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STUDY OF BIOCHEMICAL MARKER TARC FOR HODGKIN LYMPHOMA IN HUMAN AND ITS RELATION WITH CLINICO–PATHOLOGICAL BEHAVIOR

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ABSTRACT

Back ground: Lymphomas can affect any organ in the body and present with a wide range of symptoms and is a curable disease in most patients. In the present study, TARC is the main parameter to prognosis of Hodgkin lymphoma, its positive Hodgkin Reed-Sternberg (HRS) cells has been found in Hodgkin patients. TARC serum levels are significantly high in classical Hodgkin Lymphoma (cHL) patients, so, identification of sensitive biomarker to improve the prognosis related Hodgkin lymphoma is needed. **Aim of the work:** The aim of the present study was to discuss the prognosis utility of serum TARC in patients for Hodgkin lymphoma during and post therapy the clinical advantage of this marker will be decreased or normal during or post therapy. TARC is a marker used for diagnosis and in follow up the patients for Hodgkin lymphoma. **Results:** Serum TARC was significantly in most patients for Hodgkin lymphoma. The receiver operating characteristic curve (ROC) curve showed the best cutoff values for TARC was 150 ng / l. Area under the curve of TARC was 0.84, to differentiate patients with complete response from those with partial response. The area under the ROC curve (AUC) was 0.826 with sensitivity 81.3% and specificity 74.4%. To differentiate patients with early stage from those with late stage, the area under the ROC curve was 0.840 with sensitivity 88.0% and specificity 75.0%, and to differentiate patients with B-symptoms from those with no B-symptoms, the area under the ROC curve was 0.860 with sensitivity 86.0% and specificity 75.0%. **Conclusion:** Results revealed that serum TARC may be used as potential prognostic marker for Hodgkin lymphoma patients.

KEYWORDS: Hodgkin lymphoma patients, thymus and activation-related chemokine (TARC).

INTRODUCTION

Lymphoma is type of cancer of the lymph system, which is a part of the immunity. (Shankland et al., 2012). Lymphomas can impact any organ in the body with broad range of symptoms, they are divided into Hodgkin lymphoma and non-Hodgkin's lymphoma (NHL), they arise from lymphocytes at different stages of evolution, the features of subtype lymphoma cancer to explain the cell from which they produced (Armitage et al., 2017). Hodgkin's lymphoma ranged for approximately 30% of all malignant lymphoma (Diehl et al., 2003). In Egypt, the recurrence of malignant Lymphoma varies between 7.8% to 12% of cancer cases as the registries of various cancer centers indicated (ElBolkainy et al., 1984). In the NCI-Egypt cancer pathology registry, the ratio of NHL to HL was 2.3: 1 and HL constituted 30.3% of all types of lymphoma cases (Mokhtar and Khaled, 2002). Hodgkin lymphoma is characterized by the Presence of a rather low number of neoplastic cells, either multinucleated (Reed Sternbergcells, RSCs) or mononucleated (Hodgkin cells and variants, HCs) (viviani et al., 2017). It is chronic, progressive, neo plastic disorder of lymphatic tissue with the painless and enlargement of lymph nodes with progression to extra lymphatic zones such as spleen and liver. It may metastasize to bone marrow and other organs. zones which more initially influenced are usually the lymph glands of the neck or groin, commonly on one side (Goodman and Snyder, 2007). Around age (25-30) years and after (55) years, men are typically diagnosed for Hodgkin lymphoma more than women. Hodgkin lymphoma can happen in children and adults, but less than 5 years little develop to this disease, but 10% of Hodgkin lymphoma cases happen in children 16 years old and younger (Goodman and Fuller, 2009). There are two subtypes of Hodgkin's lymphoma, classic and nodular lymphocyte-predominant, classic Hodgkin's lymphoma which classified to four categories based what the cell resemble under a microscope, these are Nodular-sclerosis Hodgkin lymphoma, lymphocyte-rich Hodgkin

