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A Study of Determinants of Pulmonary Fibrosis in Covid-19 Survivors

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Abstract:
The COVID-19 pandemic has mainly affected the lungs, including many other organs. Many of the patients later developed pulmonary fibrosis. This study was planned to determine the pulmonary fibrosis determinants in post-COVID survivors. Hospital-based, cross-sectional study done over one year. A pre-designed proforma was used to collect necessary information, and follow-up HRCT and other investigations were evaluated. Out of 87 patients, 41.3%(n=36) developed pulmonary fibrosis; the majority, i.e.,66.6%(n=24), were males. Most of them, 49.42%(n=43), belonged to the age group of 51-70 years, among which 48.83%(n=21) developed fibrosis. Among the study subjects, 57.47% (n=50) had different comorbidities, of which 52% (n=26) developed pulmonary fibrosis. The proportion of diabetes was 31/50, out of which 67.7% (n=21, p=0.036) developed pulmonary fibrosis, while 80% (n=4, p=0.014) of patients with thyroid disorders developed pulmonary fibrosis. A total of 27 patients were treated in ICU, out of which 66.67% (n=18) developed pulmonary fibrosis. Pulmonary fibrosis developed more when steroids were not used on 9/19, 47% (n=9), compared to those where steroids were used on 27/68, 39.7% (n=27). Most patients, i.e.,>90% fibrotic, had raised inflammatory markers.
About half of the survivors had post-COVID-19 pulmonary fibrosis. This study emphasized the relationship between pulmonary fibrosis and many factors, such as age, comorbidities, ICU admission, steroid usage, inflammatory markers, and secondary infections.

Keywords: Post-Covid, Pulmonary-Fibrosis, Comorbidities, Inflammatory-Marker.

INTRODUCTION

Novel Corona Virus Disease (COVID-19) originating from China has rapidly crossed borders, infecting

people throughout the whole world [1]. According to WHO data, there has been a total of 31,132,906 confirmed cases of COVID-19, including 96,2008 deaths worldwide, among which there are 5,562,663 confirmed cases and 88,935 deaths in India. India is second after the United States of America [2]. The WHO report revealed a mortality rate of 3–4 %. However, it seems that the mortality statistics are underestimated. However, because COVID-19 infection is a highly contagious disease and has affected a large population, the total number of deaths caused by this virus has exceeded that caused by any of its predecessors [1].

Studies revealed that women are less susceptible to viral infection than men, possibly because of the protection of the X chromosome and sex hormones, which play a vital role in innate and adaptive immunity [3]. At the same time, men tend to be associated with bad lifestyle habits such as smoking and underlying diseases. As a result, the majority of critical or mortal patients are male. As the body's immunity declines with age, elderly patients are more likely to develop severe ailment or even die. Therefore, when the patient is male, over 65 years old, and smoking, the patient has a higher chance of developing critical illness or death. When patients are combined with primary diseases such as diabetes and hypertension, the body is in a state of stress for a long time, and immunity tends to be low. Moreover, long-term history of diabetes and hypertension will damage the vascular structure, and it is more likely to develop into a critical disease in infection. Patients suffering from chronic heart disease are more likely to be infected due to their weakened heart function and low immunity.

When infected with SARS-CoV-2, patients are more likely to have acute cardiovascular events and develop severe diseases. When the patient has previous respiratory diseases, such as chronic obstructive pulmonary disease, the patient's lung function is damaged. They have lower resistance to the virus and are prone to developing ARDS [4].

Although pulmonary fibrosis can happen in the absence of a definite inciting agent and without a clinically apparent initial acute inflammatory phase, it is more often correlated with severe lung injury. This may occur due to respiratory infections, chronic granulomatous diseases, medications, and connective tissue disorders. Pulmonary fibrosis is analogous with permanent pulmonary architectural distortion and irreversible lung dysfunction. Available clinical, radiographic, and autopsy data have showed that pulmonary fibrosis is related to severe acute respiratory distress syndrome (SARS) and MERS disease, and current evidence suggests that pulmonary fibrosis could be a complication of SARS-CoV-infection 2.4.

An initial phase of lung injury is followed by acute inflammation and an attempt at repair [5]. This process can result in the restoration of normal pulmonary architecture or lead to pulmonary fibrosis with architectural distortion and irreversible lung dysfunction [6]. The repair process involves regeneration by native stem cells and connective tissue deposition to replace areas of defect [7].

