Original Article

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Pathology Section

Histopathological Profile of Lung Lesions- An Autopsy Study at a Tertiary Care Centre, Kerala, India

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ABSTRACT

Introduction: Autopsy plays a crucial role in understanding and identifying pulmonary pathology, encompassing non neoplastic lesions, neoplastic conditions and the secondary implications of the lungs in terminal events of cardiovascular diseases. Pathological analysis confirms diagnosis and identifies the prevalence of lesions, contributing significantly to medical understanding and patient care.

Aim: To estimate the prevalence of lung pathology in autopsy specimens through Histopathological Examination (HPE).

Materials and Methods: A cross-sectional one-year study was conducted to determine the histopathological alterations in 132 lung autopsy specimens from Medicolegal autopsies received in the Department of Pathology at a tertiary care centre in Government Medical College, Cochin, Kerala, India from January 2021 to December 2021. Autopsy specimens of the lung were fixed in 10% formalin. Following gross examination, tissue sections were processed with paraffin and subjected to staining, with microscopy findings recorded. The data was numerically coded and entered into a Microsoft Excel spreadsheet. Statistical Package for Social Sciences (SPSS) version 21.0 was used for descriptive statistics and graphical representations of findings.

Results: The mean age of the study population, comprising 132 autopsy cases, was 49.41±52.12 years and the male-to-female ratio was 3.71:1. Most cases 97/132 (73.50%) involved sudden deaths where the cause remained unknown. Significant microscopic findings found in 117 (88.63%) cases were as follows: Pulmonary oedema and congestion: 61 (46.21%), Pneumonia: 17 (12.87%), Diffuse Alveolar Damage (DAD): 12 (9.09%), Chronic venous congestion: 8 (6.06%), Tuberculosis: 7 (5.30%), Emphysema: 7 (5.30%), Pulmonary fibrosis: 1 (0.75%), Fat embolism: 1 (0.75%) and Pulmonary arterial hypertension: 1 (0.75%). Neoplastic lesions were identified in 7 (5.30%) cases, with primary lung cancers accounting for 3 (2.27%) cases. There were 10 cases of Real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), positive Coronavirus Disease 2019 (COVID-19) autopsies, of which 6 (60%) exhibited DAD, while 4 (40%) showed changes of bronchopneumonia.

Conclusion: Non neoplastic lesions such as pulmonary oedema, DAD and infections contributed to mortality in most cases. DAD was the most common lung finding in more than half of COVID-19 deaths. The prevalence of pulmonary neoplastic lesions in autopsies underscores their epidemiological significance in a particular geographical area.

Keywords: Coronavirus disease 2019, Diffuse alveolar damage, Lung autopsy, Pneumonia, Tuberculosis

INTRODUCTION

Autopsy is considered the definitive diagnostic test, maintaining its status as the gold standard for determining the cause of death. Autopsy pathologists are tasked with investigating a broad spectrum of sudden, unexpected and clinically unexplained deaths stemming from various natural causes [1]. Diagnosing lung diseases can pose a significant challenge to clinicians, even with access to advanced diagnostic techniques. Timely pathological diagnosis, complemented by clinical and radiological observations, are vital for enhancing patient survival [2]. The rapid progression of the disease results in less time for diagnosis; many lesions remain unidentified until after the patient has died and an autopsy has been performed [3].

Examining the lungs during an autopsy provides crucial insights into various patterns of lung injury, including DAD, stages of fibrosis, stages of interstitial pneumonitis, infectious processes and other specific pathologies. Through gross examination, valuable information is obtained about pleural lesions, the presence of collapsed or hyperinflated lungs, scarring, fibrosis, bullae, consolidation, nodules, infarction, all of which offer hints to establish a diagnosis [4]. The patterns of injury indicate damage to lung structures such as the alveolocapillary membrane, airways and blood vessels, either individually or in combination. Histologically, many diseases with distinct causes show similar tissue reactions, aiding in compiling a comprehensive list of potential diagnosis. Additionally, different disease states can affect various combinations of pulmonary microanatomy simultaneously, with conditions primarily targeting the pulmonary interstitium often also damaging small airways and vice versa [4].