lymphoma, Mixed-cellularity Hodgkin lymphoma and Lymphocyte-depleted Hodgkin lymphoma (Goodman and Snyder, 2007). A history of infectious mononucleosis as a result of this infection by Epstein–Barr virus (EBV) may increase the risk of Hodgkin lymphoma, but the accurate contribution of Epstein–Barr virus remains broadly unknown (Gandhi et al., 2004). Ideal markers must be specific, sensitive, and plain to assay and interpret with rapid turnaround high reproducibility and comparability between laboratories. Serum protein estimation by Enzyme-linked immuno sorbent assay (ELISA) exploits an established technology used in the diagnostic laboratory. Furthermore, while tissue markers could be applied routinely to the diagnostic biopsy to provide prognostic information, they have no applicability in monitoring disease response. In contrast, biomarkers based on blood have possibility to supply information on disease response and exhibit of early relapse (Gandhi et al., 2006). One potency biomarker for Hodgkin lymphoma is the chemokine thymus and activation-regulated chemokine (TARC). This is highly expressed by malignant Hodgkin Reed-Sternberg cells which excreted into the serum (Hnatkova et al., 2009). High (TARC) levels in chord with immune regulatory cytokines and chemokines contribute in the inflammatory of Hodgkin lymphoma microenvironment, promoting tumor initiation, maintenance and progression (Aldinucci et al., 2010). Thus, (TARC) might be a potential marker for an early response assessment. (TARC) levels are elevated in the most patients with HL at diagnosis, and rapidly turn to normal through treatment (Plattel et al., 2012).

Subjects and Methods

In this research, patients were collected from Clinics of Damietta, Mansoura during the interval between November 2015 and April 2016, this study was proceed on eighty four patients they were diagnosed Hodgkin lymphoma during and post-therapy. Included criteria, All Egyptian patients were diagnosed by Hodgkin lymphoma and with age ranging from 18 to 70 years old regardless to sex, social status or occupation. Excluded criteria, Patients who diagnosed as Epstein–Barr virus (EBV), Human Immunodeficiency Virus (HIV) and auto-immune diseases were positive.

Samples collection

Three ml venous blood were withdrawn from each individual, was collected and coagulated in room temperature 10-20 mins, centrifugated 20 min at the speed of 2000-3000 rpm, for separation of serum which was transferred into another tube and kept frozen at -20°C to detect tumor marker TARC which was done using ELISA (enzyme-linked immune sorbent assay) kit by (ELISA plate analyzer, ELIZA read well touch, Rebonik, India).

Reagent preparation

All reagents were allowed to reach room temperature (the reagents should not be dissolving at 37°C directly and mixed thoroughly by swirling before pipetting, and avoid foaming**.**

Statistical analysis

All statistical analysis of the data was done by statistical package for the social sciences (SPSS), version 20.0 on Microsoft Windows XP (SPSS Inc., Chicago, IL, USA). Optimal biomarker cut-off levels for patients were determined by using the Receiver Operating Characteristic (ROC) method. Differences in biomarker levels were calculated with the unpaired t-test. Baseline biomarker levels were correlated to Ann Arbor stage and response for treatment. Kaplan–Meier analysis was used to calculate OS. Boxplot which appears the interquartile range, the whiskers specify the highest and lowest values, and the line across the box indicates the median value.

