Original Article

ERA'S JOURNAL OF MEDICAL RESEARCH

VOL.9 NO.2

DOI:10.24041/ejmr2022.24

PLACENTAL ALKALINE PHOSPHATASE AS A THRESHOLD CONCEPT FOR EARLY DETECTION OF PRIMARY LUNG CANCER

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Received on : 12-01-2022
Accepted on : 16-12-2022

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ABSTRACT

The biochemical existing tool of diagnostic methods to lung cancer cases need to be improved. In order to validate an early screening of primary tumor patients, a developed a simple procedure or technique was demanded. The aims of this study were to provide an overview of alkaline Placental Alkaline Phosphatase activity in lung cancer. Using heating inactivation method regarding the measurement of Placental Alkaline Phosphatase activity as an early diagnosis marker in lung cancer cases. Total alkaline phosphatase and Placental alkaline phosphatase activity were measured in patients of Lung cancer patients who were classified according to the site of tumor by histological picture. ALP isoenzymes were identified by heat inactivation, and compared with the most frequently applied method (ELISA). Monitoring of the Total ALP and Placental ALP activity in the studied groups using two different methods were shown a highly performance of heating method by an experimental assessment to confirm the accuracy and validity of the proposed method. The distribution of serum placental ALP isoenzyme activity in patients and control groups which was measured by two different methods were found to be (20.2-43.1) IU/L respectively (measured by heating method) and (394.3- 454.5) pg/mL measured by ELISA method) respectively. Placental ALP isoenzyme showed a high significant activity in lung cancer patients than healthy control with p value less than (0.05). That application of the heat inactivation method yields similar indication to the ones obtained by the highly and specific enzyme-linked immunosorbent assay. The results of detection Placental alkaline phosphatase in serum were in excellent agreement and could have a potentially extensive application for Placental alkaline phosphatase quantification.

KEYWORDS: Placental Alkaline Phosphatase, ALP Isoenzymes; Predictor Marker ; Lung Malignancies.

INTRODUCTION

The majority of Alkaline Phosphatase Isoform detection techniques have several benefits and drawbacks (1). It is often regarded as having a high equipment cost, a slow sample speed of processing, physically huge instruments, and higher sample volume requirements. Additionally, most detection techniques lack sensitivity and specificity, particularly when it comes to differentiating between intestine and placental alkaline phosphatase.

The goals of this research are to establish a placental alkaline phosphatase detection method that can be used in any concise laboratory and to offer testing that is both affordable and easy to use. This research was based on the heating stability of placental alkaline phosphatase then detection of the isoenzyme effectively by spectrophotometry.

The performance of the research experiment was evaluated in this study of Placental alkaline phosphatase test and compared to highly sensitive method (ELISA) measurements for confirming the accuracy and validity of the proposed method.

This research work encourages and gives some knowledge on the potential application of placental alkaline phosphatase isoenzymes as an easy-to-use, accessible, and inexpensive biomarker for lung cancer detection. Moreover, research was examine the possibility of using Placental alkaline phosphatase can serve as a diagnostic marker with baseline data without the requirement for sophisticated facilities. In this study, it might be provide proper diagnosis tool and interpretation of diseases or complication association

with such cases by assessing the applicability of the method in clinical assay as tumor marker through examination of primary lung malignancy.

AIM

The aims of this study were to provide an overview of alkaline Placental Alkaline Phosphatase activity in lung cancer.

OBJECTIVE

Using heating inactivation method regarding the measurement of Placental Alkaline Phosphatase activity as an early diagnosis marker in lung cancer cases. Also to provide an overview of the confidence levels those are currently applied.

MATERIALS AND METHODS

For a total of (207) samples—83 patient samples, 74 healthy control samples, and (50) pregnant samples—the current work included a case-control study. Lung cancer patients were chosen from the oncology department at Al Hussein Teaching Medical City. All patients underwent a thorough clinical history review, physical examination, and pertinent laboratory tests. The WHO's most recent clinical practice guidelines were used to determine the diagnoses of the cancer-related clinical conditions. Depending on evaluation of test results for the patient examination of the tumor with histological diagnosis, the kind of lung cancer was determined. Most patients were newly diagnose, majority of them were not taking cancer therapy (Chemotherapy, Hormonal therapy and radiotherapy).

