The Egyptian Journal of Hospital Medicine (July 2017) Vol.68 (3), Page 1533-1540

The Impact of Comorbidities on the Outcome of Tuberculous Patient in Respiratory Intensive Care Unit

Mona Mansour Ahmad[1], Hossam EL Dien M Abdel-Hamid[1], Marwa Hassan AL Makawy[2]
1 Chest Department, Ain Shams University Hospital, 2 Abbassia Chest Hospital, Cairo, Egypt

ABSTRACT

Aim of the work: there are limited data regarding active pulmonary tuberculosis (APTB) patients requiring ICU admission. This study aimed to determine the mortality rate and risk factors associated with TB patients with comorbidities requiring respiratory intensive care unit (RICU) admission**. Patients and methods:** a combined retrospective-prospective study was conducted from November 2014 to October 2016 and from November 2016 to April 2017 on adult patients with APTB admit to the RICU of Abbassia Chest Hospital for a period of more than 24 h. Demographic, clinical and therapeutics characteristics as well as outcome (RICU morality) were obtained from the medical records. **Results:** in this study a total of 43 patients were considered (median age 45 years for non survived patients and 36 years for survived patients). The RICU morality rate was 81.4%. Respiratory failure was the most common cause of admission to RICU 37,2% (16 patient). Mechanical ventilation (MV) was needed in 69.8% of patients (30 patients). Death rate in the diabetic patients was14.29%, in patients with renal disease it was 20% , in case of HIVit was 17.14% and in case of malignancy it was 8.57%.There was highly significant mortality rate accompanying LCF and the ratio was 31.43%,in case of respiratory failure type II it was 94.28% and in mechanical ventilation it was 80%. Non survived patients had high significant APACHE SCORE 21.4±6.2 and the main cause of death was mainly ventilatory 80%(28 patients).

Conclusion: the present study showed a very high mortality rate among TB patients with comorbidities requiring respiratory intensive care unit (RICU) admission and identified associated co morbidities, risk factors and a predictor of RICU mortality.

Keywords: active pulmonary tuberculosis, mortality, respiratory intensive care unit, co morbidities.

INTRODUCTION

According to the World Health Organization, more than 2 billion people (one third of the world's population) are currently infected with the tuberculosis (TB)bacillus , it continues to be a leading cause of burden and death among infectious diseases worldwide **(1).**

Several non-communicable diseases (NCDs), such as DM, alcohol use disorders and smoking-related conditions, are responsible for a significant proportion of TB cases **(2).** NCDs may complicate treatment and management of TB, due to clinical challenges (e.g. among people with DM) as well as behavioral challenges (e.g. among people with alcohol use disorders) **(1).** Smoking also affects the chance of cure from TB. Severity of TB at the time of diagnosis and risk of relapse has been linked to smoking. In addition, few studies have been found that smokers have a higher risk of death from TB and other poor treatment outcomes than nonsmokers **(3).**

Nicotine is hypothesized to act directly on nicotinic acetylcholine receptors on macrophages to decrease intracellular tumor necrosis factor-α production and, thus, impair intracellular killing of M. tuberculosis **(4).**There is an evidence that DM leads to delay culture conversion **(5)**and that the risk of death during TB treatment is increased **(6)** as the risk of relapse **(7).**

The association between silicosis and pulmonary TB has been well documented. Silicosis is caused by the inhalation of crystalline silica particles, almost always due to occupational environments, including mining, sandblasting, quarrying, ceramic working and iron smelting**(8)**, but silicosis and silica dust exposure are not deemed risk factors for relapse or re-infection**(9).**

Low BMI at the time of diagnosis has also been linked to risk of treatment failure, death during TB treatment and relapse **(10).** Other chronic conditions, such as autoimmune and systematic disorders, chronic renal failure, liver failure, certain malignancies and wide range of immune-suppressant treatments, are also associated with TB (11).