A chest CT scan showed GGO with irregular interlobular septal thickening and reticular pattern with traction bronchiectasis [8]. The process described is typical of pulmonary fibrosis following acute lung injury, such as those occurring in severe acute respiratory syndrome (SARS) with diffuse alveolar damage, acute fibrinous, and organizing pneumonia [9].

Restrictive lung dysfunction and abnormal carbon monoxide diffusion capacity were commonly reported in patients recovering from SARS.

Assessing the long-term consequences of COVID-19 thus appears crucial. We, therefore, stress the importance of (a) setting up specific follow-up strategies in COVID-19 patients showing pulmonary involvement to assess the possible progression toward lung fibrosis and (b) treating patients at risk from

the early phases with therapies preventing the development of future lung fibrosis [4].
In this study, we determined the determinants of pulmonary fibrosis in post-COVID survivor patients and learned its prevalence.

METHODS

A hospital-based, cross-sectional study was done at the Department of Respiratory Medicine, a tertiary care teaching hospital in North India. The Institutional Ethical Committee of our University (Ref. code: -107thECM 11 B-Thesis/P18) approved this study. For one year, patients were enrolled as pre-defined proforma after obtaining written consent from the study participants. One hundred twenty-one patients attending the IPD and OPD in the Department of Respiratory Medicine were screened for the study based on previous COVID-19 infection symptoms and considering the inclusion and exclusion criteria. Finally, 87 patients tested positive for the novel coronavirus by nasopharyngeal swab, admitted to the hospital, or treated at Home and discharged after recovery or having 2 RT-PCR negative reports of covid 19. With a follow-up CT after discharge, they were enrolled in our cross-sectional study. Not all patients with pulmonary fibrosis have evidence of COVID-19 infection. All follow-up cases of pulmonary fibrosis before March 2020/COVID-19, Patients without baseline reports, and active covid 19 pneumonitis are excluded from the study.

STATISTICAL ANALYSIS

Data analysis was conducted by utilizing descriptive statistics and comparing among the various groups. Discrete (categorical) data was summarized in proportions, percentages (%), and frequency analysis. Chi-square and other appropriate tests were used to find associations and relations. Odds ratio and logistic regression analysis were utilized to assess the risks present for various explanatory variables. The means of descriptive statistics were used, including percentage, means ± Standard Deviation (SD), and 95% Confidence Interval. P-value < 0.05 -were considered to be Significant.

RESULTS

In our study of 87 post covid survivors, patients were included. All the patients are broadly categorized according to post-pulmonary fibrotic and non-fibrotic groups; out of 87 patients, 41.3%(n=36) developed pulmonary fibrosis, among which the majority, i.e.,66.6%(n=24), were males. Most of them, 49.42%(n=43), belonged to the age group of 51-70 years, among which 48.83%(n=21) developed fibrosis. Among the study subjects, 57.47% (n=50) had different comorbidities, of which 52% (n=26) developed pulmonary fibrosis. The proportion of diabetes was 31/50, out of which 67.7% (n=21, p=0.036) developed pulmonary fibrosis, while 80% (n=4, p=0.014) of patients with thyroid disorders developed pulmonary fibrosis. A total of 27 patients were treated in ICU, out of which 66.67% (n=18) developed pulmonary fibrosis. Pulmonary fibrosis developed more when steroids were not used on 9/19, 47% (n=9), compared to those where steroids were used on 27/68, 39.7% (n=27). Most patients, i.e.,>90% fibrotic, had raised inflammatory markers.

Table 1: Comparison of fibrotic and non-fibrotic COVID survivors based on gender
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Table 2: Comparison of fibrotic and non-fibrotic COVID survivors based on age
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Table 3: Comparison of fibrotic and non-fibrotic COVID survivors based on Covid severity

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DISCUSSION:

This observational study was conducted at the Department of Respiratory Medicine, King George's Medical University, Lucknow, to determine the determinants of pulmonary fibrosis in post-COVID survivor patients. We finally included 87 patients as per the inclusion and exclusion criteria.

