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TO STUDY THE LONG-TERM OUTCOMES OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME INTENSIVE CARE UNITS IN A TERTIARY CARE HOSPITAL IN SOUTH TAMILNADU

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ABSTRACT :

Background: Acute Respiratory Distress Syndrome (A.R.D.S.), a syndrome described more than 50 years ago by Ashbough was a disease entity that has gain significant prominence over the past few years. Acute Respiratory Distress Syndrome as a term was first coined 50 years ago by Dr. Ashbaugh and his colleagues. He had initially described a case series of 12 patients who had tachypnea, with refractory hypoxemia and bilateral opacities seen on a chest radiograph

Aim: To determine 6 months outcomes of patients with A.R.D.S.To determine the mortality of patients with A.R.D.S., 6 months after discharge.To calculate the percentage of patients with A.R.D.S. who return to work in the study period.

Results: In our study population, 44.5% of patients were given steroids during their course of stay. The benefit of steroids in A.R.D.S is still an area of uncertainty. However its use was associated with a lower distance walked in the 6 minute walk test at 3 months,

Conclusion:

Patients with A.R.D.S. at 6 months had a mortality of 5 % and residual morbidity in terms of spirometry abnormalities and a lower walking distance than predicted in the 6- minute walk test. The disease was also associated with significant direct and indirect expenditure.

Keywords: OPC poisoning,Hypokalemia,mechanical ventilation,

INTRODUCTION:

Acute Respiratory Distress Syndrome (A.R.D.S.), a syndrome described more than 50 years ago by Ashbough was a disease entity that has gain significant prominence over the past few years. In the past, there were very few survivors with a paucity of strategies to combat the severe respiratory failure. However, over the past few decades, and thanks to the work of many researchers into this illness, there has been a drastic improvement in mortality of patients with A.R.D.S. This is in part due to the use of newer ventilatory strategies, such as a low tidal volume ventilation strategy and other improvements in intensive care. Though there is still scope for research into further improving the short-term outcomes, due to the increased population of survivors, the long-term effects of the

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illness are slowly coming to light.

A large cohort study done in a western population noted significant morbidity in survivors even up to 5 years after the illness. However, we have almost no data on the same in India and risk factors for these long term sequalae are yet to be clearly defined. As the first step to tackling any problem is to identify it, we decided to follow up our patients who had survived this illness. This study was done to assess the clinical profile, long term mortality, abnormalities in pulmonary function on spirometry, exertional capacity and overall economic burden of patients with acute respiratory distress syndrome admitted in the intensive care units and general medicine wards.

The entity we now call Acute Respiratory Distress Syndrome has existed far before the term was coined in 1967.One of the earliest descriptions was given by Dr. René Laennec, who after inventing the stethoscope, described a condition of pulmonary edema without heart failure in 1816. A condition which at the time, was almost universally fatal.(1) Multiple names have been used for the term since then including shock lung, respiratory lung, double pneumonia and so on.

Acute Respiratory Distress Syndrome as a term was first coined 50 years ago by Dr. Ashbaugh and his colleagues. He had initially described a case series of 12 patients who had tachypnea, with refractory hypoxemia and bilateral opacities seen on a chest radiograph. It was again associated with a high mortality and there were no clear outlines for diagnosis or treatment. He described a variety of causes, from severe infections to burns which gave rise to this disease.

Now in 2017 a considerable amount of progress has been made regarding A.R.D.S.(2), with new definitions, management strategies and information regarding short term outcomes. Though the complex pathophysiology is not yet fully understood, the benefits of this knowledge are clearly seen in the change in mortality due to A.R.D.S, as seen in a large epidemiological study by Cochi et all in the U.S.A. The mortality rate was noted to decrease from 5.01 to 2.82 per 100,000 person years between the time frames of 1999 to 2013.

