Article

Body Mass Index effect on Interleukin-2 , its receptor and Liver Functions Tests in Iraqi ovary and uterine Cancers Patients.

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Abstract

Interleukin-2 was first identified as a potent T-cell growth factor and Interleukin-2 has a multifaceted role in activating the immune system by interacting with various types of cells. When Interleukin-2 binds to its receptor (Interleukin-2 Receptor), it triggers crucial signaling pathways such as Janus Kinases/Signal Transducer and Activator of Transcription Proteins (JAK/STAT), phosphoinositide-3-kinase/Protein kinase B (PI3K/AKT) and Mitogen-Activated Protein Kinases (MAPKs). This study aimed to the Body Mass Index effect on Interleukin-2 and its receptor in Iraqi patients with ovary and uterine cancers. Methods: Serum IL-2 and IL-2R levels were measured in patients with ovarian cancer (n = 40), uterine cancer (n=40) and controls (n = 40). Results: Serum IL-2 and its receptor, were elevated in patients compared to controls ($p < 0.001$). Conclusion: The role of IL-2 and IL-2R within the tumor microenvironment remains a fascinating and vital area of exploration. Their multifaceted interplay mediating both immune activation and regulation has profound implications on the immune response to various cancers such as ovarian and uterine cancer.

Keywords: Ovary Cancer, Uterine Cancer, IL-2, IL-2R, BMI and Liver Function.

Introduction

Ovarian cancer poses a significant health threat to women, contributing substantially to both morbidity and mortality rates. Over the past four decades, there has been a concerning rise in ovarian cancer-related deaths among women aged 65 and older (1). Despite ongoing research, the exact causes of ovarian cancer remain elusive. Various hypotheses have been proposed regarding the origins of epithelial ovarian tumors (2).

One such hypothesis, the incessant ovulation theory, suggests that the repetitive process of ovulation may lead to continuous proliferation and repair of the surface epithelial cells. This persistent cycle increases the likelihood of abnormal repair processes, potentially resulting in the development of malignant cells and subsequent ovarian cancer formation (3).

Several risk factors have been identified, including personal and family history of breast and ovarian cancer, cigarette smoking, obesity, advancing age, and prolonged use of high-dose estrogens (2). Additionally, dietary factors may also play a role in ovarian cancer development (4).

Uterine cancer ranks among the prevalent female cancers globally, exhibiting significant diversity in both morbidity and mortality rates. Research indicates a correlation between elevated body mass index (BMI) and the occurrence of uterine cancer. (4). while the exact cause of uterine cancer remains elusive, various risk factors have been identified, including obesity, metabolic syndrome, diabetes mellitus, and hypertension. (5,6)

Obesity, often assessed through body mass index (BMI), is linked to reduced survival rates in numerous cancers such as breast and colorectal cancer (7). Additionally, it is associated with an increased likelihood of developing uterine cancer (8).

Interleukin-2 (IL-2) and its receptor (IL-2R), were identified for their influential role in promoting the growth and functionality of human T cells. Their multifaceted activities have garnered considerable attention for potential cancer therapies (9). IL-2 operates in a complex manner within the immune system, interacting with diverse cell types, resulting in varied and sometimes opposing effects that can either enhance or suppress subsequent immune responses (10). Upon binding to its receptor (IL-2R), IL-2 initiates key signaling pathways, notably the JAK/STAT pathway. The IL-2R comprises α (CD25), β (CD122), and γ (CD132) subunits (11), forming a transmembrane glycoprotein receptor found on the surface of T and B cells, among other immune cells (12). This receptor's pivotal role in immune responses is highlighted by its ability to bind IL-2, triggering a series of events culminating in the activation and proliferation of these cells (13).

The liver enzymes Alkaline phosphatase (ALP), Alanine aminotransferase (ALT), and Aspartate transaminase (AST) are frequently assessed in clinical settings to diagnose liver diseases, as they are discharged into the bloodstream following liver damage (14).

