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Investigation of the Correlation between DPD Activity and Renal and Liver Function Parameters in Cancer Patients Treated by 5-Fluorouracil

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Abstract

Background: Cancer is a disease that refers to abnormal cell growth, uncontrollably with the ability to spread to other parts of the body."5-Fluorouracil (5-FU), is a commonly used anticancer treatment for different types of cancers with a seriousside effect.Dihydropyrimidine dehydrogenase (DPD) enzyme responsible for the degradation of pyrimidine bases and 5-FU in the body. **Aim:** This study aimed to determine the relationship between DPD and BMI with Renal and Liver function parameters in 5-fluorouraciltreated cancer patients.

Materials and Methods: This study included (88) samples divided into three groups. Group 1 included (28) Control,which is composed of two subgroups, (13) healthy as a (negative control)with age range (27 - 74) years, and (15) patients with cancer (untreated patients with 5-FU) as a (positive control)with age range (24 - 76) years. Group 2 included (30) Colon cancer(treated with 5-FU)with age range (30 - 85) years. Group 3 (30) Stomach cancer (treated with 5-FU)with an age range (16 - 70) years.

All the volunteers were selected to investigate the variations in biochemical levels in the sera of cancer patients treated with 5-FU. The sera's concentrations of (DPD, Urea, Creatinine, Albumin, and Total Protein) were measured in blood samples from all volunteers.

Results: The current study findings show no Significant Correlation between the concentration of DPD and all the studied variables for all study groups ($p>0.01$). Asignificant positive correlation between the BMI and serum Creatinine [($r = 0.688$, $p = 0.005$)] in Colon cancer. Also, our findingsa significant positive correlation between Blood Urea with Age [($r = 0.708$, $p = 0.003$)] and serum Creatinine [($r= 0.800$,$p =0.0003$)] in patients with Stomach Cancer.Moreover a significant positive correlation between Albumin and Total Protein [($r = 0.760$, $p = 0.001$)] in patients with Colon Cancer .Using Pearson's correlation coefficients.

Conclusion:the DPD activity had No Correlation with Age,BMI, Renal function parametersfor all study groups.the relationship between increasing age, renal function parameters, showed a

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direct correlation between urea and age. whereas Serum urea and Creatinine levels showed a statistically significant increase between years of age, in patients with Stomach Cancer.

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Key world:Dihydropyrimidine dehydrogenase; 5-Fluorouracil; Renal function; Liver function; Chemotherapy toxicity;

Introduction

Dihydropyrimidine dehydrogenase (DPD) "EC 1.3.1.2" encoded with the Dihydropyrimidine dehydrogenase gene (DPYD)(Wigle et al. 2019**).** DPD enzyme is responsible for stimulating the degradation in the catabolism pathway, of pyrimidine bases (uracil and thymine), into 5,6-dihydrouracil and 5,6 -dihydrothymine, respectively**(van Kuilenburg et al. 2018).**also stimulate the reduction of Fluoropyrimidine includes 5-Fluorouracil"(5-FU)" into Fluoro-beta-alanine "(FUH2)" in the human body **(Hishinuma, Gutiérrez Rico, and Hiratsuka 2020).** "5-Fluorouracil (5-Fu)" is an anticancerdrugwidely used to treat many cancers in the human body, breast, head gastric, neck, Colon, colorectal cancer**(Ishiguro et al. 2020)**.In twenty to forty percent of some patients, is not well tolerated treated by these drugs; occurs toxicity medium to severe (fatal) leading to death, such as "(diarrhea, nausea, vomiting, bone marrow suppression, inflammation of the mouth, mucositis and Hand-Foot syndrome) **(Coenen et al. 2019)**.The current study identifies the Correlation between DPD enzyme and BMI with renal and liver function parameters in 5-fluorouracil-treated cancer patients.

Materials and methods

Patient's selection

This research is conducted after collecting samples from the National Cancer Center and Al-Yarmouk Teaching Hospital; all of them are from Baghdad, Iraq. From (January 2020 to May 2020), after taking consent from the Patients and institutional ethical approval.

This research included (88) samples divided into three groups; **Group1** included (28) Control, Which is composed of two subgroups, (13) healthy as a (negative control)with age range (27 - 74) years, and (15) patients with cancer (untreated with 5-FU) as a (positive control)with age range (24 - 76) years. **Group2** included (30) patients with Colon cancer(treated with 5-FU)with an age range (30 - 85) years. **Group3** (30) patients with Stomach cancer(treated with 5-FU)with

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age range (16 - 70) years.