AIM AND OBJECTIVES OF THE STUDY:

To study the long term physical and quality of life outcomes of patients with Acute Respiratory Distress Syndrome who are admitted to the medical intensive care unit and Emergency medicine opd and in a tertiary care hospital in South India.

- To determine 6 months outcomes of patients with A.R.D.S.

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- To determine the mortality of patients with A.R.D.S., 6 months after discharge
- To calculate the percentage of patients with A.R.D.S. who return to work in the study period.
- To determine the direct medical costs (hospital bill including medicines) as well as the indirect costs (wages lost during hospitalization as well as time to return to work)
- To assess the quality of life reported by the patients after an episode of A.R.D.S 6 months after discharge.
- To identify risk factors that may predict mortality and morbidity.
- To assess the average distance walked on a the 6-minute walk test and outcomes of spirometry in survivors of A.R.D.S., 6 months after illness.

MATERIALS AND METHODS:

This study was conducted in the sree mookambika college of medical sciences University Teaching Institute in south India. However only patients from South India admitted under the medical units and emergency medicine ward were included in the study. This was for ease of follow up and to minimize loss to follow up.Patients presenting to the emergency department or admitted into the intensive care unit or in medical wards were screened for recruitment in the study. The following were the inclusion and exclusion criteria.

Inclusion Criteria are All patients satisfying the Berlin definition of A.R.D.S,Patients informed consent is necessary,Patients should be older than 16 years of age,All eligible patients were recruited consecutively during the study period. Exclusion criteria:Patients not consenting for follow up.

Primary Outcome is To determine the 6 months outcomes of patients with A.R.D.S Secondary Outcomes are To determine the mortality of patients with A.R.D.S., 6 months after discharge,To calculate the percentage of patients with A.R.D.S. who return to work in the study period,To determine the direct medical costs (hospital bill including medicines) as well as the indirect costs (wages lost during hospitalization as well as time to return to work),To assess the quality of life reported by the patients after an episode of A.R.D.S 6 months after discharge,To identify risk factors that may predict mortality and morbidity,To assess the average distance walked on a 6-minute walk test and outcomes of spirometry in survivors of A.R.D.S., 6 months after illness

The data was collected from the patient or patient’s relative if the patient was unable to furnish the necessary information by direct and telephonic interview using the standard Clinical Research Form (CRF) designed for this study (Annexure 11.3) by the principal investigator. Some of the required data required was collected from the electronic health records of the hospital (Clinical Workstation, Version; Christian Medical College) Department of Computerized Hospital Information Processing Services).

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Baseline demographics data included age, gender, hospital number, source of admission, date of admission and discharge, duration of hospitalization, education, occupation, dependency for activities of daily living, income and socioeconomic class- Modified Kuppuswamy socioeconomic scale (Annexure 11.8). Other patient variables including co-morbidities, use of alcohol, smoking and use of tobacco were also collected. Disease variables included etiology of the A.R.D.S., severity of the A.R.D.S, associated hypotension, secondary infections and complication including an acute kidney injury.Treatment variables included duration of invasive and noninvasive ventilation, use and total dose of steroids, use of paralytics, prone ventilation and vasoactive medications.

Need for interventions such as dialysis, transfusions and their number needed, and tracheostomy were also recorded. The total cost of medical treatment, including medications was recorded.
At review, data on the patients 6-minute walk test and its comparison to predicted models, their spirometry function, a SF 36 quality of life questionnaire and St. George Respiratory questionnaire were all collected. Additional outcomes of loss of wages, duration to return to work and whether they returned to their original work or not was also collected at review .

Statistical analysis was done using the statistical package for social sciences (SPSS).Different statistical methods were used as appropriate. Mean ± SD was determined for quantitative data and frequency for categorical variables. The independent t- test was performed on all continuous variables. The normal distribution data was checked before any t-test. The Chi-Square test was used to analyze group difference for categorical variables.A p- value < 0.05 was considered significant.

