Original Article

Acute respiratory distress syndrome: A study of autopsy findings

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ABSTRACT

Context: In this autopsy study, the various morphological patterns of acute respiratory distress syndrome (ARDS) have been analyzed and compared along with their etiopathogenesis. **Aims:** We aimed to study the prevalence and clinicopathological correlation of ARDS based on age, gender, hospital stay, symptoms, clinical diagnosis, gross, and microscopy findings. **Subjects and Methods:** Total 130 cases of ARDS were studied over a period of 5 years. Age, gender, hospital stay duration, symptoms, clinical diagnosis, gross and microscopic lung finding, clinicopathological correlation, and cause of death were documented and analyzed. Special stains were done whenever required. **Statistical Analysis:** This is an observational study, and simple statistics such as mean, median, and standard deviation have been used for continuous variables. **Results:** The prevalence of ARDS among the adult autopsy was 6.05%. Majority of the cases were in the age group of 18–30 years (36.9%), with a male: female ratio of 1.7:1. Chief complaints were fever (71%), breathlessness (54.6%), and chills (43.8%). The main clinical diagnoses were ARDS (41.6%), sepsis (28.3%), acute febrile illness (17%), and lower respiratory tract infection (12.5%). Most of the patients had a hospital stay of <1 day. Associated conditions mostly included chronic alcoholism (16.1%), pregnancy (16.1%), and chronic smoking (10.7%). Major findings on gross examination were intrapulmonary hemorrhage (38.5%), ARDS (33%), pulmonary edema (13%), and pneumonia (15.3%).On microscopy, major findings were hyaline membrane (84.6%), intrapulmonary hemorrhage (76.1%), pulmonary edema (75.3%), organizing fibrin (55.3%), and bronchopneumonia (36.2%). **Conclusion:** Infections were one of the major predisposing causes of ARDS. Due to the short interval, the underlying cause for ARDS often goes undiagnosed.

KEY WORDS: Acute respiratory distress syndrome, hyaline membrane, intrapulmonary hemorrhage

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical manifestation of acute lung injury (ALI). Diffuse alveolar damage (DAD) is the histological counterpart of the term ALI. Some even consider acute fibrinous and organizing pneumonia as one of the subtypes of the broad spectrum of ALI, however, some believe that organizing pneumonia is a subacute phenomenon.[1] Signs and symptoms associated are so vague that clinically diagnosing true ARDS with DAD is problematic.

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This study focuses on the prevalence of ALI in adult autopsies, causes, and comorbid conditions associated with ALI. This study also includes detailed morphological appearances of gross and microscopic lung findings seen in ALI. A detailed distribution was done based on age, sex, hospital stay duration, clinical features, comorbid illness, radiological findings, gross, and histological lung features for adult autopsies having ALI.

SUBJECTS AND METHODS

Methodology

This study was carried over a period of 5 years, which includes 4 years of retrospective and 1 year of prospective arms. The study period was from January 1, 2013, to December 31, 2017. The study was performed in a tertiary care hospital. All adult medical autopsies where final cause of death was ARDS on histopathological examination were thoroughly analyzed and documented. Autopsy records were used anonymously and the identity of the individuals was not revealed anywhere in the study.

Parameters such as age, gender, hospital stay duration, clinical symptoms with history, clinical diagnosis, postmortem examination findings, gross and microscopic lung findings, any significant pathological findings in other organs, clinicopathological correlation, and cause of death were studied.

Detailed gross appearance of lung included *in situ* findings, weight of each lung, pleural surface examination, lung consistency and appearance along with inspection of airways, blood vessels, and hilum.

Minimum five or more hematoxylin- and eosin-stained slides from each lobe were studied by two or more pathologists. Special stains such as periodic acid–Schiff, Ziehl–Neelsen stain, and Gomori methenamine silver were done wherever required.

Microscopic findings were studied thoroughly by two or more pathologists. All significant findings in pleura, alveolar spaces, interstitium, bronchi, bronchioles, blood vessels (bronchial and pulmonary), and lymphatics were noted.

Subject selection criteria

Individuals with age more than or equal to 18 years and with final cause of death of ARDS after histopathology examination were included.

Subject exclusion criteria

All cases with age below 18 years were excluded. Newborns were excluded since their etiopathogenesis also includes intrapartum and congenital causes.

Statistical analysis

This is an observational study with simple statistics such as mean, median, and standard deviation used for continuous variables.