Postmortem analysis of lung specimens provides valuable insights into the diverse factors contributing to prevalent respiratory infections such as bronchitis, bronchopneumonia and other types of pneumonia [5]. Some cases of active tuberculosis are not identified until after the patient has died and an autopsy has been performed [6]. Pulmonary oedema arises from fluid accumulation in the interstitium and alveoli of the lungs, which can be caused by inherent lung issues or systemic factors. It is traditionally categorised into two types: cardiogenic, resulting from acute left ventricular failure and manifesting as high-pressure oedema typically triggered by events like myocardial infarction; and non cardiogenic, characterised by low-pressure fluid build-up and arising from acute lung injury or conditions such as Acute Respiratory Distress Syndrome (ARDS) [7].

The COVID-19 infection leads to either localised or widespread inflammation in the alveoli and interstitial spaces of the lungs, causing respiratory failure primarily due to DAD and severe capillary congestion, which is the main cause of mortality [7]. Bronchopneumonia and organising pneumonia frequently manifest in patients with prolonged COVID-19 illness duration [8]. The features of COVID-19 infection include the presence of fibrinous exudates, hyaline membrane deposition, hyperplasia of type II pneumocytes and the infiltration of lymphocytes, indicative of a transition from

exudative to proliferative DAD and to fibrosis [9]. People with co-morbidities such as cardiovascular diseases and obesity are at a higher risk for multiple system involvement [8,10]. Histopathological examination of lung autopsy not only gives significant importance to diagnose the respiratory cause of death but also enriches our knowledge about lung histology [11]. The aim of the present study was to estimate the prevalence of pulmonary lesions identified in autopsies of patients who died from respiratory diseases or other causes and to shed light on the principal causes of death due to pulmonary involvement.

MATERIALS AND METHODS

The present study was a one-year cross-sectional study conducted on 132 lung specimens from routine autopsies received in the Department of Pathology at a tertiary care centre Government Medical College in Cochin, Kerala, India from January 2021 to December 2021. The specimens of lung from the Forensic Medicine Department were received in 10% formalin. The details of the autopsy cases were collected from the requisition forms. Institutional Ethical Committee clearance was obtained for conducting the study (IEC no. 50/2021).

Inclusion criteria: Specimens of whole lungs, lobes, or tissue bits from adult medicolegal autopsies above 18 years of age were included in the study.

Exclusion criteria: The decision was to exclude autolysed specimens; therefore, 8 poorly preserved specimens were omitted, resulting in a total of 132 included specimens.

Sample size calculation: It was based on a study conducted by Amin NS et al., in which the proportion of histopathological lesions in the lung among autopsy specimens was 43% [12]. Using the sample size estimation formula $N=4pq/d^2$, where 4 represents the square of the Z-value of the alpha error at 5% (approximated to 1.96), p is the proportion from the previous study (43%), q is 100-p (57%) and d is the relative precision of 20% (8.6). Therefore, the minimum sample size required for the present study was determined to be 132.

Study Procedure

The lung specimens were fixed in 10% formalin, with universal precautions observed during handling. On gross examination, parameters such as colour, volume (collapsed or inflated), consistency, presence of bullae, consolidation, nodules, infarction, oedema, congestion, abscess formation, scarring, hilum and bronchi were assessed. A minimum of four sections, with additional sections as needed, were taken from representative areas for microscopy. In addition to Haematoxylin and Eosin (H&E) stains, special stains for Acid Fast Bacilli (AFB) and Grocott-Gomori Methenamine Silver stain (GMS) and Periodic Acid Schiff (PAS) for fungal hyphae were performed when necessary. Pulmonary lesions were examined microscopically, the relative frequency of various lesions and available clinical data were recorded.

STATISTICAL ANALYSIS

Data were numerically coded and entered into a Microsoft Excel spreadsheet. Further statistical analysis was conducted using SPSS software version 21.0. Quantitative variables were summarised using frequency and percentage.