In our study, 87 patients, 62 (71.26%) were male, and 25 (28.73%) were female. Halpin et al. [10] conducted a study and reported that males (52%) are more common among COVID survivors. Jin Jian-Min [11] is also consistent with our results. Similar results were reported in the study done by Zhou [12] et al. from China. According to them, it was referenced that expression of ACE2 was more predominantly present among Asian men, which can be the reason for the higher prevalence of COVID-19 in this subgroup of patients as compared to in women and patients of other ethnicities—developed fibrosis. T, Macdonald reported similar observations that the most severe COVID-19 disease is reported among the elderly, and this population may be at increased risk for the development of post-infection (COVID) fibrosis. Similarly, O'Driscoll [13] et al. also reported from the multicentre multination-metanalysis that the infection fatality ratio is lowest among the 5-9-years age group with a log-linear increase by age among individuals aging more than 30 years treated as severe covid 19 infections.

In our study, out of all 87 patients, nine were below 30 years old, where 11.1% (1) patients developed fibrosis and 88.9% (8) did not. Of 30 patients of the 31 to 50 age group, 36.67% (11) developed fibrosis, and 63.33% (19) did not. Out of 43 patients in the 51 to 70 age group, 48.83% (21) patients developed fibrosis, and 51.17% (22) patients without fibrosis. The odds ratio of this age group is 2.5. Of 5 patients above 70 years, 60.0% (3) developed fibrosis. George P et al. [14] showed that the main risk factors for severe COVID-19 are aging and male sex.

Out of 87 patients, 13 (14.94%) patients were mild, 37 (42.52%) patients were moderate, severity of 37 (42.52%) patients were severe. COVID-19 infection is more early developed in comorbid patients than in healthy ones.

In our study, 31 (35%) patients had diabetes mellitus, 19 (21.8%) patients had hypertension, 9 (21.8%) patients had Chronic Kidney Disease, 8 (10.3%) patients had Thyroid disorder, 11 (12.6%) patients had Asthma /COPD, 7 (12.6%) patients had malignancy and 2 (2.29%) patients had had CAD. George P et al. [15] showed that primary risk factors for severe COVID-19 are comorbidities such as diabetes and hypertension

Among the 87 patients, 76 (87.3%) had Cough, 73 (83.9%) had fever, 70 (80.4%) had SOB, 39 (44%) had Sore Throat, 36 (41.3%) had body pain, 16 (18.39%) had loss of smell/taste, and 14 (16%) had Diarrhea.

Out of 87 patients, 21 (24.1%) were treated at Home, with a mean duration of treatment of 7.47-3.51 days; 39(44.8%) were treated at the ward, with a mean duration of stay of 18.35-4.3 days; and 27 (31.0%) were treated at the ICU, with a mean duration of stay of 13.7 8.5 days.

Out of 87 patients, the CRP of 4 (4.59%) patients was below 20, the CRP of 47 (54.0%) patients was

between 20 and 100, the CRP of 31 (35.63%) patients was above 100, where data of 5 (5.74%) patients was not available. D Dimer of 7 (8.04 %) patients was below 0.5, and D Dimer of 74 (85.05 %) patients was above 0.5, where data of 6 (6.89 %) patients were not available. Serum ferritin of 11 (12.64 %) patients was 20 to 250, and serum ferritin of 70 (80.45 %) patients was above 250, where data from 6 (6.89 %) participants were not available. S. LDH of 2 (2.90%) patients was below 100, S. LDH of 11 (12.64 %) patients was 100 to 250, and S. LDH of 70 (80.45 %) patients was above 250, where data of 6 (6.89%) patients were not available. Similarly, the PCT of 23 (26.43%) patients was below 0.5, and the PCT of 58 (66.66%) patients was above 0.5, where data of 6 (6.89 %) patients were not available.

In our study, post-COVID outcomes of all 87 patients, fibrosis was found in 36 (41.37%), and no fibrosis was found in 51 (58.62%) patients. Mehrdad Nabahati et al. [16] reported that 37.8% of patients had fibrosis post covid, similar to our results. In the study by Han et al. [17], fibrotic changes were seen in 35% of the patients over the six months of follow-up, which was lower than our results. Another study by Ali et al.[18] showed that 32% of COVID patients developed pulmonary fibrosis with-in-a-month follow-up, which was less than that we found in this study. Antonio et al.[19] in studying severe cases, which stated that in early lung fibrosis, the rate reaches as high as 62%.

