Study of Cardiovascular Dysfunctions in Interstitial Lung Disease patients by Correlating the Levels of Serum NT PRO BNP and Microalbuminuria (Biomarkers of Cardiovascular Dysfunction) with Echocardiographic, Bronchoscopic and High-Resolution Computed Tomography Findings of These ILD Patients

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ABSTRACT

Aim: More than 150 known factors associated with ILD and prevalence are uncommon with usual clinical presentation of exertional dyspnea and cough, with finding on examination often limited to fine inspiratory crackles on auscultation. Diagnosis can be made by combination of clinical, radiological and pathological features.

Methods: This is a prospective study constituting 60 cases of ILD conducted to study the cardiovascular dysfunctions associated with interstitial lung diseases with special reference to serum NT PRO BNP and microalbuminuria as bio-markers of cardiovascular dysfunction and co-relating the level of serum NT PRO BNP and microalbuminuria with echocardiographic, bronchoscopic and HRCT findings in ILD patients.

Results: When the correlation between major 2D Echo findings, raised serum NT PRO BNP and microalbuminuria was made it was found that out of total 24 cases of PAH all 24 cases (100%) had raised serum NT PRO BNP and 23 cases (95.83%) had microalbuminuria, out of total 8 cases of diastolic dysfunction all these 8 cases (100%) had raised serum NT PRO BNP and 4 cases (50%) had microalbuminuria, out of 26 cases of normal 2D Echo 4 cases (15.38%) had raised serum NT PRO BNP and 2 cases (7.69%) had microalbuminuria.

Result: Pulmonary hypertension is a very important predictor of mortality; early detection can help in inducing early intervention and can delay mortality. Hence 2D Echo, serum NT Pro BNP and microalbuminuria evaluation should be included in the evaluation of all ILD cases.

Key Words: ILD, Serum NT PRO BNP and microalbuminuria, Cardiovascular dysfunction, Clinico-radiological profile of patients

INTRODUCTION

Interstitial lung diseases refer to a broad category of lung disease rather than a specific disease; it includes various illnesses with diverse causes, treatment and prognosis. But these disorders are grouped due to similarity in their clinical presentation, plain chest radiographic appearance and physiological properties. More than 150 known factors associated with ILD and prevalence are uncommon with usual clinical presentation of exertional dyspnea and cough, with finding

on examination often limited to fine inspiratory crackles on auscultation.

Diagnosis can be made by combination of clinical, radiological and pathological features. The causes of interstitial lung diseases are daunting, but they are linked by many common features: clinical presentation, radiographic appearance, physiologic abnormalities, and, in some instances, histological findings^{1,2}.

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ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 24.04.2020

Revised: 02.06.2020

Accepted: 21.06.2020

Published: 05.07.2020

Nevertheless, a specific diagnosis can be made in many patients from the results of a careful history and certain laboratory tests. Bronchoscopy with bronchoalveolar lavage (BAL) and, often, transbronchial biopsy are useful in the diagnosis of some causes of interstitial infiltration. Thoracoscopic or open-lung biopsy is required for a definitive diagnosis of the remaining cases.

Histopathological confirmation by biopsy is not required in most of the cases. The prominent feature in ILD is fibrosis in the interstitium which produces derangement of alveolar architecture and loss of functional alveolar capillary units ^{3,4}.

An interstitial lung disease hallmarks are progressive dyspnea and cough, an abnormal chest radiograph, and impaired pulmonary function tests. However, 5% to 10% of symptomatic patients eventually diagnosed as having interstitial lung disease, at the time of presentation, have normal chest radiographs. There are also dyspneic patients with or without abnormal chest radiographs in whom routine pulmonary function tests (flows, volumes, and diffusing capacity) are normal. In this situation, exercise testing, which stresses the cardiopulmonary systems and measures gas exchange, un-masks abnormalities. Furthermore, high-resolution computed tomography (HRCT) scans and BAL can detect abnormalities in the presence of normal radiographs and physiologic tests in patients at high risk for development of interstitial lung disease, such as patients with connective tissue disease, asbestos exposure, or hypersensitivity pneumonitis and patients taking drugs known to injure the lung ^{5,6}.

