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ORIGINAL ARTICLE

THE LEVELS OF C-REACTIVE PROTEIN AND ALPHA -1ANTITRYPSIN IN SERA OF PATIENTS WITH GASTROINTESTINAL CANCERS DURING DIAGNOSIS

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ABSTRACT: Although new approaches to the early detection of cancer are continually improving, still many patients come to the health centres when the disease has become incurable. For this reason early diagnosis is crucial. Biochemical tumor markers have been attracting more and more attention in the diagnosis of malignant diseases. Acute phase reactant proteins such as C-reactive protein (CRP) and Alpha-l antitrypsin (AIAT) have been considered as biochemical tumor markers useful at initial diagnosis, staging, and monitoring of cancer diseases after surgery. A significant increase of CRP and A1AT was found in the initial stages of gastrointestinal cancer groups as compared to healthy blood donors. The concentration progressively increases with increasing severity of cancers. The aim of present study was to find the usefulness of estimation of CRP and A1AT in the early diagnosis of gastrointestinal cancers. CRP was measured by latex turbidimetry method and A1AT by turbidimetry method. Statistical analyses was done using SPSS version 10.0 (SPSS Inc., USA) and MedCalc. The levels of serum CRP and A1AT can easily be determined prior to the treatment in the patients with gastrointestinal cancers. The findings were useful in the early diagnosis of gastrointestinal cancers and in complex preoperative diagnostic procedure to estimate the advanced stage of disease initially, suggesting an opinion about the treatment of patients who had not underwent any therapeutic procedure yet.
KEYWORDS: Gastrointestinal cancers, CRP, A1ATU.

INTRODUCTION

C-reactive protein (CRP) is a critical component of the immune system that our bodies make when faced with a major infection or trauma, its level rise dramatically during inflammatory processes occurring in the body. It plays an important role in innate immunity, as an early defence system against infections. CRP is used mainly as a marker of inflammation and infection. Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments (Jain *et al.,* 2011). CRP appears after an injury, infection, or inflammation and disappears when the injury heals or the infection or inflammation goes away (Fleming and Monte, 2004). The inflammation signalled by CRP is influenced by genetics, sedentary lifestyle, too much stress, and exposure to environmental toxins such as second hand tobacco smoke. Diet has a huge impact, particularly one that contains a lot of refined, processed and manufactured foods (Weil, 2013). Chronic systemic inflammation is an underlying cause of many diseases such as atherosclerosis, cancer, obesity, digestive system diseases etc. Inflammatory bowel disease (IBD) characterizes a range of chronic ailments affecting the digestive tract. It has been known to be a serious and life-long condition affecting many young people between the ages of 15 and 25 years old (Vermeire *et al.,* 2005). Ulcerative colitis (UC), a disease that has become relatively stabilized among people, and a second form, Crohn's disease (CD) have been determined to be steadily escalating by the researchers (Isaacs *et al.,* 2005). UC inflames the mucosal lining of the colon, affecting it in a continuous way, while CD distresses the entire gastrointestinal tract from the mouth to the anus in a discontinuous, transmural manner described as "cobblestone" (Angerio *et al.,* 2005). Recent research has associated the presence of IBD with the elevation of C-reactive proteins (CRP). An increased CRP level measurement is direct evidence that the body has started to mobilize its defences (Mazlam and Hodgson, 1994). Its role as an indicator of the disease corresponds directly with its presence in simultaneously inducing and inhibiting inflammation (Aqbal *et al.,* 2007). CRP is produced in hepatocytes as a

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systemic response to the cytokines released from leukocytes infiltrating within the tumor microenvironment, in particular IL-6. IL-6 indirectly influence the binding of CRP to phospholipids on tumor cells, activating the classical C1q pathway of the complement system acting as an opsonin, which may sometimes lead to tumor cell lysis. Thus, CRP is not only a response to the tumor microenvironment, but it may also contribute to disposing of the tumor cell whether it is alive or dead (Chang *et al.,* 2009). C-reactive protein (CRP) is a representative marker for inflammatory conditions, in many cancers, it has been reported that chronic inflammation is involved with malignant change, and the risks of cancer are increased when pre-diagnostic CRP levels are high (Erlinger *et al.,* 2004).

