Pak. J. Chest Med. 2021;27(04)

Original Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

Frequency of Cor-Pulmonale in Asthma patients visiting a tertiary care hospital in Peshawar

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Article History:

Received:	June 24, 2021
Revised:	Aug 22, 2021
Accepted:	Nov 28, 2021
Available Online:	Dec 02, 2021

Author Contributions:

MI AB MYK conceived idea, AB MU ZU drafted the study, MI SA ZI collected data, AB ZI AU did statistical analysis, AB ZI MYK interpretation of data, AB MYK critical review manuscript, all approved final version to be published.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

How to cite this article:

Idress M, Basit A, Umar M, Ali S, Iqbla Z, Ullah Z, Khan MY. Frequency of Cor-Pulmonale in Asthma patients visiting a tertiary care hospital in Peshawar. Pak J Chest Med 2021; 27(4):283-289.

ABSTRACT

Background: Cor-pulmonale, also known as right sided heart failure is the anatomical and physiological deterioration of right ventricle of heart secondary to respiratory diseases. Long-term pulmonary disorders cause hypoxia, which leads to cor-pulmonale. COPD is one of the most common causes of Cor-pulmonale and respiratory disorders with Cor-pulmonale has strong association for hospital admission and poor mortality rate. The prevalence of Cor-pulmonale varies in various country depending on the burden of respiratory diseases and other associated risk factors. There is very limited information of cor-pulmonale in asthmatic's patients in Pakistan.

Objective: The aims of this study were to determine the frequency of Cor-pulmonale in patients presented with asthma to OPD in a tertiary care hospital MTI-Lady Reading Hospital, Peshawar.

Methodology: This was a cross-sectional study conducted at the Pulmonology unit, Lady Reading Hospital-MTI Peshawar; from 15 Jan 2020 to 15 Jun 2020. Based on criteria for inclusion, 130 patients were selected through convenience sampling technique. Basic demographics like age, gender, duration of asthma and weight on weighing scale in standing position was noted. All patients underwent chest X-ray and then echocardiography. Data regarding Cor-pulmonale was recorded as per operational definition.

Results: Mean and SDs for age were 37.22+13.289, weight 77.79+5.662, height 5.498+0.0816, BMI 28.299+2.0568, duration of asthma 2.55+0.694. There were 73 (56.2%) patients under the age of 40, and 57 (43.8%) patients above the age of 40. There were 94 (72.3%) males and 36 (27.7%) females among the patients. A total of 25 participants (19.2%) had a family history of the disease. As per Cor-pulmonale in patients with asthma, 27 (20.8%) patients were recorded with Cor-pulmonale.

Conclusion: In our study we found that 20.8% of asthmatic patients were suffering from Cor-pulmonale. Men were seen slightly more effected than female. It was recorded more frequently as the duration of asthma advances among the participants. Alarming findings also noted that Cor-pulmonale was found in relative younger age group in our study as compared to data from other studies.

Key words: Cor-Pulmonale; Asthma; Oxygen Therapy

Introduction

Cor-pulmonale is an end stage result of long standing respiratory diseases, which due to hypoxia causes pulmonary hypertension resulting in right ventricular hypertrophy (RVH) and ultimately right ventricular heart failure. Therefore, in chronic cor-pulmonale the mechanism which leads to RVH ultimately results in right heart failure. In recent years chronic Cor-pulmonale is also considered as a cause of congestive heart failure.(2)(4) Cor pulmonale was classically defined as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs except when these pulmonary alterations are the result of diseases that primarily affect the left side of heart."(3) Therefore, early diagnosis and management of Cor-pulmonale is of great significance to physicians, pulmonologists and cardiologists. Analysis of cardiovascular epidemiology in Pakistan also reflected that chronic cor-pulmonale forms a significant proportion of cardiovascular cases.

