USE OF ECG AND OTHER CLINICAL VARIABLES FOR DETECTING PULMONARY HYPERTENSION IN COPD PATIENTS- A CROSS-SECTIONAL OBSERVATIONAL STUDY

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ABSTRACT

BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) has emerged as a leading cause of mortality worldwide. Pulmonary Hypertension (PH) is a frequent complication associated with COPD and it is prevalent among 10% - 30% of the COPD patients with moderate-to-severe disease. However, PH-associated with COPD is poorly diagnosed due to the lack of specific clinical investigations and sensitive markers. Despite being the most common techniques, the use of non-invasive techniques like echocardiography and electrocardiography for diagnosing PH in COPD is controversial.

MATERIALS AND METHODS

The cross-sectional observational study was conducted for a period of two years in a super speciality hospital in south India. The subjects were classified based on the status of PH. Apart from routine laboratory investigations, pulmonary function test, transthoracic 2D-echo with colour Doppler and electrocardiography were performed for all the participants. Different clinical and demographic variables were compared between COPD subjects with and without PH and their significance were studied.

RESULTS

The study included a total of 44 subjects with a mean age of 61.3 ± 10.84 . PH was detected in 11 subjects based on the 2D ECHO Doppler findings. On comparison of the various ECG findings between the two groups, only P axis $> 60^\circ$ ($P = 0.0336$) showed a significant variation and $V1-R/S > 1$ (0.0507) showed a trend towards significance.

CONCLUSION

ECG may not be an accurate non-invasive tool for diagnosing PH in COPD patients.

KEYWORDS

COPD, Pulmonary Hypertension, Electrocardiography, Right Ventricular Hypertrophy.

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BACKGROUND

Chronic obstructive pulmonary disease (COPD) is the most prevailing cause of mortality worldwide.¹ According to the 2013 report by World Health Organisation, 65 million people have moderate-to-severe COPD globally. The disease is estimated to cause more than 30% total deaths by the next 10 years and it is projected to become the third leading cause of death worldwide by 2030.² Reports indicate that 90% of the COPD deaths occur in the low- and middle-income countries.³

A population-based survey has reported an overall prevalence of 8.2 in the Chinese population and the disease was found to be prevalent among individuals of 40 years of age.⁴ Studies based on Indian population have reported that 30 million Indians suffer from COPD.⁵ A review of the India-based population studies by Jindal et al have reported that the estimated prevalence of COPD is 5% in men and 2.7% in women.⁶ A systemic review has found that the prevalence of chronic bronchitis in the rural Indian population ranges between 6.5% and 7.7%.⁷

Pulmonary hypertension (PH) is a frequent complication noted in patients with COPD, which further increases the risk of disease exacerbation and decreases the survival.⁸ PH is reported to be prevalent among 10% - 30% of the patients with moderate-to-severe COPD.⁹ Though PH associated with COPD is a well-recognised entity, it confers poor diagnosis. Moreover, the precise estimation of the incidence of PH is difficult since most of the cases have been reported in patients with advanced COPD disease.¹⁰

Studies have reported the lack of specific clinical investigations and sensitive markers to accurately distinguish COPD patients with PH.⁹ Echocardiography and electrocardiography are the two commonly used techniques for the diagnosis of PH. The principal non-invasive technique employed for the diagnosis of COPD is electrocardiography (ECG), but the method holds technical limitations in a significant portion of the COPD patients. Several studies have noted variations like longer PR interval, taller R-wave in lead I, leftward deflection in the T-wave axis, incomplete right bundle branch and larger S-wave in lead I for COPD patients with PH.^{9,11} There are contradictory findings on the efficacy of ECG in distinguishing COPD patients with PH. Alkukhun et al have reported that ECG can significantly distinguish between advanced COPD patients with PH and those without PH.¹¹

There is a lack of clear consensus to differentiate COPD patients with and without PH. The present study was conducted to compare clinical and demographic variables

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among COPD patients with and without pulmonary hypertension, and to explore the risk associated with different variables in COPD patients with PH.

