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Original Research Article

PROGNOSTIC SIGNIFICANCE OF SERUM LACTATE DEHYDROGENASE LEVELS IN HIV PATIENTS WITH PNEUMOCYSTIS JIROVECIII PNEUMONIA

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ABSTRACT

Background: HIV-induced immunodeficiency frequently leads to opportunistic infections including Pneumocystis jiroveciii pneumonia (PJP). lactate dehydrogenase (LDH) levels are usually elevated in cases of PJP. The purpose of this study was to assess the predictive value of LDH in PJP patients as well as its link with HIV progression as measured by CD4+ lymphocyte counts.

Materials and Methods: A prospective observational study was carried out over a two-year period at the Kamineni Academy of Medical Sciences and Research Centre in Hyderabad, India. 51 HIV-positive patients with PJP were included in this study on the basis of a predefined inclusion and exclusion criteria. Comprehensive pathological and radiological assessments were carried out including a complete blood profile, LDH levels, renal and liver function tests, viral load and CD4/CD8 counts. HRCT chest imaging and arterial blood gas analysis was also done. The relationship between LDH levels and CD4 counts was analysed with an emphasis on LDH as a prognostic marker.

Results: The average CD4 count for the patients was 130.47 ± 48.39 cells/mm³. LDH levels showed a substantial negative correlation with CD4 counts ($p < 0.001$). The study found that LDH levels >372 U/L had 100% sensitivity and 89.20% specificity in predicting adverse outcomes, resulting in a 27.5% mortality. Youden's index (J=0.9189) revealed >372 U/L as the best LDH threshold, resulting in an 82.4% positive and 100% negative predictive value.

Conclusion: LDH can be a valuable diagnostic tool, especially in situations where invasive testing is impossible or risky. This is important in resource poor setting in developing countries including India.

Keywords: CD4/CD8, HIV, Lactate Dehydrogenase, Liver Function Test, Pneumonia, Pneumocystis jiroveciii pneumonia.

INTRODUCTION

Immunodeficiency caused by the human immunodeficiency virus (HIV) commonly leads to lung infections, including Pneumocystis jiroveciii pneumonia (PJP), bacterial pneumonia, and granulomatous diseases such as tuberculosis and fungal infections. Of these, PJP continues to be a significant consequence in individuals with weakened immune systems.[1] It is linked to significant illness and death in HIV-positive people. Before the development of efficient therapies, PJP was a prominent factor contributing to mortality in individuals with AIDS. Over the past three decades, comprehension of HIV/AIDS and PJP has seen substantial breakthroughs, however, there are notable areas of research that need to be bridged.[2]

Due to its association with AIDS and frequent need for invasive diagnostics PJP garners significant attention. It is one of the uncommon but life-threatening fungal infection and primarily affects individuals with acquired immunodeficiency yndrome and low CD4 counts. The appearance of PJP in previously healthy young men was an early sign of the HIV in earlier phase of epidemic. Although Antiretroviral Therapy (ART) has reduced incidence of PJP in people with HIV it still remains a concern for those with uncontrolled HIV or severe

immunodeficiency.[3] The highest incidence of PJP is seen in individuals with CD4+ T-cell counts below 200 cells/mm.[4] PJP is caused by Pneumocystis jiroveciii which is an opportunistic pathogen affecting immunocompromised hosts. The typical symptomatology includes shortness of breath, fever, and dry cough which usually develop gradually. Diagnosis usually depends upon microscopy, PCR and specialized staining.[5]

Lactate dehydrogenase (LDH) is an enzyme involved in glucose metabolism. It converts lactate to pyruvate and exists as isoenzymes (LDH1-5) linked to various organs. It is significant in infectious diseases particularly among immunocompromised individuals like those with HIV.[6] Many studies have shown that elevated LDH levels correlate with poorer outcomes in lung conditions such as tuberculosis.[7] Its role in HIV-related PJP is relatively less studied.[8] Some studies have shown that lower LDH levels indicate a positive treatment response due to alveolar cell damage by Pneumocystis jiroveciii. Although PJP has extensively researched particularly in cases of HIV infections still knowledge gap remains. For instance role of LDH in early diagnosis, screening in mild cases and predicting disease severity based on HIV stages has not been extensively researched. Studying LDH in HIV patients with PJP could enhance prognosis and may allow for cost-effective risk assessments.[9]

Early identification of PJP and appropriate intervention are critical components of effective HIV PJP care. Delay in proper diagnosis and appropriate management may cause catastrophic consequences such as respiratory failure and need for assisted ventilation.[10] Many studies have concluded that there exists a strong correlation between elevated serum LDH levels and PJP, particulalry in cases of HIV. However further studies are needed to uncover biomarkers that improve prognostic accuracy and guide treatment choices. LDH levels may indicate disease severity and inflammation. Its estimation may provide important information about patient prognosis and therapy responsiveness. This study aims to assess the predictive value of serum lactate dehydrogenase (LDH) levels in diagnosing Pneumocystis jiroveciii pneumonia (PJP) in HIV-positive patients and its correlation with HIV progression as measured by CD4+ lymphocyte counts.

