Association between Systemic Inflammation and Clinicopathological Characteristics in Patients with Colorectal Cancer

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ABSTRACT:

BACKGROUND:

Colorectal cancer is a major cause of mortality and morbidity. The interplay between systemic inflammation and the local immune response was recognized as the seventh hallmark of cancer, and it has been demonstrated to be involved in the initiation, development, and progression of several types of malignancies. systemic immune-inflammation index, was reported as prognostic factors in some malignant tumors, including Colorectal cancer.

AIM OF STUDY:

To investigate the relationship between systemic immune-inflammation index and clinicopathological characteristics (sex, age, site of tumor, T stage, N stage, M stage, Clinical (TNM) stage, Duke stage, Grade, Lympho-Vascular Invasion and Carcino-Embryonic Antigen level) of colorectal cancer.

METHOD:

cross-sectional study was conducted, involving seventy patients with Colorectal cancer who were diagnosed by histopathological proof, to evaluate the relationship by dividing the patients into two groups depending on cut-off values: (1) those with high marker level, (2) those with low marker level.

RESULTS:

The study involved 70 patients who are 38 males and 32 females. Their mean age was 53 years. Tumor site was in 40% of them in the left colon. The majority (67.1%) of patients have no metastasis and moderately differentiated tumors, 22 of 38 patients (58%) have positive lymphovascular invasion. Only 53 patients (75%) have a recorded pretreatment Carcino-Embryonic Antigen level and the mean was 13.07 ng/ml. There was a statistically significant association between systemic immune inflammation index and T stage and presence of metastasis, thereby clinical and Duke stages, as the value of systemic immune inflammation index is higher in advanced stages. Higher values of systemic immune inflammation index were associated with higher grade and with positive lymphovascular invasion also.

CONCLUSION:

Elevated systemic immune-inflammation index is associated with higher stages and with lympho-vascular invasion of colorectal cancer. It is furtherly associated with higher grade of disease. Systemic immune inflammation index is easily accessible, and its association with poor prognostic indicators (like stage or presence of metastasis) warrant further investigation.

KEY WORDS: Systemic immune inflammation index, Colorectal cancer.

INTRODUCTION:

Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second most common cause of cancer death in western Europe and North America. The long-term survival of patients having colorectal cancer is dependent on pathological stage and complex interactions between tumor- and patient-related factors. The host inflammatory response is a determinant of cancer outcome. Several studies examined a variety of methods to assess the local inflammatory response in colorectal tumors and to explore relationships with both clinicopathological characteristics and survival.[1] In particular, the host inflammatory responses, both systemic and local, are important determinants of cancer outcome. A marked systemic inflammatory response has been reliably associated with decreased survival in a number of solid malignancies, including colorectal cancer, and has now been rationalized into a simple and reliable prognostic tool.[2]

Immunity, Inflammation, and Cancer

The presence of leukocytes within tumors, observed in the 19th century by Rudolf Virchow,

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gave the first clue of a possible connection between inflammation and cancer. A role of inflammation in tumorigenesis is now generally accepted, and it has become evident that an inflammatory microenvironment is a crucial element of all tumors, including those in which a direct contributing relationship with inflammation is not yet confirmed.[3]

A completely different type of inflammation is that follows tumor development. Most solid malignancies initiate an intrinsic inflammatory response that make up a protumorigenic microenvironment.3 In addition to cell-autonomous proliferation, specific oncogenes, such as RAS and MYC family members, prompt a transcriptional program that leads to remodeling of the tumor microenvironment through recruitment of leukocytes, expression of tumor-promoting chemokines and cytokines, and induction of an angiogenic switch.[4]

Immune Cells in Tumorigenesis

According to these different forms of inflammation, the tumor microenvironment has innate immune cells (including neutrophils) and adaptive immune cells (T and B lymphocytes) together with cancer cells and their surrounding stroma. These various cells communicate with each other by means of direct contact or cytokine and chemokine production and act in autocrine and paracrine manners to regulate tumor growth [5]