In interstitial lung disease. There are characteristic changes in the lungs' mechanical properties and the failure of the movement of gases at the alveolar-capillary interface. Assessment of ventilatory function and the mechanical properties of the lungs as well as exchange of gas, especially during exercise, are vital components of the initial assessment of patients with suspected interstitial lung disease. Additionally, serial functional tests allow the doctor to assess the severity of the disease and the therapeutic intervention results. Beyond radiologic imaging and physiological testing, most patients with suspected interstitial lung disease require invasive studies to establish a final diagnosis. These studies range from bronchoscopy with bronchoalveolar lavage (BAL) to surgical lung biopsy. A poor candidate for the operative risks of a surgical biopsy might undergo bronchoscopy with BAL in search of specific diagnostic features or a typical BAL cell pattern to strengthen the clinico-radiological diagnosis ¹⁻³.

RHC remains the gold standard for haemodynamic pulmonary circulation evaluation and should be conducted in of patient with PH evidence found by non-invasive investigations including clinical results (systolic murmur indicating tricuspid insufficiency), Lung capacity loss for carbon dioxide (DL, CO), severe exercise desaturation and free-flow oxygen

replacement, radiological signs and TTE results indicating PH, as well as elevated levels of BNP or NTpro-BNP ⁵⁻⁹.

An interstitial lung disease hallmarks are progressive dyspnea and cough, an abnormal chest radiograph, and impaired pulmonary function tests ⁴.

This is a prospective study constituting 60 cases of ILD conducted to study the cardiovascular dysfunctions associated with interstitial lung diseases with special reference to serum NT PRO BNP and microalbuminuria as bio-markers of cardiovascular dysfunction and co-relating the level of serum NT PRO BNP and microalbuminuria with echocardiographic, bronchoscopic and HRCT findings in ILD patients.

MATERIAL AND METHODS

Interstitial lung diseases refer to a broad category of lung disease rather than a specific disease, it includes variety of illnesses with diverse causes, treatment and prognosis. But these disorders are grouped due to similarity in their clinical presentation, plain chest radiographic appearance and physiological properties.

The study was conducted in patients admitted to TB and CHEST ward of the department of pulmonary medicine, SCBMCH, Cuttack.

Selection criteria

All cases of ILD based on clinico-radiological and pathological assessment.

Exclusion criteria

A detailed history was taken; physical examination was done in all patients. Routine blood checks up and urine investigations, sputum for AFB, *x-rays*, sputum for gram stain and culture sensitivity studies were conducted. Additional tests include USG, ANTIBODY profile, complement study and other marker study was also done in appropriate cases.

HRCT thorax, ECG, PFT, 2D-ECHO, Serum NT-Pro BNP, 24-hour urine microalbumin and bronchoscopy was done with patient's consent in all patients to further support the evidence in our diagnoses. The procured data was in the proforma and the same was taken up for statistical analysis.

Statistical analysis

For statistical analysis, the comparison between the average values was performed and the relation of continuous data was evaluated by student 't' and 'F' tests. A p-value of 0.05 or less than that was considered statistically significant and statistical calculations were performed using SPSS 16.

RESULTS AND DISCUSSION

The present study was conducted in the Department of Pulmonary Medicine in Netaji Subhash Chandra Bose Medical College and hospitals, Cuttack, Odisha from September 2012 to August 2014. A total of 60 cases were studied with their consent.

Table 1: Age Sex Distribution

Age (years)	Male n (%)	Female n (%)	Total n (%)
25-35	4 (6.67)	5 (8.33)	9 (15)
36-45	10 (16.67)	8 (13.33)	18 (30)
46-55	3 (5)	4 (6.67)	7 (11.67)
56-65	11 (18.33)	6 (10)	17 (28.33)
>65	5 (8.33)	4 (6.67)	9 (15)
25 to >65	33 (55)	27 (45)	60 (100)

Table 1 shows the age range is between 25 to >65 with male predominance of 33 with 55% and female being 27 with 45%. Peak incidence is between 36 to 45, which means about 30%, but this depends on the etiology of the disease.

Figure 1: Chest X-ray pattern.