Samples collection included draw 5 milliliters from venous blood and put in a plain tube let at the room's temperature. Serum was separated and isolated by centrifuged at (3000 round per minute)separate serum and stored in the deep freeze at (-20°C)until assayed.

Measurement of Biochemical parameters in study groups; Using Human DPYD(Dihydropyrimidine Dehydrogenase)ELISA Kit (MyBioSource/USA). While the Urea, Creatinine, and Albumin levels were determined using the (BioSystems/Spine)Kit, total proteins level was determined using (Spineact/Spine) Kitall by using the colorimetric method.

Statistical analysis

The data was specific as mean ± SD, one-way-ANOVA, we used to show a significant dissimilarity between Groups when P-value was considered **(P<0.01)**. Also, Pearson's correlation coefficients to identify the statistical relationship, or association, between the concentration of DPD and the studied clinical variables.

Result and Discussion

Demographic elements for the study groups:

Demographic data in **Table [1]** showed**;** the age range (30 - 85) years in Colon patients and the age range (16 - 70) stomach patients. While the age range (27 - 74) year for (-ve) control healthy and age range (24 -76) year (+ve) control untreated patients.

Table 1: Demographic elements for the patient groups.

Characteristics		(-ve) control healthy	(+ve) controluntreated	Colon cancer (treated)	Stomach cancer (treated)
Number		13	15	30	30
Age	Range	27 - 74	24 - 76	30 - 85	70 - 16
Gender	Male no.(%)	46%	7%	40%	53%
	Female no.(%)	54%	93%	60%	47%

Table [2] shows,Mean ±SD (54.27 ± 15.31), and age range (30 - 85) years in Colon patients, (53.13±14.85) and age range (16 -70) stomach patients group, while the control subgroup; Is (42.08±16.01)and age range (27-74) year for (-ve) control healthy and, (52.87±14.27) and age range (24-76) year (+ve) control untreated patients.

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Table 2: Mean value of BMI and age of the studied groups.

Groups		G1	G2	G3	G4	P-value
Parameters		Control (-ve) Healthy	Control (+ve) untreated	Colon Cancer (treated)	StomachCancer (treated)	
Age (year)	(mean ± SD)	(42.08 ±16.01)	(52.87±14.27)	(54.27±15.31)	(53.13±14.85)	0.14
	range	27 - 74	24 - 76	30 - 85	16 - 70	
BMI kg/m2	(mean ± SD)	21.09 - 28.52 a	18.37 - 43.75 b,c	14.98 - 29.73 a,b,d	12.76 - 32.27 c,d	0.002
		(25.07±2.56)	(29.29 ±7.29)	(24.13±3.97)	(21.87±5.24)	

*** Significant using ONEWAY-ANOVA (LSD) at 0.01 level.**

a, Refers to significant difference within G1 and G2.
b, Refers to significant difference within G1 and G3.
c, Refers to significant difference within G2 and G3.
d, Refers to significant difference within G3 and G4.

Findings,the Mean value of BMI is significantly decreased **(P<0.01)** in the patient's colon and stomach cancer [(24.13±3.97),(21.87±5.24)] respectively. Compared with the controls (25.07±2.56) for negative control and (29.29±7.29) for positive control.Are shown in **Figure [1].**

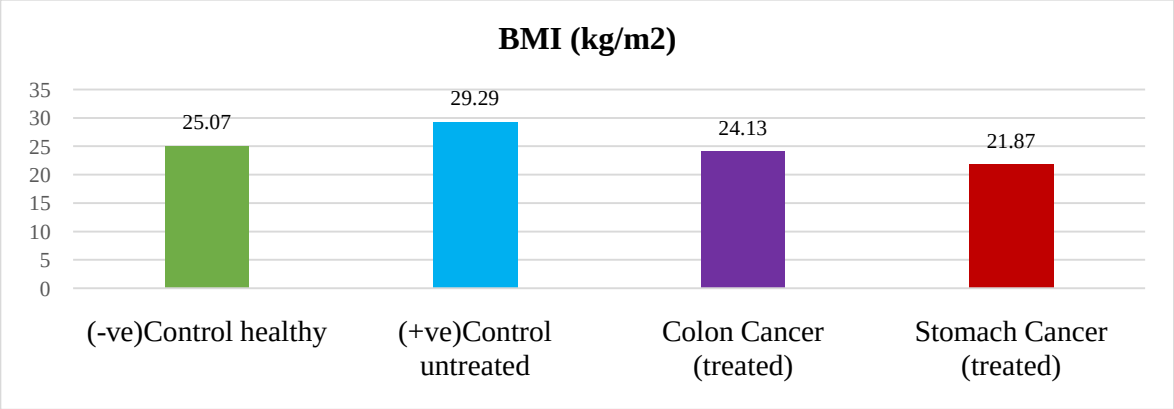

Figure 1: the mean value of BMI of the studied groups.