RESULTS

The study was proceed on eighty four patients for Hodgkin Lymphoma divided according to pathology, stage, symptoms and response to treatment, In the study there were 48 (75.2%) males and 36 (24.8%) females all were patients for Hodgkin Lymphoma with average age <35 years 34 patients (40.5%) and >35 years 50 patients (59.5%). Patients were classified to nodular sclerosis 45 (53.5%) and mixed cellularity 23 (27.3%) which were appear as the most frequent subtype followed by lymphocyte depletion 10 (9.5%) then nodular lymphocyte predominant 6 (7.1%), according to the histological WHO classification. Patients classified to four stages, in the study stage (I) were the most frequent stage 38 (45.5%) patients followed by stage (III) 28 (33.3%) patients then stage (II) 14 (16.7%) patients and 4 (4.8%) patients were distributing for stage (IV). Patients were classified as indicated in Ann Arbor stage to early stage without bulky lesions (I- II) 52 (61.9%) patients and in advanced stage with bulky lesions (III- IV) 32 (38.1%) patients. B symptoms varied between patients, 22 (26.2%) patients were with B symptoms, and 62 (73.8%) patients were with no B symptoms. Most of Patients presented with complete response 48 (55. 1%) followed by which presented with partial response 34 (24.4%), the poly chemotherapy treatment frequently used was ABVD (adriamycin/bleomycin/vinblastine/ dacarbazine) followed by many types of chemotherapy, patients were treated with ABVD only were 24 (38.1%), patients were treated initially with ABVD and/or other chemo-therapy (following therapy strategies for HL patients BEACOPP (bleomycin / etoposide / adriamycincyclophosphamide / vincristine / procarbazine / prednisone), DHAP (dexamethasone / highdosearaC / cisplatin), ICE (ifosfamide / carboplatin / etoposide), IGEV (ifosfamide / gemcitabine / vinorelbine / dexamethasone), MINE (mesna, ifosfamide, mitoxantrone, and etoposide) 42 (50.0%) most patients in this group were not treated by radiotherapy ABVD therapy and involved-field radiation Therapy (IFRT) 10 (11.9%), Patients were treated by ABVD only were classified according to count of cycles, patients were

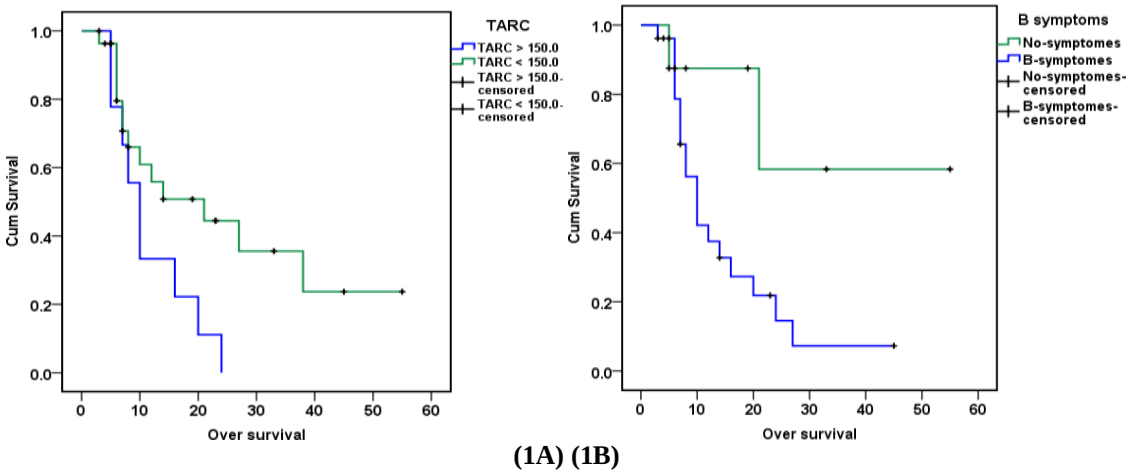
treated by two cycles 4(12.5%), patients were treated by four cycles 8 (25.0%), patients were treated by six cycles 12 (37.5%) and patients were treated by eight cycles 8 (25.0%) as indicated in (Table1). most frequent subtype Nodular Sclerosis was with a mean value 263.38±75.30, Mixed Cellularity sub type was with a mean value 257.04±78.21, Lymphocyte-Depletion subtype was with a mean value 235.30±69.71 and Nodular Lymphocyte Predominant subtype was with a mean value 204.13±68.92. There is no difference in pathology and parameter, TARC was showed significant (p value < 0.05). Early stages (stage I –II) was with a mean value 206.61±65.83 showed in TARC and in advanced stages (stage III–IV) was with a mean value 322.97±84.88 showed in TARC. The relation between Parameter and stages showed that TARC was extremely significant (P value < 0.0001***). With respect to the value of TARC and it is relation to symptoms which are 219.68 ± 69.20 in cases of no-B symptoms and 318.96±103.84 in cases of B-symptom. The relation between Parameters and symptoms showed that TARC was very high significant (P value < 0.001**). 48 patients achieved complete response with a mean value 229.63±71.12 in TARC and 34 patients with partial response with a mean value 293.01± 92.34 in TARC, TARC was showed high significant (p value<0.01) as indicated in (Table2). Kaplan Meier method was to estimate the distribution of over survival was done using individual patient information, the best chosen cut off of TARC was (150 ng/l), Patients with TARC <150 were more response than patients with TARC >150, there was significant difference (x^2=4.179: p<0.04) among detection of quality of over survival distributions for different levels of TARC_150 in Hodgkin lymphoma as indicated in (Figure1A). There was significant difference (x^2=4.117: p<0.042) among detection of quality of over survival Comparisons for different levels of symptoms in Hodgkin lymphoma as indicated in (Figure 1B). The cut off of serum TARC in early stages vs. late stages was 150 ng/l yields AUC was 0.84, with sensitivity 68.8% and specificity 80.8% as indicated in (Figure 2). Optimal biomarker cut-off levels between patients were determined using (ROC) method. Differences in biomarker levels between categorical variables were calculated using the unpaired t-test, using ROC curve we assessed the diagnostic of serum utility of TARC, the cut off of serum TARC in B symptoms vs. no B symptoms was 150 ng/l yield AUC was 0.789, with sensitivity 77.8% and specificity 72.4% as indicated in (Figure 3).