A1AT is a 52-kDa serpin, in medicine, it is considered as the most prominent serpin. The terms α_1-antitrypsin and Protease inhibitor (P_i) are often used interchangeably. Several means by which A1AT plays role in malignancy and inflammations have been proposed so far: In equilibrium hypothesis it is assumed that changes in the ratio of a particular protease to its cognate inhibitor account for the increased potential of tumor formation (El-Akawi *et al.,* 2008). Neutrophil elastase and A1AT constitute a pair including protease and protease inhibitor counterpart which are in equilibration. Perturbation of this equilibration causes tissue damage and provides a favourable environment for carcinogenesis and tumor progression. The finding of a high serum concentrations of protease inhibitor even in the advanced stage of cancer at first glance was paradoxical, since inhibitors such as A1AT are supposed to counteract the destructive activity of proteolytic enzymes (e.g. trypsin). However, it became clear that the role of protease inhibitors is rather complex and that, in most types of cancers, they play important role in modulating the dynamics of the proteolysis, in which proteases, inhibitors, regulators, cytokines and growth factors interact with each other (Andolfatto *et al.,* 2003).

Peracaula *et al.,* (2010) suggested that acute-phase proteins might play important role as sensor of diseases. Both level of acute-phase protein and glycosylation have reported to be altered in the inflammation and other diseases including cancer. Factors that promote acute phase protein synthesis and enhance the expression of specific glycosyltransferases, such as sialyltransferases and fucosyltransferases, may be up-regulated in some tumors which could explain the changes in acute-phase proteins level and specific *N*-glycosylation modifications of some acute-phase proteins in cancer. Hence the present study aims to assess the role of acute phase proteins (CRP &A1AT) in diagnosis of gastrointestinal cancers to predict and evaluate the disease in terms of its presence, severity, and therapeutics.

MATERIAL AND METHODS

2.1. Clinical data

The subjects included 150 patients suffering from esophageal, gastric, and colon cancer diagnosed by endoscopic examination and biopsy and who have not previously received any anticancer therapy. Fifty healthy subjects with no cancer comprised the normal control group.

The hematological and biochemical profile of each cancer patient and each healthy subject was evaluated. All patients and healthy control subjects were recruited from the Department of Radiotherapy, SMS Medical College and Hospital, Jaipur from July 2011 to December 2012. This study was approved by the Ethics Committee and the institutional research committee of the hospital. Written informed consent was obtained from all patients and healthy subjects.

2.2. Inclusion criteria

Healthy subjects were identified as individuals not suffering from any physical ailment or acute illness, not hospitalized for any disease in the past two years, and not addicted to smoking, tobacco, or alcohol consumption. Patients were identified as individuals suffering from esophageal, gastric, and colon cancers currently diagnosed by endoscopic examination and biopsy and who have not previously received any anticancer therapy.

2.3. Exclusion criteria

Healthy subjects with any type of gastrointestinal infections, acute illness, recent hospitalization, or addiction to smoking, alcohol, or tobacco are excluded from this study. Cancer patients who have received radiotherapy, chemotherapy or surgery were excluded.

2.4. Study design

2.4.1. Clinical history

Each patient was first examined by obtaining a brief clinical history related to diet, lifestyle, initial symptoms, or any previously received treatment.

The patients and healthy subjects were categorized as follows:

Group 1: 50 normal healthy subjects; Group 2: 50 patients with esophageal cancer; Group 3: 50 patients with gastric cancer; Group 4: 50 patients with colon cancer.

During initial diagnosis of cancer clinician viewed reports of biopsy, upper gastrointestinal radiographs, colonoscopy, fibre optic esophagoscopy, gastroscopy, computed tomography, chest X-ray, ultrasonography *to assess primary and metastatic tumours.*

2.4.2. Sample Collection

Blood samples were collected prior to administering any therapy in gastrointestinal cancer patients and as part of a routine investigation in healthy subjects. The samples placed in a plain vial were allowed to clot. Serum was separated by centrifugation at 3,485 *g* for 10 min and stored at –20 °C until further assay was performed.

