JKKI
SCIENTIA EST BASIC VITAE

Jurnal Kedokteran dan Kesehatan Indonesia

Indonesian Journal of Medicine and Health

Journal homepage: https://journal.uii.ac.id/JKKI

Correlation between transduction signal route with serum dehydrogenase lactate level in non-Hodgkin's lymphoma

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Original Article

ARTICLE INFO

Keywords:
non-hodgkin lymphoma;
lactate dehydrogenase;
pPI3K;
pAKT;
pMTOR

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DOI: 10.20885/JKKI.Vol12Iss3.art5

History:
Received: July 1, 2020
Accepted: December 25, 2021
Online: December 30, 2021

ABSTRACT

Background: PPI3K/pAKT/pMTOR expression is important in NHL patients. The cascade of biomarker signals regulates translational events, cell survival, cytoskeleton organisation, and ion transport. pPI3K/pAKT/pMTOR enhance gene transcription increasing lactate dehydrogenase (LDH). LDH is one of the important markers in plasma people with non-Hodgkin's lymphoma (NHL).

Objective: This study aims to determine the correlation between the expression of kPI3K, pAKT, and pMTOR and serum LDH levels in NHL patients.

Methods: This study was used an observational approach with a cross-sectional design. The expression score of pPI3K, pAKT, and pMTOR was obtained from medical records and expressed in histoscore obtained from multiplication between intensity (1=weak, 2=medium, 3=strong) with an express area (1=<20%, 2=20-50%, 3=50-80%, 4=>80%). The correlation between the histoscore of pPI3K, pAKT, and pMTOR expressions with LDH levels was statistically analysed using Pearson correlation tests.

Results: The mean of pPI3K, pAKT, and pMTOR expression respectively were 5.29 + 2.95; 4.71 + 2.26 and 7.62 + 1.86. There was a weak correlation between pPI3K expression and serum LDH levels in NHL patients (r=0.293). A very weak correlation occurred between pAKT (r=-0.064) and pMTOR (r=-0.172) with serum LDH in NHL patients.

Conclusion: There is a weak correlation between pPI3K expression and serum LDH levels in NHL patients. There is a very weak correlation between pAKT and pMTOR with serum LDH in NHL patients.

Latar Belakang: *Ekspresi pPI3K/pAKT/pMTOR penting dalam penderita LNH. Cascade sinyal biomarker ini meregulasi peristiwa translasi, survival sel, organisasi sitoskeleton, dan juga transpor ion. pPI3K/pAKT/pMTOR meningkatkan transkripsi gen yang mengakibatkan peningkatan LDH. Lactate Dehydrogenase (LDH) merupakan salah satu penanda penting pada plasma penderita limfoma non-hodgkin (LNH).*

Tujuan: *Mengetahui korelasi ekspresi pPI3K, pAKT, dan pMTOR dengan kadar LDH serum pada pasien LNH.*

Metode:*Penelitian ini menggunakan pendekatan observasional dengan rancangan cross sectional. Nilai ekspresi pPI3K, pAKT, dan pMTOR didapatkan dari rekam medis dan dinyatakan dalam histoscore nilai histoscore didapatkan dari perkalian antara intentas (1=weak, 2=medium, 3=strong) dengan luas ekpresi (1=<20%, 2=20-50%, 3=50-80%, 4=>80%). Korelasi antara histoscore dari ekspresi pPI3K, pAKT, dan pMTOR dengan kadar LDH dilakukan dengan menggunakan uji korelasi pearson.*

Hasil: : *Rerata ekspresi pPI3K, pAKT, dan pMTOR secara berurutan adalah 5.29 + 2.95; 4.71 + 2.26 dan 7.62 + 1.86. Terdapat korelasi yang lemah antara ekspresi pPI3K dengan kadar LDH serum di pasien LNH (r=0.293). Korelasi yang sangat lemah terjadi antara pAKT (r=-0.064) dan pMTOR (r=-0.172) dengan LDH serum di pasien LNH*