RESULTS

In the present study out of 2147 adult autopsies, 130 autopsies were included with final cause of death as ARDS. The prevalence calculated was 6.05%. Most cases were in the younger age group (18–30 years), and the mean age was 38.93 ± 15.29 years.

As per Table 1, nonspecific signs and symptoms such as fever and breathlessness were most prevalent. Among associated conditions, chronic alcoholism and pregnancy were most common [Table 2].

In 92 out of 130 cases (70.8%), the hospital stay duration was <1 day. On laboratory investigations, thrombocytopenia was seen in 60 out of 103 cases (58.3%), raised total count in 54 out of 102 cases (52.9%), deranged kidney function test in 53 out of 80 cases (66.3%), deranged liver function test in 41 out of 75 cases (85.5%), deranged serum electrolytes in 37 out of 68 cases (54.5%), abnormal coagulation profile in 24 out of 29 cases (82.7%), and abnormal pH in 25 out of 30 cases (83.4%). On chest X-ray, fluffy opacities were seen most commonly (15 out of 27 cases). On microbiological studies, leptospirosis was seen in 7 cases while viral hepatitis, dengue, and malaria each in 3 cases.

In 41.6% of cases (50 out of 120), ARDS was found concomitantly with DAD [Table 3]. Lung findings on gross examination included intrapulmonary

Table 1: Major clinical signs and symptoms (*n*=130)

Clinical symptoms	Total cases, *n* (%)
Fever	93 (71)
Breathlessness	71 (54.6)
Vomiting	38 (29.2)
Generalized body ache	29 (30)
Icterus	22 (16.9)
Loose motions	20 (15.3)
Cough with expectoration	16 (12.3)
Abdominal pain	14 (10.7)
Dry cough	13 (10)
Headache	11 (8.4)

Table 2: Associated clinical conditions (*n*=130)

Associated conditions	Total cases, *n* (%)
Chronic alcoholism	21 (16.1)
Pregnancy	21 (16.1)
Chronic smoking	14 (10.7)
Diabetes mellitus	12 (9.2)
Hypertension	11 (8.4)
Tuberculosis history	10 (7.7)
Chronic kidney disease	5 (3.8)
COPD	5 (3.8)
Seropositive (HIV)	4 (3)
Autoimmune conditions	4 (3)

COPD: Chronic obstructive pulmonary disease

hemorrhage in 50 out of 130 cases (38.5%), ARDS in 43 out of 130 cases (33%), pneumonia in 19 out of 130 cases (15.3%), pulmonary edema in 17 out of 130 cases (13%), fibrocavitatory lesion in 12 out of 130 cases (9.2%), tubercles in 10 out of 130 cases (7.7%), and bronchiectasis and lung abscess each in 2 out of 130 cases (1.5%).

On microscopic examination of pleura, it was thickened fibrotically in majority. On microscopic examination of the lung parenchyma, hyaline membrane was one of the most common findings [Table 4]. DAD-specific findings such as hyaline membrane and intra-alveolar fibrin were often seen in an overlapping manner based on the stage of pathogenesis. On microscopic examination of other organs for significant pathological findings, acute tubular necrosis in kidney was seen most commonly [Table 5].

Table 3: Major clinical diagnosis (*n*=120) (since 10 cases were brought dead)

Clinical diagnosis	Total cases, *n* (%)
ARDS	50 (41.6)
Pneumonia	24 (20)
Sepsis	28 (23.3)
AFI (unknown reason)	20 (17)
AKI	17 (14.1)
Hepatic encephalopathy	16 (13.3)
Hepatitis	14 (11.7)
Acute gastroenteritis	7 (5.8)

AKI: Acute kidney injury, ARDS: Acute respiratory distress syndrome, AFI: Acute febrile illness

Table 4: Notable microscopic findings (*n*=130)

Microscopic findings	Total cases, *n* (%)
Hyaline membrane	110 (84.6)
Intrapulmonary hemorrhage	99 (76.1)
Pulmonary edema	98 (75.3)
Intra-alveolar fibrin	72 (55.3)
Bronchopneumonia	47 (36.2)
Fibrin thrombi	41 (31.5)
Type 2 pneumocyte hyperplasia	12 (9.2)
Epithelioid cell granuloma and caseous necrosis	10 (7.7)
Bacterial colonies	10 (7.7)

Table 5: Significant findings in other organs (*n*=130)