*CRP was estimated by latex turbidimetry method and *A1AT was estimated by turbidimetry method.

Reference values:

CRP values up to 5 mg / l for healthy men and women; A1AT New born: 124-348 mg/dl, Adults: 90-200 mg/dl.

2.5. Data analysis

Data were analyzed using SPSS version 10.0 (SPSS Inc., USA) and MedCalc to estimate the significance of the observed differences and calculate the percentage.

RESULTS AND DISCUSSION

Mean serum value of CRP & A1AT were given in Tables (1A) and (1B) and Figure (1) in esophagus, gastric and colon cancer patients as compared to healthy control subjects.

Table 1: Statistical evaluation of serum CRP & A1AT in healthy control subjects and gastrointestinal (esophagus, gastric and colon) cancer patients before therapy. **1A)** Mean ± SD of serum CRP&A1AT in healthy control subjects and gastrointestinal (esophagus, gastric and colon) cancer patients before therapy

	C-reactive protein Mean±SD (Range)	%P	%N	Alpha-1antitrypsin Mean±SD (Range)	%P	%N
Control	3.98±0.85 (2.1-4.9)			141.35±33.86 (91.5-199.1)		
Esophagus	19.10±18.89 (2.8-68.5)	62%	38%	190.95±79.67 (103.1-356.8)	26%	74%
Gastric	16.65±18.31 (2.1-71.7)	46%	54%	181.17±74.29 (90.8-352.2)	20%	80%
Colon	23.59±27.41 (2-98.8)	66%	34%	181.04±82.44 (101.3-350.9)	28%	72%

1 B): p value of serum CRP & A1AT in healthy control subjects, and gastrointestinal (esophagus, gastric and colon) cancer patients before therapy

Cancer v/s Control	C-reactive protein		Alpha-1antitrypsin	
	't'	'p'	't'	'p'
Esophagus v/s Control	5.653	0.0001	4.051	0.0001
Gastric v/s Control	4.884	0.0001	3.448	0.0008
Colon v/s Control	5.054	0.0001	3.148	0.0022

Mean serum value of C-reactive protein in esophagus cancer patients were (19.10±18.89 mg/L), in gastric cancer patients were (16.65±18.31mg/L), and in colon cancer patients was (23.59±27.41mg/L). Mean serum value of C-reactive protein was significantly higher in esophagus cancer patients (t=5.653, p<0.001), in gastric cancer patients, (t=4.884, p=<0.001) and in colon cancer patients (t=5.054, p<0.001) as compared to healthy control subjects (3.98±0.85mg/L). For CRP the percent positive cases in three cancers were given as: 62% percent in esophagus cancer, 46% in gastric cancer and 66% in colon cancer.

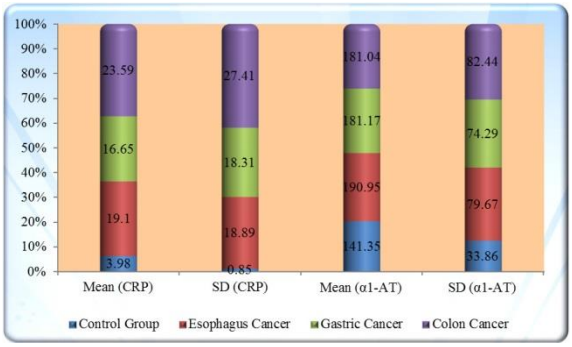

Figure 1: Statistical evaluation of serum CRP and A1AT in healthy control subjects and gastrointestinal (esophagus, gastric and colon) cancer patients before therapy.