MATERIALS AND METHODS

The 2-year cross-sectional observational study included both male and female inpatients diagnosed with COPD at a super specialty hospital in south India. The diagnosis of COPD was made as per World Health Organisation definition and evidence of pulmonary function tests. The study was approved by the Institutional Ethics Committee and informed consents were obtained from all the participants. Subjects with diabetes mellitus, hypertension, pulmonary diseases like bronchial asthma, tuberculosis, suppurative lung diseases, restrictive lung diseases, interstitial lung diseases and heart diseases like congenital heart disease, valvular heart disease and coronary heart disease were excluded.

Detailed history was collected and clinical examination of the subjects were performed using a structured proforma. Routine investigations carried out for all the subjects included: haemoglobin, total count, differential count, erythrocyte sedimentation rate and urine examination. Pulmonary function test (PFT), reversible airway test and transthoracic 2D-echo with colour Doppler and electrocardiography (12-lead) were also performed for all the participants. The ECG parameters considered for computation were: P-wave axis $> 60^\circ$, P-pulmonale, QRS axis $> 90^\circ$, lead V1-R/ S > 1 , lead V6-R/ S > 1 , clockwise rotation, intrinsicoid deflection and ST-T changes.

Computerised spirometry was performed using KIT MICRO, Data Management Software Version 6.1 A. Among the PFT parameters, forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio and forced expiratory volume in one second (FEV1) were analysed. Transthoracic 2D-echo with colour Doppler was performed using H. P. SONOS 2000, system No. 2406A (HP, US). Patients were considered to have right ventricle/ right atrium (RV/RA) dilated or right ventricular hypertrophy (RVH) if the right ventricle (RV) thickness was 5 mm or more and right atrial enlargement (RAE) if right atrial diameter (inferior-superior) was 5.5 cms or more. The evidence of PAH was looked for with Doppler studies. The subjects were classified into two groups based on the presence and absence of PH.

Statistics

Data with normal distribution are represented as mean $\pm$ SD and those without normal distribution as median (range) and categorical data as counts. The variables with normal distribution were compared by independent 't' test and without normal distribution by Mann-Whitney U test and categorical variables by chi-square test. The risk estimate done by odds ratio was also verified. P value < 0.05 was considered statistically significant. All the statistical analysis was performed using MedCalc Software Version 14.8.1.

RESULTS

Out of the 50 enrolled subjects, 6 were excluded due to the lack of sufficient data. A total of 44 subjects with COPD were included in the study. The mean age of the subjects was 61.3 ± 10.84 with a male-to-female ratio of 1: 0.22. The average duration of illness was 6 years, ranging from 2 - 20 years. Among the subjects, 11 were found to be positive for PH and

33 were negative based on 2D ECHO Doppler findings. The comparison of demographic and clinical variables of the PH positive and negative groups are provided in Table 1.

Upon comparison the variables like FEV1/ FVC ratio, RV/RA dilated or RVH and P axis $> 60^\circ$ were noted to differ significantly between the two groups. Additionally, V1-R/ S > 1 (P value of 0.05) showed a trend towards significance. However, other variables like age, gender, duration of illness, smoking, FEV1, P-pulmonale, QRS axis $> 90^\circ$, V6-R/ S > 1 , clockwise rotation, intrinsicoid deflection and ST-T changes showed uniform distribution.

FEV1/ FVC was significantly higher in subjects with positive PH (57.61 ± 12.29) than those with negative PH (47.21 ± 13.02) (P= 0.025). A significantly higher number of subjects with RV/ RA-Dilated or RVH belonged to the group without PH (n= 28) (< 0.0001). None of the subjects with PH had RV/ RA-dilated or RVH. Similarly, P axis was $> 60^\circ$ in a significant number of subjects belonging to the PH positive group (n= 10) and was $< 60^\circ$ in a significant number of subjects belonging to the PH negative group (n= 17) (P=0.0336). V1-R/ S was > 1 and < 1 majorly in subjects negative for PH (n= 12 and n= 21), but was not statistically significant.