Pathological findings	Total cases, *n* (%)
ATN	24 (18.5)
Fatty liver	20 (15.4)
Hepatic necrosis	14 (10.8)
Pyelonephritis	10 (8.4)
Glomerulosclerosis	10 (8.4)
Tubulointerstitial nephritis	6 (4.6)
Perforation peritonitis	5 (3.8)
Massive cerebral edema	5 (3.8)
Hepatitis	5 (3.8)
Cirrhosis	4 (3)
Kidney tuberculosis	4 (3)
Old healed infarct	4 (3)
Acute coronary insufficiency	4 (3)
Myocarditis	4 (3)

ATN: Acute tubular necrosis

On summarizing all the data, infectious predisposing conditions for ARDS and noninfectious predisposing conditions were seen in 87 out of 130 cases (67%) and 43 out of 130 cases (33%), respectively. Infectious conditions both of known and unknown etiologies accounted for around 48 out of 87 cases (55.1%) and 58 out of 87 cases (66.6%), respectively. Among known infectious conditions, tuberculosis was most common, 18 out of 48 cases (37.5%). Other infectious etiologies were leptospirosis and adenovirus (4 out of 48 cases each); dengue virus, candida, and hepatitis E (3 out of 48 cases each); malaria and typhoid (2 out of 48 cases each); and finally, one case of *klebsiella pneumoniae*, cytomegalovirus, and swine flu virus (H1N1) each.

DISCUSSION

The prevalence calculated for ARDS in the present study was 6.05%, while a similar study by Sachdev and Pandit had a prevalence of 3.15%.[2] The difference occurred because the present study was exclusively done on adult autopsies while the study by Sachdev and Pandit included both adult and pediatric autopsies.[2] The studies done by Estenssoro *et al*. and Singh *et al*. reported a prevalence of 6.8% and 7.4%, respectively.[3,4] Both the above studies were prospective and carried out over a period of 1 year and included exclusively patients of intensive care unit.

In the present study, the mean age was 38.93 ± 15.29 years; almost similar mean age was seen in the study by Magazine *et al*., 42.92 ± 13.91 years; both the studies were performed on adult population.[5] There were other Indian studies with a similar mean age like 37.9 years and 39.2 ± 2.5 years by Bhadade *et al*. and Vigg *et al*., respectively.[6,7] However, studies carried in the United States of America by Rubenfeld *et al*. and Sheu *et al*. had a mean age of 60.6 years and 60 years, respectively.[8,9] The mean age is less in Indian studies due to higher incidence of tropical and vector-borne infections.

The main clinical symptoms seen in the present study were fever (71%, n = 93/130) and breathlessness (54.6%, n = 71/130). The study by Sachdev and Pandit also showed a predominance of symptoms like fever (68.6%) followed by breathlessness (60.8%).[2] Other studies by Schell-Chaple *et al*. also had fever (65%) as one of the most predominant symptoms in the early days of ARDS onset.[10]

The present study had some associations with clinical conditions such as chronic alcoholism and pregnancy (16.1%, n = 21/130 each) followed by chronic smoking (10.7%, n = 14/130). A retrospective study from the United States showed an association of 7% between chronic alcoholism and ARDS.[11] Other studies by Magazine *et al*. and Calfee *et al*. showed an association of 14% and 19% with chronic alcoholism, respectively.[5,12] Similarly for smoking, studies by Magazine *et al*. and Calfee *et al*. showed an association of 15.3% and 36%,

respectively.[5,12] The variation is due to the fact that the history of alcoholism and smoking is given by the patient or its relatives, so there are high chances of getting a biased information. It has also been seen that smoking and alcohol have a superadded effect when both coexist due to increased free radical effect.[5,12] The present study also had an association with pregnancy 16.1%; a similar study done in the United States by Rush *et al*. showed an association of 9% with pregnant females.[13] The increased prevalence of ARDS in pregnancy among Indians could be attributed to the fact that a large population still living in a rural setup where there is less access to both basic medical and intensive care facilities which is further compounded by the prevailing unhygienic practices, malnutrition and tropical infections.

In the present study, ARDS was diagnosed clinically in 41.6% (n = 50/120) of cases which turned out to be DAD on light microscopy. Other studies where ARDS was diagnosed clinically and DAD was present on histopathology were by Lorente *et al*. showing an association of 34.3%.[14] The study by Lorente *et al*. was done exclusively on deaths in an intensive care unit, thus their prevalence was less comparatively.[14] Other studies by Lorente *et al*. and Pinheiro *et al*. found a correlation of 48% and 50% between clinical diagnosis and histological examination, respectively.[14,15] In the present study, we also found a clinical diagnosis of acute febrile illness (AFI) of unknown etiology in 17% (n = 20/120) of cases. Similarly, the study by Bhadade *et al*. reported AFI of unknown cause in 27% of cases.[6] Due to decreased hospital stay in most, proper workup was not done.