It is safe to assume that tumor promoting inflammation and antitumor immunity live together at different points along the pathway of tumor progression and that environmental and micro environmental conditions transcribe the balance between the two.5 Neutrophils can play both tumor-promoting and tumoricidal functions. B lymphocytes are also essential providers to immune-mediated tumor growth, and conventional macrophages and dendritic cells are important for antigen presentation and T cell activation during antitumor immunity. [6]

the presence of tumor-infiltrating lymphocytes that recognize tumor antigens and the favorable prognosis for some patients whose tumors display increased infiltration with activated T cells. Such infiltration is more obvious in tumors that have microsatellite instability or have a mutator phenotype and thus express tumor antigens that exhibit bigger variations from normal counterparts. [7]

Lastly, cell-mediated immunity may be reflected by lymphocyte count, while systemic inflammation may be suggested by neutrophilia. Experimental and clinical evidence showed that platelet activation may act as chemo-attractants for cancer cells, encourage the establishment of optimized conditions for metastasis, promote the transition of epithelium to mesenchyme in tumor cells, and increases circulating tumor cells level. Consequently, Systemic immune inflammation index (SII), calculated as the neutrophil count multiplied by platelet count divided by the lymphocyte count,[8] may represent an easily measurable and inexpensive marker of systemic inflammation. [9] However, Hu et al reported that systemic immune inflammation index an integrated indicator based on peripheral lymphocyte, neutrophil, and platelet counts, was a powerful prognostic marker for patients with hepatocellular carcinoma. Another study found that SII is a more powerful tool for predicting survival outcome in patients with CRC. It might assist the identification of high-risk patients among patients with the same TNM stage. [10]

METHOD:

Study design:

Hospital based, cross-sectional study was conducted to evaluate the association between systemic immune-inflammation index (SII) and clinico-pathological characteristics in patients who have been newly diagnosed with colorectal cancer.

Study population:

A sample of a total of (70) patients with CRC who were newly diagnosed on a basis of a histopathological exam of a biopsy from an open surgery.

Data collection:

The study was started on the 1st of November, 2017 and was ended on the 31st of October, 2018. The patients were picked up from the daily visits to different consultation clinics of the Oncology Teaching Hospital. Each patient was interviewed and the data were collected. We asked the help of the statistic department as well as the pathology and laboratory in our hospital in order to complete our data.

The collected data are: (1) name, age and sex. (2) site of the primary tumor identified by imaging or endoscopy: whether it was right side of colon; left side or rectum. (3) T stage (local invasion of tumor), N stage (lymph node involvement), M stage (distant metastasis), grading (degree of differentiation), clinical staging and duke staging. (4) presence of lymphovascular invasion. 3 and 4 are assessed by histopathological exam of obtained tissue biopsy. (5) serum carcinoembryonic antigen level obtained from the lab by Immuno assay system, Siemens, immulite **2**000 XPi. (6) pretreatment complete blood count and differentials obtained for patients and control groups (to calculate the value of **S**ystemic

Immune-**I**nflammation **I**ndex (SII= Neutrophil count X Platelet count ÷ Lymphocyte count)) by Hematology system, Siemens, ADVIA 2120i.

Exclusion criteria: (affecting Blood counts)

pregnant, breast feeding, obese (body mass index [BMI] >40 and >35 for females and males, respectively), excessively thin (BMI <8), drinking alcohol, recent treatment for anemia, incomplete data, corticosteroid use, recent chemotherapy or any drug that may affect blood counts, recent surgery, deep venous thrombosis, concurrent cancer (another preceding primary), active infection (by history), have renal impairment, diabetic or have been admitted to the hospital recently.[11] More than 225 patients were seen but only 70 are eligible and the others were excluded.

seventy healthy persons served as a control group to calculate the cut-off points for SII. The control group was age and sex-matched with cases group in order to get rid of sex and age variations that may affect the results.[12,11]

Statistical analysis:

Collected data were introduced into excel sheet and loaded to IBM-SPSS v.24 for analysis. Descriptive statistics were presented through frequency distribution table. The cut-off points for SII level, to discriminate between patients with high from those with low level, were estimated by using receiver operating characteristic (ROC) curve and Youden index (J). [13] Chi-square test was used to find out any association between studied variables. P value less than 0.05 is considered as discriminating point of associationsignificance.

