Original Article

Correlations between the Maximum Standard Uptake Value of Positron Emission Tomography/Computed Tomography and Laboratory Parameters before and after Treatment in Patients with Lymphoma

Edip Ucar[1], Hulya Yalcin[2], Gamze Hande Kavvasoglu[1], Gul Ilhan[1]

[1]Department of Internal Medicine, Tayfur Ata Sokmen Medical School, Mustafa Kemal University, Antioch, Hatay 31100, Turkey
[2]Department of Nuclear Medicine, Tayfur Ata Sokmen Medical School, Mustafa Kemal University, Antioch, Hatay 31100, Turkey

Abstract

Background: After the first examination of patients with lymphoma diagnosis, important laboratory tests such as complete blood count; albumin, kidney and liver function tests; uric acid; β2-microglobulin; C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); and lactate dehydrogenase (LDH) examinations are recommended. In this study, our aim was to find the relationship between laboratory parameters and the maximum standard uptake value (SUV_{max}) of positron emission tomography/computed tomography (PET/CT) in patients with lymphoma at the diagnosis and after treatment.

Methods: Thirty-four lymphoma patients treated at Mustafa Kemal University Internal Medicine Clinic between 2014 and 2017 were included in this retrospective study. Results of CRP, ESR, LDH, albumin, and white blood cell (WBC) count were recorded before each PET scan test, and each parameter was analyzed for correlation with SUV_{max} measurements.

Results: Spearman's correlation test showed that the after-treatment SUV_{max} values were significantly correlated with the after-treatment LDH, ESR, and CRP values (for LDH, ESR, and CRP, R^2: 0.453, 0.426, and 0.351; $P = 0.007$, 0.012, and 0.042, respectively). On the other hand, albumin and WBC count did not show a significant correlation with the after-treatment SUV_{max} values (all $P > 0.05$).

Conclusions: CRP, ESR, and LDH values may also be good predictors in patients for whom PET/CT imaging cannot be performed.

Key words: Albumin; C-reactive Protein; Erythrocyte Sedimentation Rate; Lactate Dehydrogenase; Lymphoma; Maximum Standard Uptake Value; Positron Emission Tomography/Computed Tomography; White Blood Cell Count

Introduction

Worldwide, about 75% of all lymphomas are non-Hodgkin and 25% are Hodgkin's lymphoma; but in Turkey, this ratio is 80% for non-Hodgkin and 20% for Hodgkin's lymphoma.[1] Among cancer-related deaths, lymphoma is the ninth-most common cause of death in men and the sixth-most common in women.[2] According to 2008 data from the Turkish Ministry of Health, lymphoma is the seventh-most common cause of death in men and the eighth-most common in women.[3]

After the first examination of patients with lymphoma diagnosis, it is recommended to perform important laboratory tests such as complete blood count; albumin, kidney and liver function tests; uric acid, β2-microglobulin; C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); and lactate dehydrogenase (LDH) examinations.

Computed tomography (CT) and magnetic resonance imaging are commonly used for lymphoma as imaging

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.237392

Address for correspondence: Dr. Hulya Yalcin, Department of Nuclear Medicine, Tayfur Ata Sökmen Medical School, Mustafa Kemal University, Antioch, Hatay 31100, Turkey
E-Mail: hulyapekeryalcin@gmail.com

Received: 28-02-2018 **Edited by:** Qiang Shi
How to cite this article: Ucar E, Yalcin H, Kavvasoglu GH, Ilhan G. Correlations between the Maximum Standard Uptake Value of Positron Emission Tomography/Computed Tomography and Laboratory Parameters before and after Treatment in Patients with Lymphoma. Chin Med J 2018;131:1776-9.

techniques, but guidelines recommend that positron emission tomography (PET)/CT should be performed instead of CT at the time of diagnosis. Therefore, staging with PET/CT is important in predicting early- and advanced-disease treatment success.[1] CRP is an acute-phase reactant produced in the liver[4] and also has an important role in diagnosis, prognosis, and follow-up of all types of lymphoma.[5] ESR is an inflammation indicator showing the amount of sediment forming in a vertical tube over a 1-h period. It is also an acute-phase reactant. Several studies showed that elevation of ESR is related with infection, malignant neoplasms, and inflammatory diseases.[6] LDH is a common enzyme in several types of cells, which is released in response to any kind of tissue damage. It is recommended that serum LDH should be assessed in lymphoma patients at diagnosis, after treatment, and during follow-up.[7] PET scanning is a type of nuclear medicine imaging which has an important role in cancer detection, staging, metastasis, and treatment evaluation, and disease relapse determination.[8]

This study was to determine the relationship between laboratory parameters and maximum standard uptake value (SUV_{max}) measurements in patients with lymphoma at the diagnosis and after treatment.