In the present study, 58.8% (n = 60/103) of cases had thrombocytopenia; the study done by Sachdev and Pandit found thrombocytopenia in 65.6% of cases.[2] Among other coagulation parameters available, prothrombin time (PT) was found to be raised in some 82.7% cases in present study (n=24/29), similar finding was also seen in the study by Sachdev *et al*.[2] In the present study, an association between ARDS and renal disease was seen in 17.9% of cases. The study done by Darmon *et al*. found an association with renal disease of 10.4%.[16] Total counts were increased in 52.9% (n = 54/102) of cases in the present study. The study done by Wanahita *et al*. based on conditions associated with increased total counts found an association with ARDS of 29% of cases.[17] This discrepancy is because the present study was exclusively done on ARDS while the latter was done exclusively on patients with high counts. High counts indicate that infections are one of the most important predisposing factors for ARDS.

The lungs on gross examination were mostly boggy voluminous, and the cut surface had a characteristic angry red-looking congested appearance [Figure 1], thus making an impression based on gross examination was difficult. In only 33% (n = 43/130) of cases, it correlated with DAD on microscopy, while it was often misdiagnosed for intrapulmonary hemorrhage (38.5%, n = 50/130).

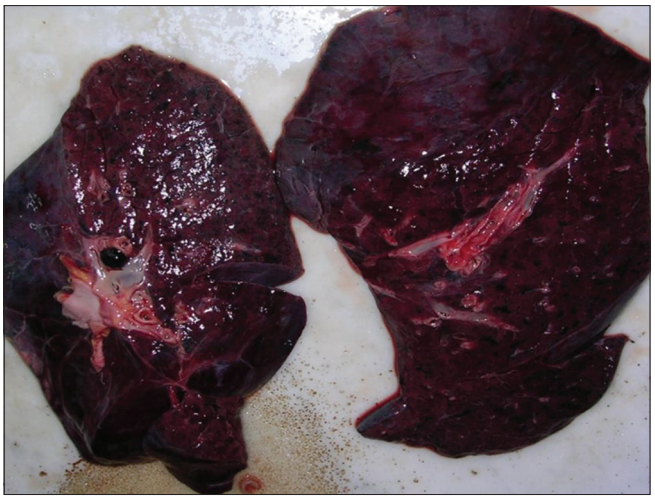

Figure 1: Lungs on gross (fresh state) – Angry red looking

Another common mimic for ARDS on gross examination is bronchopneumonia. The study by Sachdev and Pandit also showed a predominance of bilateral hemorrhagic consolidation on gross examination in most cases.[2]

On lung microscopy, hyaline membrane [Figure 2] alone was seen in 47.7% (n = 62/130) of cases, hyaline membrane with intra-alveolar fibrin in 36.9% (n = 48/130) of cases, and only intra-alveolar fibrin in 15.4% (n = 20/130) of cases. Most cases in the present study were in the exudative phase. The study by Sachdev and Pandit also showed hyaline membrane (94.4%) as the most common finding.[2] Like the present study, Sachdev and Pandit and Thille *et al*. also found most cases in exudative phase.[2,18] There is no clear demarcation between each and every phase of ARDS, and they often overlap. Thus, there always lies an interobserver variability.

The acute exudative phase of ARDS/ALI is seen in the 1st week from the day of insult, and the most characteristic feature of this phase is the hyaline membrane. The exudative phase is followed by the proliferative phase [Figure 3], characterized by fibroblast proliferation and fibrin deposition within the alveolar space along with Type 2 pneumocyte hyperplasia and hyaline membrane at the verge of disappearance. In the present study, we found Type 2 pneumocyte hyperplasia in 9.2% (n = 12/130) of cases; similarly, the study by Beasley *et al*. also noted reactive Type 2 pneumocyte hyperplasia as a minor feature in the initial days postinsult.[19] After the proliferative phase, there are two possibilities either complete resolution or else fibrosis. These findings are least common at autopsy, since by this time, most of the patients are cured. In the present study, we found bronchopneumonia in 36.2% (n = 47/130) of cases along with ARDS, and in the study by Soeiro Ade *et al*., they found an association with bronchopneumonia in 33.9% of cases.[20] Other common lung pathologies often seen in association with ARDS included pulmonary

