

Histopathological Analysis of Lung Infections during Pre and Post COVID-19 Eras: Insights from a Four-Year Autopsy Study at a Tertiary Care Hospital in Tirunelveli, Tamil Nadu, India

YOGAMBAL MUTHUREDDY¹, MAHALAKSHMI KANDASAMY², SELVAM ABATHU KATHA PILLAI³, SWAMINATHAN KALYANASUNDARAM⁴



ABSTRACT

Introduction: Autopsies are routinely useful in establishing the cause and time of death. The Coronavirus Disease-2019 (COVID-19), a pandemic viral infectious disease, has affected many countries worldwide. In developing countries like India, infectious lung pathology has been a significant cause of death even before the COVID-19 era. However, the emergence of COVID-19, there has been an increase in lung infections due to factors such as prolonged hospital stays, assisted ventilation, lung damage, and immune suppression, affecting both morbid patients and survivors.

Aim: To describe the histopathological spectrum of infective lesions of lung in autopsy during Pre COVID-19 and COVID-19 era in a tertiary care hospital of Tirunelveli, Tamil Nadu, India.

Materials and Methods: This cross-sectional study was conducted in the Department of Pathology at Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India, between January 2018 and December 2021. Data including age, sex, COVID-19 status, clinical history, histomorphological patterns, and identification of infectious agents, were collected from clinico-pathological and autopsy documents. A total of 627 lung specimens were available, with 41 specimens being autolyzed, leaving 586 specimens for inclusion in the study. Gross morphology and microscopic features were documented, and diagnoses were made based on these findings.

Results: The study included a total of 586 specimens, of which 76 (12.9%) were reported as infective pathology. Among these cases, 29 (38.1%) cases were reported in the pre COVID-19 period, and 47 (61.9%) were reported during the COVID-19 period.

Of the 76 cases, 41 (53.95%) were male, and 35 (46.05%) were female. The number of cases reported during the post COVID-19 period (47 cases, 61.84%) was higher than the number reported during the pre COVID-19 period (29 cases, 38.16%). In both periods, the majority of cases (10 cases, 13.1% in the pre COVID-19 period; 13 cases, (17.1%) in the post COVID-19 period) were observed in individuals aged 60 years and above, followed by those in the age group of 50 to 59 years (7 cases, 9.2%). Similarly, in the pre COVID-19 period; 10 cases, 13.2% in the post COVID-19 period). Among the 76 cases, interstitial pneumonia (9 cases, 11.8%) was the most common finding in the pre COVID-19 period, followed by bronchopneumonia (seven cases, 9.2%). In the COVID-19 period, Tuberculosis (TB) was the most common finding (17 cases, 22.4%), followed by pneumonia with consolidation (10 cases, 13.2%). Additionally, the number of cases diagnosed with pulmonary TB during the COVID-19 period (17 cases, 22.4%) was higher than that during the pre COVID-19 period (6 cases, 7.9%). During the post COVID-19 period, there has been a drastic increase in the number of pneumonia cases compared to the pre COVID-19 era, and this increase is statistically significant with a p-value of 0.04.

Conclusion: Pneumonia (lobar pneumonia, interstitial pneumonia, and bronchopneumonia) is the most common histopathological lung lesion in the present study. Compare to pre COVID-19 era, there is increased number of infective lesions during COVID-19 era. There was a drastic increase in pathological findings of Kochs lesion during COVID-19 era.