RESULTS

Severity of A.R.D.S.:

Category	N	Percent
200-300 (Mild)	22	20.0
100-200 (Moderate)	50	46.4
<100 (Severe)	37	33.6

Most patients had Moderate severity of A.R.D.S. (46.4%). The next most common subgroup was severe (33.6%) followed by mild 20%.

Mortality of survivors of A.R.D.S.:

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The mortality at 6 months after discharge was 5%. 2 patients were reported to have passed away due to an acute coronary syndrome and a pulmonary embolism. 1 patient had a fall from stairs and later developed an intracranial bleed. One patient had a probable cerebrovascular accident with a hypertensive emergency. Another patient had a probable pneumonia 3 days after going home and passed away due to the same. One patient passed away in her sleep, with no clear cause known.

6-month Mortality of A.R.D.S. survivors in our cohort

Category	Frequency	Percent of group
200-300 (Mild) (n=22)	2	9.1%
100-200 (Moderate) (n=51)	3	5.9%
<100 (Severe) (n=37)	1	2.7%
Total (n=103)	6	5%

Quality of Life of Survivors of A.R.D.S. at 6 months

SF 36 Quality of Life Questionnaire

Category	Physical	Physical role	Emotion role	Vitality	Mental	Social	Body	General

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	functi on				healt h	Role	pain s	Healt h
Mild (n=20)	73.3+/- 22.3	78.8+/- 37.4	81.9+/- 36.6	60+/- 19.9	75.6+/- 14.8	82.2+/- 19.8	81.8+/- 17.2	63+/- 19.7
Moderate (n=45)	78+/-23	78.3+/- 36.8	90.4+/- 28.1	64.1+/- 19.6	78.1+/- 16	87.6+/- 17.6	85.4+/- 18.5	65.1+/- 16.5
Severe (n=36)	77.6+/- 22.5	66+/- 46.4	80.6+/- 37.7	64+/- 19.3	74+/- 16.4	85.5+/- 19.2	84.8+/- 20.5	66.3+/- 20.5
Total (n=10 1)	76.9+/- 22.6	74+/- 40.6	83.2+/- 33.5	63.3+/- 19.4	75.8+/- 15.9	85.8+/- 18.5	84.3+/- 18.9	65.1+/- 19

P value								
Mod/Mild	0.6	1.00	1.00	1.00	0.86	0.84	1.00	1.00 1.00 1.00
Severe/Mild	0.85	1.00	1.00	1.00	1.00	1.00	1.00	
Severe/Mod	1.00	1.00	0.59	1.00	0.75	1.00	1.00	

*The SF-36 values have component scores ranging from 0-100, with lower scores showing more disability in the component

Table 6B: St George Respiratory Questionnaire

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P value							
Mod/Mild	0.6	1.00	1.00	1.00	0.86	0.84	1.00
Severe/Mild	0.85	1.00	1.00	1.00	1.00	1.00	1.00
Severe/Mod	1.00	1.00	0.59	1.00	0.75	1.00	1.00

*The SF-36 values have component scores ranging from 0-100, with lower scores showing more disability in the component

DISCUSSION:

Acute respiratory Distress syndrome (A.R.D.S.) was a dreaded medical condition for many years, with as many as one in ten patients admitted in an ICU affected by it(9). Significant improvement in critical care and better understanding of the condition , has reduced the mortality from 60 to 25% over the last 20 years(1). The long term morbidity following A.R.D.S. is however, a growing problem, affecting patients even up to 5 years after the illness (4). A large cohort in Canada by Herridge et al has been pivotal in identifying the long-term morbidity of survivors(4). Such reports on A.R.D.S. in the Indian population is however, lacking.