PATIENTS AND METHODS

This is a retrospective-prospective study design started in October 2016 in which adult patients (> 16 years) with active pulmonary TB previously or subsequently admitted to the respiratory ICU (RICU) of Abbassia Chest Hospital between november 2014 to October 2016 (retrospective part) and between November 2016 to April 2017 (prospective part). Patients who stayed at RICU less than 24 hours or presenting with inactive pulmonary TB or extra pulmonary TB were excluded. The Abbassia Chest Hospital is a special, tertiary care hospital with 600-bed

Received: 11 / 6 /2017 DOI: 10.12816/0039700
Accepted: 20 / 6 /2017

occupancy in which 100 of them for TB, 32 ICU beds; 3 of them were isolated for active pulmonary TB.TB treatment in the hospital is according to WHO and national guidelines [12].

The following data were obtained from the medical records:

- **Demographic characteristics:**

o Age, sex, special habits of medical importance (smoking and drug addiction) and comorbidities.

- **Stain for acid fast.**
- **Tuberculin test.**
- **Radiological features:**

o Unilateral or bilateral lung infiltration

- **Mechanical ventilation:**

o The need and outcome of mechanical ventilation was recorded.

- **Respiratory failure and multiple organ failure occurrences.**
- **Scores:**

o APACHE II (Acute Physiology and Chronic Health Evaluation) score and Glasgow coma score.

- **RICU stay:**

o Causes, type of admission (early or late), length of stay and recorded complications during RICU stay.

- **Laboratory investigations on admission:**

White cell count, hemoglobin, coagulation profile, liver and renal function tests, electrolytes and arterial blood gas analysis.

The study was done after approval of ethical board of Ain Shams university.

Statistical analysis

The collected data were coded, tabulated and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 18.0.

Descriptive statistics were done for numerical parametric data as mean±SD (standard deviation) and minimum and maximum of the range and for numerical non parametric data as median and 1st& 3rd inter-quartile range, while they were done for categorical data as number and percentage..

Inferential analysis was done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non parametric data. Inferential analysis was done for qualitative data using Chi square test for independent variables. The level of significance at P value < 0.050 was considered significant, otherwise is not significant. P-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

RESULTS

A total of 43 patients were included during this study period from November 2014 to April 2017. 35 of 43 stud

ied patients (81.4%) died in RICU.

Demographic characteristics

The baseline demographic characteristics are shown at tables below.

Table 1: showing the median age of servivors and non servivors.

Variable	Outcome	N	%	Mean	SD	Min	Median	Max
Age	**Died**	35	81.4	45.51	17.72	19	45	77
	Discharged	8	18.6	41	16.82	22	36	62

Table1showed that the median age of servivors was 36 and non servivors was 45.

Table2: showing the sex, marital status, smoking and addiction status of survivors and non survivors.

Variable	Sub variable	Frequency	Percent %
Sex	**Male**	**34**	**79.1**
	Female	**9**	**20.9**
Marital status	**Single**	**13**	**30.2**
	Married	**25**	**58.1**
	Other	**5**	**11.6**
Smoking status	**Smoker**	**28**	**65.1**
	Non smoker	**15**	**34.9**
Addiction status	**IV**	**4**	**9.3**
	Tablet	**2**	**4.7**
	Hashish	**2**	**4.7**
	Many	**1**	**2.3**
	No	**34**	**79.1**

Table 2 showed that 79.1% of patients were male, 58.1% married, 65.1%, smokers and the majority were not addict (79.1%) .

Table 3: showing the proportions of co morbidities of the patients.

Variable	Sub groups	Frequency	Percent
DM	Yes	8	18.6
	No	35	81.4
IHD	Yes	9	20.9
	No	34	79.1
RF	Yes	8	18.6
	No	35	81.4
CLD	Yes	11	25.6
	No	32	74.4
HIV	Positive	8	18.6
	Negative	35	81.4
HCV	Positive	6	14.0
	Negative	37	86.0
Malignancy	Positive	3	7.0
	Negative	40	93.0

Table 3 showed the co morbidities of the patients. There were 18.6 % DM, 20.9 % IHD, 18.6% RF, 25.6 % CLD, 9.3 %, 18.6 % positive HIV patients, 14% positive HCV and 7% had malignancy.

Clinical characteristics

The clinical characteristics include causes of ICU admission, need to mechanical ventilation, respiratory failure, co morbidities accompanying non survivals, cause of death and predictors of death.