Figure 1 shows that the most common pattern on chest x ray is reticular in 43.33% of cases followed by nodular in 33.33% and reticulonodular in 30% of cases. Consolidation was seen in 6.67% and calcification in 3.33% cases. It has been seen that the location of lesion on chest x rays, lower zone being the predominant one in 45% cases followed by multiple zones in 41.67% cases.

Figure 2: correlation between etiology, raised serum NT PRO BNP and microalbuminuria.

The above Figure 2 shows that 28.33% of cases with UIP pattern, 20% of cases with NSIP pattern, 11.67% of cases with OLD and 3.33% of cases with HP pattern had raised serum NT PRO BNP levels. While microalbuminuria is observed in 21.67% of cases with UIP pattern, 15% of cases with NSIP pattern, 8.33% of cases with OLD pattern and 3.33% of cases with HP pattern. Statistical correlation between etiology raised serum NT PRO BNP and microalbuminuria was carried out and it has been found the critical value of t (with 4 degrees of freedom using the 0.05 significance level) is 2.77. This means that for the probability value to be less than or equal to 0.05, the absolute value of the t statistic (2.25) must be 2.77 or greater, but it is less than that, so we fail to reject the null hypothesis and there to have significant level of p at >0.05. For further confirmations of variation between them, F-value was calculated and table value or critical value of F (4,4) at 5 % level of significance is 6.388. The computed F statistics is 1.779 less than tabulated or critical value. Hence we fail to reject the null hypothesis and concluded that all sets of data do not differ. Hence it may be inferred that the test parameters are almost identical and applied within the same populations.

Figure 3: Correlation between major 2D Echo findings, raised serum NT PRO BNP and microalbuminuria.

The above Figure 3 shows that serum NT PRO BNP was raised in all of the cases with pulmonary artery hypertension and diastolic dysfunction and also in 4 cases having normal 2D Echo findings. While microalbuminuria was present in all but one cases of PAH, 4 cases of Diastolic dysfunction and in two instances having normal 2D Echo findings. Statistical correlation between major 2D Echo findings, raised serum NT PRO BNP and microalbuminuria was performed and it has been found the critical value of t (with 3 degrees of freedom using the 0.05 significance level) is 3.18. This means that for the probability value to be less than or equal to 0.05, the absolute value of the t statistic (3.576) is greater than 3.18, so we reject the null hypothesis and there having significant level of p at <0.05. For further confirmations of variation between them, F value was calculated and table value or critical value of F (3,3) at 5 % level of significance is 9.276. The computed F statistics is 1.73 less than tabu-

lated or critical value. Hence we fail to reject the null hypothesis and concluded that all sets of data do not differ. Hence it may be inferred that the test parameters are almost same and was employed within the same populations.

Figure 4: Correlation between etiology, PAH detectable in 2D ECHO, raised serum NT PRO BNP and microalbuminuria.

The above Figure 4 shows that out of 19 cases of UIP pattern 11 cases(57.89%) had PAH, 17 cases(89.47%) had raised serum NT Pro BNP, 13 cases(68.42%) had microalbuminuria. Out of 17 cases of OLD pattern 5 cases(29.41%) had PAH, 7 cases(41.18%) had raised serum NT Pro BNP, 5 cases(29.41%) had microalbuminuria. Out of 14 cases of NSIP pattern 7 cases(50%) had PAH, 12 cases(85.71%) had raised serum NT Pro BNP, 9 cases(64.28%) had microalbuminuria. Out of 9 cases of UIP pattern only 1 case(11.11%) had PAH, 2 cases (22.22%) had raised serum NT Pro BNP, 2 cases (22.22%) had microalbuminuria.

Statistical correlation between etiology, PAH +Ve and serum NT PRO BNP was performed and it has been found the critical value of t (with 4 degrees of freedom using the 0.05 significance level) is 2.77. This means that for the probability value to be less than or equal to 0.05, the absolute value of the t statistic (2.418) must be 2.77 or greater, but it is less than that, so we fail to reject the null hypothesis and there having a significant level of p at >0.05. For further confirmations of variation between them, F-value was calculated and table value or critical value of F (4,4) at 5 % level of significance is 6.388. The computed F statistics is 1.286 less than tabulated or critical value. Hence we fail to reject the null hypothesis and concluded that all sets of data do not differ. Hence it may be inferred that the test parameters are almost same and was used within the same populations.