Out of 36 patients with fibrosis, 24 (67%) were male and 12 (33.33%) were female. Similarly, out of 51 patients with non-fibrosis, 38 (74.50%) were male, and 13 (25.49%) were female. Other authors, i.e., Patil SV [20] et al. and Ali RMM5 et al., also reported that fibrosis is more developed in males.

It has been noted that post-COVID-19 pulmonary fibrosis was highly correlated to patient age, as those who developed pulmonary fibrosis were mostly in higher age groups than lower. In our study, out of all 87 patients, nine were below 30 years.

In our study, out of 13 patients of mild severity, 7 (53.8%) patients had fibrosis, and 6 (46.2%) had no fibrosis. Out of 37 patients of moderate severity, 9 (24%) had fibrosis, and 28 (76%) had no fibrosis. Thirty-seven patients were severe, 20 (54.5%) had fibrosis, and 17 (45.5%) had no fibrosis. Ali RMM et al. [21] found that the mild group showed less liability for post-COVID-19 fibrosis that developed only in 7 patients (18.4%). In contrast, the severe group (CT-SS of 18–25) (42 patients) showed a higher incidence of post-COVID-19 pulmonary fibrosis seen in 18 patients (42.8%). That matches the study of Zhou F. et al. [22], who stated that disease severity is directly proportional to lung tissue destruction and is also correlated with mortality.As per the data of the World Health Organization (WHO), 80% deloped mild SARS-CoV-2 infections , 14% develop severe symptoms, and 6% become critically ill.

In our study, fibrosis is more common in comorbid patients. Out of 37 patients with no comorbidity, 10 (27.02%) were diagnosed with fibrosis; out of 50 patients with comorbidity, 26 (52.0%) were diagnosed with fibrosis. Out of 87 patients, 50 had different comorbidities, among which diabetes mellitus was the most common (31/50). Among diabetes post-COVID, fibrosis developed in 21/31(67.74%), significant (p=0.036) with an odd ratio of 3.59.

In our study, fibrosis was more developed in patients treated in the ICU than in the ward or Home. Out of 21 patients with treatment taken at Home developed fibrosis years where 1 (11.1%) of patients developed fibrosis, and 8 (88.9%) patients did not. Out of 30 patients in the 31 to 50 years age group, 11 (36.67%) developed fibrosis, and 19(63.33%) were not developed fibrosis. Out of 43 patients in the 51 to 70 age group, 21 (48.83%) patients developed fibrosis, and 22 (51.17%) did not. Out of 5 patients above 70 years, 3 (60.0%) patients developed fibrosis, and 2 (40.0%) did not develop fibrosis. This matches a study by Wong et al. [23], who stated that older people are more likely to develop pulmonary fibrosis following MERS. Low incidence was noted in the 45–60 years of age (7 patients out of 25; 28%), and the 25–45-

year age group showed a minor incidence (5 out of 25 patients; 20 %); Das K.M. et al. also noticed this.[24] that correlated age with MERS and SARS-CoV-2 pulmonary fibrosis development.

Out of 39 patients treated at the ward, fibrosis was developed in 12 (30.76%) patients; out of 27 patients treated in ICU, it developed fibrosis in 18 (66.67%). Fibrosis is more common in ICU patients. Yu M [25] et al. reported that patients with fibrosis had a longer duration of stay in the hospital with a increased rate of ICU admission than those without fibrosis. Our study shows that out of 87 patients, 78.16% (68) were treated with steroids, 78.16% (27) patients developed fibrosis, and out of 21.84% (19) patients who had not used steroids, 47.3 % (9) patients developed fibrosis. Fanshawe [26] et al. also demonstrated a dramatic improvement in the patient's symptom severity, radiology, and pulmonary function after completing the course of corticosteroids and concurrent personalized pulmonary rehabilitation.

Early corticosteroid treatment was well tolerated and associated with rapid and significant improvement.

