [IL-8] = 33.67 pg/ml (n=35). There was no significant difference between the [IL-8] of CRC patients and the control group ($p > 0.05$). When data was analyzed to see if there is a correlation between CEA and IL8 it was found that the correlation was not significant(r=0.19). The results showed no significant difference ($p > 0.05$) in CEA levels of smokers (12.68 ng/dl) and non-smokers (23.05 ng/dl).

DISCUSSION

The present study was conducted to compare the CEA and IL-8 levels of a cohort of patients with CRCs to determine their potential to be used as diagnostic and prognostic evaluators in CRCs. Most CRCs are diagnosed at later stages of the disease and identification of early markers of CRCs is vital to reduce the associated motility rates. Among markers of CRCs, CEA holds a prime position and is used

TABLE 1. Demographic and clinical characteristics of patients.

Variables		*Patients (P)*	*Controls (C)*
	Age (Years)	41-82	24-50
	Mean	65 +/- 11	32 +/- 7
Gender	Male	24 (68.6%)	25 (71.5%)
	Female	11 (31.4%)	10 (28.5%)
Histology	Adenocarcinoma	32 (91.4%)	
	Singlet-ring cell carcinoma	1 (2.86%)	
	Not available	2 (5.71%)	
Grade	Well-differentiated	3 (8.6%)	
	Moderately differentiated	25 (71.4%)	
	Not available	7 (20%)	
Location	Right sided	3 (8.57%)	
	Left sided	30 (85.7%)	
	Transverse colon	2 (5.71%)	
Stage	I	1 (2.9%)	
	II	3 (8.5%)	
	III	18 (51.4%)	
	IV	6 (17.1%)	
	Not available 7	(20%)	
Mean CEA		21.3 ng/dl	
Mean IL8	38.16 pg/ml		33.67 pg/ml

in the diagnosis of CRCs. With emerging evidence from research done on Caucasian populations, the inflammatory cytokine, IL-8 could be considered as a potential marker elevated in CRCs. However, data on CEA and IL-8 levels in CRC patient populations of the South Asian region is scarce.

Development of CRCs is multifactorial. Mutations in the key genes in the cell cycle, cell signaling, and epigenetic mechanisms have been identified in CRCs. *KRAS* mutations are found in 35%-45% of CRC cases[17]. A positive correlation has been observed between the presence of *KRAS* mutations and increased CEA levels in CRC patients[18]. Microsatellite instability has been reported in 10–20% of CRC patients[18]. In addition to the genetic aberrations, other factors such as nutritional deficiencies, obesity, smoking, use of excessive alcohol and sedentary lifestyle are known to play key roles in the development of CRCs[19]. Metabolic syndrome is also known to be associated with increased prevalence of CRCs[20]. In this regard reduced BMI has been shown to reduce the risk of CRCs [19,21]. Excess body fat have shown to induce a pro-inflammatory response and increases the risk of CRCs[20].

Once developed assessing prognosis is equally important as early diagnosis to better treat the CRCs. Among multiple factors, tumor stage is still regarded as the most important prognostic factor in CRCs[22]. Tumor budding and tumor border configuration have also been considered as additional morphological features of CRC prognosis[23]. At molecular level, presence of certain genetic aberrations has shown to be prognostically unfavorable. Microsatellite instability has appeared as an adverse predictive factor to adjuvant chemotherapy. Mutations in the *KRAS* and *BRAF* genes are known prognostic and predictive biomarkers in metastatic CRCs treated with cetuximab and panitumumab[24-26]. *BRAF* mutation has been significantly associated with females, right-sided tumours, older age and high grade[27-30]. The presence of mutant *BRAF* is known to delay the response to panitumumab or cetuximab[30].

The cytokine, transforming growth factor beta (TGF-β) has been identified as an indicator in the prognosis of CRCs. TGF-β levels have shown a positive correlation with tumor size, differentiation, and invasion of the advanced CRCs[28,29].