Statistical correlation between etiology, PAH +Ve and PAH -Ve was performed and it has been found the critical value of t (with 4 degrees of freedom using the 0.05 significance level) is 2.77. This means that for the probability value to be less than or equal to 0.05, the absolute value of the t statistic (2.449) must be 2.77 or greater, but it is less than that, so we fail to reject the null hypothesis and there to have significant level of p at >0.05. For further

confirmations of variation between them, F-value was calculated and table value or critical value of F (4,4) at 5 % level of significance is 6.388. The calculated F statistics is 1.286 less than tabulated or critical value. Hence we fail to reject the null hypothesis and concluded that all sets of data do not differ. Hence it may be inferred that the test parameters are almost same.

Statistical correlation between etiology, PAH +Ve and microalbuminuria was performed and it has been found the critical value of t (with 4 degrees of freedom using the 0.05 significance level) is 2.77. This means that for the probability value to be less than or equal to 0.05, the absolute value of the t statistic (2.23) must be 2.77 or greater, but it is less than that, so we fail to reject the null hypothesis and there having significant level of p at >0.05. For further confirmations of variation between them, F value was calculated and table value or critical value of F (4,4) at 5 % level of significance is 6.388. The calculated F statistics is 1.37 less than tabulated or critical value. Hence we fail to reject the null hypothesis and concluded that all sets of data do not differ. Hence it may be inferred that the test parameters are almost same.

Statistical correlation between etiology, PAH -Ve and serum NT PRO BNP was performed and it has been found the critical value of t (with 4 degrees of freedom using the 0.05 significance level) is 2.77. This means that for the probability value to be less than or equal to 0.05, the absolute value of the t statistic (4.06) must be 2.77 or greater, but it is greater than that, so we reject the null hypothesis and there having significant level of p at <0.05. For further confirmations of variation between them, F value was calculated and table value or critical value of F (4,4) at 5 % level of significance is 6.388. The calculated F statistics is 3.14 less than tabulated or critical value. Hence we fail to reject the null hypothesis and concluded that all sets of data do not differ. Hence it may be inferred that the test parameters are almost same.

Statistical correlation between etiology, PAH -Ve and microalbuminuria was performed and it has been found the critical value of t (with 4 degrees of freedom using the 0.05 significance level) is 2.77. This means that for the probability value to be less than or equal to 0.05, the absolute value of the t statistic (3.628) must be 2.77 or greater, but it is greater than that, so we reject the null hypothesis and there having significant level of p at <0.05. For further confirmations of variation between them, F value was calculated and table value or critical value of F (4,4) at 5 % level of significance is 6.388. The calculated F statistics is 1.764 less than tabulated or critical value. Hence we fail to reject the null hypothesis and concluded that all sets of data do not differ. Hence it may be inferred that the test parameters are almost same.

Figure 5: Distribution on HRCT.

Figure 5 illustrates the pattern of distribution of lesions on HRCT thorax with septal thickening being the most common with 56.67% followed by nodules and honey combing with 50% and 46.67% respectively.

Figure 6: Multiple ill defined small centrilobular nodules with ground glass opacities in bilateral lung parenchyma in a case of subacute hypersensitivity pneumonitis.

Figure 7: Numerous centrilobular micronodules distributed in bilateral lung parenchyma with calcified mediastinal nodes in a case of silicosis.

Figure 8: Salt and pepper type of pigmentation of skin in a case of systemic sclerosis.

Figure 9: Interlobular and intralobular septal thickening, traction bronchiectasis and subpleural honeycombing in a case of UIP-IPF.

This is a prospective study constituting 60 cases of ILD conducted to study the cardiovascular dysfunctions associated with interstitial lung diseases. The age range was between 26-83 yrs with the mean age of 50.53 yrs. with a male predominance of 33 with 55% and female being 27 with 45%. Peak incidence was in between 36 to 45 of about 30%. Most of the patients with UIP and NSIP were females with 20% and 21.67%, respectively. And in males OLD was more commonly seen in 28.33% of cases.