RESULTS:

Descriptive analysis for the data of the patients is summarized in Table (3.1) the patient group included 38 males and 32 females. Their ages ranged from 23 to 79 years with mean age of 53 years. 46 of them are below 60 years and 24 patients age above 60 years. Tumor site was in 40% of them in the left colon and around 25% in right colon. 47.1% of tumors were staged as T3, 38.6% were N0, 67.1% have no metastasis, 34.3% have stage III and 35.7% have Duke stage C. The majority (67.1%) of patients have moderately differentiated tumors, 22 of 38 patients (58%) have positive lymphovascular invasion. Only 53 patients have a recorded pretreatment CEA level and the mean was 13.07 (0.2-152) ng/ml.

Table 1.1: Distribution of Studied Cases According to Their Basic Characteristics.

Parameters		Count	Percent
Age	<=60 yrs.	46	65.7%
	>60 yrs.	24	34.3%
	Mean 53.63yr (23-79)		
Sex	Male	38	54.3%
	Female	32	45.7%
Tumor site	Lt colon(from splenic curvature)	28	40.0%
	Rt colon(to splenic curvature)	17	24.3%
	Rectum	25	35.7%
T stage	1	3	4.3%
	2	13	18.6%
	3	33	47.1%
	4	21	30.0%
N stage	0	27	38.6%
	1	20	28.6%
	2	22	31.4%
	3	1	1.4%
M stage	0	47	67.1%
	1	23	32.9%
Clinical stage	I	8	11.4%
	II	15	21.4%
	III	24	34.3%
	IV	23	32.9%
DUKE stage	A	3	4.3%
	B	20	28.6%
	C	25	35.7%
	D	22	31.4%
Grade	well differentiated	13	18.6%
	moderately differentiated	47	67.1%
	poorly differentiated	10	14.3%
LVI n(38)	-ve	16	42.1%
	+ve	22	57.9%
CEA (ng/ml)	n(53)	Mean 13.07 (0.2-152)	

Data extracted from the results of complete blood count for patients and control groups, in order to obtain SII value, are shown in table (3.2) with statistically significant higher levels in patients than control group.

Table 3.2: Patients and control immune markers.

	Patient n =70		Control n = 70		
	range	Mean ± SD	range	Mean ± SD	P value
Absolute Neutrophil count $X10^9/L$	2.58-17.86	6.45 ± 2.9	1.7-7.41	3.94 ± 1.07	0.000*
Platelet count $X10^9/L$	141-879	345.62 ± 122.46	155-385	258.1 ± 51.23	0.000*
Absolute Lymphocyte count $X10^9/L$	0.68-3.4	1.78 ± 0.66	1.1-3.79	2.34 ± 0.65	0.000*
SII	274.16-11288.21	1537.52 ± 1464.83	179.58-1291.13	469.4 ± 223	0.000*

The optimum cut-off points for SII is obtained by using ROC curve and Youden index. It was 735.6 as shown in the figure (3.1).

* p value < 0.05 (statistically significant)

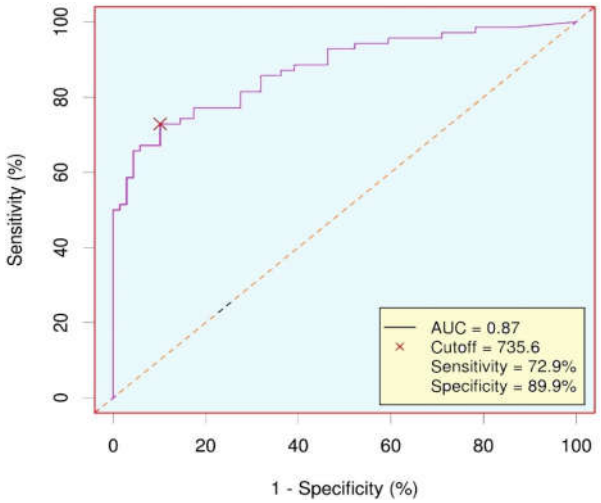

Figure 3.1: The optimum cut-off point of SII using Youden index and ROC curve.