RESULTS

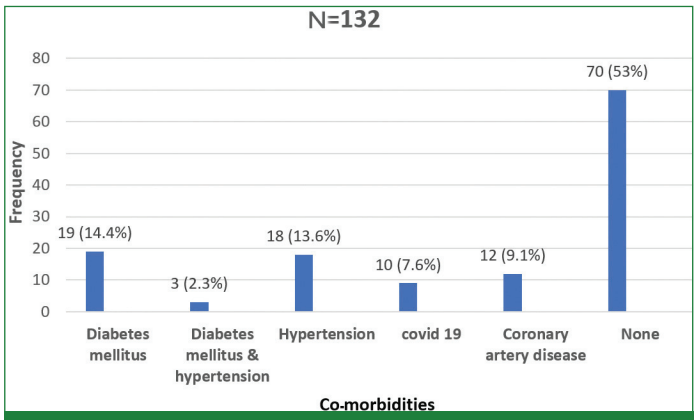
The adult autopsy cases in the study ranged in age from 18 to 88-year-old, with a mean age of 49.41 years and a standard deviation of ±52.12. Out of the 132 autopsy cases, the majority (48.50%) were in the age group of 31-40 years, followed by 41-50 years (15.90%), 20-30 years (14.40%) and 51-60 years (10.60%). The distribution of age among the patients in the autopsy cases is shown in [Table/Fig-1].

Age (years)	Frequency	Percentage
18-30	19	14.4
31-40	64	48.5
41-50	21	15.9
51-60	14	10.6
61-70	5	3.8
71-80	5	3.8
81-90	4	3
Total	132	100

[Table/Fig-1]: Distribution of age of the patients in autopsy cases.

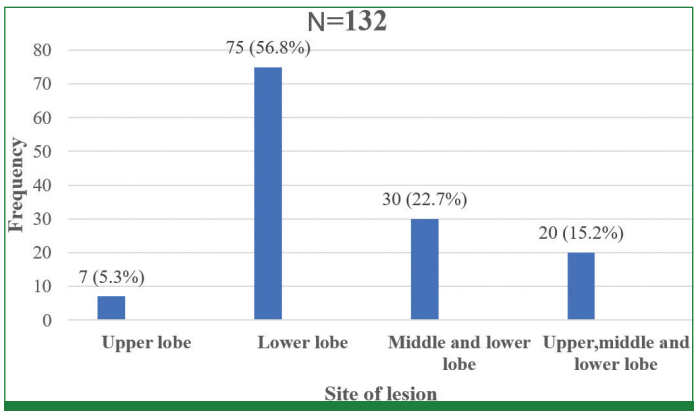
Of the 132 autopsy specimens, 104 (78.80%) cases were males and 28 (21.20%) were females, resulting in a male-to-female ratio of 3.71:1. Among the 132 cases, the cause of death for the majority, 97 (73.50%) was sudden death, while the remaining 35 cases (26.50%) were attributed to other causes such as underlying illness, suicide, electrocution, drowning, road traffic accidents, burns, etc.

Among the 132 cases, 70 cases (53%) had no associated co-morbidities. Diabetes mellitus was present in 19 cases (14.40%), hypertension in 18 cases (13.6%) and 3 cases (2.30%) had both diabetes and hypertension. RT-PCR positive COVID-19 infection was observed in 10 cases (7.60%). A history of ischaemic heart disease and coronary artery disease was seen in 12 cases (9.10%). The distribution of co-morbidities in autopsy cases is shown in [Table/Fig-2].



[Table/Fig-2]: Distribution of co-morbidities in autopsy cases.

The most common macroscopic finding was oedema and congestion, observed in 89 cases (67.40%), followed by congestion alone in 29 cases (22%). Collapse and consolidation were observed in 4 cases (3.03%). Out of the 14 cases (10.60%) with gross white lesions, seven cases showed multiple caseous lesions and necrosis suggestive of tuberculosis. Among the 132 autopsy cases, 75 cases (56.8%) showed macroscopic lesions in the lower lobe of the lung, while 30 cases (22.7%) had lesions in both the middle and lower lobes. The site of lung lesions in the lobe-wise distribution in the study is shown in [Table/Fig-3].