Multiple metabolic changes have been observed during cancer due to a variety of mechanisms that are often unclear. Mainly, it alters energy metabolism, resulting in an involuntary loss of body weight due to Anorexia (appetite loss) and disorders in muscle mass.Anorexia is a medical condition linked to chronic diseases, such as cancer. Anorexia represented about 41% of cancer

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patients was reported.

Cancer-related Anorexia has been linked to many factors: increased releasing pro-inflammatory substances (Cytokines) causing loss of weight., anticancer treatments (e.g., chemotherapy, radiotherapy), changes in gut microbiota, and tumor-derived catabolic factors **(Molfino et al. 2021).**

Weight changes, muscle loss, are some of the most common side effects in patients with cancer **(Escamilla and Jarrett 2016).** Weight loss and cancer are closely linked; it is expected to lower the patient's activity level, reflecting on the fat storages and muscle energy stores**(Beauvillain de Montreuil C, Goldwasser F, Hébuterne Xavier, Lemarié E 1980).**

Therefore, a decrease (BMI) in patients with Colorectal Cancer (CRC) correlated with an increased risk of hematologic toxicities. As a side effect of result from cancer treatment(5-FU), like anemia (deficiency of red blood cells (RBC) or hemoglobin (Hb) in the blood, and Neutropenia (low neutrophils in the blood). However, decreasing BMI can have been linked to an increased likelihood of nausea, vomiting, in addition to peripheral neuropathy**(Abdel-Rahman 2019).**

Table [3] showedThe BMI classifications are (Severely underweight, underweight, Normal weight, Overweight, and Obesity class I, II, III), as illustrated in **Table [3].**The World Health Organization (WHO) and National Institute of Health (NIH) today using this classification **(Weir and Jan 2019)**.

Table [3]Classifications of BMI for all studied groups.

Groups	G1	G2	G3	G4	Status
BMI range (Kg/m2)	Control (-ve) Healthy N=13	Control (+ve) untreated N=15	Colon Cancer (treated) N=30	Stomach Cancer (treated) N=30	
under 16.5	0%	0%	7%	20%	Severely underweight
16.5- 18.4	0%	7%	0%	0%	underweight
18.5 - 24.9	38%	27%	47%	53%	Normal weight
25 - 29.9	62%	13%	47%	20%	Overweight
≥ 30	0%	0%	0%	0%	Obesity
30 - 34.9	0%	40%	0%	7%	obesity class I
35 - 39.9	0%	7%	0%	0%	obesity class II
≥ 40	0%	7%	0%	0%	obesity classIII

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The Correlation Between Level of DPD and Clinical Variables For All Study Groups.

The statistical correlation analysis between the concentration of DPD and the studied clinical variables was performed on all groups generally, as shown in **Table [4]** using Pearson's correlation coefficients.

Table 4: The Correlation Between Level of DPD And Clinical Variables For All Study Groups.

DPD					
Groups		**G1**	**G2**	**G3**	**G4**
Parameters		**Control (-ve) Healthy**	**Control (+ve) untreated**	**Colon Cancer (treated)**	**Stomach Cancer (treated)**
Age (year)	**r**	-0.455	0.122	0.378	0.234
	p value	0.118	0.666	0.165	0.401
BMI (kg/m2)	**r**	0.258	0.075	0.368	0.252
	p value	0.395	0.790	0.177	0.364
Blood Urea	**r**	-0.098	0.153	0.099	-0.181
	p value	0.750	0.587	0.749	0.518
S.Creatinine	**r**	-0.618	0.298	0.378	-0.050
	p value	0.024	0.281	0.203	0.859
Albumin	**r**	-0.277	0.376	-0.272	-0.176
	p value	0.360	0.168	0.326	0.529
Total Protein	**r**	0.305	0.113	-0.157	-0.261
	p value	0.310	0.689	0.576	0.347

*** Significant Correlation at 0.01 level .**

The current study results showed the correlation coefficient of DPD level with [Age, BMI, Urea, Creatinine, Albumin, and Total protein] in patients and control groups.Findings, No- Significant Correlation between the concentration of DPD and all the studied variables for all study groups ($p>0.01$), as shown in **Table [3]**.