It has been shown that average overall survival (OS) of CRC patients for 1-year is 74.6%, while 5-year and 10-year is 43.8% and 33.0% respectively[30]. The OS of CRC patients is determined by the sex, age at diagnosis, local site of tumor and the stage. Clinical parameters such as elevated levels of lactate dehydrogenase, white blood cell, serum albumin, liver transaminases, haemoglobin, platelets are used as predictive markers for OS[31].

For years, CEA has been serving as a diagnostic marker for CRCs. CEA is a complex glycoprotein present in 90% of colorectal cancers which contributes to the malignancy of CRCs[32]. [CEA] of >2.41 ng/mL has been suggested as the cut off value for the diagnosis of CRCs[33]. In addition, the preoperative CEA measurements are routinely used in CRC patients to predict the spread of the disease[34]. Inline with previous findings, more than 82.5% of the patients in our cohort had CEA levels >2.41 ng/mL. This result highlights the importance of the usage of CEA in the diagnosis of CRCs.

Previous studies support the utility of pre-operative CEA levels as a factor for prognostic and prediction of OS[34,35]. In addition, determination of CEA before resection is important in the assessment of postoperative surveillance[36]. An elevated preoperative CEA suggests that the marker would be useful for surveillance. It is recommended that serum CEA levels should be evaluated every 3 months for at least 3 years after the diagnosis in patients with stage II or III CRCs[36]. CEA is also used for monitoring the disease during systemic therapy[37]. However, as a prognostic factor, CEA has shown controversial findings. Some studies have indicated that CEA level in serum tends to be higher in well-differentiated CRCs than poorly differentiated CRCs[38,39], while some support the idea that there is no correlation between the CEA levels and the differentiated stage of CRCs[40]. Supporting the latter, the results of our study showed that there is no correlation between the CEA levels and the stage of differentiation of the CRC. Apart from the controversial findings, CEA as a marker has other drawbacks: it has been found that CEA levels can be increased by many other factors such as use of tobacco[38], emphasizing the importance of identifying novel markers for CRCs. However, no correlation was observed between elevated CEA levels and smoking among our patients' cohort ($p<0.05$).

Emerging research identifies cytokines as potential candidates to be used as markers in the diagnosis, prognosis and predicting overall survival of CRCs. IL-8 is a neutrophil chemotactic factor, produced by immune cells as well as tumor cells[41]. It is classified as a member of the neutrophil-specific CXC chemokine family and plays a key role in the initiation and amplification of inflammatory processes. The pathophysiology of cancers now attributes significant roles to inflammatory processes. It is well known that cancer cell proliferation, invasion and metastasis in CRCs are promoted under inflammatory conditions[42].

IL-8 has been reported to be correlated with the initiation and development of CRCs[43]. In addition, IL-8 is known to play a role in angiogenesis

and apoptotic resistance in CRC via activation of CXCR1/2, Akt and MAPK signaling pathways[44]. This study clearly observed an increase in the [IL-8] in CRC patients compared to that of controls. However, the difference was not significant (p<0.05). This result is partly on par with the previous investigations[45], but not strong enough to recommend IL-8 as a biomarker for CRCs. However, the clear difference in [IL-8] in patients of CRCs than controls leave the potential of IL-8 as a candidate biomarker for CRCs which needs further validation by higher sample numbers.

CONCLUSIONS

This study shows that most of the CRCs are diagnosed at the moderately differentiated stage with high CEA values. The findings of this study are in favor of using CEA as a diagnostic marker but provide no evidence of a correlation between high CEA and IL-8 levels. Though not significantly different from that of controls, elevated IL-8 could be a potential marker for CRCs which needs further validation by higher sample numbers.

Ethical standards:

This study was conducted according to Declaration of Helsinki together with the ethical clearance obtained from the Ethics Review Committee of the Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka.

Informed consent:

A written informed consent was obtained from all the subjects before obtaining the blood samples.

Availability of data and materials:

Data are available. The confidentiality of the patients is maintained.

Conflict of interest:

The authors declare that they have no conflict of interest.

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Author contributions:

W M M S Bandara: conceptualization, data analysis and manuscript preparation. F T Muhinudeen: conducting experiments. A J I S Rathnayake: conceptualization, data analysis and manuscript preparation. S L Malaviarachchi: conceptualization and patient recruitment.

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