Materials & Methods

Blood samples of about 5 mL were collected from 80 patients and divided into two groups G1: 40 Ovary Cancer and G2: 40 Uterine Cancer, G1 divided into two groups: A (23) Ovary Cancer with BMI ≥ 25 kg/m^2 and G1 B (17) Ovary Cancer with BMI< 25 kg/m2. G2 divided into two groups: G2 A (23) Uterine Cancer with BMI ≥ 25 kg/m^2 and G2 B (17) uterine Cancer with BMI<25 kg/m^2. G3 control BMI<25 kg/m^2 and age range for all groups about (40-60) years all sample patients Collected from oncology teaching hospital in the medical city from October 2022 to April 2023.

IL-2 and IL-2R were estimated by Kit Elisa (EH 0189) and (EH0081) respectively.

Statistical Evaluation

The investigation's findings were displayed as mean ±SD to compare the patient and control groups, a t-test was run. Significant P values of 0.05 and 0.001 were also discovered (22).

Results and Discussion

Table(1): IL-2R, IL-2, GPT, GOT and ALP Levels in all Studied Groups

	Gynecologic cancer Mean ± SD	Health control G3	*P-value*

Parameters	Ovary cancer G1 No.40	Uterine Cancer G2 No.40	No.40 Mean ± SD	G1& G2	G1& G3	G2 & G3
IL-2R(Pg/ml)	799.7± 105.6	708.5± 182.3	468.2±39.67	<0.001	<0.001	<0.001
IL-2 (Pg/ml)	100.2± 19	97.2±19.14	47.6±7.06	<0.001	<0.001	<0.001
GPT (U/ml)	16.3 ± 0.61	27.04± 1.75	7.3±1.44	<0.001	<0.001	<0.001
GOT (U/ml)	20.4±0.74	20.98± 0.07	18.18±2.7	<0.001	<0.001	<0.001
ALP(U/ml)	91.06±3.1	116.95±2.9	55.5±6.6	<0.001	<0.001	<0.001

**P-value*< 0.001 significant

Table(2): IL-2R, IL-2, GPT, GOT and ALP Levels in Ovary Cancer Groups

Parameters			
	Ovary Cancer BMI≥ 25Kg/m² No.17	Ovary Cancer BMI< 25 Kg/m² No.23	*P-value*
IL-2R (Pg/ml)	768.61± 89.8	788.91± 118	0.29
IL-2 (Pg/ml)	99.82± 18.37	100.57±20.1	0.88
GPT (U/ml)	20 ± 3.6	20.8± 6.4	0.7
GOT (U/ml)	14.6±4.6	17.7± 7.0	0.09
ALP(U/ml)	86.8±3.2	94.9±3.0	0.2

Table(3): IL-2R, IL-2, GPT, GOT and ALP Levels in Uterine Cancer Groups

Parameters			
	Uterine **Cancer** BMI≥ 25 Kg/m² No.17	Uterine **Cancer** BMI< 25 Kg/m² No.23	*P-value*
IL-2R (Pg/ml)	801.5± 111	52.2± 6.44	0.001
IL-2 (Pg/ml)	85.8± 6.3	105.7±21	0.004
GPT (U/ml)	20.3 ± 2	21± 9	0.81
GOT (U/ml)	20±3	32± 19	0.01
ALP	127±21	108±31	0.03

Table(4): Correlation between IL-2R and Liver Function Tests in Ovary Cancer

	Factors	**GPT**	**GOT**	**ALP**
IL-2R	**R person**	-0.048	0.22	-0. 478*
	P	0.851	0.381	0.04