Our results of CRP in esophagus cancer patients were in accordance with studies of (Guillem *et al.*, 2005) they observed the mean CRP level in patients with esophageal cancer has been found to be elevated compared to patients with benign pathology. Gockel *et al.*, (2006) found an elevated pretreatment CRP in 56.4 % of esophagus cancer patients (our value was 62%) in their study patients were associated with decrease survival compared to patients with normal CRP levels. Zingg *et al.*, (2010) showed

that an elevated serum CRP level was independent prognostic indicator for survival in patients with esophageal cancer.

Our results of CRP in gastric cancer were similar to studies of Tsavaris *et al.,* (2005); Kim *et al.,* (2009) and Lukaszewicz-Zajac *et al.,* (2011) they found elevated levels of CRP in patients with gastric cancer compared to healthy controls ($p<0.001$). Significantly higher levels of CRP were also observed in gastric cancer patients when compared with healthy subjects, in studies of Choi *et al.,* (2009).

Our results of CRP in colon cancer were similar to studies of Erlinger *et al.,* (2004) they observed CRP to be elevated in patients with colorectal cancer compared to controls ($p<0.01$). Kemik *et al.,* (2010) found elevated CRP concentrations are associated with tumor length, tumor depth, lymph node metastasis, liver metastases, and Duke's stage. Contradictory reports, were given by Zhang *et al.,* (2005), they carried out a prospective cohort study of participants in the Women's Health Study where baseline CRP levels were not significantly ($p>0.05$) associated with colorectal cancer risk, suggesting that low-grade inflammation might not increase the risk of colorectal cancer. Heikkila, (2007) found higher CRP concentrations only in patients with advanced, but not with newly diagnosed, breast, gastrointestinal tract and prostate cancers when compared with controls and with benign diseases.

Groblewskaa *et al.,* (2012) suggested that cancer initiation and tumor development are closely linked with inflammation. C-reactive protein (CRP) and interleukin-6 (IL-6) are acute-phase proteins involved in cancer development. They play potential roles in the growth and progression of malignant tumors, including esophageal cancer. Otake *et al.,* (2009) found adiposity and smoking are strongly and positively correlated with circulating levels of CRP. Expanded adipose tissue mass increases the secretion of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, and the signal to hepatic synthesis of CRP predominantly under control of interleukin-6 is enhanced.

Wang *et al.,* (2009) suggested elevated CRP has been associated with progressive disease and worse survival for patients with malignancies. They reported examples of infectious causes of gastric cancer are Helicobacter pylori (H. pylori) bacterial infection. Noninfectious conditions include gastroesophageal reflux for Barrett's esophagus, and inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, predisposing to colon cancers. CRP was the first of the so-called acute phase proteins, which appeared in the serum of patients with infections or inflammation, during the acute and chronic stages. The linkage of inflammation and cancer was first reported by Rudolf Virchow in 1863, when he identified leucocyte infiltration in neoplastic tissues, and suggested that the sites of chronic inflammation were the origin of cancer. Since then, approximately 25% of all cancer patients are reported to have an association with chronic inflammation of either infectious or non-infectious causes.

Aqbal et al., (2007) studied as a result of its active presence in gastrointestinal disease, CRP has a role as an effective inflammatory marker and a possible pro and anti-inflammatory agent. As a pro-inflammatory mediator, CRP can initiate the elimination of targeted cells by interacting with both the humoral and cellular immune responses of inflammation. CRP functions as an anti-inflammatory agent by preventing the adhesion of neutrophils to endothelial cells and the inhibition of neutrophil chemotaxis. Trichopoulos *et al.,* (2006) suggested that chronic inflammation is functionally involved in colorectal carcinogenesis. The inflammatory response promotes carcinogenesis by damaging DNA, stimulating angiogenesis and cell proliferation and inhibiting apoptosis. Bruce *et al.,* (2000) demonstrated that elevated concentrations of CRP are strongly associated with the development of colon cancer in individuals believed to be free of this disease at baseline. The inflammatory component of chronic infections is a key element in the carcinogenic risk among carriers.