Our study also shows that out of 87 patients, 69 patients had radiology reports/films at the time of COVID-19 infection. Of 69 patients, 58 (84%) had GGO, and 24 (34%) had consolidation. Fibrosis is more common in patients having consolidation (p-0.036). Our results are consistent with the available literature. Rabab Yasin [27] et al. conducted a study to Predict lung fibrosis in post-COVID-19 patients after discharge with follow-up chest CT findings. The study included two hundred and ten patients whocame to be positive for the novel coronavirus by nasopharyngeal swab, admitted in indoor facility, and discharged after recovery from the ailment. Patients who has at least a one-time chest CT scan after discharge were enrolled. In accordance with presence of fibrosis on follow-up CT thorax after discharge, patients were categorised into 2 groups and assigned as the "non-fibrotic group" (without evident fibrosis) and the "fibrotic group" (with evident fibrosis). Moreover, it was concluded patient's age, initial CT thorax severity score, consolidation/crazy-paving score, and ICU admission were independent risk factors co-related with post-COVID-19 fibrosis ($p<0.05$). Chest CT severity score revealed sensitivity of 86.1%, a specificity of 78%, and an accuracy of 81.9% at a cut-off point 10.5.

LIMITATIONS

We screen the patient at one point; thus, the natural history of post-COVID changes or fibrosis cannot be interpreted.

CONCLUSION

Based on our study, we arrived at the following conclusions. Covid infection is more common in older people, urban areas, offices, and homemakers. In patients having previous comorbidities, post-COVID pulmonary fibrosis is common; it is also more common in males than females in the 51-70 years of age group; patients with multiple comorbidities and patients with diabetes mellitus have more common post-fibrosis compared to the other comorbidities. As per receiving investigation and treatment, patients having consolidation on chest radiology are more prone to post-COVID covid fibrosis, patients with secondary bacterial infection and with raised inflammatory markers are prone, and patients who have been treated in ICU and patients who needed treatment for a long time are more prone to post-COVID covid fibrosis. Patients treated with steroids have a lower frequency of post-fibrosis compared to others who are not receiving steroids for moderate to severe COVID-19 infection. So, as per the results, we recommend HRCT thorax, spirometry/impulse oscillometry, and a 6-minute walk test in patients with post-COVID

symptoms of breathlessness, cough, and chest pain. Adequate treatment of comorbidities, vaccination, and following COVID-19 preventive measures like physical distancing, wearing masks, and hand washing.

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LIST OF TABLES:

Table 1:- Comparison of fibrotic and non-fibrotic covid survivors based on gender

Gender	Fibrosis Group	Non-Fibrosis Group	Total	Odds ratio
Male	66.67% (24)	74.50% (38)	71.26% (62)	0.68
Female	33.33% (12)	25.49% (13)	28.73% (25)	1.46
Total	100% (36)	100% (51)	100% (87)	

Table2 :- Comparison of fibrotic and non-fibrotic covid survivors on the basis of age

Age	Fibrosis Group	Non-Fibrosis Group	Total
Below 30 years	11.1% (1)	88.9% (8)	9
31 to 50 years	36.67% (11)	63.33% (19)	30

51 to 70 years	48.83% (21)	51.17% (22)	43
Above 70 years	60.0% (3)	40.0% (2)	5
Total	41.37% (36)	58.62% (51)	87

Table 3 :- Comparison of fibrotic and non-fibrotic covid survivors on the basis of Covid severity

Covid Severity	Number	Fibrosis Group n (%)	Non-Fibrosis Group n (%)	p-value
Mild	13	53.8% (7)	46.2% (6)	0.062
Moderate	37	24% (9)	76% (28)	0.120
Severe	37	54.5% (20)	45.5% (17)	0.322
Total	87	41.3% (36)	58.7% (51)	0.098

Table 4 :- Comparison of fibrotic and non-fibrotic covid survivors on the basis of single & multiple Co-morbidities

Co-morbidity	Fibrosis Group N=36	Non-Fibrosis Group N=51	P value	No of patients N (%)
Single comorbidity	42.85% (12)	57.15% (16)	0.035	28
Multiple comorbidities	63.63% (14)	36.37% (8)	0.011	22
Total Co-morbid patients	52.0% (26)	48.0% (24)	0.083	57.48% (50)
No comorbidity	27.02% (10)	78.38% (27)	0.089	42.52% (37)

Table 5 :- Comparison of fibrotic and non-fibrotic covid survivors on the basis of place of treatment.