DETERMINATION OF PLACENTAL ALKALINE PHOSPHATASE (PALP) FROM TOTAL ALKALINE PHOSPHATASE AFTER HEAT INACTIVATION

For all sera samples (patients and control) 0.5 mL were heated at 65 ℃ for 30 minutes using water bath for the separation of placental alkaline phosphatase from the rest of alkaline phosphatase isoenzymes due to their heating stability (2)**.** The ALP activity in each aliquot of the heated samples was measured after they had cooled to room temperature. Each aliquot's residual activity is calculated as a percentage.

Measurement of serum alkaline phosphatase and placental alkaline phosphatase by using Kinetic method (3) and spectrophotometer technique. Principle was performed following the Colorimetric determination of the ALP activity (4). Finally, the sandwich approach was used to conduct an ELISA, or enzyme-linked immunosorbent assay.

The Real Statistics Resource Pack for Mac (Release 7.2) of the Excel 2016 resource pack was used to establish the data analysis for this project. Copyright (2013 – 2020) (2013 – 2020) www.real-statistics.com (5) Charles Zaiontz.

RESULTS

Activity of Total ALP and Placental ALP isoenzyme were measured in a (207) subject. Serum Placental ALP activity was measured by Heating and sensitive sandwich ELISA which has a minimal detectable level of 0.4 pg/ml.

The mean age of the participants in the 30 to 79 age range was shown in Table 1. For the patient group, there were 50% men and 50% women in the study, while for the control group; there were 53% men and 47% women. According to the origin of the disease, the study covered four primary forms of lung cancer: squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and non-small cell carcinoma, as indicated in figure (1).

Total ALP and Placental ALP activity were measured in a total of 30 patients of lung cancer group with histopathological diagnoses. Lung cancer was classified according to site of tumor by histological picture of WHO classification. Study group were divided base on the site of tumor to: Adenocarcinoma types (% = 47); Squamous cell carcinoma (% = 30); Small cell carcinoma (% = 17); and Non-small cell carcinoma (% = 7)

Characteristics	Patient group	Control group
Age (Mean/years)	60	50
Gender% (male/female)	50/50	53/47
Smoking state (Yes/No)%	77% / 23%	13% / 87%
BMI	25.02	28.22
Type of cancer (%) (Primary- Metastasis)	93% - 7%	/
Lung Cancer (%)	64 %	/
Site of lung cancer (%)	Adenocarcinoma 47%	/
	Squamous cell carcinoma 30%	
	Small cell carcinoma 17%	
	Non-small cell carcinoma 7%	

Table 1: Demographic characteristics of the study participants

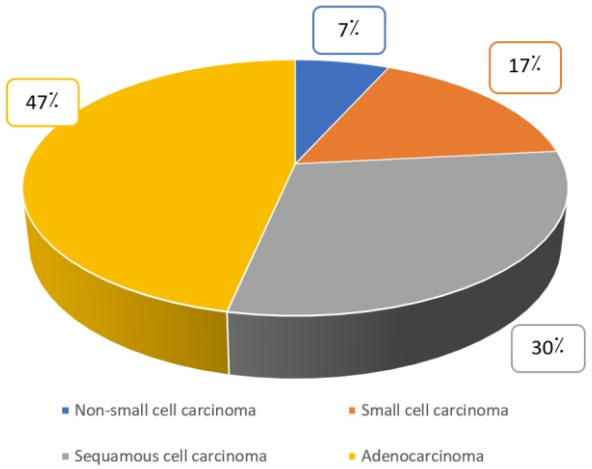

Fig. 1 : Histopathological groups of Lung Cancer Patients based on the site of Tumor according to WHO classification.

DISTRIBUTION OF SERUM TOTAL ALP AND PLACENTAL ALP ISOENZYME ACTIVITY IN STUDIED GROUPS

The distribution of serum placental ALP isoenzyme activity was shown in Table (2). The confidence levels of placental ALP isoenzyme activity which measured by two different methods were found to be (20.2-43.1) IU/L (measured by heating method) and (394.3-454.5) pg/mL measured by ELISA method) respectively. Placental ALP isoenzyme showed a high significant activity in lung cancer patients than healthy control with p value less than (0.05).

Activity (U/L)	Median (Confidence level) By (Heating) U/L		Median (Confidence level) By (ELISA) pg/ml	
	Patients	Control	Patients	Control
PALP Median (range)	31.65 (20.2-3.1)	20.04 (17.2-2.9)	424.4 (394.3-454.5)	370.1 (324.5-415.8)
p value	0.025		0.024	

Table 2: The Confidence levels of Placental ALP Isoenzyme activity in Lung Cancer Patients Group Compared to Healthy control group.