Table 4: showing the mortality rate of cases, causes of ICU admission and mechanical ventilation use.

Variable	Sub variable	Frequency	Percent
Causes of ICU admission	Ventilatory	16	37.2
	Circulatory	7	16.3
	Metabolic	8	18.6
	Many	12	27.9
Mechanical Ventilation use	Mechanically Ventilated	30	69.8
	Not mechanically ventilated	13	30.2
Outcome	Died	35	81.4
	Discharged	8	18.6

Table 4 showed that the mortality rate of the cases was 81.4%, the majority of patients 37 % admitted for ventilator cases and 18.6 % for metabolic one, 69.8% were mechanically ventilated.

Table 5: showing a comparison between the outcomes of the studied groups as regarding the co-morbidities.

Variables			Died	Discharged	P	Sig.
DM	No	N	30	5	0.15	Not sig.
		%	69.77	11.63		
	Yes	N	5	3		
		%	11.63	6.98		
	All	N	35	8		
		%	81.4	18.6		
IHD	No	N	29	5	0.33	Not sig.
		%	67.44	11.63		
	Yes	N	6	3		
		%	13.95	6.98		
	All	N	35	8		
		%	81.4	18.6		
RF	No	N	28	7	1	Not sig.
		%	65.12	16.28		
	Yes	N	7	1		
		%	16.28	2.33		
	All	N	35	8		
		%	81.4	18.6		
Hepatic F	No	N	24	8	0.021	Sig.
		%	55.81	18.6		
	Yes	N	11	0		
		%	25.58	0		
	All	N	35	8		
		%	81.4	18.6		
HIV	Negative	N	29	6	0.63	Not sig.
		%	67.44	13.95		
	Positive	N	6	2		
		%	13.95	4.65		
	All	N	35	8		
		%	81.4	18.6		

Table 5 showed that data was significantly correlated as regarding hepatic failure only, while the other co morbidity showed no significant correlation with the outcome.

Table 6: showing the causes of death.

Cause of death N=35	Circulatory	Ventilatory	P
	7 (20%)	28 (80%)	<0.0001

Table 6: showed that there was a significant correlation between the ventilator related death and mortality, p <0.0001, as predictor of death.

Table 7 showing the difference between the two groups as regarding APACHE score, as predictor of death.

Variables	Outcome			P
	Died N=35	Discharged N=8	Total N=43	
APACHE (Mean±SD)	21.4±6.2	17.7±3.9	20.5±5.9	0.005*

Table7 showed a significant difference between the two groups as regarding APACHE score, as predictor of death.

Table 8: showing the mortality rates in patient with respiratory failure, as predictor of death.

Respiratory F	**Type I**	**N**	**2**	**2**	**0.15**	**Not sig.**
		%	**4.65**	**4.65**		
	Type II	**N**	**33**	**6**		
		%	**76.74**	**13.95**		
	All	**N**	**35**	**8**		
		%	**81.4**	**18.6**		

Table 8 showed high mortality rate in patient with respiratory failure type II.

DISCUSSION

Across the world, tuberculosis (TB) remains an important public health problem, especially in developing countries.Despite the availability of curative therapy, a large proportion of patients with TB are being hospitalized. In hospital mortality rates remain high, particularly among patients with TB requiring intensive care unit (ICU) [13]**.** Pulmonary TB requiring ICU care is rare accounting to 1-3% of all TB cases, but commonly known to be of markedly bad prognosis [14,15]**.** This study aimed to evaluate the retrospective-prospective basis, the mortality rate, risk factors cause of death associated with mortality among ICU patients with active pulmonary TB.The mortality rate for ICU patients with TB is difficult to compare because different definitions of estimation are used (ICU morality, in-hospital morality, 30-day and 180-day mortality) by previous studies [15- 17]**.**The RICU mortality rate in the current study in active pulmonary TB population was 81.4% ; it was considered 14.29% , 17.14% ,20% ,31.34% , 17.14%,11.43% ,8.57% in DM, IHD, RF ,LCF, , HIV, HCV, malignancy respectively. The mortality rate may be judged comparable with previous TB ICU mortality rates. The mortality rates previously studied were 38% by **Sandrine *et al,*** [18]**,** also **Erbes *et al.*** [15] found a mortality rate of 66%, while greater than 90% of their patients required mechanical ventilation. The median age of the patients in this study for discharged patients was 36 years and for non servived patients was 45, However, the median age range varied in literature from 41 to 63 years [17, 19]**.**