The Correlation Between BMI and Clinical Variables For All Study Groups.

The statistical correlation analysis between the BMI and the studied clinical variables was performed on all groups generally, as shown in **Table [5]**using Pearson's correlation coefficients.

The current study results showed a significant positive correlation between the BMI and S.Creatinine [($r = 0.688$, $p = 0.005$)] in (Colon Cancer treated). Are shown in **Figure [2].**

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Table 5: The Correlation Between BMI And Clinical Variables For All Study Groups.

BMI					
Groups		**G1**	**G2**	**G3**	**G4**
Parameters		**Control (-ve) Healthy**	**Control (+ve) untreated**	**Colon Cancer (treated)**	**StomachCancer (treated)**
Age (year)	**r**	-0.484	0.080	-0.019	0.605
	p value	0.094	0.778	0.948	0.017
Blood Urea	**r**	0.202	-0.266	0.584	0.199
	p value	0.509	0.338	0.022	0.477
S.Creatinine	**r**	-0.276	0.098	0.688	0.253
	p value	0.362	0.727	0.005*	0.363
Albumin	**r**	0.308	-0.362	0.252	-0.233
	p value	0.307	0.185	0.364	0.403
Total Protein	**r**	0.318	0.046	0.218	0.073
	p value	0.290	0.870	0.435	0.795

*** Significant Correlation at 0.01 level .**

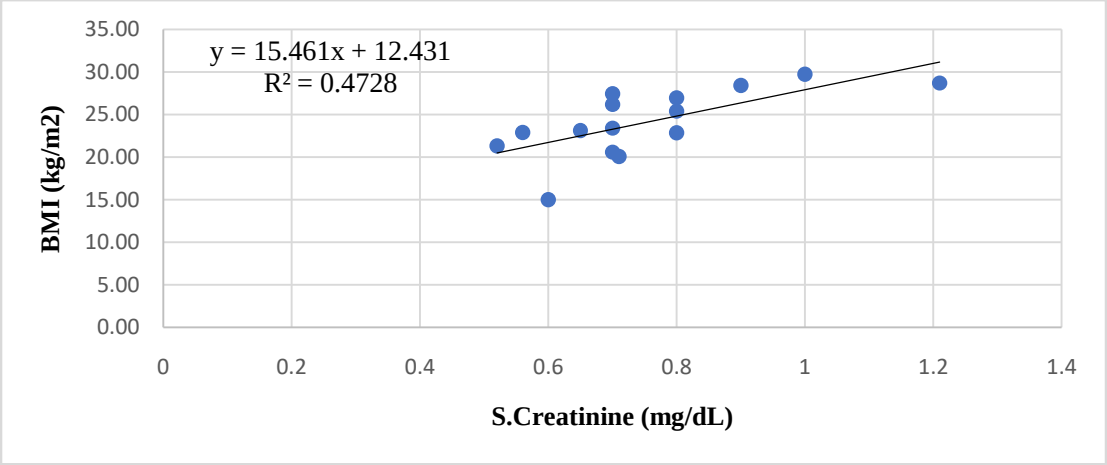

Figure [2]: The Correlation Between BMI and S.Creatinineforthe patient with Colon cancer.

This result agreed with a previous study**(Ahmed, Fadlalla, and Bakheit 2018).**showed a positive correlation or direct relationship between BMI with Serum Creatinine concentrations in both genders age equal to 45 or above.

The Correlation Between Blood Urea and Clinical Variables For All Study Groups.

The statistical correlation analysis between Blood Urea and the studied clinical variables was performed on all groups generally, as shown in**Table [6]** using Pearson's correlation coefficients. The current study results showed a significant positive correlation between Blood Urea and Age

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[(r = 0.708, p = 0.003)]are shown in **Figure [3].**whereas, we are finding a significant positive correlation between Blood Urea and S.Creatinine [(r= 0.800,p =0.0003)] in patients with Stomach Cancer (treated). Are shown in **Figure [4].**

Table [6]: The Correlation Between Blood Urea And Clinical Variables For All Study Groups.