Treatment was taken at	Fibrosis Group N=36	Non-Fibrosis Group N=51	Total	p-value
Home	28.57% (6)	71.43% (15)	**21**	**0.07**
Ward	30.76% (12)	71.79% (28)	**39**	**0.07**
ICU	66.67% (18)	33.33% (9)	**27**	**<0.01**

LIST OF FIGURES:

Figure 1: Shows that out of 36 patients of fibrosis, 66.67% (24) patients were male and 33.33% (12) patients were female.

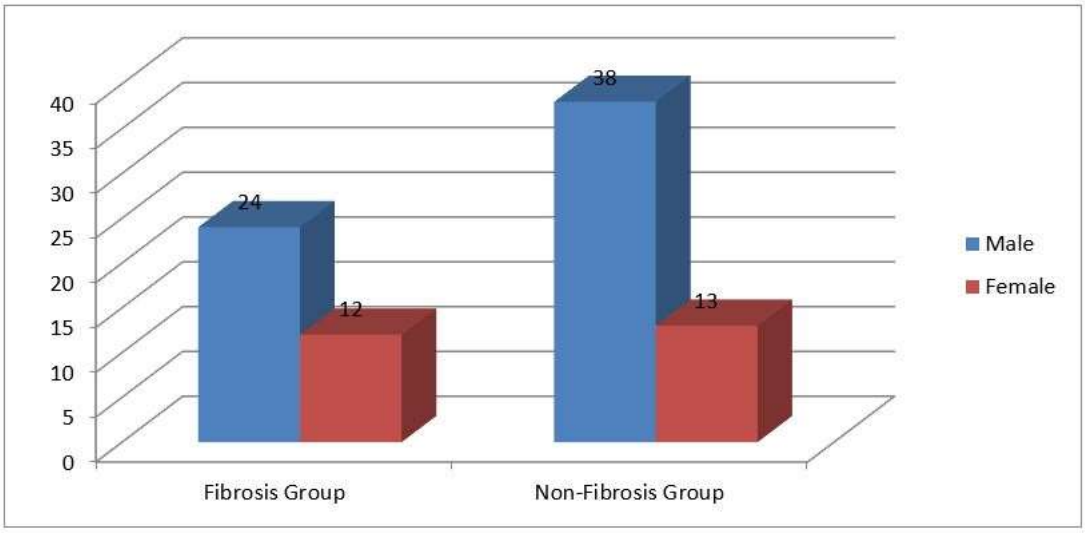


Figure 2 :- Shows comparison of fibrotic and non-fibrotic covid survivors on the basis of age.

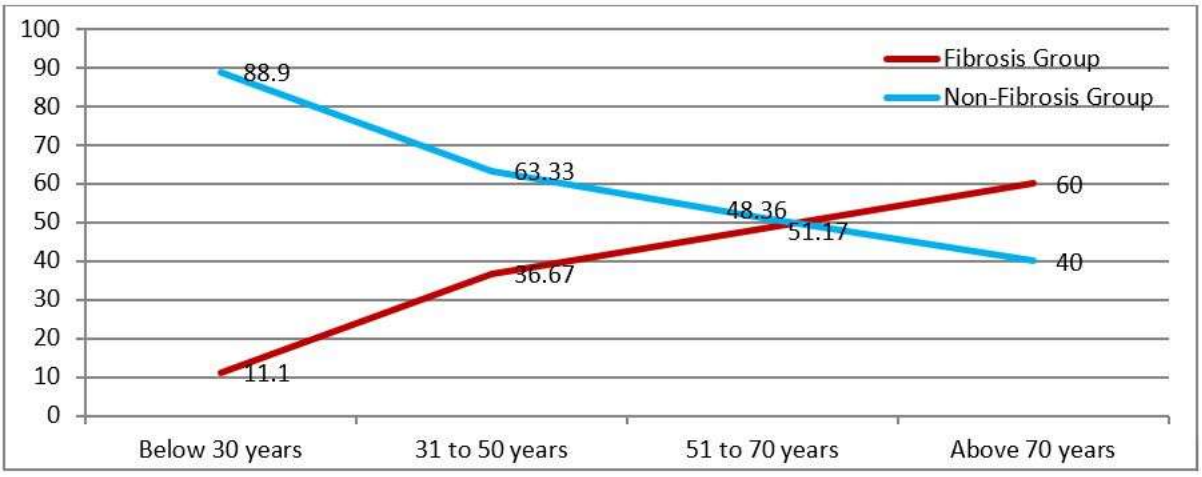


Figure 3 :- Shows comparison of fibrotic and non-fibrotic covid survivors on the basis of Covid severity.