MATERIALS AND METHODS

This prospective hospital-based observational study was conducted in the department of internal medicine of Kamineni Academy of Medical Sciences and Research Centre in Hyderabad, Telangana. 51 HIV patients with PJP were included in this study on the basis of a predefined inclusion and exclusion criteria over a period of 2 years extending from September 2019 to September 2021. The study was approved by the Institutional ethics committee of the hospital and written informed consent was obtained from the participants. Patients aged > 18 years with HIV and PJP were included and patients aged <18 years with elevated LDH with infections other than PJP were excluded from this study.

A detailed history and examination of recruited HIV patients with PJP were performed. The complete blood profile (CBP), serum lactose dehydrogenase (LDH), serum renal function test (RFT), serum liver function test (LFT), serum HIV viral load, serum CD4 and CD8 count. Further, sputum stain (AFB test), arterial blood gases (ABG) test, chest x-ray, Bronchoalveolar lavage (BAL), and high-resolution computed tomography (HRCT) chest were conducted on all the recruited patients as per the standard protocol.

Serum Lactate Dehydrogenase (LDH), Renal Function Tests (RFT), Liver Function Tests (LFT), HIV viral load, CD4 and CD8 lymphocyte counts, arterial blood gas (ABG) analysis was done in all cases. LDH levels were assessed as a non-specific marker of tissue injury, often elevated in cases of Pneumocystis jiroveciii pneumonia (PJP). RFT and LFT were done to evaluate systemic involvement including renal impairment and hepatocellular or cholestatic liver dysfunction which may be attributable to HIV infection or its complications.

HIV disease status was monitored through viral load quantification and CD4/CD8 counts with a focus on immunosuppression severity. ABG analysis was performed to detect respiratory compromise with particular attention to hypoxemia and hypercapnia. High-resolution computed tomography (HRCT) of the chest and bronchoalveolar lavage (BAL) analysis was done in all cases. Characteristic pulmonary changes such as ground-glass opacities and BAL specimens were examined microscopically. Molecular techniques was used to confirm the presence of Pneumocystis jiroveciii.

Respiratory failure was categorized into hypoxemic and hypercapnic types. Hypoxemic respiratory failure was defined by a partial pressure of arterial oxygen (PaO2) below 60 mmHg on room air or a PaO2 to FiO2 ratio of 300 mmHg or less while the patient was receiving oxygen at a flow rate of 10 L/min or higher for at least 15 minutes. Hypercapnic respiratory failure was characterized by a partial pressure of arterial carbon dioxide exceeding 45 mmHg . Lactic acidosis was identified by a blood pH of 7.35 or lower and a serum bicarbonate ($HCO3^-$) level of 20 mmol/L or less, along with elevated blood lactate levels . Sepsis was diagnosed when two or more of the following criteria were met: a temperature above 38°C or below 36°C, a heart rate exceeding 90 beats per minute, a respiratory rate above 20 breaths per minute and a leukocyte count greater than 12 × 10^9/L or less than 4 × 10^9/L or the presence of more than 10% immature bands. Septic shock was defined by the need for vasopressor support, including agents such as dobutamine, norepinephrine, epinephrine, phenylephrine, angiotensin II, or vasopressin.

The data was recorded in a Microsoft Excel data sheet and then analyzed using the SPSS V.22 software. Categorical data was presented using frequencies and percentages. Continuous data was presented using the mean and standard deviation. A Pearson correlation analysis was conducted to determine the relationship between two quantitative variables and qualitative variables, respectively. P value less than 0.05 was taken as statistically significant.

RESULTS

Among 51 patients there were 30 (58.8%) males and 21 (41.2%) females with a male to female ratio of 1:0.7. The mean age of the patients was 46.33 ± 9.76 years. The largest percentage of patients fell in the age group of 41-50 years (27%) while 31-40 years had 4% of patients (Table 1).