Blood Urea					
Groups		**G1**	**G2**	**G3**	**G4**
Parameters		**Control (-ve) Healthy**	**Control (+ve) untreated**	**Colon Cancer (treated)**	**StomachCancer (treated)**
Age (year)	**r**	-0.144	0.257	-0.010	0.708
	p value	0.639	0.355	0.971	0.003*
S.Creatinine	**r**	-0.062	0.006	0.257	0.800
	p value	0.842	0.983	0.355	0.0003*
Albumin	**r**	0.339	0.470	0.141	-0.090
	p value	0.216	0.077	0.616	0.749
Total Protein	**r**	0.359	0.235	0.252	-0.149
	p value	0.188	0.398	0.365	0.597

*** Significant Correlation at 0.01 level .**

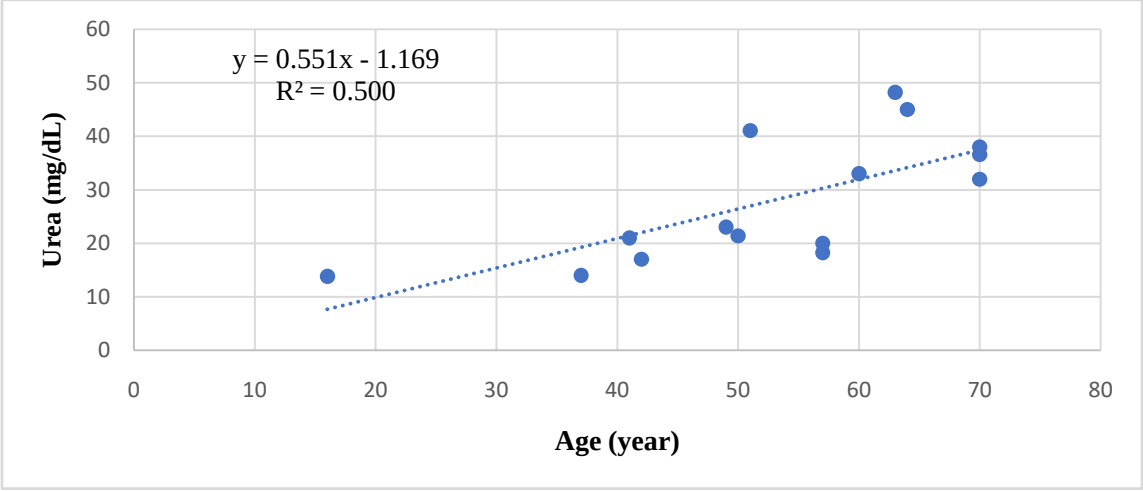

Figure [3]: The Correlation Between Blood Urea and Age for patients with Stomach Cancer (treated).

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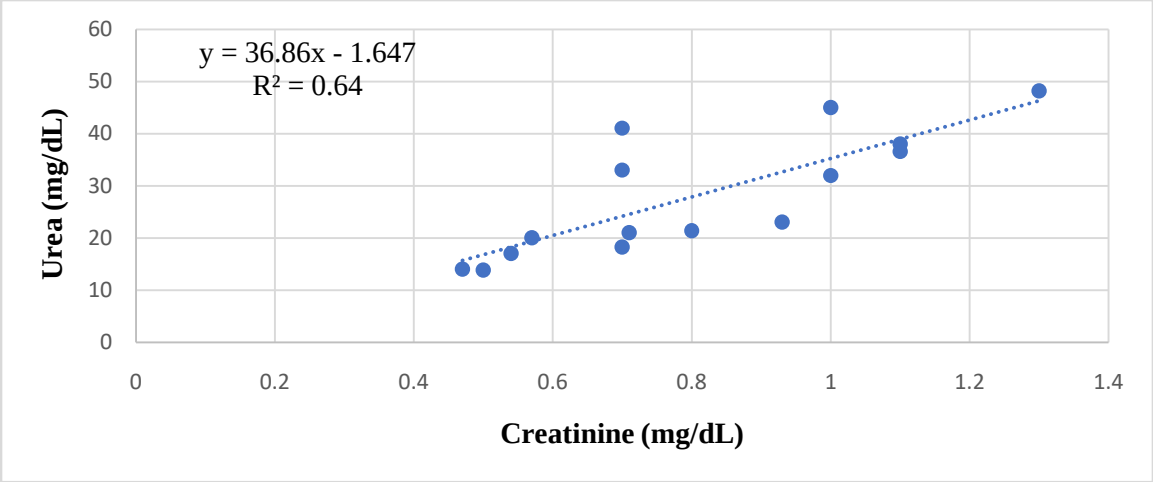

Figure [4]:The Correlation BetweenUrea and Creatinine for patients with Stomach Cancer (treated).