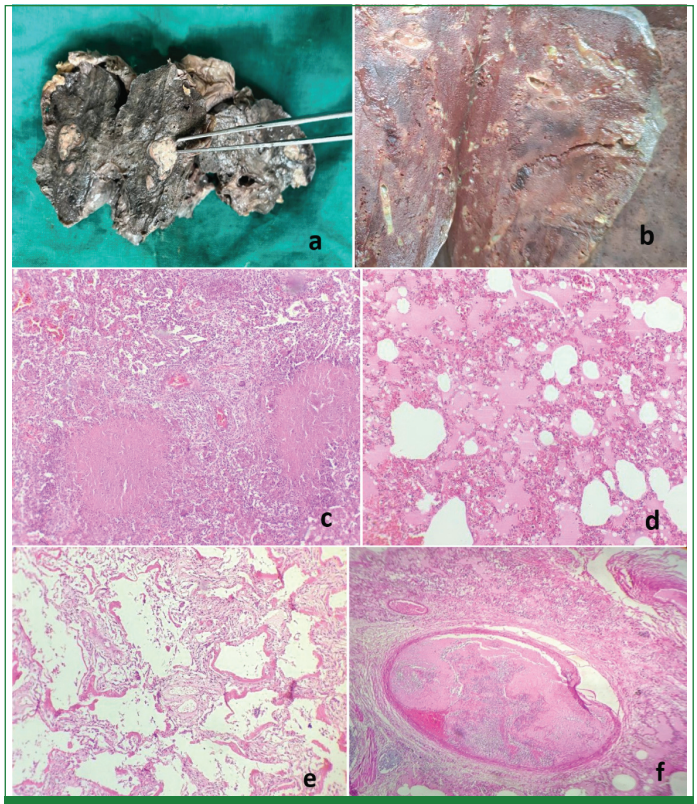
[Table/Fig-3]: Distribution according to site of lung lesion in autopsy cases.

In the present study, 11.37% of the cases were histologically unremarkable, whereas 88.63% of the cases showed histological changes of pulmonary pathology, which were further subclassified based on the type of the lesion encountered. This distribution shows the prevalence of various microscopic diagnosis in the study population given in [Table/Fig-4].

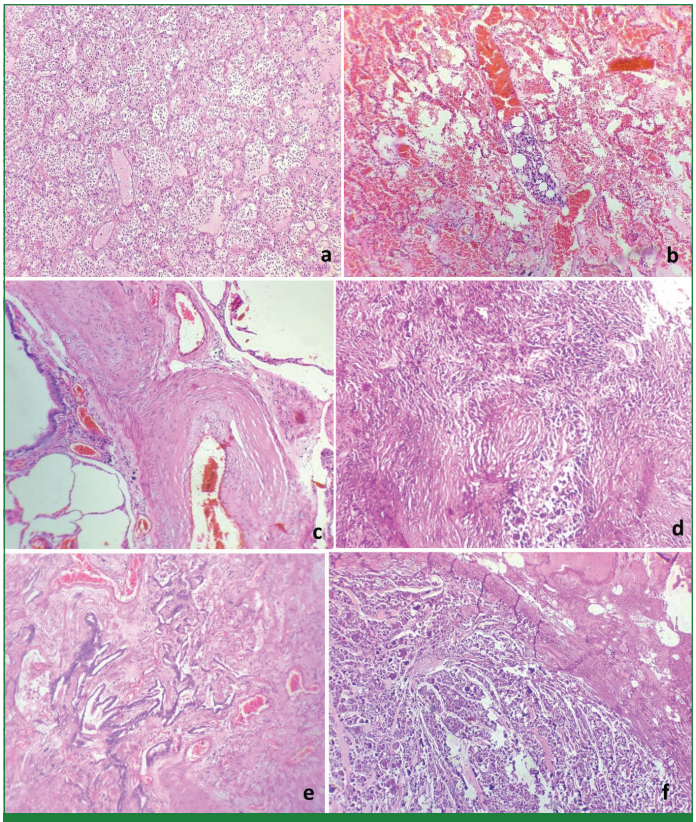
Microscopic diagnosis	Frequency	Percentage
Pulmonary oedema/congestion	61	46.21
Chronic venous congestion	8*	6.06
Emphysema	7*	5.30
Acute Respiratory Distress Syndrome (ARDS)/Diffuse Alveolar Damage (DAD)	12	9.09
Pneumonia	17*	12.87
Tuberculosis	7	5.30
Fat embolism	1	0.75
Pulmonary hypertension	1	0.75
Pulmonary fibrosis	1	0.75
Neoplastic lesions	7	5.30
No specific lesion/normal	15	11.37

[Table/Fig-4]: Microscopic findings in lung in the study (n=132).
*Overlap of findings in these lesions with pulmonary congestion and oedema