Keywords: Aspergilloma, Coronavirus disease-2019, Pneumonia, Tuberculosis

INTRODUCTION

The worldwide impact of the COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-COV-2) virus has been substantial on clinical, social, and economic fronts [1,2]. The virus induces a strong immunological response and cytokine storm that results in an excessive inflammatory reaction [3]. As a result, immunosuppressive treatments, including the use of steroids, have been recommended in severely and critically ill patients to reduce morbidity and mortality associated with COVID-19 [4]. However, in some instances, the inappropriate use of immunosuppressive drugs or steroids in COVID-19 treatment has resulted in complications, such as opportunistic infections. Respiratory system pathology is the second most frequent cause of sudden and unexpected death across the globe. Prior to the COVID-19 pandemic, congestion, oedema, and interstitial pneumonia

were the most commonly observed respiratory conditions, along with other infections [5]. In the pre COVID-19 era, lung infections were primarily associated with elderly individuals and those with weakened immune systems. Compared to the pre COVID-19 era, the involvement of the lungs due to infectious causes increased during the COVID-19 pandemic. This was attributed to immune suppression caused by the virus, prolonged assisted ventilation, and extended hospital stays [6]. In developing countries, the lockdown's effects, limited medical access, fear of hospital stay, and economic crisis led to a rise in chronic infections like TB and opportunistic infections during the COVID-19 period. Notably, the lungs were the primary organ affected by COVID-19, which contributed to the increased incidence of lung infections during this time [7].

In light of these developments, the authors conducted a retrospective analysis of clinico-pathological, autopsy findings, and histopathological

findings of lung specimens from our institute, a tertiary care center in Tirunelveli. The analysis was conducted for two periods: pre COVID-19 (January 2018 to December 2019) and COVID-19 (January 2020 to December 2021) to evaluate the trend and nature of lung infections during these periods. The present analysis of the lung infection trends before and during the COVID-19 pandemic can provide valuable insights to help develop more effective treatment protocols and preventative measures. Additionally, understanding the COVID-19 induced injury to the lungs and raising awareness about pandemic management can aid in mitigating the burden of lung infections during such pandemics.

MATERIALS AND METHODS

This study was conducted as a retrospective cross-sectional study in a year 2022 from January to December (1 year) in Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India. The data were collected for four years between 2018 to 2021. This study was conducted in academic and for research purpose to find out the histopathological spectrum of infectious lesions in lung autopsy specimens during this pre COVID-19 and COVID-19 era. For this study, a total of 627 lung specimens were received over a four-year period from January 2018 to December 2021, irrespective of age and sex. However, 41 specimens were excluded due to autolysis and not being received in formalin, leaving 586 specimens for analysis. Among these specimens, 309 were received during the pre COVID-19 period (January 2018 to December 2019), and 277 were received during the COVID-19 period (January 2020 to December 2021).

Procedure

Out of the 586 specimens analysed, 76 were histopathologically reported as infectious lesions, including interstitial pneumonia, lobar pneumonia, granuloma, and fungal infections. Both whole organ lung specimens and portions of the lung were included in the analysis. It should be noted that all 76 cases were analysed irrespective of their COVID-19 positive status or the cause of death. Among these 76 cases, 11 were portions of the lung. Since this study is purely retrospective in nature and involves record and histopathological analysis, no interventions were made, and patient identities were kept anonymous. As a result, ethical clearance was not required for this study. All the clinical data were taken from autopsy records and hospital records. Most of the specimens were received in portion, fixed in 10% formalin. Gross examination of the specimen includes weight of the specimen, size, colour change, texture and any

specific change with description. Routine tissue processing, paraffin block preparation, section cutting, slide staining using haematoxylin and eosin were done. After mounting slides were viewed under light microscope.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel and analysed using open epi software. Chi-square test was used to find the association between various parameters during pre COVID-19 and COVID-19 era. Results were expressed as proportions and percentages.

RESULTS

The study included a total of 586 specimens, out of which 309 were received during the pre COVID-19 period (January 2018 to December 2019) and 277 were received during the COVID-19 period (January 2020 to December 2021). Histopathological examination was performed on all specimens. Among these 586 specimens 76 (12.9%) were reported as infective pathology which further included 29 (38.1%) cases reported during the pre COVID-19 period, and 47 (61.9%) cases reported during the COVID-19 period. The age-wise and sex wise distribution of these lung lesions is presented in [Table/Fig-1].