Several physiologic and functional changes in the kidney have been identified as age-related. Including; (Reduced kidney size, changed tubular structure, renal artery vascular changes., increased glomerular sclerosis, and a changed vascular flow pattern) are some of the anatomic anomalies seen in the aging kidney and are some causes of renal dysfunction**(Meyer and Bellucci 1986).**

Age is an important factor affecting kidney function in cancer patients, especially in the older.however, older patients have more comorbid conditions and are less tolerant of treatment toxicity than younger patients. Renal function impairment is frequent in older patients **(Ohara et al. 2012).**

To understand the impact of aging on renal function parameters. Our findings on the relationship between increasing age, renal function parameters, showed a direct correlation between urea and age.whereas Serum urea andCreatinine levels showed a statistically significant increase between years of age, in patients with Stomach Cancer (treated).

The Correlation Between Level of Albumin And Clinical Variables For All Study Groups.

The statistical correlation analysis between Albumin and the studied clinical variables was performed on all groups generally, as shown in **Table [7]** using Pearson's correlation coefficients.

The current study results showed a significant positive correlation between Albumin and Total Protein [(r = 0.760, p = 0.001)] in patients with Colon Cancer (treated),are shown in

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Figure [5].

Table[7]: The Correlation Between Creatinine And Clinical Variables For All Study Groups.

Albumin					
Groups		**G1**	**G2**	**G3**	**G4**
Parameters		**Control (-ve) Healthy**	**Control (+ve) untreated**	**Colon Cancer (treated)**	**StomachCancer (treated)**
Age (year)	**r**	-0.351	-0.048	-0.094	-0.223
	p value	0.239	0.865	0.740	0.424
Blood Urea	**r**	0.339	0.470	0.141	-0.090
	p value	0.216	0.077	0.616	0.749
S.Creatinine	**r**	0.339	0.086	0.271	0.100
	p value	0.216	0.760	0.329	0.723
Total Protein	**r**	0.229	0.430	0.760	0.615
	p value	0.411	0.110	0.001*	0.015

*** Significant Correlation at 0.01 level .**

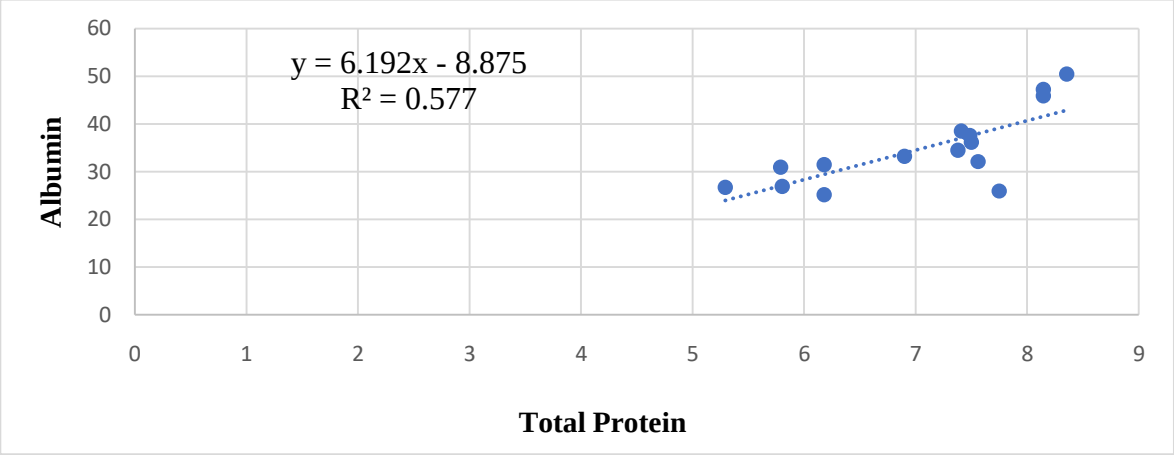

Figure [5]:The Correlation Between Albumin and Total Protein for patients with Colon Cancer (treated).

The prevalence of hypoalbuminemia is generally high in cancer patients. Therefore, there was strong interest in the role of hypoalbuminemia in colorectal cancer patients. According to basic and clinical studies, (hypoalbuminemia, starvation, and cancer cachexia) are side effects of the body's systemic inflammatory reaction to Cancer**(Nazha 2015)**

In cancer patients, hypoalbuminemia is an ordinary phenomenon. Hypoalbuminemia is common in cancer patients with digestive tract cancers linked to elevated catabolism, obstruction of the digestive tract, and the continuing systemic inflammatory reaction caused by Cancer. According