Methods

Ethical approval

The study was designed according to the *Declaration of Helsinki* and, as it is a retrospective study, patient consent was not taken.

Patients

Thirty-four lymphoma patients treated at Mustafa Kemal University Internal Medicine Clinic between 2014 and 2017 were included in this retrospective study. These patients were treated with various chemotherapy regimens and were followed up with PET scan before and after treatment.

Laboratory tests

Results of CRP, ESR, LDH, albumin, and white blood cell (WBC) count were recorded before each PET scan (Biograph MCT, Siemens, Germany). Serum CRP concentrations were measured by nephelometric immunoassay, which is a chemical quantitative analysis method for measuring agglutination of particles based on scattered light (OQIY21; Siemens BN™ II System, Germany).[9] ESR determinations were performed with infrared spectroscopy, which is one of the most common and widely used methods to analyze the interaction of infrared light with matter (Mindray BC-6800, China). LDH activity was measured by spectrophotometric monitoring (2P56-21; Abbott ARCHITECT c800, USA). Serum albumin levels were studied by photometric method (7D53-23; Abbott ARCHITECT c800, USA).

Positron emission tomography/computed tomography imaging

All the 34 patients underwent PET/CT scans before and after treatment. PET/CT scan images were obtained using a Biograph MCT PET-CT scanner (Siemens, Germany) after intravenous injection of 376.29 ± 66.60 MBq 18F-fluorodeoxyglucose (18F-FDG). Before the injection, patients fasted for at least 6 h and blood glucose levels were under 200 mg/ml. After injection, during the waiting period, all patients stayed in a quiet room. All patients were told to empty their bladders. Whole-body 18F-FDG PET/CT imaging at 1 h was acquired from the skull base to the mid-thighs in supine position. CT imaging was first performed using the integrated PET/CT scanner with the use of a standardized protocol using 120 kV, which automatically calculated mAs for patient weight, with a tube rotation time of 0.75 s per rotation, a pitch of 0.85, and a section thickness of 3.3 mm. Afterward, PET/CT images were acquired immediately for 3 min per bed position. PET/CT images were reconstructed using CT data for attenuation correction and were regulated with iterative reconstruction and attenuation correction. The images of 18F-FDG PET/CT were evaluated by visual inspection in transaxial, coronal, and sagittal planes. Foci of intense uptake in nodes were noted. The lesion with the highest uptake was taken and SUV_{max} value for this lesion was calculated automatically by a computer according to patient's height and weight, injected dose, and imaging time. The same imaging protocol was performed after treatment.

Statistical analysis

Statistical analysis was performed by Statistical Package for the Social Sciences version 13.0 (SPSS, Chicago, IL, USA). All descriptive data were expressed as median (interquartile range). All data analyses were performed with Spearman's correlation coefficient test and the Wilcoxon test.

Results

A total of 34 patients (19 males and 15 females) with a mean age of 49 ± 17 years were enrolled in this study. Thirteen patients had Hodgkin's lymphoma and 21 had non-Hodgkin's lymphoma (NHL). Seven of Hodgkin's lymphoma were nodular sclerosing type, while 6 were mixed; 16 of 21 NHL were diffuse B-cell lymphoma, one was small lymphocytic lymphoma, three were follicular lymphoma, and one was mantle cell lymphoma.

Table 1 shows the SUV_{max} values and CRP, ESR, LDH, WBC count, and albumin levels before and after treatment. When we compared the before- and after-treatment laboratory parameters with before-treatment PET/CT imaging SUV_{max} values, there was no correlation (Spearman's correlation test: for before-treatment parameters: LDH, ESR, WBC count, albumin, and CRP, R^2: 0.211, 0.050, −0.317, −0.257, and 0.101, P = 0.232, 0.770, 0.055, 0.148, and 0.378, respectively; and for after-treatment, R^2: −0.210, −0.320, −0.150, 0.101, and 0.780, P = 0.925, 0.860, 0.935, 0.578, and 0.661, respectively). We also found no correlation between after-treatment SUV_{max} values and before-treatment blood values (Spearman's correlation test: for LDH, ESR, WBC count, albumin, and CRP, R^2: 0.276, −0.120, −0.170,