During the pre COVID-19 period, the majority of the cases of infective lung pathology were observed in individuals above the age of 60 years (10 cases, 13.1%). In the COVID-19 period, the majority of cases were observed in individuals above the age of 60 years (13 cases, 17.1%) [Table/Fig-1]. Among these 76 cases Interstitial pneumonia 9 (11.8%) is the most common finding in pre COVID-19 period, followed by bronchopneumonia 7 (9.2%), TB 6 (7.9%), Pneumonia with consolidation 5 (6.6%) and aspergillus infection 2 (2.6%) [Table/Fig-2].

During COVID-19 is the most common finding 17 (22.4%), followed by pneumonia with consolidation-Gross appearance and histopathology of TB depicted in [Table/Fig 3a and 3b]. The gross appearance of bronchopneumonia with patchy discolouration is depicted in [Table/Fig-4] 10 (13.2%), Interstitial pneumonia 9 (11.8%), bronchopneumonia 6 (7.9%) and aspergillus 5 (6.6%) [Table/Fig-5] depicts the Haematoxylin and Eosin (H&E) examination of Lobar pneumonia while [Table/Fig:6] depicts the H&E examination of Aspergilloma. Out of the 47 cases, 26 cases were COVID-19 positive, 10 cases were COVID-19 symptomatic positive cases. For 11 cases, COVID-19 status was not specified [Table/Fig-7]. The comparative analysis of baseline parameters and diagnosis of lung infections between the pre COVID-19 and COVID-19 eras reveals several

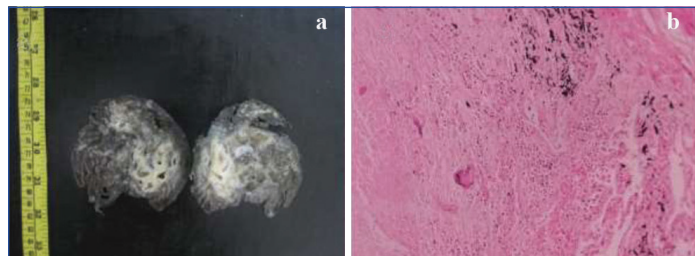
Age (years)	Pre COVID-19 period-cases	Percentage (%)	Males	Females	COVID-19 period-cases	Percentage (%)	Males	Females
0-09	2	2.6%	2	0	2	2.6%	1	1
10-19	4	5.3%	3	1	1	1.3%	1	0
20-29	1	1.3%	0	1	5	6.6%	3	2
30-39	2	2.6%	1	1	7	9.2%	6	1
40-49	3	4%	1	2	9	11.9%	5	4
50-59	7	9.2%	4	3	10	13.2%	6	4
≥60	10	13.1%	6	4	13	17.1%	7	6
Total	29	38.1%	17 (22.3%)	12 (15.8%)	47	61.9%	31 (40.8%)	16 (21.1%)

[Table/Fig-1]: Age and sex wise distribution of lung lesions with infective pathology.

Diagnosis	Pre COVID-19 period-cases	Percentage (%)	COVID-19 period-cases	Percentage (%)
Tuberculosis	6	7.9%	17	22.4%
Pneumonia with consolidation	5	6.6%	10	13.2%
Interstitial pneumonia	9	11.8%	9	11.8%
Bronchopneumonia	7	9.2%	6	7.9%
Aspergillus	2	2.6%	5	6.6%
Total	29	38.1%	47	61.9%

[Table/Fig-2]: Histopathological findings in infective lung lesions.