Research of Aleksandrova *et al.,* (2010) gives further credence to the hypothesis that chronic low-grade inflammation may be involved in colon carcinogenesis. Inflammation has been hypothesized to play an important role in carcinogenesis, particularly for colorectal cancer. This was supported by studies which have shown that persons with chronic inflammatory bowel disease have a higher risk of colorectal cancer than the general population (Jess *et al.,* 2005; Canavan *et al.,* 2006).

Mean serum value of Alpha-1antitrypsin in esophagus cancer patients was (190.95±79.67mg/dl), in gastric cancer patients (181.17±74.29 mg/dl), and in colon cancer patients (181.04±82.44 mg/dl). Mean serum value of Alpha-1antitrypsin was significantly higher in esophagus cancer patients ($t=4.051$, $p<0.001$), in gastric cancer patients, ($t=3.448$, $p<0.001$) and in colon cancer patients ($t=3.148$, $p<0.01$) as compared to healthy control subjects (141.35±33.86 mg/dl). For Alpha-1antitrypsin the percent positive cases in three cancers were

given as: 26% percent in esophagus cancer, 20% in gastric cancer and 28% in colon cancer.

Our results were in agreement with observations of Ganji *et al.*, (2012) who observed significant increase in serum AAT in malignant esophageal cancer patients compared to benign tumors and healthy controls ($p<0.05$). Bujanda *et al.*, (2013) reported that Alpha-1antitrypsin expression in blood could be useful for the early diagnosis and/or screening of colon cancers and found significantly higher level as compared to control in colon cancer patients ($p<0.01$).

Elevated Alpha-1 antitrypsin levels were also observed in previous studies (Stamatiadis *et al.*, 1990; Saito *et al.*, 1991; Solakidi *et al.*, 2004). A1AT is a member of the serine protease inhibitors (serpins) family. Tumor cells synthesize and release not only an intact native form of A1AT, but also a variety of cleaved and/or degraded forms of alpha-1 antitrypsin. A1AT has multiple effects on tumor cell viability and play diverse roles in tumorigenesis. Liver cells are the major source of synthesis and secretion of A1AT into the blood. Moreover, it has been demonstrated that A1 AT is expressed and secreted by many types of malignant cells as a response to inflammation. A significant correlation between serum levels and cancer stage has also been reported, additionally A1AT blood levels testing is done as one of the important indicators for the efficacy of cancer treatment (El-Akawi *et al.*, 2013). A1AT protects tissues from enzymes of inflammatory cells, especially neutrophil elastase, the concentration rise many fold upon acute inflammation. It plays major role in the normal physiological processes such as angiogenesis, intravascular fibrinolyis, and wound healing. However it may also participate in pathological conditions such as tumor invasion and metastasis which require degradation of the basement membrane, stimulation of angiogenesis, and migration [38]. Liver cells are the major source of synthesis and secretion of (α_1-AT) into the blood. Apart from synthesis in the liver, A1AT may also be synthesized and secreted by the epithelial cells of stomach, intestine, pancreas, and respiratory tract. Additionally, it can be produced by certain cancer cells, including cancers of gastric, colon, and lung. A1AT augments in the serum of gastrointestinal tract cancer patients (Ganji *et al.*, 2012). A1AT in colorectal carcinoma is related to the invasive and metastatic capacity. It may thus serve as a biologic marker for prognosis of colorectal carcinomas at relatively early stages (Karashima *et al.*, 2006).

Mean serum value of acute phase reactant protein level in metastatic esophagus cancer patients (n=8) were given in Table (2) and Figure (2) CRP (42.37±20.04mg/L) and A1AT (268.26±102.00mg/dl). Mean serum value of acute phase reactant protein level in nonmetastatic esophagus cancer (n=42) were CRP (14.72±15.21mg/L), and A1AT (176.23±66.50mg/dl). Mean serum value of CRP ($t=2.921$, $p<0.01$) and A1AT ($t=2.121$, $p<0.05$) were significantly higher in metastatic cancer patients than nonmetastatic cancer patients. Our results were according to following studies. Nozoe *et al.*, (2001) studied the significance of preoperative elevation of serum CRP as an indicator of prognosis in patients with esophageal carcinoma. The mean size of the tumors and the proportions of lymph node metastasis and lymphatic invasion were significantly larger in patients with preoperative elevation of serum CRP than in patients without preoperative elevation of serum CRP. The preoperative serum elevation of CRP can be used as a marker of malignant potential of the tumor in esophageal carcinoma.