In comparison with frequently cited population-based registry from New Mexico, reports have a prevalence of 80.9 per 100,000 in males and 67.2 per 100,000 in females and compared to Muhammed Shafeeq K *et al*¹ reported on clinico-radiological profile of ILD of 70 patients and same pattern were included in this study. The mean age of study population was 52.4 years. 34 (48.6%) were males and 36 (51.4%) were females.

Whereas Tiyaas and Zarir *et al*² reported that the mean age of the patients was 48 years and the male: female ratio was 1:2. Gagiya *et al*³ reported the mean age of the patients was 43.57 years. In this study 66.5% male patients, while 33.5% were female patients. Jindal *et al*⁴, the study showed peak incidence between 30 to 59 years, and out of which male and female incidence was 42.4% and 57.4%. Our study showing male predominance tallied with Gagiya *et al*³ studied in 2012 on ILD patients.

Raised ESR was the most common abnormal lab parameter in 76.67% of cases followed by hypoalbuminemia in 66.67% of cases, raised serum NT PRO BNP in 63.33%, microalbuminuria in 48.33%, leucocytosis was seen in 43.33% of patients. Hyperglycemia and anemia was seen in 11.67% and 15%, respectively. ANA was positive in 16.67% and RF in 6.67% of patients. Anti scl 70 was positive in 11.67% and anti ds DNA was positive in 5% patients. Muhammed Shafeeq K *et al*¹ reported that ANA was positive in 11 patients, RA factor in 8, Anti-ds-DNA in 2, Anti-scl-70 was seen in 3 patients. Tiyaas and Zarir *et al*² showed the blood counts, a predominance of either neutrophils (n=230 patients; mean±SD=2) or lymphocytes. The ESR was raised (>100 mm at the end of first hour) in all the patients. Antinuclear

antibody was detected in patients with ILD secondary to collagen vascular disease. Anti-topoisomerase (SCL-70) was positive in patients with systemic sclerosis and ILD, anti-double stranded deoxyribonucleic acid was positive in 4% patients with systemic lupus erythematosus (SLE) and ILD. Gagiya *et al*³ reported that hemoglobin less than 10% was found in 36.63% and white blood cells more than 11,000/cmm in 6.66% of cases. Elevated ESR was found mainly in the collagen disease group and in some idiopathic group patients with elevated ESR.

The latter study showed its correlation with other similar studies and proved that incidence of anemia (36.63%) closely resemble to Jindal *et al*¹⁰ (39.30%) study. As compared to latter study (6.66%), slightly increased incidence of leucocytosis was found in Jindal *et al*¹⁰ (14.70%) study. Rheumatoid factor was positive in 16.65% cases as compared to Jindal *et al*¹⁰ study (8.4%) and M. Turner *et al*¹¹ study (19%) cases have Rheumatoid factor positive.

Our study tallied with Tiyas and Zarir *et al*² when comparing elevated ESR and with Muhammed Shafeeq K *et al*¹, when comparing ANA and RF. But our study showed higher incidence of leucocytosis and hypoalbuminemia may be due to high incidence of infection and nutrition deficiency.

The location of lesion on chest x rays showed that lower zone was predominantly affected (45%) followed by multiple zones (41.67%). The pattern of distribution on chest X-ray showed that most common pattern on chest x ray is reticular (43.33%) followed by nodular (33.33%) and reticulonodular (30%). Consolidation was seen in 6.67% and calcification in 3.33%. In Muhammed Shafeeq K *et al*¹, reticular pattern was 43%, Reticulonodular- 29%, Nodular pattern 10%, Consolidation 10%, Mediastinal widening was seen 10%. Tiyas and Zarir *et al*² observed that the chest radiograph of the patients showed ground-glass appearance at the bases in 82% of the patients and in Gagiya *et al*³ majority of patients showed reticular (16.65%) or reticulonodular (60%) Ground glass (10%) and honey-combing (13.32%) pattern on chest X-ray.

Muhammed Shafeeq K *et al*¹ has observed Ground glass opacity in 46%, Septal thickening 69%, Honey combing 43%, Nodules 16% of total included patients and Mediastinal nodes was seen 11.4% and in Tiyas and Zarir *et al*² showed ground-glass appearance in 90% and Honey-combing was observed in 43% of the patients and in Gagiya *et al*³ was studied in honey combing appearance and which was 13.32%, that resemble to Johnston *et al*¹² studies (15.10%). Incidence of Reticular and Reticulonodular patterns were 76.65%.