Our study was a prospective cohort, of patients who developed A.R.D.S., done in a tertiary care hospital in south India. All patients that satisfied the Berlin criteria for A.R.D.S(6) were followed up after discharge for a minimum of 6 months.
The age and gender distribution of our cohort were similar to the cohort by Herridge et all. (50).Almost all patients were independent for their activities of daily living prior to illness. Being independent for activities of daily living prior to illness was one of the predictors of mortality in a prospective cohort study from Taiwan by Wang et al.(66) . It has also been associated with an impaired quality of life as reported in a quality of life questionnaire among A.R.D.S. survivors at 6 months after illness(73). This associationcould not be ascertained in our study as there were only very few patients who passed away.Our patients predominantly fell into the normal and pre-obese categories of B.M.I. A higher. B.M.I. is a possible risk factor for the development of A.R.D.S. (36). In the Canadian cohort by Herridge et al, 32% of patients were noted to have a BMI over 30, as compared to 20.8% of patients in out cohort. Obesity has been associated with an impaired quality of life among A.R.D.S. survivors at 6 months. (73) However our study found a BMI > 30 to be associated with a greater odd of return to work at 6 months.

The most common cause of A.R.D.S. in our population was infections (93%)..In the cohort by Herridge et al, infectious were the causative factors for nearly 70 % of cases.(75)This is

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similar to other studies done on A.R.D.S. in India. One study done in the Pondicherry Institute of Medical sciences noted that 67% of patients enrolled in the study had A.R.D.S. due to infectious diseases. Another epidemiological study done in a tertiary hospital in Karnataka,(20) which looked at 150 patients meeting the AECC criteria, noted that 90 % of all cases of A.R.D.S were due to infections. Probable reasons for the higher proportion of infectious etiologies in our cohort were the recruitment of patients from only medical wards, so trauma and burns related A.R.D.S. were not included. Another explanation could be the higher prevalence of endemic diseases such as scrub typhus which have a strong association with A.R.D.S.

The most common infectious etiology for A.R.D.S. in our study was pneumonia. It comprised of 44% of all cases in our cohort. This was consistent with the international cohort by Herridge et al where more than 50% of all surviving patients with A.R.D.S. were due to pneumonia.

Scrub typhus was a significant causative factor for A.R.D.S, occurring. in nearly 25% of our patients. This is similar to the Karnataka cohort where 22% of the patients also had A.R.D.S. secondary to scrub typhus.The table below shows the co-morbidities noted in our cohort compared to those seen in a tertiary Centre in Karnataka, in an epidemiological study by Magazine et al and in the Canadian cohort.

The proportion of diabetes seen in our patients was significantly higher than noted in the epidemiological study by Magazine et al. This is also higher than the average Indian prevalence of 8.8%. This is probably due to a higher likelihood of diabetics requiring hospitalization. Prior studies have shown no conclusive relationship between diabetes andA.R.D.S. Hypertension was also noted to be significantly higher among patients in our cohort than other studies in India. The reason for this is not known.

The prevalence of respiratory diseases was similar in all 3 studies. However the study by Magazine et al included all patients with A.R.D.S. , whereas ours recruited only patients who survived A.R.D.S.(76). In the cohort by Margret Herridge et all, 11% of patients were noted to have a pulmonary disease, far more than in our study. The possible reasons for this difference are the different (more infectious) etiologies in our populations and under-reporting of prior pulmonary diseases in our population.

Other complications such as hypotension and acute kidney injury as per the RIFLES criteria were common in our population affecting 53.6% and 59% of our population respectively the number of patients requiring renal replacement therapy was only 4.6% of our cohort compared to 13% in the Canadian cohort.Health care associated infections were also noted to be common, seen in 22.7% of our population. Comparative data with the Canadian cohort was not available.

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Though noted to be of benefit in patients with severe A.R.D.S. in conjunction with prone ventilation, paralytics were used in only 2 patients with severe A.R.D.S. in our study,(77), In the study by Herridge et all , use of paralytics was associated with a lower distance walked in the 6-minute walk test at 6 months, and 60% of survivors had history of paralytic use during admission. This may be one of the reasons for the better 6-minute walk test in our cohort though

In our study population, 44.5% of patients were given steroids during their course of stay. The benefit of steroids in A.R.D.S is still an area of uncertainty. However its use was associated with a lower distance walked in the 6 minute walk test at 3 months, but not at 6 months in the cohort by Herridge et all.(50). The percentage of patients who received steroids in the Canadian cohort was 36%, lower than that of our population.