Factors	PH Positive (N=11)	PH Negative (N=33)	P value
Age	62.0 $\pm$ 12.1*	61.0 $\pm$ 10.5*	0.7764
Gender (M/F)	10/1	26/7	0.6517
Duration of Illness	5 (3-10) #	6 (2-20) #	0.0805
Smoking (Y/N)	10/1	23/10	0.3149
FEV1	1.15 $\pm$ 0.41*	1.06 $\pm$ 0.26*	0.4088
FEV1/ FVC	57.61 $\pm$ 12.29*	47.21 $\pm$ 13.02*	0.025
RV/ RA-Dilated or RVH (Y/N)	0/11	28/5	< 0.0001
P-pulmonale (Y/N)	3/8	14/19	0.5918
P axis $> 60^\circ$ (Y/N)	10/1	16/17	0.0336
QRS axis $> 90^\circ$ (Y/N)	7/4	16/17	0.6011
V1-R/ S > 1 (Y/N)	0/11	12/21	0.0507
V6-R/ S > 1 (Y/N)	3/8	13/20	0.7174
Clockwise rotation (Y/N)	1/10	8/25	0.5174
Intrinsicoid deflection (Y/N)	6/5	10/23	0.2776
ST-T changes (Y/N)	1/10	7/26	0.6517

Table 1. Comparison of Demographic and Clinical Variables in Subjects With and Without PH

*mean $\pm$ SD, # median (range).

No significant association was noted on comparison of variables like age, gender, smoking, FEV1/ FVC and P-pulmonale in COPD patients with PH (Table 2). However, the incidence of PH was found to be 4.35 times higher in smokers than non-smokers. Males were 63% less likely than females to be associated with PH. Three patients had normal FEV1/FVC ratio ($\geq 70\%$) and hence were excluded from the analysis. The incidence of PH was found to be 61% lesser in the FEV1/ FVC ratio $< 50\%$ or severe group when compared to mild-to-moderate group. Presence of P-pulmonale was found to be 49% less likely to be associated with PH than its absence. There was no difference in the incidence of PH across different age groups (≤ 35 to ≤ 60 and > 60).

Factors	Odds Ratio	95% Confidence Interval	P value
Age			
> 60	1	0.2540 to 3.9371	1
<= 35 to <= 60	1		
Gender			
Male	0.3714	0.04040 to 3.4152	0.3816
Female	1		
Smoking			
Yes	4.3478	0.4887 to 38.6791	0.1875
No	1		
FEV1/ FVC			
Severe	0.3889	0.08238 to 1.8359	0.233
Mild and Moderate	1		
P-Pulmonale			
Yes	0.5089	0.1140 to 2.2712	0.3761
No	1		
Table 2. Risk Estimate of Demographic and Clinical Variables in Subjects with PH			

DISCUSSION

The incidence of PH noted in the current study in COPD patients was around 25% (n= 11). The recent studies conducted in south Indian population by Reddy et al (2016) and Mahishale et al (2015) have reported a higher frequency of PH in COPD patients.^{12,13} The prevalence reported by Reddy et al was 50% and by Mahishale et al was 41.96% (involving 2040 COPD patients). Researchers have noted that frequency and degree of PH is directly proportional to the severity of COPD.^{12,13} Reddy et al have found that PH accounted for 83% in subjects with severe COPD compared to only 24% in those with mild COPD.¹² However, the present study did not observe a similar trend.

COPD patients with PH are more susceptible to death due to increased risk of right heart failure with systemic congestion. The disease is also associated with ankle oedema, inability of the right ventricular output to meet the peripheral demand during exercise, renal problems and other complications.^{14,15} Currently, there is a lack of precise treatment and effective cure for the disease.¹⁵ Dave et al have indicated COPD as a late onset disease. They have also noted that maximum number of COPD patients belonged to the 51-60 years' age group with a mean age of 54.8 ± 5 years.¹⁶ The mean age noted by Soliman et al (2015) was 62 ± 9.16 years.¹⁷ In concurrence with their findings, the present study has noted a mean age of 61.3 ± 10.84 years in COPD patients. Compared to other studies, Sertogullarindan et al have reported a higher mean age of 67 ± 10 years.¹⁸