Cor-pulmonale is rarely reported secondary to asthma but the presence of hypoxia, hypercapnia, fluid retention with related electrocardiographic evidence of right ventricular strain has been observed.(5)(6) Asthma affects 5-10% of the global population making total burden of around 23.4 million people, including 7 million children.(7) The World Health Organization (WHO) estimated that fifteen million disability-adjusted life-years are lost each year, with 250,000 asthma related deaths.(8)

With advances in asthma treatment such as steroid plus LABA (Long-acting beta agonist), Leukotriene antagonist, and Anti IGE, the main goal of asthma therapy is to have total control. Despite the availability of the medications mentioned above, we still see Asthmatic patients developing Cor-pulmonale, as mentioned in the literature. (7–9)

A study conducted by Tarlo SM, et al. has showed that frequency of Cor-pulmonale among asthmatic patients was 16.67%.(9)(10)

Among asthmatic population of Pakistan, no such research has been carried out. Furthermore, literature evidence suggests diversity in results in different populations. so,(7,9) there is a dire need of same study that represent our asthmatic population to determine the frequency of cor-pulmonale in patient with asthma. According to a study on Pakistani population the prevalence of asthma is increasing.(11)(12) The results of this study will help in estimating the real burden of this morbidity in our asthmatic population. Therefore, this research will assist to improve preventive approaches like educating and counseling asthmatic patients to take regular medication, to prevent serious long-term complication like Cor-pulmonale.

Objective:

Objective of the present study was to determine the frequency of cor-pulmonale in patients presenting with asthma to the outdoor department.

Methodology

This cross-sectional study was conducted at department of Pulmonology, LRH, Peshawar from 15 Jan 2020 to 15 Jun 2020. For this study, strict inclusion and exclusion criteria was followed. Inclusion criteria includes patients having age from 18 to 60 years from both genders. Disease related criteria was Asthma as per operational definition for ≥ one year. Exclusion criteria included any cardiac disease (Congenital valvular heart disease,

Table 1. Descriptive Statistics (n≥130)

Numerical Variables	Minimum	Maximum	Mean	Std. Deviation
Age	18	62	37.22	13.289
Weight	62	95	77.79	5.662
Height	5.4	5.7	5.498	.0816
Body Mass Index	23.0	34.5	28.299	2.0568
Duration of Asthma	1	4	2.55	.694

Table 2. Age group of study cases

Age Groups	Frequency	Percent
< 40 Years	73	56.2%
> 40 Years	57	43.8%
Total	130	100.0%

Hypertension, Ischemic Heart Disease, Rheumatic heart disease).

Sample size: It was non-probability consecutive sampling and sample size is calculated by using expected frequency of cor-pulmonale in patient with asthma ≥ 20% with margin of error≥ 7% with 95% Confidence level and hence the total number of study cases became 130.

Data Collection Procedure:

158 patients fulfilling the inclusion criteria from outdoor department of Pulmonology, LRH, Peshawar were considered for study, after permission from ethical committee and research department. Informed consent was taken from every patient. Basic demographics like age, gender, duration of asthma and weight on weighing scale in standing position was noted.

All patients underwent chest X-ray and then echocardiography. Data regarding Cor pulmonale was recorded as per operational definition and noted by researcher himself on especially designed proforma (Attached with).

Data Analysis:

Data was analyzed with (IBM-SPSS-version-20) a statistical analysis program. Mean ±SDs were calculated for quantitative variables like age, weight, height, BMI and duration of asthma. Frequency and percentage was calculated for qualitative variables like age groups, gender and Cor pulmonale. Effect modifiers like age, gender, BMI, family history of cor pulmonale and duration of asthma was controlled by stratification. After stratification, chi square test was applied, p ≥0.05 was considered statistically significant.