Table 2: Comparison of serum CRP& A1AT in esophagus cancer patients with and without metastasis

ESOPHAGUS CANCER (n=50)	CRP (Range)	A1AT (Range)
With METASTASIS (n=8)	42.37±20.04 (4.9-68.5)	268.26±102.00 (124.2-356.8)
Without METASTASIS (n=42)	14.72±15.21 (2.8-48.3)	176.23±66.50 (103.1-355.1)
't'	2.921	2.121
'p'	0.0053	0.0391

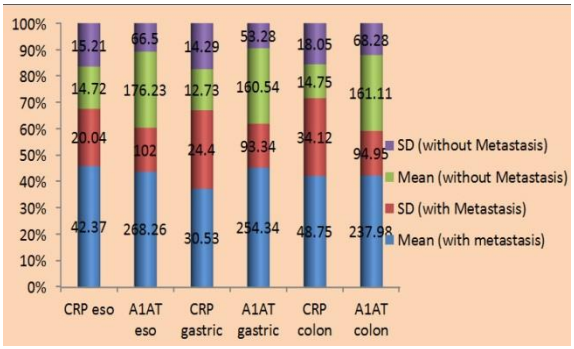

Figure 2: Comparison of serum CRP and A1AT in gastrointestinal (esophagus, gastric and colon) cancer patients with and without metastasis.

Shimada *et al.*, (2003) studied acute-phase reactions in tumour progression and tumour recurrence. A correlation has been established between elevated serum CRP concentrations and malnutrition as well as impaired immunity in patients with oesophageal cancer. The authors

found that elevated serum levels of the protein, in addition to the synthesis by hepatocytes as a response to the tumour, may be at least in part due to the production of CRP by the tumour itself. Guillem *et al.,* (2005) gave contradictory results no significant correlation could be found between CRP levels and baseline characteristics such as age, gender, histology, cancer localization, tumor depth, lymph node status or metastatic spread. Gockel *et al.,* (2006) evaluated C-reactive protein (CRP) as an acute-phase reactant and a known indicator of the malignant potential of the tumour, the significance of preoperative CRP as a parameter of the perioperative course and long-term prognosis in patients with squamous cell carcinoma and adenocarcinoma of the oesophagus patients was investigated. Tumour extension and the number of lymph nodes affected by metastatic spread were significantly increased in the group with elevated CRP levels. The correlation between acute-phase protein and biological behaviour in oesophageal cancer may be attributable to an inflammatory reaction, the endogenous response to tumour invasion. The production of CRP is regulated by proinflamatory cytokines which serves as autocrine growth factors in neoplastic processes. Our results of A1AT in metastatic esophagus cancer were according to studies of Ganji *et al.,* (2012); Saito *et al.,* (1991) and Shirao *et al.,* (1992). They suggested that it should be kept in mind that most squamous cell carcinoma of esophagus is diagnosed in the late stages of tumorigenesis due to late referral of patients to clinics. Thus determining augmented A1AT levels in the early stages remains to be investigated in future studies. One way for elucidation A1AT level in early stages of malignancies would be establishing definite relationship between inflammatory diseases and cancers. In addition most malignancies exhibit increased production of cytokines. A1AT is an acute phase reactant. This means that it will be elevated in acute and chronic inflammatory conditions, infections, and with some cancers (Pagana and Pagana, 2007).

In our study mean serum value of tumor markers and acute phase reactant protein level in metastatic gastric cancer patients (n=11) were given in Table (3) and Figure (2) CRP (30.53±24.40mg/L) and A1AT (254.34±93.34mg/dl). Mean serum level of tumor markers and acute phase reactant protein level in nonmetastatic gastric cancer (n=39) were CRP (12.73±14.29mg/L), and A1AT (160.54±53.28mg/dl). Mean serum levels of CRP ($t=2.116$, $p<0.05$) and A1AT ($t=2.777$, $p<0.01$) in metastatic gastric cancer patients were significantly higher than nonmetastatic cancer patients.