Table (1): Clinicopathological characteristic of patients.

Clinical features		**No**	**Percent**
sex	male	48	57.2 %
	female	36	42.8 %
Age	<35	34	40.4%
	>35	50	59.5%
stages	I	88	45.2%
	II	41	16.7%
	III	88	33.3%
	IV	1	4.8%
pathology	Nodular sclerosis	14	(48.5%)
	Mixed Cellularity	88	(27.3%)
	Lymphocyte Depletion	41	(9.5%)
	Nodular Lymphocyte Predominant	6	(7.1%)
B-symptoms	No B-Symptoms	62	73.8 %
	B-Symptoms	22	26.2 %
response	Partial response	48	57.4 %
	Complete response	34	11.4 %
Therapy type	ABVD and/or other chemotherapy	42	50.0%
	ABVD+RT	10	11.9%
ABVD only	Digit of cycles of ABVD		
	2 cycle	4	12.5%
	4 cycle	8	25.0%
	6 cycle	12	37.5%
	8 cycle	8	25.0%
	Total	32	38.1%

Table (2): Demographic characteristic of patients.

First variable	Second variable	TARC		
		mean	SD	P value
pathology	Nodular Sclerosis	263.38	75.30	< 0.05
	Mixed Cellulariy	257.04	78.21	
	Lymphocyte Depletion	235.30	69.71	
	Nodular Lymphocyte Predominant	204.13	68.92	
Ann prop stage	Early (I – II)	206.61	65.83	<0.0001***
	Advanced (III-VI)	322.97	84.88	
symptoms	B-Symptoms	318.96	103.84	<0.001**
	No-symptoms	219.68	69.20	
response	Partial response	293.01	92.34	<0.01*
	Complete response	229.63	71.12	<0.01*



(1A) (1B)

Figure (1): Kaplan–Meier curves for estimation of over survival in patients of Hodgkin lymphoma (A) with serum TARC concentrations<150 ng/l and >150 ng/l at prognosis (p<0.04) (B) with symptoms at prognosis (p<0.042).

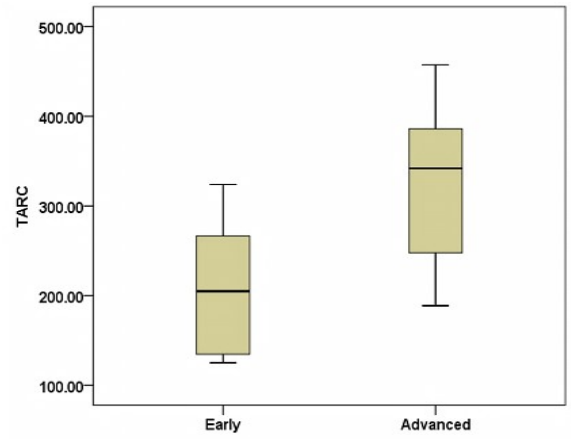


Figure (2): Boxplot of serum TARC in patients. The box appears the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value.