Sex distribution was in line with data from previous studies as male patients (34 male patient ,79.1%) were seen more often than females (9 female patient, 20.9%) [15, 17]**.** One possible explanation for this disparity might be higher exposure of males to droplet infections due to a greater prevalence of outdoor occupations. Aggravating factors such as smoking, exposure to air pollutants and industrial exposure may also predispose males to tuberculosis [17]. At the current study, there was no significant difference between survivors and non-survivors as regards patient sex.The same results are in agreementwith those of **Erbes *et al.*** [15].This discrepancy may be related to difference in disease severity, comorbidities and need for mechanical ventilation between both studies. However, **Fouda *et al.*** [20] reported that there was a significant difference between survivors and non-survivors as regards patient sex as female sex showed risk factor of mortality, but it was not a predictor of non survival.

In the current study there were 38 patients presented as a new TB case (88.4%) ,4 TB defaulter cases (9,3%) and only one MDR case (2,3%) . There was low number of MDR cases. This result is in line with the result of F**ouda *et al.*** [20] who detected only 4% TB resistant cases (2 MDR and 2 XDR cases) and only 3% of TB resistant cases had comorbidities. This may be due to the number of non involved TB cases in the current study because they were not in the current study inclusion criteria , also a number of cases died before determination of TB resistance type.

At the current study there were 19 drug addict of 43 case considering that 4 of them were intra venous drug addict , 7 were tablet addict ,6 were hashish addict ,2 of them were addict to all drugs. Drug addiction had high non significant mortality rate of 34.29%.This result is in line with the result of **Fouda *et al.*** [20] who proved a mortality rate of 24,3% and **Fremond *et al.*** [21] who proved that the epidemiologic factors are associated with injection and non-injection drug use (e.g., homelessness, incarceration) contribute to the high prevalence of TB among drug users

In the current study there were 28 smoker ; 22 of them were non survived and represented 62.8% of the mortality rate. This result is in line with the result of **Fouda *et al.*** [20] who proved a mortality rate of smoking equals to 59.5% .Cigarette smoking confers a relative risk of about 1.5 to 2.0 for the development of tuberculosis [25]**.** Smoking has been found to be associated with

both risk of relapse of TB and TB mortality. Passive smoking also increases the risk for TB [22]. Cigarette smoking, including passive smoking, has been associated consistently with an increased risk of M tuberculosis infection, subsequent disease development and poor treatment outcomes [23].

Bilateral lung infiltration non significantly affected rate of death in the current study in 46.51% of the patients and unilateral lung infiltration 53.39% and mortality rate was 80%, 82.8% respectively.A previous study of **Raquel *et al.*** [24] showed that the majority of patient presented with severe radiographic alterations; a possible reflection of a protracted disease process, however, it did not significantly impact the mortality rate. A history of pulmonary tuberculosis was associated with clinical suspicion of tuberculosis, although the radiological patterns were not associated with that suspicion [26].

The current study involved 43 patient, 41 (95.34%) of them were smear positive for acid fast bacilli with death rate 0f 94.29%. Smear negative patients were2 (4.65%) and they all died. In a previous study, pulmonary TB patients with a positive smear for AFB for M. tuberculosis presented higher mortality rates and a similar trend could be seen in those with positive cultural examination. This was also reported by **Valade *et al.*** [27], while **Silva *et al.*** [16] reported the opposite, with smear-positive sputum as a protective factor (in view of more timely diagnoses). It could be argued that there was a higher mycobacterial burden in these patients, probably representing a longer disease process. Although. There were 41 smear positive patients, but there were only 38 tuberculin positive of them; 33 patient were non survived which represent a mortality rate of 88.57%. This may be due to presence of immune compromised cases in our study , leading to a tuberculin negative result although they were smear positive. Mechanical ventilation in the current study affected rate of death significantly 80% This is the same as previous studies **(Lee *et al.*** [28]**; Erbes *et al.*** [15]**; Sandrine *et al.*** [18]**; Fouda *et al.*** [20] **)**. They showed a death rate of 83,3%, also **Levy *et al.*** [29] and **Lin *et al.*** [25] studies showed that the outcome of TB and respiratory failure requiring mechanical ventilation was poor; they reported in-hospital mortalities 33 to 67% which is nearly the same of the current study. Fatalities remain high in patients admitted to the ICU with tuberculosis, mechanical ventilation and vasopressor requirement on admission are considered predictors of death [18].Also, **Frame *et al.*** [14] evaluated the factors associated with the development of respiratory failure and the need for MV. Gram-negative pneumonia or sepsis, Chronic Obstructive Pulmonary Disease (COPD), history of poor compliance with tuberculosis treatment and cancer were predictors of respiratory failure.