Table 3: Comparison of serum CRP&A1AT in gastric cancer patients with and without metastasis

GASRTIC CANCER (n=50)	CRP (Range)	A1AT (Range)
With METASTASIS (n=11)	30.53±24.40 (2.4-71.7)	254.34±93.34 (101.2-352.2)
Without METASTASIS (n=39)	12.73±14.29 (2.1-68.2)	160.54±53.28 (90.8-341.2)
't'	2.116	2.777
'p'	0.0395	0.0078

Our results were in agreement with findings of Kim *et al.,* (2009), who revealed significant differences in lymph node metastasis and serum concentrations of CRP. They suggested preoperative serum CRP levels might be markers of tumor invasion, LN metastasis, and TNM stage. Lukaszewicz-Zajac *et al.,* (2011) evaluated that CRP levels correlated with clinicopathological features of gastric cancer, such as tumor stage, depth of tumor invasion and the presence of lymph node metastasis. Wu *et al.,* (1996) gave the first study assessing diagnostic criteria for IL-6 and CRP in sera of gastric cancer patients, especially in comparison with classic tumor markers— CEA and CA 19-9. It shows extensive tumor invasion and early spread to metastasis sites. Serum levels of all the proteins tested varied according to nodal metastases (N factor) and the CRP concentrations were correlated with the presence of lymph node metastasis. Cancer invasion begins with inflammation around the tumor cells therefore CRP levels might be higher in the sera of patients with invasive cancer than those in noninvasive tumors.

Ilhan *et al.,* (2004) suggested angiogenesis was required for tumour growth and progression and it was involved in metastasis. The process could result from an imbalance between positive and negative angiogenic regulators released by both tumour cells and host cells. Tumour vascularisation correlated directly with the prognosis of cancer patients in many carcinomas. Gastric cancer is a major malignant disease. Gastric adenocarcinoma is associated with a high incidence of serosal invasion, direct invasion into the neighbouring organs, peritoneal dissemination, lymph node metastasis, and liver metastasis. These lesions have led to a low resection rate and a poor prognosis. CRP may contribute directly to the proinflammatory state. CRP could stimulate monocyte release from inflammatory cytokines which might directly act as a proinflammatory stimulus to phagocytic cells.

Our results of A1AT in metastatic gastric cancer were similar to studies of Solakidi *et al.*, (2004) they found significantly higher level (p<0.01) of A1AT in gastric cancer patients correlated with advanced stage. Sun *et al.*, (2004) postulated neutrophil elastase and alpha 1-antitrypsin a pair of protease and protease inhibitor counterparts. The imbalance between the two counterparts is generally thought to cause tissue damage, which could create a favourable tissue environment for carcinogens and tumour progression. Conversely, raised concentrations of neutrophil elastase might promote the development, invasion, and metastasis of many cancers. Several mechanisms of carcinogenesis have been postulated. Excess neutrophil elastase might facilitate cancer development by causing tissue damage and air trapping, which foster longer carcinogen exposure, might promote cancer progression by degrading the intercellular matrix barrier, and might directly lead to cancer development through the tumour-necrosis-factor signalling pathway. Analysis of the serum level of these proteases may also be useful in complex preoperative diagnostic procedure to estimate the stage of both cancers before surgical intervention.

In our study mean serum levels of tumor markers and acute phase reactant protein in metastatic colon cancer patients (n=13) were shown in Table (4) and Figure (2), CRP (48.75±34.12mg/L) and Alpha-1antitrypsin (237.98±94.95mg/dl). Mean serum levels of tumor markers and acute phase reactant protein in nonmetastatic colon cancer (n=37) were CRP (14.75±18.05mg/L), and Alpha-1antitrypsin (161.11±68.28mg/dl). Mean serum levels of CRP (t=3.032, p<0.01) and Alpha-1antitrypsin (t=2.499, p<0.05) were significantly higher than nonmetastatic cancer patients.