Table 1: Gender and Age Distribution of studied cases

Variable		Category	Frequency (n)
Gender Distrbution	Male	30	58.8%
	Female	21	41.2%
Male: Female Ratio = 1:0.7			
Age Group (years)	≤30	3	5.88%
	31–40	8	15.69%
	41–50	18	35.29%
	51–60	14	27.45%
	Above 60	8	15.69%
Age (Mean ± SD) = 46.33 ± 9.76 years			

The mean CD4 cell count was 130.47 ± 48.39 cells/mm³ (indicating a significantly immunocompromised state) while the mean CD8 count stood at 732.04 ± 249.99 cells/mm³, with a CD4/CD8 ratio of 0.19 ± 0.09. Serum LDH was elevated with a mean value of 373.51 ± 155.34 U/L . Mean Hemoglobin levels were 11.20 ± 1.52 g/dL while total leukocyte count (TLC) was 8999.02 ± 3409.37 cells/mm³. Liver function parameters such as SGPT and SGOT were recorded at 41.02 ± 11.79 U/L and 49.14 ± 33.53 U/L respectively, and alkaline phosphatase (ALP) levels averaged 227.37 ± 50.44 U/L. Mean serum creatinine was found to be 1.08 ± 0.22 mg/dL. The viral load in these patients was also notably high with a mean of 10845.43 ± 4157.48 RNA copies/ml (Table 2).

Table 2: Characteristics of patients with respect to Laboratory parameters

Parameters	**(Mean ± SD)**
CD4 (cells/mm^3)	130.47 ± 48.39
LDH (U/L)	373.51 ± 155.34
Hemoglobin	11.20 ± 1.52
TLC	8999.02 ± 3409.37
S. Creatinine	1.08 ± 0.22
SGPT	41.02 ± 11.79
SGOT	49.14 ± 33.53
ALP	227.37 ± 50.44
Viral Load (RNA copies/ml)	10845.43 ± 4157.48
CD8 (cells/mm^3)	732.04 ± 249.99
CD4/CD8	0.19 ± 0.09

In this study, the mean CD4 count of patients was found to be 130 cells/mm3 with a minimum value of 11 cells/mm3 and a maximum value of 200 cells/mm3. With the increase in LDH value the CD4 level decreased significantly. Pearson correlation indicated a negative moderate correlation. The mean CD8 count of patients was 732 cells/mm3 with a minimum value of 289 cells/mm3 and a maximum value of 1480 cells/mm3. Likewise, the mean CD4/CD8 ratio was 0.19 with a minimum of 0.01 and a maximum of 0.51 with a similar trend of negative moderate correlation. However, there was no significant correlation observed between LDH and viral load (Table 3).

Table 3: Correlation of LDH with CD4 count, CD4/CD8 and Viral load

Variables	**N**	**P-value**	**Pearson-correlation**
CD4	51	<0.001**	-0.585**
CD4/CD8	51	0.001**	-0.470**
Viral load	51	0.103	0.473
**values are significant at p < 0.001			

The analysis of LDH cutoff values in relation to their diagnostic performance for Pneumocystis jiroveciii pneumonia in HIV patients demonstrated notable variations in sensitivity, specificity, and predictive values at different thresholds. At the LDH level of ≥200 U/L, the sensitivity was exceptionally high at 100% (95% CI: 76.8–100.0), However, the specificity was 0% (95% CI: 0.0–9.5), with a positive

predictive value (+PV) of 27.5%. At a higher threshold of >372 U/L, both sensitivity and specificity remained high at 100% (95% CI: 76.8–100.0) and 89.2% (95% CI: 78.1–98.3) respectively, indicating an excellent balance of correctly identifying both positive and negative cases, with a +PV of 82.4% and a negative predictive value (–PV) of 100.0%. In contrast, at a very high cutoff of >799 U/L, the sensitivity dropped to 0.00% (95% CI: 0.0–23.2), while specificity reached 100.0% (95% CI: 90.5–100.0). However, due to the complete absence of sensitivity, this threshold was clinically unhelpful for diagnosing the condition. At Youden's index the threshold of LDH was identified at >372 U/L, yielding a sensitivity, specificity, PPV, and NPV of 100%, 89.20%, 82.4%, and 100% respectively (Table 4).