Table(5): Correlation between IL-2 and Liver Function Tests in Ovary Cancer

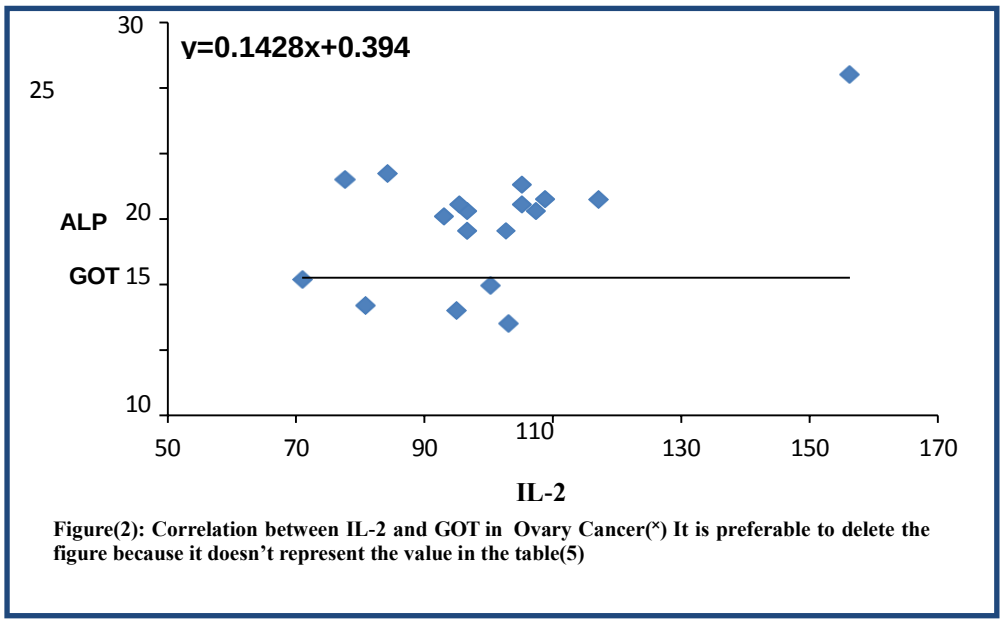
	Factors	**GPT**	**GOT**	**ALP**
IL-2	**R** person	0.134	0.570*	0.12
	P	0.597	0.013	0.635

Table(6): Correlation between IL-2R and Liver Function Tests in Uterine Cancer

	Factors	**GPT**	**GOT**	**ALP**
IL-2R	**R** person	0107	0.33	0.082
	P	0.671	0.192	0.755

Table(7): Correlation between IL-2 and Liver Function Tests in Uterine Cancer

	Factors	GPT	GOT	ALP
IL-2	R person	0.212	-0.467	0.244
	P	0.415	0.06	0.346

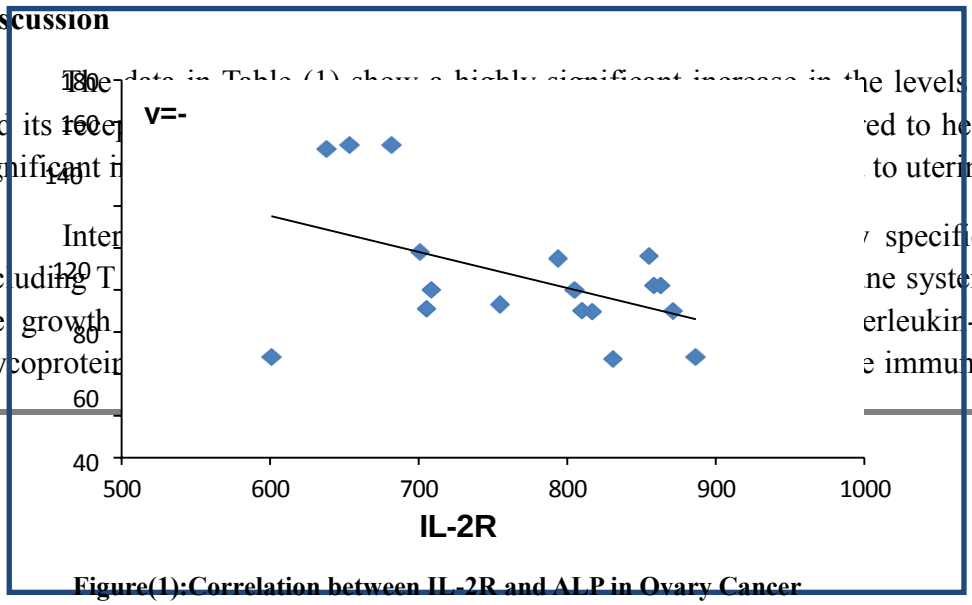


Figure(2): Correlation between IL-2 and GOT in Ovary Cancer(ˣ) It is preferable to delete the figure because it doesn't represent the value in the table(5)

Discussion

The data in Table (1) show a highly significant increase in the levels of interleukin-2 and its receptor in patients with uterine cancer compared to healthy controls, a significant increase in the levels of interleukin-2 and its receptor in patients with uterine cancer.