On HPE of 132 lung specimens, 61 cases (46.21%) showed pulmonary oedema and congestion. Changes of Chronic Venous Congestion (CVC) were seen in 8 cases (6.06%), Emphysema in 7 (5.30%) cases. There was overlap of findings as combined findings of pulmonary oedema with CVC were seen in 4 (3.03%) cases, pulmonary oedema with emphysematous changes were seen in 6 (5.30%) cases and pulmonary oedema with pneumonia in 8 (6.10%) autopsy cases. Pneumonia was seen in 17 (12.90%) cases which included both lobar and bronchopneumonia. Granulomatous inflammatory lesion and caseous necrosis consistent with tuberculous bronchopneumonia were found in 7 (5.30%) cases. The gross and microscopy images of lung lesions in the study is shown in [Table/Fig-5a-f, 6a-f].



[Table/Fig-5]: Gross and microscopy images of lung lesions in the study. a) Gross image of lung showing multiple caseous lesions; b) Gross-congestion and oedema; c) Caseating granuloma in Tuberculosis (H&E,10X); d) Pulmonary oedema (H&E,10X); e) DAD, ARDS. (H&E, 10X); f) Intravascular thrombi formation in COVID-19 infection lung (H&E,10X).



[Table/Fig-6]: Microscopic findings in lung in the study- images. a) Lobar pneumonia - red and grey hepatisation. (H&E,10X); b) Fat embolism in vessel-lung (H&E,10X); c) Medial hypertrophy of artery in pulmonary arterial hypertension (H&E,10X); d) Pulmonary fibrosis- extensive fibrosis (H&E,10X); e) Primary adenocarcinoma lung (H&E, 10X; f) Lung metastasis from follicular carcinoma thyroid (H&E, 10X).

The ARDS and DAD associated with multi-organ failure were seen in 12 (9.10%) of cases. Out of the 12 cases of DAD, 6 cases had COVID-19 infection as a co-morbidity. There were 10 cases of COVID-19 deaths in the study. The primary pulmonary findings in COVID-19 deaths were massive capillary congestion in all 10 (100%) cases, exudative DAD associated with hyaline membrane and type II pneumocyte hyperplasia in six cases. Four cases showed superimposed bronchopneumonia. Other findings in COVID-19 deaths were interstitial congestion, alveolar haemorrhage in three cases, platelet and fibrin thrombi in two cases.

Neoplastic lesions were seen in 7 (5.30%) out of 132 cases. There were three cases of primary lung adenocarcinoma, two cases of adenocarcinoma metastasis to lung and two cases of thyroid neoplasm metastasis to lung were found. Other lesions in the present study included one case each of pulmonary arterial hypertension (0.75%), pulmonary fibrosis (0.75%) and fat embolism (0.75%). In 15 cases (11.40%), there was no specific pathology seen.

DISCUSSION

The present study on pulmonary findings of medicolegal autopsies aimed to identify the prevalence of pulmonary pathology and the incidental lung lesions that may have contributed to fatalities associated with cardiorespiratory failure. In the current study, histopathological changes in the lungs were present in 88.63% of cases. This is similar to the findings from previous studies by Khare P et al., and by Chauhan G et al., where the prevalence of lung pathology was 65.10% and 87.47%, respectively [13,14]. The current study examined 132 autopsy cases, with patients ranging in age from 20 to 88 years. A significant portion of cases 64 (48.5%) fell within the 31 to 40 year age group and males 104 (78.8%) outnumbered females 28 (21.2%). Tahir TM et al., reported that 68.14% of cases in their study were between 20 and 49 years-old [2]. The cause of death was unknown in 97 (73.50%) cases in the present study. Road traffic accidents, suicide, poisoning and drowning were the known causes seen in 35 out of 132 (26.5%) cases. Co-morbidities present in 52 (39.39%) cases included,

diabetes mellitus, hypertension, ischaemic heart disease, coronary artery disease and COVID-19 infections.

The gross morphology of lung lesions in the study varied from congestion, heaviness, frothy appearance, whitish lesions to collapse and consolidation. Congestion and oedema were the most common gross findings, seen in 89 cases (67.40%). The second most common finding was congestion alone in 29 (22%) cases. Similar observations were seen in a study conducted by Khare P et al., which observed congestion in 42.85% of cases [13].