India-based population studies have noted a higher prevalence of COPD in males due to the increased use of tobacco. The present study has also found increased occurrence of COPD in male subjects (82%) than females (18%). The prevalence reported by Reddy et al and Mahishale et al in male patients were 85% and 74% respectively.^{12,13} However, studies have indicated that female mortality associated with COPD has surpassed men in countries like US and Turkey, where smoking is more common in females.^{18,19} Joppa et al (2006) have concluded that the results of the pulmonary function test like FEV1 and FEV1/ FVC ratio did not differ significantly between COPD subjects with and without PH.²⁰ Similarly, the current study results of FEV1 did not differ significantly between COPD

subjects with and without PH. Whereas, Sertogullarindan et al (2012) have highlighted the significant role of FEV1 % in the development of PH in moderate and very severe COPD subjects.¹⁸ The study by Joppa and Colleagues observed lower FEV1 in patients with PH than those without the condition with a trend towards significance (P= 0.052).²⁰ A similar observation was also noted by Fayngersh et al.²¹ Contrary to the observation of Joppa et al, the present study has noted a significantly higher FEV1/ FVC ratio (57.61 ± 12.29) in COPD patients with PH. PH-positive subjects demonstrated a mean moderate FEV1/ FVC ratio, whereas those without PH had a mean severe FEV1/ FVC ratio. This observation correlates well with the previous study finding. A similar study conducted by Keller and Colleagues on 89 patients with COPD has shown that COPD patients without PH had significantly higher (< 0.001) mean FEV1/ FVC ratio (53 ± 11) compared to COPD patients with PH (43 ± 11).²²

Sertogullarindan et al (2012) and Fayngersh et al (2011) have suggested gender as an independent predictor of PH in COPD.^{18,21} The present study has also noticed gender as an independent risk factor for the development of PH in subjects with COPD. However, males were noted to be 63% less likely to be associated with PH than females. This observation is in line with the study by Sertogullarindan et al, which reported a higher frequency of PH in females than males with COPD.¹⁸

Current study has also concluded age and smoking as independent factors for predicting the risk for PH in COPD patients. This is in agreement with the study of Fayngersh et al (2011).²¹ The present study has found that smokers were 4.3 times more likely to be associated with PH than non-smokers.

The present study has concluded ECG as an insensitive tool for diagnosing PH in COPD patients. Among the various ECG parameters, only P axis of $> 60^\circ$ was noted in a significant number of subjects with PH. In contrast, the study by Alkukhun et al (2014) did not find any significant difference in the P-wave axis of COPD patients with and without PH. The study also noted a uniform distribution of V1-R/ S ratio and no significant difference in the QRS axis between COPD subjects with and without PH, similar to the current study.¹¹ Several previous studies have indicated ECG as an inadequate tool with poor sensitivity for diagnosing PH in COPD.^{11,23}

Literature evidence indicate that the PH may increase the possibility of right ventricular hypertrophy in subjects with COPD.⁹ Whereas, the present study has noted RVH only in a significantly lesser number of subjects with PH. Diagnosis of PH in COPD patients is often challenging, as most of the patients might be stable and they do not undergo right heart catheterisation. Moreover, the similarity in symptoms for both the diseases adds to the difficulty in diagnosing PH. Early detection is crucial to improve the treatment outcome and quality of life.¹⁴

The major limitations of the present study include single-centre-based evaluation and small sample size. The reduced sample size and single-centre evaluation limit the generalisability of the study findings. Moreover, the study has not used right heart catheterisation, which is considered as the Gold standard for evaluating PH. The preliminary study warrants more similar cross-sectional studies involving large sample size to substantiate the findings, thereby to identify precise diagnostic markers for the detection of PH.

CONCLUSION

In summary, the present study corroborating the increased incidence of PH in COPD patients, especially in male subjects underscores the need of non-invasive markers for the precise and sensitive detection of the condition. The findings also suggest ECG is not a reliable marker for PH detection.

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