Table 1: Before- and after-treatment SUV_{max} values of PET/CT and laboratory parameters of lymphoma patients (n = 34)

Items	Before treatment	After treatment	Z	P
SUV_{max}	11.25 (5.21–13.91)	3.72 (1.68–7.98)	−2.97	0.003
LDH (U/L)	235.00 (196.25–312.50)	239.00 (201.50–301.00)	−0.84	0.400
ESR (mm/h)	33 (15–66)	21 (6–40)	−2.13	0.033
WBC count (cells/μl)	6850 (5150–10,640)	7110 (4070–9520)	−0.59	0.557
CRP (mg/L)	18.00 (3.25–63.50)	5.40 (3.40–32.00)	−1.31	0.191
Albumin (g/dl)	3.60 (3.33–4.00)	4.00 (3.60–4.40)	−1.63	0.104

Data are shown as median (IQR). SUV_{max}: Maximum standard uptake value; LDH: Lactate dehydrogenase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IQR: Interquartile range; WBC: White blood cell; PET/CT: Positron emission tomography/computed tomography.

0.082, and 0.510, P = 0.114, 0.797, 0.395, 0.651, and 0.775, respectively). However, when the after-treatment SUV_{max} values were analyzed, we found that they were significantly correlated with the after-treatment LDH, ESR, and CRP values (Spearman's correlation test: for LDH, ESR, and CRP, R^2: 0.453, 0.426, and 0.351, P = 0.007, 0.012, and 0.042, respectively). On the other hand, as albumin and WBC count had other factors affecting their values, they did not show a significant correlation with the after-treatment SUV_{max} values (Spearman's correlation test: for WBC count and albumin, R^2: −0.123 and −0.312, P = 0.494 and 0.077, respectively).

Discussion

It is important to predict the biological behavior, prognosis, and follow-up results in patients with lymphoma. There are several methods used for this prediction (e.g., tumor markers and imaging techniques), but it is unclear which is the best. CT scanning is the standard for lymphoma staging which reveals the size of lymph nodes but does not indicate the metabolic state of the lymph nodes.[10] With the onset of clinical use of PET/CT, its clinical significance in lymphoma has been demonstrated in various studies.[11]

There are several prognostic indexes used to identify these high-risk patients at diagnosis including the Follicular Lymphoma International Prognostic Index (FLIPI) 4, FLIPI-2.5, the International Prognostic Index (IPI), and conventional radiological assessment. The IPI consists of patient age, performance status, serum LDH, tumor stage, and number of sites of extranodal involvement. Using these factors in aggressive NHL gives prediction of survival. Prognostic factors alter the efficacy of applied treatments since new effective therapies are now available for identified patients.

Okada *et al*.[12] reported that PET/CT gives functional and anatomical information and should be the current standard in lymphoma treatment in order to know the exact stage. Several studies mentioned that there is a relationship between higher FDG uptake and aggressiveness of NHL.[11,13] Wu *et al*.[14] and Tang *et al*.[15] found a correlation between high SUV and rapid cellular proliferation in different types of NHL. The uptake of 18F FDG in PET/CT is dependent on the subtypes of lymphoma. In our study, all patients had PET/CT 18F FDG avid subtypes of lymphoma as stated in the WHO classification in 2003.[16]

Several studies assessed the possible relationships among cancer risk, identification of patients for staging, serum CRP levels, ESR, lymphocyte count, albumin, and LDH levels.[17] It is known that cytokines can cause clinical and histopathological alterations of the disease[18] and that cytokine release and inflammatory processes can affect albumin and hemoglobin levels, as well as WBC counts.[19] In our study, we found that after-treatment SUV_{max} values are related to the results of after-treatment laboratory parameters such as CRP, LDH, albumin, ESR, and WBC count. Hasenclever and Diehl[20] found that, in advanced-stage disease, low hemoglobin, low albumin, high ESR level, and increased leukocyte levels are common. Tatcı *et al*.[8] did not observe a significant correlation between metabolic parameters and ESR, levels of albumin, and WBC count ($P > 0.05$), but they found that standard uptake value normalized by body surface area (SUV_{bsa}) and standard uptake value normalized by lean body mass (SUV_{lbm}) were higher in patients with anemia. Khalifa *et al*.[18] reported that LDH and CRP levels were significantly higher, while albumin level was significantly lower among patients with Stage IV as compared to patients with Stages I/II or III. Cao *et al*.[5] studied the association of serum CRP level with Ann Arbor clinical stage, B-symptoms, and bulk disease in lymphoma patients and found that higher CRP level was a negative prognostic factor in these patients.