ALP isoenzymes were identified by heat inactivation (10), the simplicity of the procedure and lack of expensive equipment required to perform it make it advantageous; as a result, the results were clinically applicable and usable. Previous studies show that using the heat inactivation approach produces results that are comparable to those of polyacrylamide gel electrophoresis (11). Locally, no previous studies were compared the measurements of Placental ALP activity that determined by heating method with the highly sensitive sandwich ELISA method.

DISTRIBUTIONS OF SERUM TOTAL ALP AND PLACENTAL ALP ISOENZYME ACTIVITY IN PATIENTS AND CONTROL GROUPS

The correlation between Total ALP and Placental ALP isoenzyme was assessed by using Spearmann Rank test (Figure 2). Thus, statistically significant correlation observe between Total ALP with Placental ALP isoenzyme in patients with lung cancer c (rs = 0.5, p=0.005). Placental ALP isoenzyme activity appears to contribute to normal cells but such contribution varies among the patients and healthy control groups. Hence, many variations in Placental ALP isoenzyme genotype may be associated with differences in the enzyme activity such as the environmental factors.

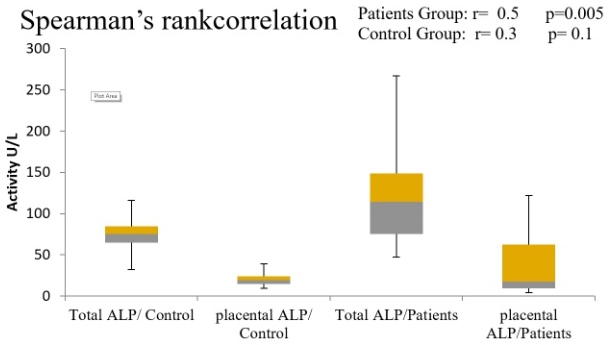

Fig. 2: Spearman`s rank Correlation Assessment of Serum Total ALP and PALP Isoenzyme Activity in Lung Cancer Patients group Compared to Healthy Control Group.

The current findings were supported by earlier research that found that the overall ALP activity of the enzyme was almost three times higher in cancer patients than in healthy individuals who were the same age (22,23).

A tumor isoenzyme has recently been extracted from the serum and tumor tissue of individuals with a variety of cancers and dubbed the Regan isoenzyme after the patient in whom it was initially discovered (24). Since it shares L-phenylalanine sensitivity and high heat stability with placental ALP, this tumor isoenzyme can be identified in serum.

Moreover Total ALP and Placental ALP isoenzyme (measured by two different methods) were examined with smoking status of the patients. Alkaline phosphatase and placental ALP elevation tend to be more marked in smoker lung cancer patients than non smoker patients; no significant differences were found comparing smoker and non smoker patients (p value >0.05) as illustrated in Table (3).

It has recently been shown that smokers have a higher activity of Placental ALP or Placental ALP-like enzymes then non-smokers (27).

	PALP By **(Heating)** U/L		TALP Median U/L		PALP By **(ELISA)** pg/ml	
	Smoker Patients	Non-smoker Patients	Smoker Patients	Non-smoker Patients	Smoker Patients	Non-smoker Patients
Median	30.4	24.07	431.47	407.91	132.66	118.93
p value	0.56		0.47		0.58	

Table 3: Mean Distributions of Serum Total ALP and PALP Isoenzyme activity in Smoker and Non-smoker Lung Cancer Patients.

Furthermore, Placental ALP activity has reported to be found in low levels in type I pneumocytes (which secrete it into the broncoalveolar fluid). Different lung conditions, including those that increase endothelial and alveolar-epithelial permeability, may lead to the appearance of Placental ALP activity in the circulation. It is believed that, for this reason, people who smoke have higher levels of Placental ALP activity in their circulation (28).

The distribution of the data was shown graphically using a box plot by presenting the data's averages and quartiles (or percentiles). Box plots display a data set's average requirement, first (lower) quartile, median, third (upper), and maximum scores in a five-number summary. The line dividing the box into two parts represents the median, which is the average value from such a set of data.

The degree by which an allocation is stretched or compressed is known as dispersion in statistics (also known as variability, scatter, or spread). The ends of the "whiskers" contain the smallest and greatest values, which are helpful for giving a visual indication of the range of measurements. For both methods and by Comparing the respective medians of each box plot, Fig (3&4) was indicated that female/patients have more PALP than male. The differences were statistically not significant with p value more than 0.05.