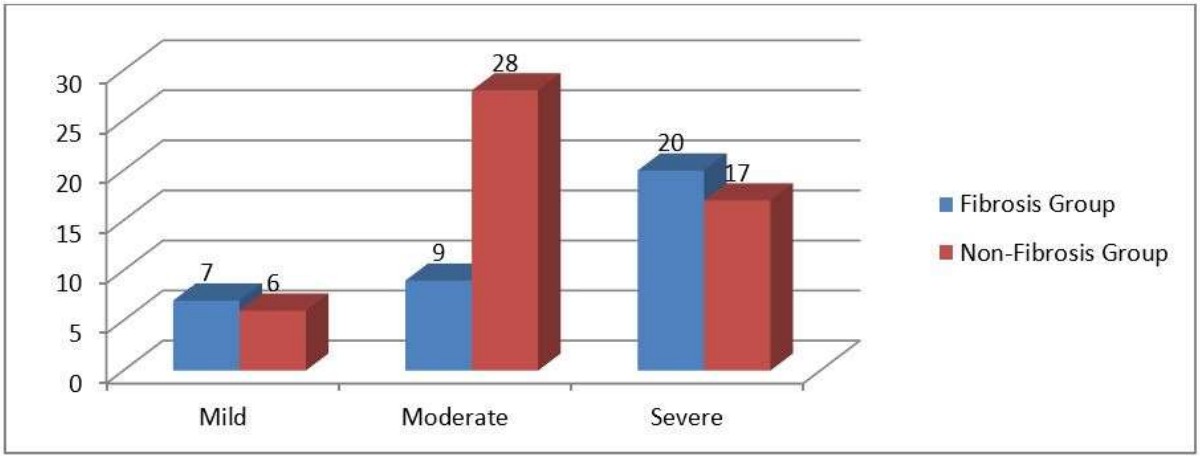
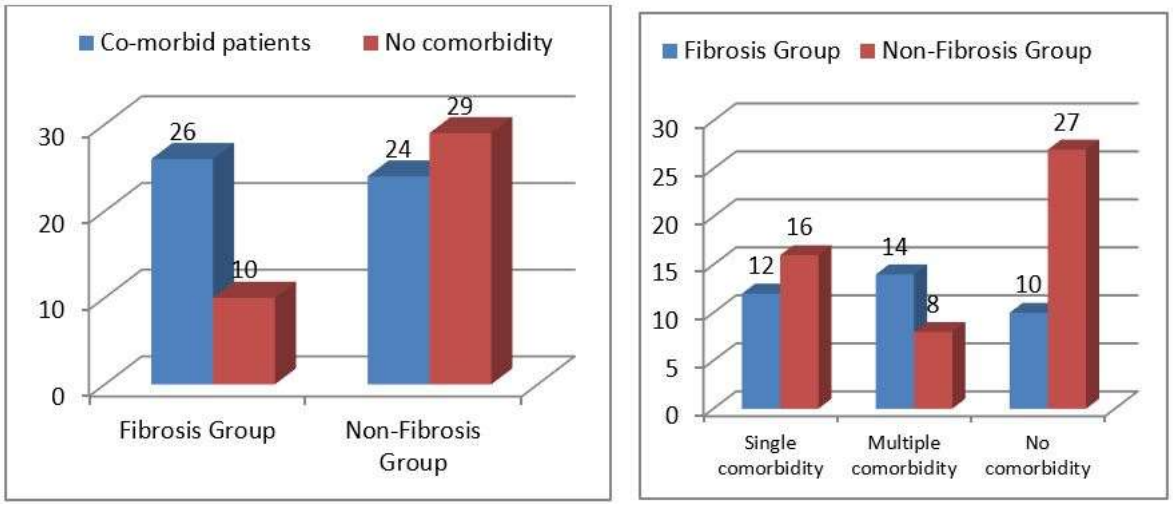


Figure 4:- Shows comparison of fibrotic and non-fibrotic covid survivors based on single & multiple Co-morbidities



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