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a group of primary lymphocytes malignancies that derived from B-lymphocytes, T-lymphocytes, and rarely from natural killer (NK) cells. NHL is very heterogeneous in histological type, symptoms, clinical course, response to treatment, and prognosis. About 85-90% of the incidence of NHL arises from B-lymphocytes and 15-20% from T-lymphocytes and very rare lymphocytes.[1,2]

Specific epidemiological studies in Indonesia ranked NHL as the sixth most common cancer in Indonesia.[3] The National Coordinating Board for Hematology of Medical Oncology in Indonesia (BAKORNAS HOMPEDIN) stated that lymphoma incidence is higher than leukaemia and ranked third fastest-growing cancer after leukaemia and lung cancer. Data from M. Djamil Hospital in 2016-2017 reported that 75 out of 602 chemotherapy patients had lymphoma. RSK Dharmais Cancer Register in 2012 reported an increasing death in lymphoma patients by 2% compared to 2010. These data show a decrease in the curative rate in lymphoma patients (98% in 2010 to 72% in 2012). According to the Ministry of Health, this condition occurs because patients come to the hospital in an advanced stage, which in turn, reducing the chances of recovery.[4]

The five-year and ten-year survival rates of NHL patients receiving standard chemotherapy were 58% and 43.5%.[5] The complete response in diffuse large B cell lymphoma (DLBCL) patients treated with regiment-CHOP (cyclophosphamide doxorubicin, vincristine, prednisone) was 65-80%. However, this is highly dependent on patients' international pre-treatment prognosis index.[6] Around 6-10% of patients who have achieved a complete response will experience relapsing.[6] In relapsed patients, the rate of standard chemotherapy response decreases to 40-50%.[5]

Study regarding signal transduction pathways in lymphoma is still growing. Studies showed that the pathways involved in lymphoma are T-cell receptor pathways, B-cell receptors, and tyrosine kinase receptor pathways. Of the three pathways, the B-cell receptor pathway is studied further. This pathway has three upstream components: phosphatidylinositol 3-kinase (PI3K), pAKT, and mammalian target of rapamycin (mTOR). Therefore, this path is known as the pPI3K /pAKT/pMTOR path. Although the pPI3K, pAKT, and pMTOR pathways are activated by B cell receptors, they can also be activated by T cell receptors and tyrosine kinase receptors. Activation of any of the three receptors converts PI3K into phosphorylated PI3K (pPI3K), which converts AKT into pAKT and then converts MTOR to pMTOR. Activation of this pathway leads to enhanced gene transcription, cell proliferation, cell survival, as well as suppression of apoptosis processes that promote malignant phenotypes.[7]

In vitro studies and clinical trials showed extracellular activation through crosslinking of cluster differentiated 20 (CD20) surface molecules will increase cell susceptibility to pPI3K/pMTOR inhibitors.[8] CD20 is a classic NHL marker that targets the monoclonal anti-CD20 antibody rituximab.[9] Rituximab is a regimen used in chemotherapy in lymphoma patients (CHOP-R). Several studies have shown that there is an increase in resistance to rituximab. Data showed that only 40% of patients respond to rituximab a second administration.[10] Another study showed that 60% of NHL patients treated with rituximab and experiencing relapsing failed to achieve a partial or complete therapeutic response. Chong et al. stated that the FiveYears Survival Rate of low-degree follicular lymphoma patients who failed to respond (or were resistant) to rituximab was 58%, while patients who responded with

rituximab (on initial treatment) was 15%. Therefore, overcoming rituximab resistance has become the focus of recent therapeutic developments in lymphoma.[11] In rituximab resistant patients, it is known that there are many phosphorylated proteins in the pPI3K/pAKT pathway.[12] This suggests that pPI3K/pAKT/pMTOR has a role in causing rituximab resistance.

One of marker cell cancer activities is the increasing rate of cell proliferation. In cancer, the increased rate of cell proliferation can be detected through increased levels of serum lactate dehydrogenase (LDH). The LDH levels are used as predictive markers as well. Increased serum LDH levels may also be observed in NHL patients. According to Hoffbrand, increased levels of LDH mean a faster and wider proliferation of cells and indicate poor prognostic.[13] In line with this statement, the National Cancer Institute also states that LDH also describes the extent of occurrence of tissue damage.[14]

The effort to suppress the progressivity of the NHL is needed. Therefore, it is necessary to conduct a study regarding the progressivity parameters (serum LDH) and affected signal pathway (pPI3K/pAKT/pMTOR) in the NHL. By knowing the influence of both parameters, multimodal therapy can be given to NHL patients optimally.