The spectrum of histopathological lesions included pulmonary congestion, oedema, pneumonia, tuberculosis, DAD, emphysema, neoplastic lesions and other abnormalities. Pulmonary oedema could be due to primary pulmonary pathology or secondary involvement of the lungs in the terminal stages of cardiovascular diseases. Pulmonary oedema and congestion were the most common findings in 61 (46.2%) cases in the study. Chauhan G et al., reported a similar prevalence of 53.32% [14]. Changes in the CVC were observed in 8 (6.06%) cases, while Shetty AC and Vijaya A noted a prevalence of CVC in 30 out of 349 cases (8.6%) [11]. The second most common histopathological lesion was pneumonia, including bronchopneumonia and lobar pneumonia, accounting for 12.87% of the 132 cases. This finding was consistent with studies by Chauhan G et al., and Patel CB et al., who reported pneumonia in 14.62% and 18.68% of cases, respectively [14,15].

Granulomatous inflammatory lesions with caseation consistent with tuberculosis were found in 7 (5.30%) cases out of the 132 autopsy cases in the present study. The increased frequency of sudden deaths due to undiagnosed tuberculosis, despite improved healthcare facilities, is a cause for concern. In a study on sudden unexpected deaths due to tuberculosis by Rastogi P et al., tuberculosis was identified as the most common cause of sudden unexpected death related to the respiratory system [16]. Tuberculosis poses a threat to the community, both during life and after death. Although it is a treatable disease, its fatality is often linked to its association with Human Immunodeficiency Virus (HIV) infection.

In a study by Garg M et al., which included a total of 115 autopsy cases, 10 cases (8.7%) of active tuberculosis were identified. Tuberculosis was the primary cause of death in 30% of patients, with 90% having pulmonary tuberculosis, 10% miliary tuberculosis and 30% extrapulmonary tuberculosis [17]. Emphysematous changes were observed in 7 cases (5.30%) in the present study. In a study of 441 autopsy cases by Dhruw D et al., only 3 cases (0.63%) of emphysema were reported [18]. Goswami PR et al., reported a higher prevalence of 15.8%, attributing the increase to tobacco consumption in the area [19]. A comparison of the proportions of lung lesions with other studies is shown in [Table/Fig-7] [13-15,18,19].

There were 7 (5.30%) cases of neoplastic lung lesions. Primary lung adenocarcinoma was observed in three cases and four cases of metastatic carcinoma with multiple pulmonary nodules were seen. All these findings were incidental in postmortem examinations and the lesions appeared as grey-white single or multiple nodular lesions macroscopically. Two cases of lung metastasis were from thyroid neoplasms, one from papillary carcinoma of the thyroid and another case from follicular carcinoma of the thyroid. Manser RL et al., observed 47 incidental lung cancers in a large series, with 28 being invasive non small cell lung cancers and 86% of those were stage I cancers [20]. A study on autopsy diagnosis of malignant neoplasms conducted by Burton EC et al., showed that 33% of undiagnosed malignancies were in the respiratory tract [21]. Although incidental lung cancer is uncommon, there are some lung cancers that remain undetected during life and do contribute to death. It is not possible to determine from the present study whether the incidental lesions detected were indolent or would have progressed to cause death had the individuals not died from co-morbid diseases. HPE of the autopsied specimens helps to highlight incidental findings [21]. Other lesions in the present study included a single case of pulmonary arterial hypertension associated with cardiac mitral valve stenosis and cardiac failure. Additionally, one case of fat embolism following a road traffic injury and bone fracture was noted.

Among the 10 autopsies of COVID-19-related deaths in the present study, more than half of the cases 6 (60%) showed predominantly a DAD pattern of lung injury, with the formation of hyaline membranes and interstitial fibrous tissue proliferation. Features of Bronchopneumonia were seen in 4 COVID-19 deaths. In a review article of 20 studies of COVID-19-related deaths by Sofizan NM et al., the major histological feature in the lung was DAD with hyaline membrane formation and microthrombi in small pulmonary vessels [22]. The authors concluded that there was a high incidence of deep vein thrombosis, despite the use of prophylactic anticoagulants in intensive care units. Carsana L et al., described the fibrotic phase of DAD and honeycombing, which were only focal in COVID-19 deaths, suggesting that progression to the fibrotic phase was rare due to the short duration of the disease [Table/Fig-8] [7-9,23]. Based on the comparison of COVID-19 pulmonary pathology findings between the present study and other studies, the prevalence and pattern of lesions varied based on the chronicity and complications of the cases.