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to previous studies, pre-therapeutic hypoalbuminemia is a significant predictor of short-term postoperative outcomes in the digestive system's various malignant tumors. Linked Hypoalbuminemia with an elevated risk of severe postoperative complications. Such as sepsis, respiratory failure, heart failure, and postoperative irregular heartbeat. **(Wu et al. 2015)**

Colorectal cancer (CRC)patients with low serum albumin concentration or" mild hypoalbuminemia" (Albumin 25–35 g/L). With malnutrition affects post-operative. Have significantly linked with a blood clot in a vein or Deep vein thrombosis (DVT). Additional to the blockage of an artery in the lungs, "Pulmonary embolism (PE)" on the other hand, patients with mild hypoalbuminemia. Occurred complications associated with the infection, such as infection in a surgical location, deep infection in the surgical site, pneumonia, and septic shock. **(Hu et al. 2019)**

Toxicity of 5-FU

Toxicities associated with treatment are listed in **Table [8]** and **Figure 6,7** for patients with cancer after treatment with 5-FU in both genders and include:

- Nausea
- Vomiting
- Diarrhea
- Mouth Sores (Mucositis)
- Mouth inflammation (Stomatitis)
- Hyperpigmentation
- Hand-Foot Syndrome (HFS)
- Hypertension
- Tiredness, and Anorexia.

Table (8): The Toxicity Level in patients Cancer After treated with 5-FU.

Groups	G1				G2			
	Colon Cancer (After treated with 5-FU) N=15				Stomach Cancer (After treated with 5-FU) N=15			
Symptoms	gender			Percent	gender			Percent
	Male	Female	Total		Male	Female	Total	
Nausea	6	8	14	93%	8	5	13	87%

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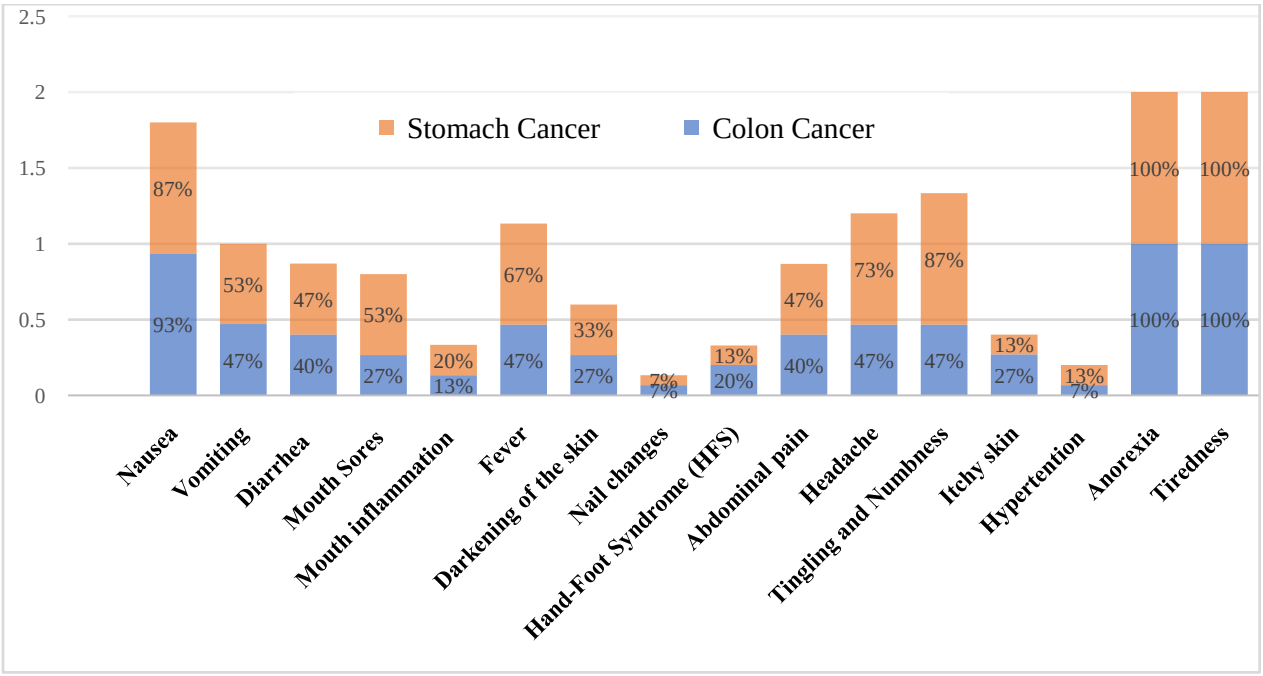
Vomiting	3	4	7	47%	5	3	8	53%
Diarrhea	2	4	6	40%	2	5	7	47%
Mouth Sores	3	1	4	27%	4	4	8	53%
Mouth inflammation	0	2	2	13%	2	1	3	20%
Fever	1	6	7	47%	5	5	10	67%
Hyperpigmentation	1	3	4	27%	4	1	5	33%
Nail changes (discoloration)	0	1	1	7%	1	0	1	7%
Hand-Foot Syndrome (HFS)	2	1	3	20%	1	1	2	13%
Abdominal pain	2	4	6	40%	4	3	7	47%
Headache	1	6	7	47%	6	5	11	73%
Tingling and Numbness	2	5	7	47%	6	7	13	87%
Itchy skin (pruritus)	2	2	4	27%	1	1	2	13%
Hypertention	1	0	1	7%	1	1	2	13%
Anorexia	6	9	15	100%	8	7	15	100%
Tiredness	6	9	15	100%	8	7	15	100%