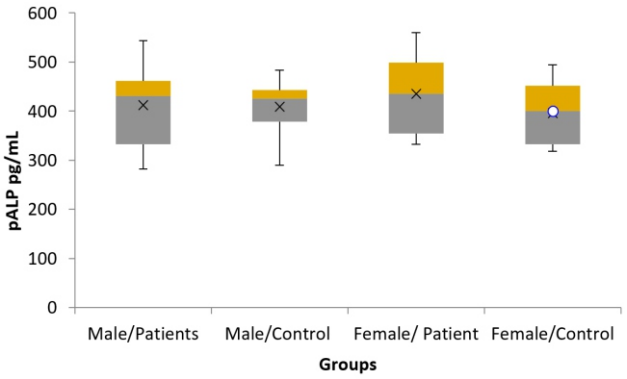

Fig. 3: Distribution of serum PLAP isoenzyme activity levels measured by ELISA methods in different sex groups in lung cancer patients compared to healthy control.

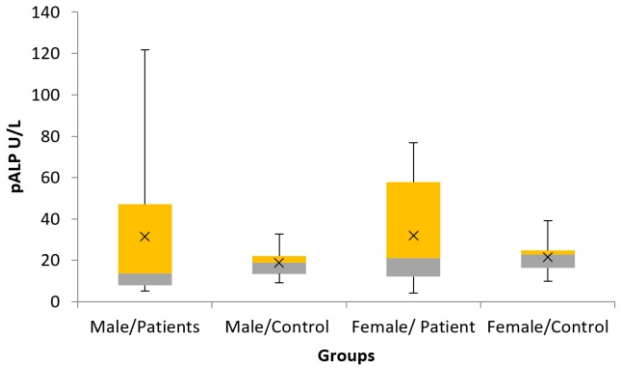

Figure 4: Distribution of serum PALP isoenzyme activity levels measured by Heating stability method in different sex groups in lung cancer patients compared to healthy control.

Contrary to the blood levels of liver, bone, and intestine alkaline phosphatases, which are much greater, placental ALP is often relatively low in healthy, non-pregnant individuals (37). There are minor levels of placental-like alkaline phosphatase in the normal testis, but the tissue unspecific isozyme (liver and bone) predominates (>95%) (38). Recently, the international group report on relevant clinical tumor indicators identified this trace expression of eutopically generated placental-like alkaline phosphatase as either a tumor marker for cancerous tumors of the testis, particularly seminomas (39). The deficiency of Placental ALP in a healthy normal population and the availability of very sensitive assays make the identification of this isozyme in normal human serum during pregnancy and under some malignant situations straightforward (40).

However, the picture also showed that there was higher variation in the level of placental ALP in the male interquartile ranges of the boxes than in the female interquartile ranges.

The Placental ALP measurements by heating were shown to have a symmetric distribution in the control groups (male and female), with the probabilities for values farther from the mean tapering off equally in both directions. Extreme values in the distribution's two tails are likewise rare. While there was some variation in the placental ALP activity in the male control.

DISCUSSION

Numerous malignancies have been found to have increased alkaline phosphatase activity, and there is evidence that some tumours may secrete different types of alkaline phosphatase into the bloodstream(6). Monitoring of the ALP activity is widely used to identify cancer metastasis to bone and liver (7). Despite being expressed throughout pregnancy and in a number of human malignancies, placental ALP's biological role is still unknown. There are data that support the use of placental ALP as an informative diagnostic parameter

in lung pathologies, including chronic obstructive pulmonary disease, tuberculosis, bronchial asthma, and lung cancer of various histological types (8) Therefore, Placental alkaline phosphatase activity have been measured and used for the clinical diagnosis of lung cancer patients. The tumor expression of the isoenzyme is an example of inappropriately high expression of embryonic genes during malignancy.