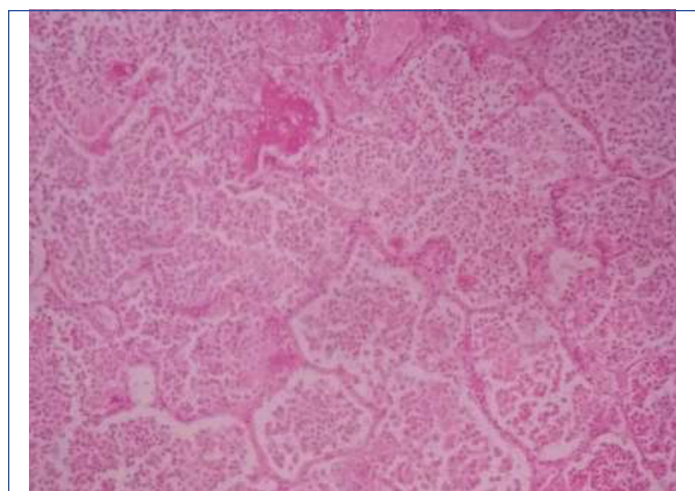
key findings. Firstly, there is a significant increase in the number of pneumonia cases during the COVID-19 era compared to the pre COVID-19 era, and this increase is statistically significant with a p-value of 0.04 [Table/Fig-8]. Although there is a significant difference in socio-demographic data between the pre COVID-19 and COVID-19 periods, these differences are not statistically significant. Furthermore, there is an observed increase in the percentage of Tuberculosis cases during the post COVID-19 period. However, this increase is not statistically significant, likely due to the smaller sample size available for analysis. Similarly, the type of specimen received did not yield statistically significant differences in the present study [Table/Fig-9].



[Table/Fig-3]: Gross: (a) grey tan to grey white areas; (b) Caseating granuloma showing langhan giant cell (H&E).



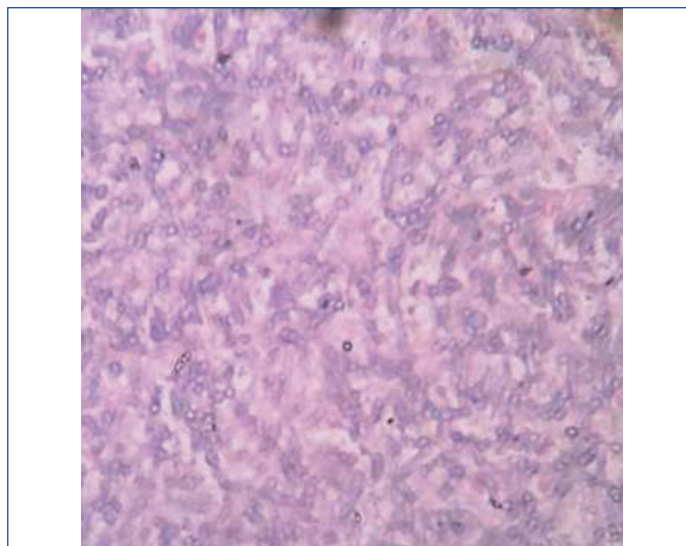
[Table/Fig-4]: Gross of bronchopneumonia showing patchy discoloration.



[Table/Fig-5]: Lobar pneumonia (H&E).

DISCUSSION

Autopsy is the detailed and careful examination of the dead body mainly done to find out the main cause of death. Most of the times cause of death having been established during ante-mortem period itself. Histopathological examination is useful to study the disease process, which may be missed during routine gross examination thus enriching the present medical knowledge. Gross examination along with histopathology gives better diagnosis. All the previous



[Table/Fig-6]: Aspergilloma (H&E).

Diagnosis	COVID-19 period-cases	COVID-19 positive	COVID-19 negative, symptomatic	COVID-19 status not specified
Tuberculosis	17	3	5	9 (5-Found dead)
Pneumonia with consolidation	10	4	5	1
Interstitial pneumonia	9	4	3	2
Bronchopneumonia	6	2	3	1
Aspergillus	5	5	0	0
Total	47	26	10	11

[Table/Fig-7]: COVID-19 status of infective lung pathology cases.