METHODS

Study design and subjects

This study was conducted in Dr. M. Djamil Padang hospital for six months. This study used an observational approach with cross-sectional data collection methods. The inclusion criteria were patients over 14 years old, had not undergone chemotherapy, and were willing to participate in the study. Exclusion criteria included patients with type 2 diabetes mellitus, obesity, autoimmune disease, other haematological diseases, multiple myeloma, and solid malignancies. The estimated sample size required in this study was 20 people. Ten patients in this study were diagnosed with chronic lymphocytic leukaemia, mantle cell lymphoma, and diffuse large B cell lymphoma. Another ten people were diagnosed with other NHL. This study has been ethically approved by the Health Study Ethics Committee of dr. M. Djamil general hospital Padang with number 353/KEPK/2019. Pearson correlation test was performed to determine the correlation between the expression of pPI3K, pAKT, and pMTOR on serum LDH levels of NHL patients.

Histoscore expression pPI3K, pAKT, and pMTOR

The histoscore for the expression of pPI3K, pAKT, and pMTOR in this study was obtained from the patient's medical record. This score was obtained from the multiplication of the intensity and distribution of immunopositive cells with IHC staining.[15] The range of intensity score were divided into three categories: one means weak, two means moderate, and three means strong. The distribution range is divided into four categories: one means <20%, two means 20-50%, three means 50-80%, and four means >80%. The final score range of this study histoscore is 0 to 12.

Serum LDH levels

The patient's serum LDH levels were obtained from laboratory assessment. LDH examination was carried out at Dr. M. Djamil Padang hospital.

RESULTS

Basic Characteristics of Study

In this study, there were 21 subjects. The study subjects were mainly males aged between 40-60 years. Most of them showed NHL morphology with the histopathological type of large cell and stage 1V (Table 1). Based on histoscore, the highest expression was found in pMTOR expression (Table 2). There were increasing serum LDH levels in NHL patients (Table 3). In the correlation test, there was no strong correlation between pPI3K/pAKT/pMTOR expression and serum LDH in NHL patients (Table 4, Figure 1).

Tabel 1. Characteristic data of the study subject

Description	n (%)
Gender	
Male	15
Female	6
Age group	
<40 years old	3
40-60 years old	12
>60 years old	6
NHL type	
Large cell (Diffuse Large B Cell Lymphoma)	16
Small cell	2
Burkitt cell	2
Mantle cell	1 (a
Stage	
I	1 (5%)
II	4 (19%)
III	6 (28%)
IV	10 (48%)

Table 2. Expression of pPI3K/pAKT/pMTOR in NHL patients

	Histoscore mean	Standard deviation
pPI3K expression	5.29	2.95
pAKT expression	4.71	2.26
pMTOR expression	7.62	1.86

Tabel 3. LDH levels in NHL patients

Levels	Mean	SD
Serum LDH (IU/L)	428.57	139.62

Tabel 4. Correlation between pPI3K/pAKT/pMTOR expression and serum LDH levels

	r value	R2 linear value	p value
pAKT	-0.064	0.005	0.784
pPI3K	0.293	0.086	0.197
pMTOR	-0.172	0.008	0.457