Microscopic diagnosis	Present study- Kerala (2024) (N=132) N (%)	Khare P et al., (Delhi-2017) [13] (N=86) N (%)	Chauhan G et al., (Gujarat-2015) [14] (N=335) N (%)	Patel CB et al., (Gujarat-2017) [15] (N=649) N (%)	Dhruw D et al., (Chhattisgarh-2020) [18] (N=474) N (%)	Goswami PR et al., (Gujarat-2021) [19] (N=139) N (%)
Pulmonary oedema, congestion	61 (46.2%)	24 (42.85%)	-	93 (26.44%)	352 (74.25%)	-
Chronic venous congestion	8 (6.06%)	-	-	92 (26.72%)	41 (8.64%)	-
*Terminal events	-	10 (17.9%)	182 (54.32%)	-	-	42 (30.2%)
Pneumonia	17 (12.9%)	5 (8.7%)	49 (14.62%)	65 (18.68%)	25 (5.26%)	47 (33.8%)
ARDS/DAD	12 (9.1%)	1 (1.8%)	-	3 (0.86%)	-	-
Tuberculosis/Granuloma	7 (5.3%)	8 (14.3%)	21 (6.26%)	5 (1.44%)	7 (1.48%)	18 (12.9%)
Emphysema	7 (5.3%)	5 (8.75%)	26 (7.76%)	15 (4.31%)	3 (0.63%)	22 (15.8%)
Neoplastic lesions	7 (5.3%)	-	7 (2.08%)	2 (0.58%)	-	7 (5%)
Normal	15 (11.37%)	26 (30.1%)	42 (12.53%)	-	33 (7%)	-

[Table/Fig-7]: Prevalence and percentage of pulmonary pathology in various studies [13-15,17,19].
*Terminal events- Congestion, pulmonary oedema, haemorrhage, changes due to cardiovascular causes [17]

Microscopic diagnosis	Present study (2024) n=10	Elsoukkary SS et al., (2020) USA n=32 [7]	Menter T et al., (2020) Switzerland n=21 [8]	Zhao L et al., (2021) Wuhan, China n=9 [9]	Carsana L et al., (2020) Italy n=38 [23]
Interstitial congestion, oedema	10 (100%)	8 (25%)	21 (100%)	9 (100%)	38 (100%)
DAD, exudative	6 (60%)	24 (75%)	8 (38%)	9 (100%)	38 (100%)

Hyaline membrane formation	6 (60%)	24 (75%)	16 (76%)	9 (100%)	33 (87%)
Type II pneumocyte hyperplasia	6 (60%)	24 (75%)	11 (52%)	9 (100%)	38 (100%)
Platelet-fibrin thrombi in vessels/coagulopathy	2 (20%)	23 (72%)	5 (23.8%)	7 (77.77%)	33 (87%)
Alveolar haemorrhage	3 (30%)	9 (28%)	3 (14.28%)	9 (100%)	20 (50%)
Bronchopneumonia organising pneumonia	4 (40%)	14 (44%)	10 (38%)	6 (66.66%)	14 (37%)
Pulmonary embolism	-	-	4 (19%)	-	-

[Table/Fig-8]: Comparison of pulmonary pathology in COVID-19 deaths (n=10/132) [7-9,23].

Limitation(s)

Information regarding the clinical details, previous illnesses and risk factors such as tobacco smoking contributing to pulmonary diseases could not be obtained in all cases.

CONCLUSION(S)

The morphology and pattern of lung pathology are varied and complex. The present study documented the prevalence of lung lesions in sudden deaths. The terminal events of pulmonary oedema and congestion were the common findings contributing directly or indirectly to mortality. Lungs are the primary site for Novel Coronavirus infection and COVID-19 pathology is currently under extensive research. The present study showed DAD as the most common histopathological finding in the majority of COVID-19 deaths. Incidental findings reveal information regarding the epidemiology of the disease in a geographical area, which is valuable in academic research. The prevalence of lung lesions of infectious aetiology in a population depends on social and epidemiological patterns. The prevalence of tuberculosis and pneumonia emphasises the clinical significance of early diagnosis and management to reduce mortality.

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