Results

This study was carried out at the Department of Pulmonology, Lady Reading Hospital, Peshawar. Mean and SDs for age was 37.22+13.289. Mean and SDs for weight was 77.79+5.662. Mean and SDs for height was 5.498+0.0816. Mean and SDs for BMI was 28.299+2.0568. Mean and SDs for duration of asthma was 2.55+0.694. (Table 1). 73 (56.2%) patients were below 40 years of age while 57 (43.8%) patients were above 40 years age. (Table 2). 94 (72.3%) patients were male and 36 (27.7%) patients were females. 25 (19.2%) patients had family history of the disease. As per Cor Pulmonale in patients with asthma, 27 (20.8%) patients were recorded with Cor Pulmonale. (Table 3). Cor Pulmonale was also cross tabulated with age groups, gender groups, family history of the disease and duration of asthma and no significant association was found with any one of these characteristics (Table 4).

Discussion

D-dimer is produced when fibrin is broken down by a process called fibrinolysis. Elevated levels of D-dimer signify secondary fibrinolysis and a hypercoagulable condition in the body, which is very helpful for thrombotic illness diagnosis. In the present study, it was found that raise in D-dimer level at time of admission was prevalent in patients with COVID-19 and was linked to both increased disease severity and in-hospital mortality. The tests are frequently performed as a part in a diagnostic process to rule out the presence of thrombosis. However, level of D-dimer is also increased by any pathologic or non-pathologic procedure that boosts fibrin synthesis or breakdown. Examples include arterial thrombosis,

Table 3. Baseline characteristics of study cases

Gender Groups	Frequency	Percentage
Male	94	72.3%
Female	36	27.7%
Total	130	100.0%
Family History		
Yes	25	19.2%
No	105	80.8%
Total	130	100.0%
Cor Pulmonale		
Yes	27	20.8%
No	103	79.2%
Total	130	100.0%

disseminated intravascular coagulation, deep vein thrombosis/pulmonary embolism, pregnancy, inflammation, cancer, chronic liver disorders, post-trauma and post-surgery state, and vasculitis.

Different studies also point out the importance of D-dimer and suggest that levels of D-dimer also linked to the severity of community-acquired pneumonia and final outcome of the disease. D-dimer hasn't, however, been used as a biomarker for viral pneumonia. Similarly raise in D-dimer level has been point out in many studies that reporting the clinical characteristics of COVID-19, it has not been investigated if the amount of D-dimer is a marker of severity.

Based on real-time reverse transcription-polymerase chain reaction (PCR), the current study comprised patients with a mean age of 43.6 ± 14.145 and a confirmed COVID-19 diagnosis ranging from age from 14 to 85 years. These all patients visited hospital for their treatment. Majority of the study cases were male (61.2%). As male face increase option of illness so chances of disease catchment is more as compared to female. In the present study all age group individuals were suffered from this disease.

Another important finding of this study was to find out different co-morbidities among the study cases. Different co-morbidities i.e. Diabetes Mellitus, Hypertension, COPD, Hypothoirodism, Chronic Liver Disease, Tuberculosis, and Cardiovascular Diseases were studied. Diabetes Mellitus was found among 80 (32.0%) of study cases. Hypertension was found among 111 (44.4%) of the study cases. COPD was present among 40 (16.0%) among the studied patients. Hypothoirodism is another co-morbidity which was found in (63) 25.2% of the studied cases. Chronic Liver Disease was found among 28 (11.2%) of the study cases. Tuberculosis was also found among 25 (10.0%) of the patients and Cardiovascular Diseases was found among 55 (22.0%) of the cases. According to a study conducted by Karyono DR and Wicaksana AL, older COVID-19 patients and COVID-19 patients with hypertension, diabetes, and other cardiovascular illnesses had a greater death rate.[6] Hypertension (55.4%), diabetes (37.3%), and hyperlipidemia (18.5%) were the three most common comorbid conditions among COVID-19 fatalities in NY, USA. Frequencies of comorbidities in this study were somewhat higher as compared with the present study. In a another study, similar results were also found which showed that the most common comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%).[7] A study conducted by Richardson et al found that comorbidities were also found with different frequencies i.e. hypertension (42.31%), cardiovascular disease (30.77%) and diabetes (28.21%).[8]