In the table below (3.3), there is no significant association between Systemic Immune Inflammation index (SII) and age, sex, tumor site, N staging and CEA level, as the p value was more than 0.05. but it was significant for T stage and presence of metastasis, thereby clinical and Duke stages, as
the value of SII is higher in advanced stages. Higher values of SII were associated with higher grade and with positive lymphovascular invasion also and the p value was significant.

Table 3.3: Association Between SII And Clinicopathological Features.

Patients` parameters		SII		P value
		735.6 or less	>735.6	
Age	<=60yr	11	35	0.40
	>60yr	8	16	
	n (mean)	19 (54.00)	51 (53.49)	0.32
Sex	Male	11	27	0.71
	Female	8	24	
Tumor site	Lt colon	4	24	0.11
	Rt colon	5	12	
	Rectum	10	15	
T stage	1	3	0	0.006*
	2	6	7	
	3	6	27	
	4	4	17	
N stage	0	12	15	0.077
	1	3	17	
	2	4	18	
	3	0	1	
M stage	0	18	29	0.003*
	1	1	22	
Clinical Stage	I	6	2	0.001*
	II	6	9	
	III	6	18	
	IV	1	22	
DUKE stage	A	3	0	0.001*
	B	9	11	
	C	6	19	
	D	1	21	
Grade	well differentiated	6	7	0.047*
	moderately differentiated	13	34	
	poorly differentiated	0	10	
LVI n(38)	-ve	8	8	0.001*
	+ve	1	21	
CEA (ng/ml) n(53)	n(mean)	14 (6.54)	39 (15.41)	0.145

* p value < 0.05 (statistically significant).

DISCUSSION:

It is recognized that clinical outcome in cancer patients varies, even at the same stage of the disease and the same treatment plan or quality, these variations are not only attributed to the characteristics of the tumor but also to the host-response factors.[14] Several reports mentioned that host factors, such as performance status, weight loss and a systemic inflammatory response are also important indicators of clinical treatment outcome.[15] Clinically, the most common reported measures of the systemic inflammatory response in cancer patients are biochemical or hematological markers.

The first report investigating the prognostic value of SII in patients with CRC was (Chen JH et al., 2017).[10] It is believed that a good understanding of the roles of neutrophils, platelets, and lymphocytes in cancer initiation and progression may assist in clarifying the association between S□ and its clinical importance. Neutrophils do not merely alter the tumor microenvironment through the extrinsic pathway, but they also secrete some inflammatory mediators to promote tumor cell proliferation, invasion, metastasis to lymph nodes and distant organs, and cellular senescence through the intrinsic pathway.

Experimental and clinical evidence revealed that platelet activation may behave as chemo-attractants for cancer cells, induce the formation of optimized conditions for metastasis, promote the transition of epithelium to mesenchyme in tumor cells, and increases circulating tumor cells level.9 Lymphopenia helps tumor cells to escape immune defense and prevents damage of cytotoxic T cells. Thus, a high SII level reflects alterations in the cancer microenvironment that

favor cancer initiation, progression, and metastasis.

We found in this study that there is a significant association between SII and M and clinical stages and this was consistent with Yang J et al., 2018 and Chen JH et al., 2017 studies.[16,10] also this study showed an association with T stage and grade of differentiation which was agreed by Chen JH et al., 2017 other than Yang J et al., 2018. Results revealed no association with Mean age, sex, site and CEA level which are similar to the results of Yang J et al., 2018 study. It is noticed that SII was not associated with N stage in this study and in Yang J et al., 2018 study also, but it was significant in Chen JH et al., 2017 study.[16,10] Both studies agree with present results in that there is no association between SII and age, sex and site of tumor.

CONCLUSION:

- Elevated SII is associated with higher stages and with lympho-vascular invasion of CRC.
- SII is furtherly associated with higher grade of disease.
- Inflammatory response is involved with CRC as neutrophil and platelet counts are elevated and lymphocyte count is reduced in patients more than in healthy individuals.
- SII is easily accessible, widely available and cost-effective marker to be done, and its association with poor prognostic indicators (like stage or presence of metastasis) warrants further investigation.

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