Table 4: Distribution of sensitivity, specificity, positive and negative predictive values

Criterion (U/L)	Sensitivity (%)	95% CI	Specificity (%)	95% CI	+PV (%)	-PV (%)
≥200	100.00	76.8 - 100.0	0.00	0.0 - 9.5	27.5	
>372	100.00	76.8 - 100.0	89.2	78.1 - 98.3	82.4	100.0
>383	92.86	66.1 - 99.8	91.89	78.1 - 98.3	81.3	97.1
>400	85.71	57.2 - 98.2	94.59	81.8 - 99.3	85.7	94.6
>420	78.57	49.2 - 95.3	94.59	81.8 - 99.3	84.6	92.1
>450	71.43	41.9 - 91.6	97.30	85.8 - 99.9	90.9	90.0
>623	28.57	8.4 - 58.1	97.30	85.8 - 99.9	80.0	78.3
>647	28.57	8.4 - 58.1	100.00	90.5 - 100.0	100.0	78.7
>799	0.00	0.0 - 23.2	100.00	90.5 - 100.0		72.5

During study period among 51 recruited patients, the study reported overall mortality of 14 patients i.e., 27.5% mortality rate.

DISCUSSION

Pneumocystis jirovecii, is an opportunist fungus, which may cause significant morbidity and mortality in immunocompromised patients. PJP is one of the most encountered HIV-associated opportunist infections.[11] The study included 51 HIV-positive, PJP-affected patients. The demographic characteristics were in line with Eid et al.[12]

Increased serum LDH levels have been linked to a variety of illnesses, including tuberculosis, PCP, toxoplasmosis, histoplasmosis, lymphoma, and bacterial pneumonia.[13] LDH levels frequently correlate with the size of radiographic infiltrates rather than the disease process. Serum LDH in PCP can be used as a predictive diagnostic to determine the severity of lung injury. According to Rahman et al,[14] LDH levels in PCP range between 361 IU/L and 1217 IU/L with greater levels associated with higher mortality. Peak LDH levels in PCP were 547 IU/L according to a study conducted by Quist and Hill.[15] Their 1995 study discovered greater rates of pulmonary TB and bacterial pneumonia. LDH levels above normal in HIV-infected patients were related with AIDS criteria, lower CD4 counts, and a higher risk of PCP, CMV, Mycobacterium avium, and bacterial pneumonia.[16]

The present study indicated a moderate negative connection between CD4 (mean 130 cells/mm^3) and CD4/CD8 ratio (0.19) and LDH. This is consistent with the study of Feng et al's findings in 193 HIV-infected PJP patients (CD4 mean 88 cells/µl, CD4/CD8 ratio 0.05).[17] This is also consistent with findings of studies done by Wang et al,[18] Memish et al,[19] and Wolfe et al.[20] Similarly Almaghrabi et al,[21] reported a median HIV viral load >1.0×10^6 RNA copies/mL in a similar group, corroborating the current findings. In this study the most efficient LDH threshold was found to be >372 IU/L with 100% sensitivity, 89.2% specificity, 82.4% PPV, and 100% NPV among thresholds ranging from ≥200 to >799 IU/L. Ramana et al,[22] discovered that a cut-off of more than 172 IU/L is useful for assessing HIV progression. Azoulay et al,[23] found that serum LDH had an 87.2% sensitivity, 92.2% specificity, 51.5% PPV, and 98.7% NPV.

The major limitation of the study was that it was a single-center retrospective analysis. prospective, multi-center case-control studies having larger sample size are required to corroborate findings of this study.

In the end it must be emphasized that While LDH is useful as a prognostic marker for PJP, it has significant limitations due to its lack of specificity. Elevated LDH levels can result from a variety of conditions, including viral infections and non-infectious sources. Although increased LDH may suggest PJP in the right clinical context it cannot confirm the diagnosis alone. Additionally, factors such as hemolysis, liver dysfunction and other co-infections which are common in HIV patients can also raise LDH levels complicating the interpretation of test results.

CONCLUSION

Since PJP cannot be cultured the diagnosis of PJP pneumonia largely relies on clinical picture and examining respiratory secretions obtained via bronchoscopy, using special staining techniques for visualization. Beta-glucan and LDH serve as noninvasive diagnostic indicators for PJP. While the beta-glucan test is costly and challenging to obtain LDH is an affordable, widely available marker that effectively assesses lung injury severity. LDH aids in PJP diagnosis when invasive methods aren't viable.

LDH levels have found to have high sensitivity and positive predictive value, though limited specificity. In resource-limited settings LDH aids in risk assessment at admission for PJP management. LDH levels as surrogate marker for diagnosis of PJP complements other diagnostic and prognostic methods effectively.

Conflict of Interest: None.

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