Figure(6): The Toxicity Ratio in patients (Colon and Stomach) Cancer After Treatment with 5-FU.

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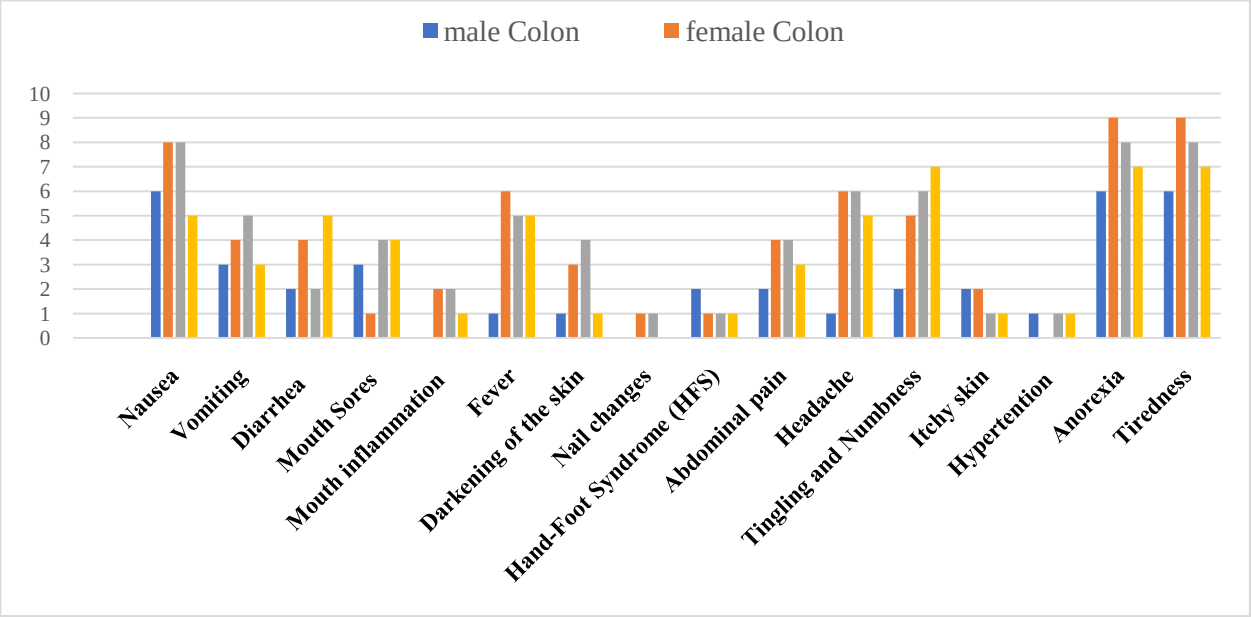

Figure(7): showing the gender-based comparison of the toxicity 5-FU for colon and stomach cancer patients.

Conclusion:

The DPD activity had No Correlation with Age, BMI, Renal function parameters for all study groups. Our study shows a positive relationship between BMI and serum Creatinine Also, between Albumin and Total Protein in Colon cancer patients (treated with 5-FU). the relationship between increasing age, renal function parameters, showed a direct correlation between urea and age. whereas Serum urea and Creatinine levels showed a statistically significant increase between years of age, in patients with Stomach Cancer.

The Toxicities associated with 5-Fluorouracil we findings:

Nausea(90%),vomiting(60%),diarrhea(63%),Mucositis(40%),Stomatitis(37%),Hyperpigmentation (30%), Hypertension(10%). Finally Tiredness, and Anorexia (100%) for both gender.

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