We classified patients into 3 groups based on the severity of their A.R.D.S. as per the Berlin criteria(6). Most patients belonged to the moderate group. This is similar to the distribution of patients in many observational studies and as described in the studies used to describe the BERLIN definition.(6). We analyzed all patients based on their outcomes to see if severity of A.R.D.S. had any long term bearing in morbidity and mortality.
There was no comparative data for the distribution of patients based on the BERLIN definition of severity in the Canadian cohort.

With regards to mortality, 2 patients in the mild A.R.D.S. group, 3 from the moderate group and 1 from the severe group died after discharge within the study period (Patients who died during hospital admission were excluded from the study). The 6-month mortality was 5% and there was no statistically significant difference between patients with different severity of A.R.D.S.
In the study by Herridge et all, which had followed up the patient cohort to 5 years. In the first year, the one-year mortality was 11% among survivors of A.R.D.S. The mortality appears to be slightly higher than that noted in our cohort. As the mortality rate in our cohort was very low, Factors associated with an increased mortality in our study could not be assessedhigher mortality was most likely due to the higher number of co-existing illness.

In the Taiwan study a one-year mortality of nearly 41% was noted after discharge, for survivors of A.R.D.S(66). However, more than half of the study population had malignancies. Other co-morbidities such as pulmonary disease (34%), cirrhosis (12%), Heart failure (15%) and chronic kidney disease (25%) were far higher than the prevalence in our cohort. As they concluded, co-morbidities were the highest predictor of mortality , with most of the deaths in the study being due to cancer related causes.(66)

With regards to return to work, 88.9% of participants who were previously in an earning occupation had returned to work in our study. This held true for all severities of A.R.D.S.

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with no significant statistical differences between each group. This was different from the numbers seen in the cohort by Herridge et al where only 32% of patients had returned by 6 months and 49% by 1 year.

The return to work rate was far higher in our population than in the Canadian cohort. This can possibly be explained by the more pressing need to return to work due to the significant costs of the hospitalization and overall lower income in our population.
Another explanation may be due to the difference in baseline characteristics, with patients in the Canadian cohort having longer hospitalizations, duration of ventilation, co-morbidities and complications such as tracheostomy which may delay early return to work.(67)

With regards to the 6-minute walk test, patients in our cohort were noted to walk a mean distance of 415mts, and around 71% of the percentage predicted for height, weight and age. There were significant inter group differences between severity of A.R.D.S., with patients in the moderate group walking less than those in the mild and severe group. The difference between groups cannot be clearly explained, as walk test distance is less in the moderate group when compared to the mild and severe group. Thus the difference may be due to other confounders . (50).
When comparing our results to those of Herridge et al, the mean distance walked in the Canadian cohort was less than that observed in our cohort, with patients only able to walk 390mts or 64% of the value predicted for their height, weight and age at 6 months. This difference may be due to the higher number of patients with co-morbidities, longer duration of ventilation and complications in the Canadian group which may have led to the slower recovery.

The walk test in the Canadian cohort was noted to significantly improve until one year and increase only slightly more after that to 76% of the predicted distance at 5 years. Unfortunately, standardized values for the 6-minute walk test in our population is still not yet available. Though values for changes in the walk test which have clinical significance have been established in COPD and ILD, similar values are not available in A.R.D.S.(48,78) The exact degree of impairment compared to the normal population is difficult to assess without normative data. This data can, however, be used for further follow up to asses for improvements.