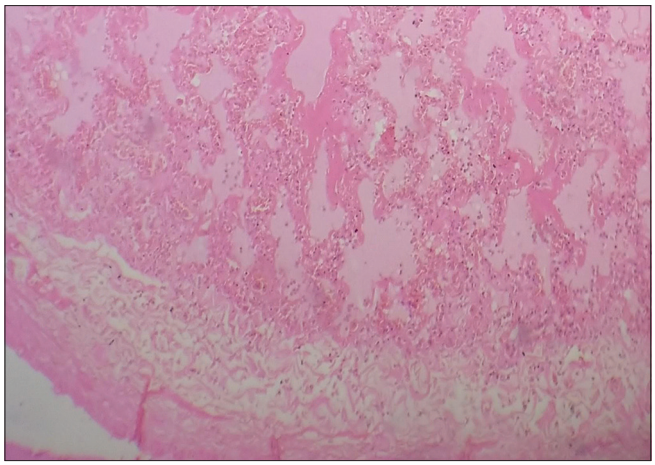

Figure 2: Pulmonary edema with hyaline membrane, ×100 view

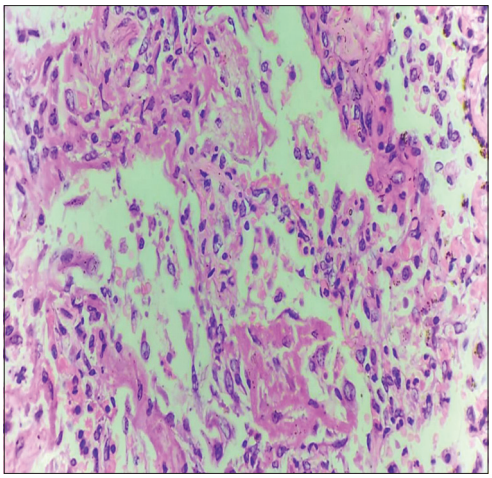

Figure 3: Fibrin balls within alveolar spaces, ×400 view

tuberculosis; in the present study, we found an association of 9.2% (n = 12/130). The study by Raina *et al*. had an association with pulmonary tuberculosis in 3.6% of cases.[21] The variation is due to the increased prevalence of tuberculosis among Indians.

After compiling everything, the underlying conditions for ARDS included both infectious and noninfectious etiologies. In 67% (n = 87/130) of cases, there were some kinds of predisposing infections. Although in many, the underlying pathogen was not elicited due to inadequate work-up. Due to lack of culture studies in many, the exact pathogen was unknown among infection-related cases. Similar predilection toward infective conditions was also seen on histopathology of other organs.

In the present study among bacterial infections, tuberculosis (37.5%, n = 18/48) was most common followed by leptospirosis (8.3%, n = 4/48). Pulmonary manifestation in Weil's disease ranges from marked intrapulmonary hemorrhage to severe respiratory failure; similarly, in the present study, all such individuals had massive intrapulmonary hemorrhage on histopathology. Other studies by Ittyachen *et al*. found an association of leptospirosis with ARDS of 2%.[22]

Among the different known causes of viral etiologies in the present study, adenovirus (8.3%, n = 4/48), HIV (8.3%, n = 4/48), hepatitis E infection in pregnant females (6.25%, n = 3/48), and dengue (NS1 antigen) (6.25%, n = 3/48) were the most predominant ones. The study by Cha *et al*. found an association between ARDS and adenoviral pneumonia of 63% (n = 12).[23] The study by Nirappil *et al*. found an association of 22% with HIV-positive individuals.[24] In the study by Mohamed *et al*., they found an association of ARDS in dengue-positive patients of 16%.[25] The reason for discrepancy of the above studies with the present study was since the above studies were done exclusively on adenovirus, HIV, and dengue-infected individuals, respectively.

Among parasitic infections, *Plasmodium vivax* was most common in the present study (4.1%, n = 2/48). Other studies like by Naha *et al*. and Sharma and Khanduri found an association of 1.88% and 1.35%, respectively, with *P. vivax*.[26,27]

CONCLUSION

Infectious etiologies contributed the most in the development of ARDS and often ARDS when diagnosed clinically may not show the features of DAD on histology.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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