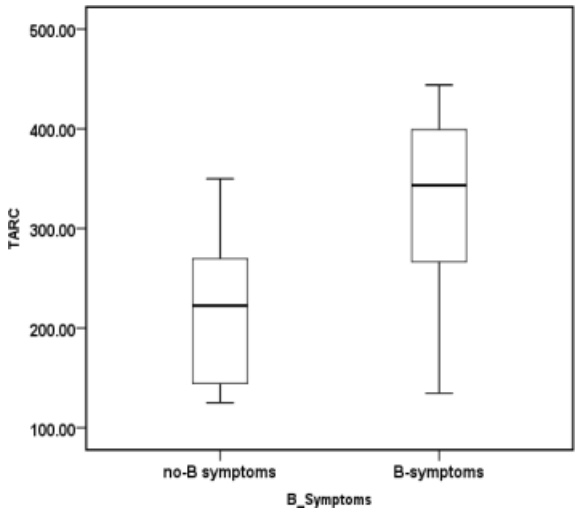


Figure (3): Serum TARC in patients. The box appears the interquartile range. The whiskers indicate the highest and lowest values and the line across the box indicates the median value.

DISCUSSION

Hodgkin's lymphoma (HL) is one type of lymphoma which produces from a specific type of white blood cells called B-lymphocytes. The infectious mononucleosis outcome infection by Epstein–Barr virus (EBV) may increase the risk of HL (Gupta et al., 2016). Treatment of the classical Hodgkin's lymphoma (HL) has been a good story, with treatment of disease by radiotherapy and treatment in advanced stages with combination of chemotherapy with/without radiotherapy leading to improvements since then (Glimelius and Diepstra, 2017). More than 95% of Hodgkin lymphoma (HL) patients in early stage and 80–90% in intermediate and progressive stages can be treated by standard chemo and radiotherapy. However, this outcome is associated with treatment of a significant proportion of patients; this can cause unnecessary treatment- related toxicity including organ damage and secondary malignancies or early progression and relapse (Sauer et al., 2013). There are an improvements in survival in the treatment of HL, concerns start to around the long-term toxicities of chemotherapy and radiation therapy (Hodgson et al., 2007), serum levels were lower compared to plasma, this makes it unlikely that serum would be more sensitive than plasma (Ouyang et al., 2013). Prognostic biomarkers for cHL can be divided into risk pre- therapy which appears disease response throughout therapy, although tissue biomarkers may be useful before to therapy, it is an impracticable source for repeated measures to observe disease response. Nevertheless, markers elevated in cHL tumor tissues may also be elevated in blood, in contrast to tissue (Shim et al., 2009). Blood- based biomarkers hold to be much more practical, patient friendly and cost-effective and might be used as serial markers during and after treatment to determine early response to treatment and disease recurrence after treatment, these biomarkers can be divided into tumor cell specific markers, secreted by Hodgkin Reed-Sternberg (HRS) cells or markers related to micro-environment (Kuppers et al., 2012 and Liu et al., 2014). The individuals' serum samples were screened for parameter to prognosis Hodgkin lymphoma including determination of thymus and activation-related chemokine (TARC) that was determined using ELISA technique. This study was conducted on eighty four patients diagnosed with Hodgkin lymphoma during, and post-therapy which indicated that TARC during and after treatment in patients with Hodgkin lymphoma related to symptoms (B symptoms n=62 patients and no B symptoms n=22 patients), according to the WHO classification, patients were classified to nodular sclerosis 45 (53.5%) and mixed cellularity 23 (27.3%) which were the most subtypes followed by lymphocyte depletion 10 (9.5%) then nodular lymphocyte predominant 6 (7.1%), stages (early stages (I – II) n=56 patients and in advanced stages (III-VI) n=32 patients), response to treatment (partial response n=34 patients and complete response n=48 patients), therapy type (ABVD only n=32 patients, ABVD and/or other chemotherapy n=42 patients and ABVD+RT (radiotherapy) n=10 patients) and number of cycles of ABVD (2 cycles n=4 patients, 4 cycles n=8 patients, 6 cycles n=12 patients and 8 cycles n=8 patients). some routine parameters were determined as hemoglobin (Hb), white blood cells (WBCs) count, red blood cells (RBCs) count, Platelets count, serum lactate dehydrogenase (LDH), serum Albumin, serum Creatinine, serum uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and erythrocyte sedimentation rate (ESR) but the more parameters were related to Hodgkin lymphoma were serum lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR) which are also increased in inflammation, pregnancy, anemia, autoimmune disorders (such as rheumatoid arthritis and lupus), infections, some kidney diseases and some cancers (such as lymphoma and multiple myeloma). The ESR is decreased in polycythemia, hyper viscosity, sickle cell anemia, leukemia, low plasma protein (due to liver or kidney disease) and congestive heart failure, the basal ESR is slightly higher in females. LDH is an