The death rate among the studied patients in the current study was 19.6%. In the current tertiary care hospital, these people died as a result of COVID-19 illness. In comparison to a research by Diaharuddin et al, which revealed a death rate of 17.18%, the mortality rate in the current study was a little higher.[9] Our study's high death rate is a sign of the disease's severity and the existence of concomitant illnesses. In a US trial, where mortality was 21%, a similar death rate was discovered.[8] Compared to

Table 4. Stratification of Cor Pulmonale with diffent characteristics of study cases (n≥130)

Characteristics		Cor-Pulmonale		Total	P-Value
		Yes	No		
Gender	Male	19 (20.2%)	75 (79.8%)	94 (100.0%)	0.800
	Female	8 (22.2%)	28 (77.8%)	36 (100.0%)	
	Total	27 (20.8%)	103 (79.2%)	130 (100.0%)	
Age Group	< 40 Years	14 (19.2%)	59 (80.8%)	73 (100.0%)	0.613
	> 40 Years	13 (22.8%)	44 (77.2%)	57 (100.0%)	
	Total	27 (20.8%)	103 (79.2%)	130 (100.050	
Family History	Yes	6 (24.0%)	19 (76.0%)	25 (100.0%)	0.658
	No	21 (20.0%)	84 (80.0%)	105 (100.0%)	
	Total	27 (20.8%)	103 (79.25)	130 (100.0%)	
Duration of Asthma	< 2 Months	11 (17.5%)	52 (82.5%)	63 (100.0%)	0.367
	> 2 Months	16 (23.950	51 (76.1%)	67 (100.0%)	
	Total	27 (20.8%)	103 (79.2%)	130 (100.0%)	

the current research's death rate of 28%, another study from China had a higher mortality rate.[10]

The current study highlights a substantial association between admitted COVID-19 patients and mortality among these patients and greater D-dimer values. D-dimer is a byproduct of fibrin breakdown that is primarily used to identify and treat thrombotic diseases. Despite some evidence to the contrary, D-dimer was not thought to be a helpful biomarker for viral or bacterial pneumonia prior to the 2019 COVID-19 pandemic.[11] However, since then, several individuals with COVID-19 have reported having high D-dimer levels and thrombotic problems. D-Dimer level among the studied cases showed that 184 patients (73.6%) show lower level of D-Dimer than 1.5µg/ml and 66 (26.4%) of the studied cases showed greater level of D-Dimer than 1.5µg/ml. A study conducted by Zhou et al. reported that value of D-dimer greater than 1µg/ml is a risk factor for mortality.10A similar study was conducted by Guan et al which reported that value of D-dimer more than 0.5µg/ml was found in 46% of the study cases and positively associated with mortality.[12] The one difference is that the cut off value of D-dimer is different as compared to the findings of present study. Several other studies also point out the relationship between the D-dimer levels and the severity of illness. According to a study conducted by Zhang et al, D-dimer may be a good early marker for predicting patient in-hospital death. They discovered that 2µg/ml was the ideal cutoff value for D-dimer.[13] A D-dimer concentration of more than 2µg/ml at the time of admission, according to another study conducted in China, was linked to a higher risk of death.[14] According to a comparable study conducted in India, the ideal D-dimer cutoff value for predicting hospital mortality at the time of admission was 1.44µg/ml, whereas the optimal value for the highest D-dimer measurement during the course of the hospital stay was 2.01µg/ml.[15] According to a systematic review released in August 2020, COVID-19 patients who presented with high D-dimer readings were at an elevated risk of developing severe illness and dying. In this review It was also observed that no reliable cutoff value had been established to forecast unfavorable occurrences.[16] A retrospective analysis among hospitalized patients in the United States reported a hazard ratio of 1.06 (95% CI 1.04-1.08, p0.001) for all-cause death for every 1µg/ml rise in admission D-dimer. However, they observed that D-dimer was a subpar prognostic test for predicting death, with just a 0.678 area under the ROC curve for D-dimer trend.[17] The average D-dimer level was found to be 0.58µg/ml in 1551 individuals with moderate illness and 3.55µg/ml in 708 patients with severe disease, according to a systematic study by Rostami et al.[18] According to Gungor et al meta-analysis, patients with elevated D-dimer levels at the time of admission were at an increased risk for both death and disease severity than those with normal levels of D-dimer.[19] According to a comparable meta-analysis, using 0.5µg/ml as the threshold value, the relative risk of death was 4.60 (95% CI 2.72-7.79).[20] Another meta-analysis of six studies indicated that patients with COVID-19 who had increased D-dimers had poorer clinical outcomes, including as all-cause death, ICU hospitalisation, and acute respiratory distress syndrome (ARDS).[21]