S. No.	Parameters	Pre COVID-19 (N=29)		COVID-19 (N=47)		p-value
1	Age (years)	N	%	N	%	0.529
	<60 y	19	35.8	34	64.2	
	>60 y	10	43.5	13	56.5	
2	Sex					0.260
	Male	17	41.5	24	58.5	
	Female	12	34.3	23	65.7	
3	Diagnosis					0.153
	Tuberculosis	6	26.1	17	73.9	
	Non-tuberculosis	23	43.4	30	56.6	
4	Diagnosis					0.04*
	Pneumonia	21	45.7	25	54.3	
	Others including tuberculosis	8	26.7	22	73.3	

[Table/Fig-8]: Comparison of baseline parameters and diagnosis between Pre COVID-19 and Post COVID-19 period.

*Threshold p-value=0.05, Significant p-value <0.05

Specimens	Pre COVID-19 (N=29)	Post COVID-19 (N=47)	p-value
Whole lung	24	41	0.290
Portion of lung	5	6	

[Table/Fig-9]: Partially received autopsy specimens of the lung.

autopsy studies of lung were generalised studies which highlighted about all histopathological spectrum of lung specimens [8-10]. During the COVID-19 pandemic, developed countries conducted autopsies on deceased COVID-19 patients revealing various COVID-19 related changes that have been extensively studied. However, there is currently a dearth of specific studies exclusively focused on lung infections during the pre and post COVID-19 periods, particularly in developing countries [11]. Despite the extensive research conducted on respiratory diseases and lung

health in general, there is a noticeable gap in understanding the specific dynamics and impacts of lung infections in the context of the pre and post COVID-19 era, particularly within developing nations [11].

The present study represents a novel contribution as it exclusively focuses on the infectious pathology of the lungs, specifically examining the trends observed during both the pre COVID-19 and COVID-19 eras. By narrowing this research scope to infectious lung diseases, the authors here, aim to provide valuable insights into this specific aspect of respiratory health. In the study conducted by Patel CB et al., it was observed that infectious disease patterns were a prevalent finding in the histopathological diagnosis across a majority of the studies [9]. The presence of infectious diseases was consistently identified as a significant contributor to lung pathology [8-10,12]. In the present study, the authors have conducted an analysis of data from previous studies focusing on the infective pathology of lung autopsy cases. In their journal article Chauhan G et al., conducted a study on 335 lung specimens [12].

Pathological lesions were observed in 285 cases, accounting for 85.1% of the total sample. In their study, pneumonia was observed in 49 cases, accounting for 14.62% of the total cases, while granulomatous (tuberculous) lesions were seen in 21 cases, representing 6.26% of the total cases [12]. In the present study during the pre COVID-19 period, the authors observed pneumonia in 21 cases, with the distribution of specific types being as follows: pneumonia with consolidation in five cases (6.6%), interstitial pneumonia in nine cases (11.8%) and broncho pneumonia in seven cases (9.2%). Additionally, the authors found that TB (granuloma) was present in six cases, representing 7.9% of the total cases. In the post COVID-19 period, we observed pneumonia in 25 cases, with the distribution of specific types as follows: pneumonia with consolidation in 10 cases (13.2%), interstitial pneumonia in nine cases (11.8%), and bronchopneumonia in six cases (7.9%). Furthermore, the authors found that TB (granuloma) was present in 17 cases, accounting for 22.4% of the total cases. The present study aligns with the findings of Sumaya et al., Amin NS et al., Momin YA et al., and Amin A et al., which indicate that pneumonia followed by TB are common findings in the examined cases [13-16]. They reinforce the presence of pneumonia and TB as commonly observed findings within the studied population [13-16]. The present study findings align with these studies, underscoring the significance of pneumonia and TB as prominent manifestations of infectious diseases in the lungs. The consistent identification of TB across multiple studies highlights [13-16] its significance as a common pathology within the examined cases, particularly during the COVID-19 era. Notably, there has been a drastic increase in the prevalence of TB cases, accounting for 17 cases (22.4%) in our study. Similar to the study conducted by Jain VK et al., the present study also observed an increase in TB cases [7]. Several factors can account for this rise, including the effects of lockdown measures and the fear of hospital stays during the COVID-19 pandemic.