Interleukin-2 is a cytokine that plays a crucial role in the activation of specific immune cells including T lymphocytes, which are responsible for regulating the immune system by promoting the growth and proliferation of these cells. The interleukin-2 receptor is a glycoprotein that is expressed on the surface of activated T cells and other cells of the immune system. When



Figure(1):Correlation between IL-2R and ALP in Ovary Cancer

IL-2 binds to this receptor, it initiates a series of events that lead to the activation and proliferation of these cells (16).

Elevated levels of interleukin-2 and its receptor signify effective immune system activity, crucial for orchestrating a balanced response against pathogens by regulating immune activation and suppression. IL-2 also plays a significant role in immune responses against tumor cells, facilitating the expansion of regulatory T cells (Tregs). However, this expansion of Tregs may potentially hinder anti-tumor immune responses.

Interleukin-2 and its receptor play pivotal roles in the onset and progression of cancer. Specifically, IL-2 contributes to the proliferation and survival of certain tumor cells, while IL-2R is involved in the formation of new blood vessels within tumors, a process known as angiogenesis (19). Furthermore, both IL-2 and IL-2R have been implicated in facilitating cancer metastasis from the primary tumor to distant sites within the body (20).

Moreover, IL-2 and IL-2R are integral components of various cancer-related pathways. For instance, IL-2 regulates critical cellular processes including proliferation, programmed cell death (apoptosis), and angiogenesis. Conversely, IL-2R is associated with tumor growth, metastasis, and evasion of the immune system (21).

Data in Table(2) Showed a non-significant elevated in IL-2 and IL-2R in Ovarian cancer serum Which has more than 25 Kg/m² of BMI as compared with Ovarian Cancer which has BMI≥ 25 kg/m², only a limited number of studies have investigated the link between obesity and ovarian cancer. Obesity, typically assessed through body mass index (BMI), has been linked to worse survival outcomes in various types of cancer, such as breast, prostate, and colorectal cancer (22,23). So in ovarian cancer, There was a slight increase in the levels of IL-2 and IL-2R in obese women.

Table (3) Shows a high significant increase in IL-2 and a significant Lowering in IL-2R in obese Women with uterine cancer and having a BMI< 25 Kg/m² as compared with uterine cancer women who have a BMI≥ 25 Kg/m². Obesity is associated with higher incidences of Uterine Cancer and previous studies showed the rate of abdominal hysterectomy performed for benign indications was increased in obese uterine patients.

So obesity plays an important role in increasing the level of IL-2, but not in IL-2R. The elevated levels of IL-2 may represent a novel biomarker for Progression of inflammation and immunity system in Cancer (24-29).

Obtained data in Tables (1) , (2) and (3) showed the levels of activity enzymes GPT, GOT, and ALP in Iraqi patients with ovary and Uterine Cancer as compared with healthy control. There were elevated significant levels of GPT and ALP in uterine and ovary cancer as compared with healthy control while there were slightly non-significant increased levels in uterine and ovary cancer with healthy control. These liver enzymes are commonly measured in clinical for Liver disease they are released in the blood after liver injury (30-34). The increased levels of GPT and ALP may be due to chemotherapy drug for uterine and ovary cancer. Data in Table 2 and three Showed the affecting of BMI in ovary and uterine cancer on (GPT,GOT and ALP). Obesity is a well-known risk factor For metabolic syndrome (35).which

can Further lead to diabetes (36), Cardiovascular disease, and cancer, overweight or obese individuals have a higher risk of developing Statuses causing abnormal liver Function (37). Data in Tables 4 and 5 showed a high significant negative correlation (-ve) between IL-2R and ALP as shown in Figure 1 and no significant positive correlation with GPT and GOT in Ovary cancer. and a high significant positive correlation (+ve) between IL-2 and GOT in the same group as in Figure 2 . There was a non-significant negative and positive correlation between IL-2R and IL-2 with liver enzymes in uterine cancer as shown in table 6 and 7.

Conclusion:

Diverse IL-2 and IL-2R as expression levels across in ovary and uterine cancer and responses to the immune system and it could be a good marker for Gynecology cancer.

Author Contributions

Sarah Ahmed and A. F. Al-Taie are both writers. I helped with research design, data collection and analysis, data interpretation, paper preparation, and critical revision.

Authors declaration

Conflicts of interest: Nil

We affirm that all of the Tables and Figures in this manuscript are our own.

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