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ORIGINAL

The evaluation of diagnostic value of serum Lactate dehydrogenase/pleural Adenosine deaminase ratio compared with pathology in diagnose of malignancy in exudative pleural effusion

Evaluación del valor diagnóstico de la relación entre la lactato deshidrogenasa sérica y la adenosina desaminasa pleural en comparación con la patología para el diagnóstico de malignidad en el derrame pleural exudativo

Abolhasan Halvani[1], Mahtab Torabi[2], Mohammad Shafiee[2], Zahra Shojaei[3]

1. Department of internal medicine, Yazd medical science, branch Islamic Azad University, Yazd, Iran
2. General Practitioner, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Medical student, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Corresponding author
Zahra Shojaei
Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
E-mail: zahrashojaaei@gmail.com

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Abstract

Background: In recent studies, it has been somewhat determined that the Lactate dehydrogenase(LDH) ratio of serum to Adenosine deaminase(ADA)of pleural fluid has a diagnostic value in malignant pleural effusions. We decided to study the diagnostic value of these enzymes by conducting a wider study and a higher statistical society.
Methods: This is a descriptive-analytic study that was conducted in a cross-sectional method. Sampling method was census and 39 patients with exudative pleural effusion were enrolled. Age, sex, biopsy report, serum LDH and ADA of pleural fluid were recorded in a preformed form. The LDH ratio of serum to ADA of pleural fluid was calculated. The collected data were entered into SPSS18, using statistical tests were analyzed.
Results: Of the 39 patients,61.5% had cancer and 38.5% had infections. There was a significant relationship between mean pleural ADA and mean ratio of serum LDH to pleural ADA in terms of type of disease. The sensitivity, specificity, positive predictive value and negative predictive value of ratio of serum LDH level to pleural ADA level were 95.8%, 80%, 88.5% and 92.3%, respectively.
Conclusions: Can be concluded that serum LDH /pleural ADA ratio are very consistent with pathological finding and can be used to diagnose of malignancy in exudative pleural effusion.

Keywords: Lactate dehydrogenase, Adenosine deaminase, pleural effusion, malignancy.

Resumen

Antecedentes: En estudios recientes, se ha determinado en cierta medida que la relación entre la lactato deshidrogenasa (LDH) del suero y la adenosina desaminasa (ADA) del líquido pleural tiene un valor diagnóstico en los derrames pleurales malignos. Decidimos estudiar el valor diagnóstico de estas enzimas realizando un estudio más amplio y una mayor relación estadística.
Métodos: Se trata de un estudio descriptivo-analítico que se realizó con un método transversal. El método de muestreo fue censal y se inscribieron 39 pacientes con derrame pleural exudativo. La edad, el sexo, el informe de la biopsia, la LDH sérica y la ADA del líquido pleural se registraron en un formulario elaborado al efecto previamente. Se calculó la relación entre la LDH sérica y la ADA del líquido pleural. Los datos recogidos se introdujeron en el SPSS18 y se analizaron mediante pruebas estadísticas.
Resultados: De los 39 pacientes, el 61,5% tenía cáncer y el 38,5% tenía infecciones. Hubo una relación significativa entre la media de ADA pleural y la media de la relación entre la LDH sérica y la ADA pleural en función del tipo de enfermedad. La sensibilidad, la especificidad, el valor predictivo positivo y el valor predictivo negativo de la relación entre el nivel de LDH sérica y el nivel de ADA pleural fueron del 95,8%, el 80%, el 88,5% y el 92,3%, respectivamente.
Conclusiones: Se puede concluir que la relación LDH sérica / ADA pleural son muy consistentes con el hallazgo patológico y pueden ser utilizados para diagnosticar de malignidad en el derrame pleural exudativo.

Palabras clave: Lactato deshidrogenasa, Adenosina desaminasa, derrame pleural, malignidad.

Introduction

Lactate dehydrogenase (LDH) is an enzyme that is almost present in all living cells. This enzyme plays a significant role in the conversion of lactate to pyruvate and vice versa. It occurs abundantly in blood cells and cardiac muscles. Since the amount of LDH increases with tissue injuries, it is known as an important factor used to assess trauma such as myocardial infarction (MI)[1,2]. Previous studies have shown that LDH can serve as a marker in cancer prognosis. Also, regarding stomach cancer, the incidence of LDH and Vascular endothelial growth factor (VEGF) in the tumor and stroma is rendered as an important factor in cancer prognosis. On the other hand, the LDH rate increases in cellular turnover leading to the use of this enzyme in follow-up of cancer patients[3,4]. Moreover, LDH is used in exploring the rate of pleural fluid absorption and its comparison with serum level to determine whether the fluid accumulated in the pleural space is exudate or transudate[5-7]. Adenosine deaminase (ADA) is an enzyme that plays a role in purine metabolism. The main function of this enzyme in humans is development and maintenance of the immune system, though other physiological roles of the enzyme are not known yet[8,9]. The low rate of ADA may indicate pulmonary inflammation, death of thymus cells, and also reduced T-cells[10,11]. ADA is additionally used in investigating the pleural fluid and ascites fluid in various differential diagnoses[12]. The most common causes of exudative pleural effusions are bacterial infections, cancers (like lung cancer, breast cancer, and lymphoma), viral infections, and pulmonary embolism[13]. The studies conducted so far have relatively demonstrated the role and diagnostic value of LDH alone in exudative pleural effusions indicating its low sensitivity[14]. Nevertheless, recent studies have relatively revealed that the serum LDH to pleural fluid ADA ratio possesses some diagnostic value[15]. Hence, this study investigated the diagnostic value of the proportion of serum LDH to pleural fluid ADA compared to pathology tests in diagnosing cancer in exudative pleural effusions.