Additionally, challenges in accessing regular Outpatient Department (OPD) services, community-level TB issues, and a significant decrease in the diagnosis of new cases of active TB have contributed to the observed increase. Furthermore, deficiencies in monitoring and uninterrupted supply of anti-TB medications, affordability of personal protective equipment for healthcare workers, and the economic consequences of the COVID-19 pandemic have played a role in the rise of TB cases. These multifaceted factors highlight the complex interplay between the COVID-19 pandemic and the management of TB. In the studies stated above pneumonia is the most common cause of death, thus correlating with the present study. Similar to Amin A et al., this study also revealed a significant observation regarding aspergillosis [16]. The authors identified two cases (2.6%) of aspergillosis during the pre COVID-19 period and five cases (6.6%) during the COVID-19 period. Importantly, we

observed an increase in the prevalence of aspergillosis during the post COVID-19 period. The increased prevalence of aspergillosis in COVID-19 patients could be attributed to the combination of diabetes and increased use of corticosteroids to combat COVID-19 infection, which increases the risk of development and aggravation of existing opportunistic fungal infections. Additionally, mechanical ventilation, catheter placement, and immunosuppressant therapies appear to play a role in the manifestation of various fungal co-infections in COVID-19 patients. The statistical analysis [Table/Fig-8] conducted in this study revealed a significant association between COVID-19 and lung infections, with a p-value of 0.04 (Threshold p-value=0.05). This finding indicates that there is a statistically significant relationship between the presence of COVID-19 and the occurrence of lung infections especially pneumonia. This significant association underscores the connection between COVID-19 and the development of lung infections. It highlights the potential impact of COVID-19 on respiratory health and the susceptibility to secondary infections. Understanding this association is crucial for effective management and prevention strategies, as it can inform clinical decisionmaking, public health measures, and interventions to minimise the risk and burden of lung infections in individuals with COVID-19.

Further research and investigation into the mechanisms and factors contributing to this association are warranted to enhance our understanding and optimise patient care outcomes. Despite significant differences in socio-demographic data between the pre COVID-19 and COVID-19 periods, these differences do not reach statistical significance, likely due to the smaller sample size employed in the study. Similarly, the type of specimen received did not yield statistically significant differences in the present study. This could also be attributed to the smaller sample size, indicating the need for a larger sample to draw more conclusive results.

Limitation(s)

In some cases, only a part of the organ was received, preventing us from providing a precise report on additional findings. Additionally, due to their compromised condition, autolysed specimens were excluded from the study. Furthermore, specimens obtained from deceased individuals of unknown identity lacked proper clinical information, significantly limiting the usability of their data in this study. However, the present analysis revealed that the specific type of specimen did not demonstrate statistical significance.

CONCLUSION(S)

Pneumonia, including lobar pneumonia, interstitial pneumonia, and bronchopneumonia, is the most commonly observed histopathological lung lesion. This finding highlights the significance of lung infections as a common cause of mortality. When comparing the pre COVID-19 era to the COVID-19 era, the authors observed an increased number of infective lesions, indicating a higher burden of infectious diseases during the pandemic. A significant increase in tuberculous etiology during the COVID-19 period emphasises the importance of prevention and pre-planning during pandemics to effectively manage and prevent the surge of treatable infectious conditions. This calls for proactive measures such as early detection, proper treatment, and comprehensive public health strategies to control the spread of TB. Furthermore, the rise in opportunistic fungal infections, such as aspergillosis, necessitates specific interventions. Proper diagnosis of the pandemic, along with strict control of diabetes and monitored steroid use, plays a crucial role in preventing life-threatening infectious conditions during the COVID-19 pandemic.

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PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India.
2. Associate Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India.
3. Assistant Professor, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India.
4. Professor and Head, Department of Pathology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Yogambal Muthureddy,
Plot No. 9, Mahalakshmi Flats, Flat D, 2nd Floor, CRR Puram, L&T Colony,
Manapakkam, Chennai-600125, Tamil Nadu, India.
E-mail: yogambaldr@gmail.com

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