Wu *et al*.[21] analyzed serum LDH, thymidine kinase, CRP, and β2-microglobulin correlation with both whole-body metabolic tumor volume and metabolic tumor burden. They found that these serum tumor markers could be clinically useful in malignant NHL because they are widely available and inexpensive. They also concluded that these could be used as independent prognostic factors.[10,11] Albumin is the most important plasma protein; it is synthesized in the adult liver and its synthesis is regulated by a variety of factors, including nutritional status, serum oncotic pressure, cytokines, and hormones.[22] Since the half-life of albumin in serum is approximately 20 days, responses to acute events are slow, which is why we could not find a correlation with SUV_{max} values and albumin after treatment. Milanovic *et al*.[23] found a relationship between serum LDH levels and tumor burden and aggressiveness in NHL. We also found the same correlation between LDH and tumor aggressiveness, and there was a good correlation between after-treatment SUV_{max} values and LDH. The correlation between CRP and

PET/CT scan results is not a well-studied issue. However, several studies found that CRP is also a poor prognostic factor in other cancers.[24] Grivennikov *et al*.[25] reported that disease metastatic potential might be determined by high serum CRP levels since CRP can stimulate angiogenesis and increase vascular permeability. Serum CRP levels can also be elevated by some comorbidities.[26] Our data show that after-treatment CRP and SUV_{max} values are significantly correlated. Since CRP is an important prognostic variable, it is also associated with SUV_{max} values. If PET/CT is not available, we recommend that CRP should be performed to follow up lymphoma patients before and after treatment.