enzyme which stimulate the transformation of lactate to pyruvate which is an important step in energy production inside the cells, many various types of cells in the body contain this enzyme, some of the organs relatively rich in LDH are the heart, kidney, liver, and muscle tissue, as cells die, LDH is liberated into the blood, some studies suggest LDH Levels as prognostic marker in Hodgkin's disease (Gocheva et al., 2010). The measurement of hematological factors such as Erythrocyte Sedimentation Rate (ESR) and Lactate Dehydrogenase (LDH) help in the prognosis of Hodgkin lymphoma (Kuruvilla, 2009). In our study correlation analysis was determined among LDH and ESR parameters and markers which showed that TARC was positively correlated to LDH, (P value 0.005, r = 0.456**), was positively correlated to ESR1 (P value 0.003, r = 0.496**) and ESR2 (p value 0.0001, r = 0.568**) respectively. The HRS cell specific (TARC) is a very specific marker for cHL disease activity (Sauer et al, 2013 and Moskowitz et al, 2015). Any changes in TARC levels during chemotherapy help in response Evaluation (Jones et al., 2013) in about 85% of patients, TARC is obvious and increased in serum at diagnosis before treatment, Pre-treatment serum TARC levels were associated with stage of disease (Niens et al., 2008). Previous studies have shown that TARC levels in HL patients are significantly correlate well with disease stage and metabolic activity, TARC is the most widely used tumor marker for diagnosis of Hodgkin lymphoma in the current study TARC levels significantly correlated with B symptoms ($p<0.001$), in stages were extremely significant ($p<0.0001$) and in response to treatment ($p<0.01$) which was similar to the results of (Wouter et al., 2016) who demonstrated that TARC levels were significantly related to B symptoms ($p=0.001$), stages ($p=0.03$) TARC decreased after treatment ($p<0.001$), higher TARC levels were observed in patients with B-symptoms ($P=0.001$). TARC consistently corresponded with clinical treatment response at the individual patient level as revealed by (Jones et al., 2013). Therefore, this marker might be used as a cancer-specific serum biomarker for various human cancers, including Hodgkin lymphoma. In patients with advanced-stage of HL, the early response after 2 courses of ABVD chemotherapy, when evaluated for 18FDG-PET scan, shows important prognostic significance (Terasawa et al., 2009). Favorable outcomes with ABVD, reporting complete response rates of 73-89%, 5-year freedom from progression (FFP) of 73-76% and 5-year overall survival (OS) of up to 90% in intermediate and advanced stage HL (Gordon et al., 2013). In the current study, the ROC curve showed that TARC had the best diagnostic performance with greater AUC=0.78, sensitivity (77.8%) and specificity (72.4%) which is in accordance with (Jones et al., 2013) who obtained that the cutoff value of TARC was AUC = 0.8552, 70% sensitivity and 84 % specificity for post-therapy respectively. the relation between markers and the clinico-pathological behavior in this study indicated that TARC was positively affected by stage of disease (P value < 0.0001***), significantly correlated to symptoms (P value < 0.001**) and the response to treatment (p value < 0.01). The results showed a significant increase in TARC levels in patients group where mounting evidence has indicated that TARC plays a significant role in disease activities, plasma thymus and activation-regulated chemokine levels related to classical Hodgkin's lymphoma tumor burden and serial levels related to response to treatment in patients with classical Hodgkin's lymphoma.

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