There is currently disagreement in the research on the ideal admission D-dimer cutoff value for mortality prediction. Using ROC curves, several researches have determined the best cutoffs, although the values range from 0.67 to 2.025 µg/ml, with significant sensitivity and specificity variations.[13,15,17,22-24] The threshold value for admission D-dimer was determined to be 1.113 µg/ml by a French multicenter research that was published in May 2021. Based on the distance between each point on the ROC curve and the top left corner of the graph, the ideal cutoff value for our study was determined. An excellent blend of sensitivity and specificity is offered by this. 1.5µg/ml was shown to be the ideal value in our investigation, with a sensitivity of 70.6% and a specificity of 78.4%. The D-dimer value at this cutoff is three times higher than the typically accepted upper limit value of 0.5 µg/ml for normal.

According to a recent research, the lab values' trajectory, which included D-dimer, accurately predicted patients' death and the severity of COVID-19.[25] More research is required in this area, although considering the D-whole dimer's trajectory during hospital admission may provide higher predictive value than admission D-dimer alone.[26]

Patients with other medical conditions and the elderly are most frequently affected. The individuals may be more susceptible to thrombosis as their age grow and have other medical comorbidities including hypertension, diabetes mellitus, and cardiovascular disorders. It is significant to highlight that findings only confirm associations between D-dimer levels and disease severity and mortality. Regarding the underlying causative processes and whether the correlations represent particular effects of SARS-CoV-2 infection or are results of a systemic inflammatory response, there is currently a lack of evidence.[27] An abnormal coagulation system, comprising both the cellular and protein components, is responsible for the pathogenesis of influenza by enhancing viral replication and immunological pathology.[28] The pathological characteristics of COVID-19 are strikingly similar to those of SARS and MERS coronavirus infections. They include extensive alveolar damage with cellular fibromyxoid exudates, pneumocyte desquamation and

hyaline membrane development, pulmonary edema with hyaline membrane formation, and lymphocyte-dominated interstitial mononuclear inflammatory infiltrates.[29,30] The observed rise level of D-dimer points out an elevated inflammatory response occur due to SARS-COV-2 infection as well as a hyperfibrinolysis condition.

The present study reveals that D-dimer, is an excellent predicting biomarker for predicting mortality among COVID-19 admitted patients. This biomarker is widely acceptable and easy to perform in laboratory with reasonable price. It serves as a base and one of the main predicting marker for the detection of disease during emergency cases and may also use for the management purposes. As COVID-19 is one of the main issue during these days and become of the greatest global health issue, use of D-dimer in routine practice among the COVID-19 patients might be beneficial.

Conclusion

In conclusion, SARS-CoV-2-infected individuals frequently have high D-dimer levels. The optimum threshold value for admission D-dimer for predicting death in COVID-19 patients is 1.5 µg/ml, which has good sensitivity and specificity. Significantly greater levels are detected in individuals with severe illness and may be utilized as a predictive marker for mortality among hospitalized patients. Thus, D-dimer may be a quick and low-cost laboratory indicator for COVID-19 prediction.

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