Materials and methods

In this descriptive-analytic cross-sectional study, a sample volume of 30 was considered to investigate the patients presenting to Internal Pulmonary Ward and Oncology Ward of Yazd hospitals. A total of 39 patients who qualified for entering the study on the basis of the inclusion criteria, i.e., affliction with exudative pleural effusions, participated in the study. First, the patients were investigated for pleural effusion and the patients with exudative pleural effusion were selected. Then, the patients underwent pleural aspiration to study protein, LDH, albumin, cell counts, ADA, Bacille de Koch (BK), and pathology. If diagnosis could not be established on the basis of these tests, pleural biopsy was done. Along with these tests and on the basis of predetermined goals, serum LDH was also requested. After determining LDH and ADA, the ratio of these two enzymes was estimated. The patients were subsequently divided into cancer and non-cancer patients. The cancer group was, in turn, subdivided into three subgroups of tuberculosis group (diagnosed on the basis of BK), parapneumonic group (on the basis of response to treatment and the appearance of pleura), and miscellaneous causes group (on the basis of exclusion of other causes). The cancer group was subdivided into pulmonary origin subgroup and metastatic subgroup diagnosed on the basis of pleural cytology or biopsy. Next, on the basis of results, the estimated ratio was compared to pathology reports from pleural biopsy which is the standard diagnostic method for differentiating the malignant exudative cases form benign exudative cases. The culled data were analyzed with SPSS20 using Mean±SD, frequencies, Kappa test, and T-test. The best cut-off point was determined by ROC curve (P<0.05).

Results

Our findings showed that of 39 patients with pleural effusion, 24 (61.5%) were affected with cancer and 15 (38.5%) had no cancer. The findings demonstrated that the mean age of the patients under study was 59.94±16.63 years with an age range of 18-86 years, mean serum LDH was 676.74±634.42 IU/L with a range of 131-3345, and the mean ADA level was 29.28±28.06 IU/L with a range of 1-96.8. The results of mean serum LDH level in the samples under study in terms of disease type suggested that the mean serum LDH was 826.75±761.45 in the cancer group and 436.73±199.09 in the non-cancer group (P=0.061) indicating no significant difference in serum LDH level between the two groups. The results of mean pleural ADA level in the samples under study in terms of disease type, cancer type, and non-cancerous diseases are presented in **table I**. The analysis of results using T-test indicated a significant difference in the mean pleural ADA in the samples under study in terms of disease type (cancerous and non-cancerous) and type of cancer (pulmonary and metastatic) (P<0.05).

Table I: Mean pleural ADA in the samples under study in terms of disease type, cancer type, and non-cancerous disease type.

Variables		Frequency	Mean±SD	P-value
Non-cancerous Disease type	Tuberculosis	6	55.33±26.05	0.602
	Miscellaneous causes	5	68.36±23.83	
	Parapneumonic	4	54.75±18.19	
Disease Type	Cancerous	24	114.96±155.17	0.000
	Non-cancerous	15	8.13±4.27	
Cancer Type	Pulmonary	4	6.47±4.54	0.037
	Metastatic	20	11.17±3.73	

The results of the study concerning the mean ratio of serum LDH to pleural ADA (cancer ratio) in the samples under study in terms of disease type, cancer type, and non-cancerous diseases are displayed in **table II**. T-test

Table II: Mean serum LDH to pleural ADA ratio in the samples under study in terms of disease type, cancer type, and non-cancerous disease type.

Variables		Frequency	Mean±SD	P-value
Non-cancerous Disease type	Tuberculosis	6	7.30±2.88	0.635
	Miscellaneous causes	5	7.66±4.41	
	Parapneumonic	4	9.96±6.25	
Disease Type	Cancerous	24	10.38±4.17	0.012
	Non-cancerous	15	59.52±22.74	
Cancer Type	Pulmonary	4	297.74±304.85	0.007
	Metastatic	20	78.41±77.68	

analysis (P<0.05) indicated a significant difference in mean serum LDH to pleural ADA ratio in the samples under study in terms of disease type (cancerous and non-cancerous), and cancer type (pulmonary and metastatic).