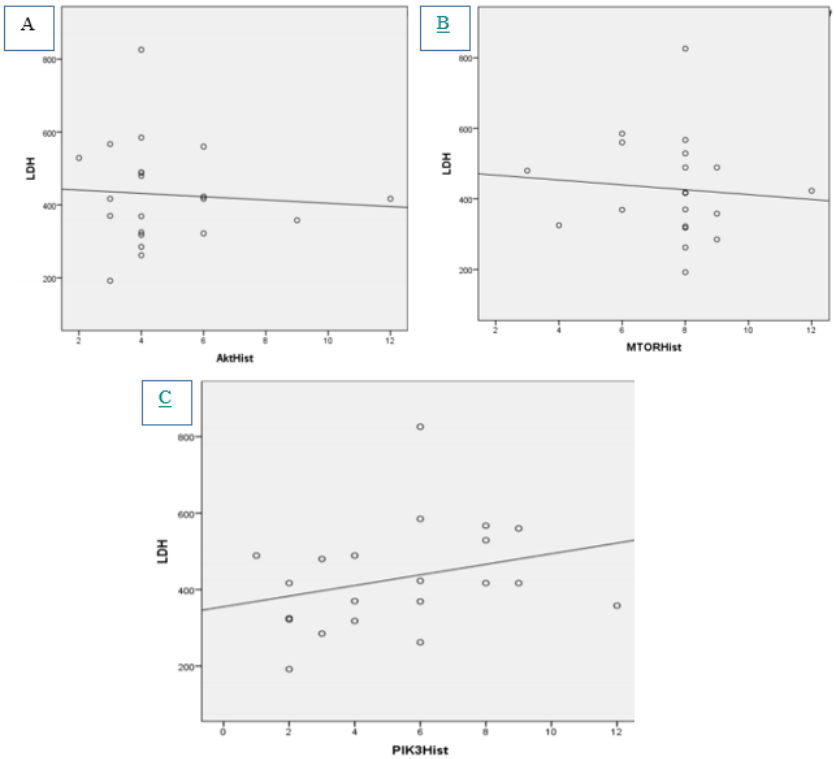

Figure 1. Correlation between pPI3K/pAKT/pMTOR expression and LDH levels in NHL patients (A=pAKT, B=pMTOR, C=pPI3K)

DISCUSSION

The dominance of NHL in male patients in the study is in line with several previous studies. A study by Zelenetz et al. showed that the proportion of NHL in men is 66%.[16] In accordance, other studies also showed a similar trend (57.1% in developing countries).[17] In contrast, a study by Broyde et al. in Israel shows that NHL cases are common in both genders (47% male and 53% female).[18] Dominance of male NHL sufferers is possible due to the role of estrogen. Research shows that inhibition in estrogen biosynthesis results in increased lymphoma growth.[19]

The dominance of the occurrence of NHL in this study occurred in the range of 40-60 years. A similar result was also reported by Menon et al. study in Uganda20 as well as the study by Perry et al. in developing countries.[17] In developed countries, the age range of patients experiencing NHL is 50-70 years.[17] The same result was reported in Sheha et al. study in patients with refractory or relapsed NHL (median age 50 years).[21] The difference in median age could be due to lifestyle factors and disease prevalence in these countries.

Diffuse Large B Cell Lymphoma (DLBCL) was the dominant type found in this study. The same result was also shown in a study by Perry et al. (42.5% in developing countries and 28.9% in developed countries) and Ten et al.[21] (53.3%). In general, the results of this study are in line with the global trend that DLBCL is the most common type of NHL. This study also shows that most patients with NHL are in an advanced stage (stages III and IV). This finding is in line with previous studies that showed that many NHL patients were diagnosed at an advanced stage in developing countries.[17,18,22] In contrast to developed countries, patients with early and advanced NHL were relatively balanced.[17] The number of stage III-IV patients in this study is understood because many patients come for treatment after their cancer is in stage II or even has entered an advanced stage. Another factor

that may play a role is the type of NHL. Large cell NHL (DLBCL), the most common NHL, is the most malignant type of NHL. This type results in rapid staging in NHL patients to advanced stages.

This study found that the mean of pPI3K histoscore in NHL patients was 5.29 (in the histoscore range 0-12). It can be seen that based on the mean score, the pPI3K histoscore in NHL patients is relatively middle (moderate) between weak (0-4) and strong (6-12). This result is different from McCall et al. that shows the pPI3K histoscore in prostate cancer patients was 60 in the range 0-300.[25] If converted to a scale of 0-12, then the score of 60 was still relatively low, equivalent to a histoscore of 2.4 on a scale of 0-12. Furthermore, the pPI3K score in patients with follicular lymphoma reported by Liu et al. showed a high level, 3 out of the range 0-3.[23]