In our study, we found that biomarkers of cardiovascular dysfunction i.e. raised serum NT PRO BNP and microalbuminuria, were observed in 63.33% and 48.33% of the total number of cases, respectively.

In our study when the correlation between etiology, raised serum NT PRO BNP and microalbuminuria was made it was found that out of total 19 cases of UIP pattern 17 cases (89.47%) had raised serum NT PRO BNP and 13 cases (68.42%) had microalbuminuria, out of total 14 cases of NSIP pattern 12 cases (85.71%) had raised serum NT PRO BNP and 9 cases (64.28%) had microalbuminuria, out of total 17 cases of OLD pattern 7 cases (41.18%) had raised serum NT PRO BNP and 5 cases (29.41%) had microalbuminuria, out of total 9 cases of HP pattern 2 cases (22.22%) had raised serum NT PRO BNP and 2 cases (22.22%) had microalbuminuria.

When the correlation between major 2D Echo findings, raised serum NT PRO BNP and microalbuminuria was made it was found that out of total 24 cases of PAH all 24 cases (100%) had raised serum NT PRO BNP and 23 cases (95.83%) had microalbuminuria, out of total 8 cases of diastolic dysfunction all 8 cases (100%) had raised serum NT PRO BNP and 4 cases (50%) had microalbuminuria, out of 26 cases of normal 2D Echo 4 cases (15.38%) had raised serum NT PRO BNP and 2 cases (7.69%) had microalbuminuria.

Findings on 2D ECHO showed that PAH with TR and diastolic dysfunction showed 40% and 13.33% incidence. Normal 2D ECHO finding was the most common presentation (43.33% of cases). There were 2 cases of global hypokinesia and 1 case each of valvular heart disease, concentric LVH, and pericardial effusion. Muhammed Shafeeq K *et al*¹ showed ECHO evidence of pulmonary artery hypertension in 17% patients. In the study of J. Behr and J.H. Ryu¹³ there was high prevalence (30–40%) of pulmonary hypertension (PH) in interstitial lung disease (ILD) patients. 2D Echo findings in our study tallied with that of study by J.Behr and J.H Ryu^{13,14}.

In our study we found that biomarkers of cardiovascular dysfunction i.e. raised serum NT PRO BNP and microalbuminuria were observed in 63.33% and 48.33% of the total number of cases, respectively.

CONCLUSION

The age range was between 26 to 83 with a male predominance of 33 with 55% and female being 27 with 45%. Peak incidence was between 36 to 45 of about 18 %, but this depends on the disease's etiology.

When the correlation between major 2D Echo findings, raised serum NT PRO BNP and microalbuminuria was made it was found that out of total 24 cases of PAH all 24 cases (100%) had raised serum NT PRO BNP and 23 cases (95.83%) had microalbuminuria, out of total 8 cases of diastolic dysfunction all 8 cases (100%) had raised serum NT PRO BNP and

4 cases (50%) had microalbuminuria, out of 26 cases of normal 2D Echo 4 cases (15.38%) had raised serum NT PRO BNP and 2 cases (7.69%) had microalbuminuria.

Finally it can be concluded that the prevalence of cardiovascular dysfunction, especially pulmonary hypertension, is high in ILD patients and 2D Echo can detect mostly moderate and severe variety of pulmonary hypertension. But 2D Echo may not be able to make early detection of cardiovascular dysfunction. Here cardiovascular bio-markers like raised serum NT PRO BNP and microalbuminuria may play an important role in predicting the presence of mild form of cardiovascular dysfunction in ILD patients so that treatment of cardiovascular dysfunction could be initiated early in ILD patients and may improve their survival. Also invasive methods like RHC may be employed to detect early forms of cardiovascular dysfunction in ILD patients. RHC could provide prognostic information with important management implications.

Since pulmonary hypertension is a very important predictor of mortality, early detection can help in inducing early intervention and can delay mortality. Hence 2D Echo, serum NT Pro BNP and microalbuminuria evaluation should be included in the evaluation of all ILD cases.

ACKNOWLEDGEMENT

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Conflict of interest: Nil

Financial support: Nil

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