Most of the Studies obtained that Total ALP and Placental ALP isozymes activity which are no differences could be detected between histological types of lung cancer. Fishman et al. (9). were first described the presence of Placental ALP in serum of a lung carcinoma patients. The heat-stable portion of ALP displayed polymorphic phenotypic differences in addition to the connection between placental ALP and lung cancer. Other study was demonstrated histochemically the activity of Placental ALP in the lining of the respiratory system's epithelia, which extends from the trachea to the alveoli which also was in order to conform with our study regarding showing not much of a difference in the distribution of Placental ALP among the lung tumor sites of various histological types (7)**.** Measurements of Placental ALP activity results were demonstrated in serum of those who have lung cancer tumors, and the present study leaves little doubt that the Placental ALP found in the healthy control group, although there might be considerable variation from one cells group to another within individual samples (12). As a tumor marker for many malignant cancers, this trace expression of ectopically produced placental alkaline phosphatase has proven to be very helpful. (13). On the other hand, many studies have been shown that trace ALP concentrations that are heat-stable and remarkably similar to placental ALP occur in testis (14, 15)**.** Additionally, this isoenzymes was discovered early on biochemically in healthy lung tissue (13). Subsequently, the use of certain monoclonal antibodies has shown the detection of placental ALP in samples from healthy lung tissue (16).

Many reasons behind serum placental-type activity in healthy control. First, the fact that placental ALP is a highly polymorphic enzyme with at least 15 rare alleles (each with a frequency of less than 1%) and three common variants (found in more than 2% of placentas assayed) could be the cause. (17). Therefore, the basal level of Placental ALP reported in healthy individuals could reflect the eutopic expression found in normal tissues, such as cervix, ovary, testis, lung, thymus and breast (18)**.** Also, It might be partially originated from neutrophils (19)**.** An example of a phagocyte is a neutrophil, which is typically present in the circulation. Neutrophils are among the first inflammatory cells to go towards the site of inflammation at the initiation of inflammation, especially when it is brought on by bacterial infection, exposure to the environment, and several malignancies (20). Following chemical cues, they move via the blood arteries and subsequently through interstitial tissue. (21) in a process called chemotaxis. Using a specific enzyme-linked immunosorbent assay with a sensitivity of 400 pg/ml by Millan and Stigbrand found that 70 % of a healthy population had Placental ALP concentrations below the limit of detection (25) **.** McLauglin et al. discovered trace amounts of placental ALP in healthy non-pregnant people utilizing a solid-phase enzyme immunoassay and a monoclonal antibody reacting solely with placental-type alkaline phosphatase (26)**.**The lungs (pneumocytes), where cellular damage brought on by cigarette smoke may release Placental ALP enzymes into the blood possibly in proportion to the duration and intensity of smoking, are where the majority of the Placental ALP isoenzyme activity found in smokers' serum likely originates (29). Smoking increases the serum levels of the PLAP isoenzyme, which may serve as a tumor pre-marker (30)**.**

Cigarette smokers have been found to have higher serum concentrations of placental ALP activity (31). To speculate on the cause of these higher levels, prior findings that Placental ALP is exclusively located on the luminal plasma membrane of respiratory bronchiolar and most likely also of alveolar epithelial cells (32) and the quantity of Placental ALP in normal lung tissue relative to other normal tissues point to a pulmonary origin for Placental ALP in smokers. The presence of extensive Placental ALP staining in the bronchiolar and alveolar lumina and in the contents of these lumina in the areas with high Placental ALP positivity demonstrated that some of the Placental ALP synthesized by the lung parenchyma was secreted into the bronchioloalveolar fluid. According to several publications, cigarette smokers have significantly higher levels of respiratory epithelial permeability (33,34). As a result, smokers may have higher blood levels of Placental ALP activity as a result of increased bronchioloalveolar liquid leaking into the pulmonary capillaries. Even with the monoclonal antibody that the present immunohistochemistry data are based on, they were unable to identify any appreciable difference in the blood levels of PALP activity among smokers and non-smokers.

It appears that hereditary factors also influence a smoker's vulnerability to lung cancer. The risk of developing lung cancer has been linked to a number of single- nucleotide polymorphisms (SNPs) (35). Additionally, some reports indicate that people with lung cancer had EGFR germline mutations. (36)**.**

CONCLUSION

Along with the recognized histological categories, PALP may be another signal for the early diagnosis of primary lung cancer. since it claimed that PALP expression is connected with prognosis, providing a further tool for classifying patients with lung cancer. Moreover, the big advantage of measurement the activity of PALP by heating inactivation method would focus on the fact that smaller tumors had somewhat higher mean concentration if the method was to be used in a clinical situation, in which small tumors might be of crucial importance.

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How to cite this article:

Hameed M.R., Abd-Alrasool Hneua R., Kadhim W. S., Fatima G., Anwar S. Placental Alkaline Phosphatase as a Threshold Concept for early Detection of Primary Lung Cancer. Era J. Med. Res. 2022; 9(2): 143-149.