Moreover, T-test analysis of results suggested no significant difference in mean serum LDH level in the samples under study in terms of disease type (cancerous and non-cancerous) and non-cancerous disease type, and cancer type (pulmonary and metastatic) (P>0.05). The correspondence between serum LDH to pleural ADA ratio and pathology findings was examined by Kappa test and gave Kappa=0.778 indicating a high correspondence. ROC curve was used to determine the best cut-off point for serum LDH to pleural ADA ratio in diagnosing cancer resulting in AUC=0.981 that is a good value. This value was tested to the power of 0.5 that was significant at P=0.000. This means that the use of serum LDH to pleural ADA index is helpful in cancer diagnosis. Given the sensitivity and specificity values given by the computer, the best cut-off point lied between 13.6 and 14.08; so, we selected 13.5 as the cut-off point in this study. Using the cut-off point obtained in this study, the following diagnostic values of serum LDH to pleural ADA ratio were acquired:

- Sensitivity=95.8%
- Specificity=80%
- Positive predictive value=88.5%
- Negative predictive value=92.3%
- Accuracy=89%

Discussion

There are countless challenges facing various sciences, especially medicine, health and experimental sciences[16-22]. The results of the study by Lee conducted on the serum LDH level in patients with pulmonary cancer showed that the serum LDH level in these patients is directly correlated with the rate of tumor spread in the patients' whole body[23]. These results are not consistent with our findings that there was no significant correlation between mean serum LDH levels in terms of disease type (cancerous and non-cancerous). The difference may be attributed to the difference in the type of tumors under study as our study examined all types of exudative pleural effusions regardless of their type while Lee's study investigated only exudative pleural effusions induced by non-small cell carcinoma. Also, the findings of the study by Hermes carried out on the role of serum LDH level in the remainders of patients with pulmonary cancer of small cell type demonstrated that the serum LDH level serves as an independent and reliable parameter in exploring the patients' survival rate[24]. Another study in 2016 revealed that the LDH to ADA ratio has great diagnostic value in diagnosing exudative effusions[15]. The results of the study above are consistent with the findings by Zhang[14] and Lumachi[25] wherein the serum LDH to pleural ADA ratio showed high correspondence with pathological findings. Besides, the results of the study by Verma (2016), performed on diagnostic value of serum LDH to pleural ADA ratio in differentiating malignant exudatives from tuberculosis, demonstrated that the LDH to ADA ratio is of great diagnostic value in differentiating malignant exudatives from TB[26]. This is consistent with our finding that indicated a significant correlation between mean serum LDH to pleural ADA ratio in terms of disease type (cancerous and non-cancerous). Furthermore, the results of this study showed that the serum LDH level was significantly higher in the malignant cancer group compared to the TB group. Although the LDH level was higher in the malignant cancer group than the infection group, the difference was not statistically significant (P=0.061). The difference may be due to disparities in the groups under study since our study examined all factors of non-cancerous exudative pleural effusions (TB, parapneumonic, and miscellaneous causes) while Verma's study explored merely TB. The study above found a significant correlation between pleural ADA and serum LDH to pleural ADA ratio between the two groups under study which was not consistent with our results. In addition, in the mentioned study, the rates of sensitivity and specificity of serum LDH to pleural ADA ratio were 98% and 94%, respectively, that were greater than those in our study, i.e., 95.8% and 80%, respectively. The difference can be attributed to the differences in sample volumes in the two studies as we investigated 39 patients with exudative pleural effusions whereas Verma explored 987 patients leading to the wide differences in the specificity of the intended index in the two studies. Finally, the study above considered a cut-off point smaller than 20 which was higher than our cut-off point that was 13.5. Moreover, in that study the mean ADA level was significantly higher in the cancer group with pulmonary origin compared to the metastatic cancer group which is not consistent with our study wherein the mean ADA level was higher in the metastatic cancer group. This inconsistency of results may be due to differences in sample volumes in the two studies since the number of samples with cancer of pulmonary origin was less than cancer of metastatic origin.

Conclusion

On the basis of our findings, it may be concluded that the use of serum LDH to pleural ADA index is beneficial

in cancer diagnosis so that it can be used in diagnosing cancers in exudative pleural effusions. The presence of high specificity (95.8%) in the correspondence between serum LDH to pleural ADA ratio and pathological results indicates that the negativity of the index can greatly reject the malignant exudative pleural effusion though, of course, a relatively low specificity (80%) suggests that the positivity of this index is not of much help in diagnosing malignant exudative pleural effusion and shows more false positive results. Ultimately, considering the significant difference in mean serum LDH to pleural ADA ratio in the samples under study in terms of disease type, it may be concluded that this index can be used in differentiating malignant exudative pleural effusion from other miscellaneous non-malignant exudative pleural effusions like infections.

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Interests conflict

The researchers declare that they have no conflict of interest.

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