The mean difference of pPI3K expression in cancer patients, including NHL, could be since not all patients are affected by the oncogenic effect of pPI3K signalling. pPI3K expression can be high in all three pathways (T-cell receptor, B-cell receptor, and receptor tyrosine kinase) if pPI3K is involved. In the B-cell receptor pathway, pPI3K is involved, but if the patient gets NHL from the T-cell receptor pathway or the receptor tyrosine kinase, pPI3K is potentially uninvolved. In the T cell receptor pathway, oncogenic effects arise from PKC beta via Ras or through NFκβ to gene transcription. Similarly, if the oncogenic effect is via receptor tyrosine kinase, the pathway may continue to JAK, then STAT, leading to apoptosis suppression and cell survival.

In this study, phosphorylated AKT (pAKT) had a histoscore mean of 4.71. This result is in line with a study by Zulvayanti et al. (histoscore 4 in the range 0-16).[24] However, the results of this study are not in line with McCall et al. in prostate cancer (40-60 in the 1-300 range)25 and Lopez-Knowles et al.26 These results suggest that pAKT levels in cancer patients vary widely and likely undergo differences in signal transduction pathways that differ in NHL cases.

Expression of pMTOR in the current study showed a high result (7.62). Similar finding with Xu et al. (pMTOR expression in 31 of 56 DLBCL patients).[37] The pMTOR complex is a phosphorilator for pAKT activation. The activated pMTOR indicates that pAKT has regulated protein synthesis and cell growth.[28] In line with this study, the high expression of pMTOR in NHL patients shows that the protein synthesis and cancer cells growth undergone by pAKT.

Serum lactate dehydrogenase (LDH) in this study demonstrated high levels (normal level <300 U/L).29 This finding is in accordance with a study conducted by Lal et al.[30] On the other hand, Benboubker et al. reported that only one-third of NHL patients had high levels of lactate dehydrogenase (LDH).[29] LDH is a prognostic marker of NHL. The high level of LDH in this study is due to the majority of patients at an advanced stage. Benboubker et al. reveal that LDH levels were related to the disease stage. This evidence indicates that the normal mean LDH level reflects most NHL patients studied at an early stage.

This study shows a weak correlation between increased pPI3K expression and serum LDH levels in NHL patients. This correlation is not statistically significant. This result is in accordance with a study conducted with the research of Uddin and Mohammad.[31] Their study also found that although Ob-R correlated with pPI3K in DLBCL patients, there was no correlation between Ob-R and LDH.[31] There is no significant correlation between pPI3K and LDH in this study due to extreme values of 2 patients (histoscore 12 with LDH 358 and histoscore 1 with LDH 358). In these two patients, the increase in LDH that occurs might be due to non-tumour factors (such as anaemia, liver problems, and others.). Further studies still needed to include more stringent inclusion criteria to exclude patients with non-tumour problems that might elevate serum LDH levels.

The correlation between the expression of pAKT, pMTOR, and LDH and in this study showed a very weak correlation and not statistically significant. The correlation absence is in line with a study by Ma et al.[32] and Xu et al.[27] in

DLBCL patients. In accordance, Luo et al.[33] also reported no correlation between XPO1 expression and LDH (XPO1 is a regulator of the pMTOR pathway). Nevertheless, other studies show a correlation between pPI3K/pAKT/pMTOR with LDH. This study shows that the inhibition in pPI3K/pAKT/pMTOR results in decreased mRNA LDH expression.[34] The absence of a significant correlation between pAKT and pMTOR in this study is likely because pPI3K activation leads to PKC Beta activation in the T cell receptor pathway, but not the pAKT pathway.

CONCLUSION

Based on the conducted study, it is concluded that there is a weak correlation between pPI3K expression and serum LDH levels in NHL patients. A very weak correlation occurs between a pAKT and pMTOR with serum LDH in NHL patients.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

ACKNOWLEDGEMENT

The study used private funds entirely. The author would like to thank Dr.dr Irza Wahid, Sp.PD-KHOM., FINASIM and Prof. dr. Nuzirwan Acang, DTM&H Sp.PD-KHOM, FINASIM, for their guidance in completing this study.

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