In conclusion, after-treatment PET/CT imaging is a good predictor of treatment success. Meanwhile, CRP, ESR, and LDH values could also be good predictors in patients who could not reach the PET/CT imaging facility or in whom PET/CT could not be performed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ar CM. Overview to lymphoma. Turkish Hematology Society. Hematology 2013;3:200-26. Available from: http://www.thd.org.tr/thdData/Books/641/lenfomalara-genel-bakis.pdf. [Last accessed on 2017 May 24].
2. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153-6. doi: 10.1002/ijc.1440.
3. Mollahaliloglu S, Basara BB, Eryilmaz Z. Turkish Ministry of Health, Health Statistical Yearbook; 2010. Available from: http://www.sbu.saglik.gov.tr/Ekutuphane/kitaplar/saglikistatistikleriyilligi2010.pdf. [Last accessed on 2013 Aug 17].
4. Li YJ, Li ZM, Xia Y, Huang JJ, Huang HQ, Xia ZJ, *et al.* Serum C-reactive protein (CRP) as a simple and independent prognostic factor in extranodal natural killer/T-cell lymphoma, nasal type. PLoS One 2013;8:e64158. doi: 10.1371/journal.pone.0064158.
5. Cao Y, Shi YX, Chen JO, Tan YT, Cai YC, Luo HY, *et al.* Serum C-reactive protein as an important prognostic variable in patients with diffuse large B cell lymphoma. Tumour Biol 2012;33:1039-44. doi: 10.1007/s13277-012-0337-z.
6. Cunha BA, Chawla K. Fever of unknown origin (FUO): CMV infectious mononucleosis or lymphoma? Eur J Clin Microbiol Infect Dis 2018;[Epub ahead of print]. doi: 10.1007/s10096-018-3262-2.
7. Alkhawtani RH, Noordzij W, Glaudemans AW, van Rijn RS, van der Galiën HT, Balink H, *et al.* Lactate dehydrogenase levels and 18F-FDG PET/CT metrics differentiate between mediastinal Hodgkin's lymphoma and primary mediastinal B-cell lymphoma. Nucl Med Commun 2018;39:572-8. doi: 10.1097/MNM.0000000000000840.
8. Tatcı E, Uslu Biner İ, Emir S, Tanyıldız HG, Özmen Ö, Alagöz E, *et al.* The correlation between pre-treatment fluorodeoxyglucose positron emission tomography/computed tomography parameters and clinical prognostic factors in pediatric Hodgkin lymphoma. Mol Imaging Radionucl Ther 2017;26:9-16. doi: 10.4274/mirt.94914.
9. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clin Chem 1999;45:2136-41.
10. Novelli S, Briones J, Flotats A, Sierra J. PET/CT assessment of follicular lymphoma and high grade B cell lymphoma – Good correlation with clinical and histological features at diagnosis. Adv Clin Exp Med 2015;24:325-30. doi: 10.17219/acem/31804.
11. Lapela M, Leskinen S, Minn HR, Lindholm P, Klemi PJ, Söderström KO, *et al*. Increased glucose metabolism in untreated non Hodgkin's lymphoma: A study with positron emission tomography and fluorine 18 fluorodeoxyglucose. Blood 1995;86:3522-7. doi://www.bloodjournal.org/content /86/9/3522
12. Okada M, Sato N, Ishii K, Matsumura K, Hosono M, Murakami T, *et al.* FDG PET/CT versus CT, MR imaging, and 67Ga scintigraphy in the posttherapy evaluation of malignant lymphoma. Radiographics 2010;30:939-57. doi: 10.1148/rg.304095150.
13. Schöder H, Noy A, Gönen M, Weng L, Green D, Erdi YE, *et al.* Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. J Clin Oncol 2005;23:4643-51. doi: 10.1200/JCO.2005.12.072.
14. Wu X, Pertovaara H, Korkola P, Vornanen M, Eskola H, Kellokumpu-Lehtinen PL, *et al.* Glucose metabolism correlated with cellular proliferation in diffuse large B-cell lymphoma. Leuk Lymphoma 2012;53:400-5. doi: 10.3109/10428194.2011.622420.
15. Tang B, Malysz J, Douglas-Nikitin V, Zekman R, Wong RH, Jaiyesimi I, *et al.* Correlating metabolic activity with cellular proliferation in follicular lymphomas. Mol Imaging Biol 2009;11:296-302. doi: 10.1007/s11307-009-0226-z.
16. Elstrom R, Guan L, Baker G, Nakhoda K, Vergilio JA, Zhuang H, *et al.* Utility of FDG-PET scanning in lymphoma by WHO classification. Blood 2003;101:3875-6. doi: 10.1182/blood-2002-09-2778.
17. Heikkilä K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. J Epidemiol Community Health 2007;61:824-33. doi: 10.1136/jech.2006.051292.
18. Khalifa KA, Alkilani AA, Ismail H, Soliman MA. Evaluation of some biochemical markers as prognostic factors in malignant lymphoma. J Egypt Natl Canc Inst 2008;20:47-54.
19. Wang X, Han H, Duan Q, Khan U, Hu Y, Yao X, *et al.* Changes of serum albumin level and systemic inflammatory response in inoperable non-small cell lung cancer patients after chemotherapy. J Cancer Res Ther 2014;10:1019-23. doi: 10.4103/0973-1482.137953.
20. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. N Engl J Med 1998;339:1506-14. doi: 10.1056/NEJM199811193392104.
21. Wu X, Pertovaara H, Korkola P, Dastidar P, Järvenpää R, Eskola H, *et al.* Correlations between functional imaging markers derived from PET/CT and diffusion-weighted MRI in diffuse large B-cell lymphoma and follicular lymphoma. PLoS One 2014;9:e84999. doi: 10.1371/journal.pone.0084999.
22. Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000;85:599-610. doi: 10.1093/bja/85.4.599.
23. Milanovic N, Matkovic S, Ristic D, Jelic S, Petrovic M. Significance of tumor burden, vascular endothelial growth factor, lactate dehydrogenase and beta-2 microglobulin serum levels in advanced diffuse large B cell lymphoma. J BUON 2012;17:497-501.
24. Hashimoto K, Ikeda Y, Korenaga D, Tanoue K, Hamatake M, Kawasaki K, *et al.* The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. Cancer 2005;103:1856-64. doi: 10.1002/cncr.20976.
25. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883-99. doi: 10.1016/j.cell.2010.01.025.
26. Koukourakis MI, Kambouromiti G, Pitsiava D, Tsousou P, Tsiarkatsi M, Kartalis G, *et al.* Serum C-reactive protein (CRP) levels in cancer patients are linked with tumor burden and are reduced by anti-hypertensive medication. Inflammation 2009;32:169-75. doi: 10.1007/s10753-009-9116-4.