With regards to spirometry, in the Canadian cohort, the values of FEV1 were only 75% of normal at 3 months but reached normal values (80%) by 6 months. The total lung capacity remained at 92 % of normal and spirometry abnormalities had resolved to normal or near normal values in the 6 month follow up.(50).In our cohort as well, mean spirometry

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values were near normal by 6 months. There was no significant difference in spirometry values between patients with different severity of A.R.D.S. Of the 78 patients who underwent spirometry at 6 months, 44% had a completely normal spirometry, 14% had values suggestive of an obstructive disease ,39% a reduced FVC indicating a possible restrictive disease and 3% a low MMEF suggestive of a possible small airway disease. Most impairments however were only mild to moderate in severity (86.4%). 5 patients were unable to do a spirometry at 6 months.The high prevalence of a reduced FVC may indicate a pulmonary restrictive disease due to fibrosis or an extra-pulmonary weakness as was previously suggested in the Canadian cohort.(4,79) The spirometry outcomes have been co-related with impairment in the quality of life questionnaire on other studies.(79)

With regards to the quality of life questionnaire, on being asked the SF 36, patients in our cohort reported impairment in the domains of physical function, vitality, mental health and general health at 6 months. The impairment reported was less than that noted in the Canadian cohort, though difference in ethnicity makes the difference harder to interpret. Also, the more significant co-morbidities and longer ventilation and tracheostomy could also be the cause for the difference.
Unfortunately, official normative data was not available for our population, making interpretation of these differences difficult, though the data can be used for comparison with future follow ups.
The St. George Respiratory Questionnaire also showed disability in all domains. This was greater than that seen in normal healthy subjects without respiratory disease based on healthy populations in Spain.(80)
Normative data for the Indian population is not currently established in India.The data from this questionnaire, like those of the SF 36, will be useful for future follow up.

With regards to overall costs of the illness, there were significant differences in the cost of hospital bills and medications among all groups in our cohort. With regards to indirect costs, there was no statistically significant difference between groups. This was as expected since the severity of A.R.D.S. was not noticed to co-relate with time to return to work. Our median costs were a hospital bill of ₹ 154,870 (101,720-154,870), medication bills of ₹ 42,780 (27,070-87,080) and loss of wages of ₹ 30,000 (10,000-60,000). This resulted in a total cost of ₹ 231,450 (146,430-387,300). We have not included the costs of accommodation and food in this study, though a prior study done on our hospital on patients with heart failure, which had a mean hospital stay of 8.79 +/- 6.5, noted that the median costs of food was ₹2000 (1000-5000) and accommodation ₹2,500.00 ₹775-₹5,000 . The difference in costs with varying severity of A.R.D.S. is expected as those who have a more severe illness are more critically ill, with a higher mortality and are more likely to require rescue measures like neuromuscular blockade, frequent arterial blood gas

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monitoring, etc.

Ours is to the best of our knowledge, the first Indian study to look at the overall economic impact of A.R.D.S. As noted, there were significant direct and indirect costs for an admission of A.R.D.S. with median total costs of ₹ 231,450, excluding those of food and accommodation. When most families on our study have and income between ₹ 6478 - ₹ 10795 per month, the health care costs associated with this illness are substantial. This along with the fact that most patients used out of pocket payments rather than any form of insurance, adds to the burden of the disease on the family. The WHO defines catastrophic health expenditure as those whose costs are more than 40% of a family non subsistence income. In our population, 78% off households had an annual income of ₹ 2,059,092 which was less than the median costs of a single admission of A.R.D.S., making it a catastrophic health expenditure.

CONCLUSION:

Patients with A.R.D.S. at 6 months had a mortality of 5 % and residual morbidity in terms of spirometry abnormalities and a lower walking distance than predicted in the 6- minute walk test. The disease was also associated with significant direct and indirect expenditure.A.R.D.S. survivors reported impairment in the domains of physical function, vitality, mental health and general health at 6 months the SF-36 quality of life questionnaires and all components of the St. George Respiratory Questionnaire.

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