Table 4: Comparison of serum CRP&A1AT in colon cancer patients with and without metastasis

COLON CANCER (n=50)	CRP (Range)	A1AT (Range)
With METASTASIS (n=13)	48.75±34.12 (3.5-98.8)	237.98±94.95 (107.2-349.7)
Without METASTASIS (n=37)	14.75±18.05 (2.0-81.3)	161.11±68.28 (101.3-350.9)
't'	3.032	2.499
'p'	0.0039	0.0159

Our results of CRP in metastatic colon cancer were according to studies of Mousavi *et al.*, (2008) and Chung *et al.*, (2003) they indicated that increased CRP in cancerous patients is significantly higher than what in control groups (p<0.01), and generally associated with larger tumor size, lymph node or liver metastases, peritoneal carcinomatosis, and advanced Dukes' stage. Also the CRP expression is inversely correlated with overall survival. These results suggested that the serum CRP level could thus be an indicator of the malignant potential and a marker of metastases in colorectal cancer and therefore can also provide valuable information when determining the treatment strategies for such patients.

Mazhar and Ngan, (2006) and Munkholm, (2003) assessed the existing evidence for a relationship between CRP and colorectal cancer. An increased risk for colorectal cancer has been demonstrated in patients with inflammatory bowel disease particularly ulcerative colitis evaluated in laboratory studies, inflammation promotes the conversion of colonic adenoma cells to adenocarcinoma cells. Pre-operative CRP levels in patients with late-stage colorectal tumours are considerably and consistently higher than those in patients with early-stage disease (p=0.01). Moreover, elevated levels of CRP or IL-6 in patients with colorectal cancer have been associated with tumour stage and recurrence and reduced survival (Wigmore *et al.*, 2001; Erlinger *et al.*, 2004).

Our results of Alpha-1-antitrypsin levels were in accordance to the studies of Bujanda *et al.*, (2013) they found Alpha-1antitrypsin was the serum marker that was most useful for CRC diagnosis (CRC group v/s the control group, P<0.0005) and have good diagnostic accuracy for CRC. Elevated serum Alpha-1antitrypsin levels have been observed in association with malignancy and inflammation. Serum levels were increased by stage and discriminated between early and advanced stages. Some authors have shown that serum Alpha-1antitrypsin levels correlated with CRC and with clinical staging. In their studies, the correlation of CEA and Alpha -1antitrypsin to the stage of disease had almost the same statistical weight. Karashima *et al.*, (1990) studied in metastatic tumor cells of colorectal carcinomas in lymph nodes and other organs, A1AT positivity was 60% and 82%, respectively. The incidence of A1AT was markedly higher in advanced adenocarcinomas than in early ones and more frequent in adenocarcinomas of right side (including transverse colon) than those of left side and rectum, regardless of their histological malignancy grades. Clinical follow-up of the patients with colorectal carcinomas suggested that A1AT positivity in Dukes' stage A/B tends to correlate with unfavourable prognosis irrespective of the grade of histologic differentiation of carcinoma, but there is no significant relation in Dukes' stage C/D. The findings suggested that A1AT in colorectal carcinoma is related to the invasive and

metastatic capacity. It may thus serve as a biologic marker for prognosis of colorectal carcinomas at relatively early stages (Dukes' stage A/B).

CONCLUSION

Serum CRP and A1AT measurements are simple, cheap, and available in daily practice. They have promising roles for the prevention and therapy of malignancies in the future.

Earlier detection of metastasis offers the possibility of additional salvage treatment.

Elevated CRP and A1AT preoperatively were associated with progressive disease such as lymph node or liver metastasis or an advanced stage, and a worse survival. Although serum CRP&A1AT are not specific biomarkers for gastric cancer, they might be a potential prognostic biomarker and a promising therapeutic target for gastrointestinal cancer patients.

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CONFLICT OF INTEREST STATEMENT

No potential conflicts of interest are disclosed.

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