The current study showed high, but non-significant death rate in the diabetic patients (14,2%). This is in agreement with the result of **Fouda *et al.*** [20]. Diabetes or even co-infection with HIV encountered in the current study as well as other studies **(Lee *et al.*** [28] **; Erbes *et al.*** [15] and **Silva *et al*.** [16] did not influence mortality rates significantly in patients with tuberculosis requiring ICU. In the present study, renal impairment was found to be a risk factor for ICU mortality (It represented 20% of mortality rate). However, it did not influence mortality rates significantly.These results are in agreement with those of **Silva *et al.*** [16]**.**

In the current study, LCF affected the death rate significantly 100% of the LCF cases died and this epresented 31.4% of the total mortality in RICU and this is the same as results of **Rajesh** and **Singh** [30] that ensured LCF patients with complications admitted in ICU have mortality rate of 69%.

HIV encountered in the current study as well as other studies **(Lee *et al.*** [28] **; Erbes *et al.*** [15] **; Silva *et al.*** [16]).They reported no significantly mortality rates in patients with tuberculosis requiring ICU. In fact, mortality in patients with TB-HIV co-infection seemed to be related to the patient's overall degree of immuno-suppression[31]**;** HIV-infected patients have been reported to be more likely to have extra pulmonary, disseminated and military tuberculosis [32]**.** In comparison with the results **Raquel *et al.***[24] who reported HIV-infected group was more likely to be admitted in the ICU for respiratory failure (73.3% versus 37.5%). In the current study co morbidities included alcohol abuse and cancer have high non significant mortality rate, however results of **Frame *et al*.** [14] and **Penner *et al.*** [13] detected that co morbidities did not impact tuberculosis mortality rate in the ICU.

As in previous studies **Tsai *et al.*** [33]**; Erbes *et al.*** [15] and **Lanoix *et al*.** [34] who stated that organ failure is negatively affecting prognosis and is associated with higher mortality rates. The need for respiratory and/or vasopressor support and the presence of acute renal failure and of multiple organ dysfunctions were associated with higher

mortality. The severity scores were significantly higher in patients that did not survive.

Co-morbidities, especially those related to immunosuppression, such as HIV infection, are considered risk factors for developing respiratory failure and requiring MV [16].**Fouda *et al.*** [20] studied that poor outcome was among group 2 having comorbidity, and it was 24.39%, mostly due to the effect of comorbid diseases which leads to change in the treatment regimen and due to poor adherence to treatment; at a previous study, four factors were independently associated with mortality: time from onset of symptoms to initiation of treatment greater than one month; number of failing organs; large number of lung lobes involved, as seen on chest X-ray and serum albumin levels greater than 20 gm/L [19].

As regard, the cause of ICU admission , pulmonary TB is a rare primary cause of acute respiratory failure (ARF)[35]. However, high mortality rates have recently been reported in patients with ARF arising from TB [28]. In the present study, respiratory failure was the most common, but non significant cause of ICU admission in 37,2% of the cases with 81.3% morality rate. This result may be due to presence of many patient admitted to ICU due to multiple causes accompanying respiratory failure which affect the result of the current study. Also, **Guy *et al.*** [36] showed that respiratory failure is a common reason for admission and death of patients with TB in an ICU. However, the leading cause of ICU admission was respiratory failure (**Lin *et al.*** [25]).

Results of the current study showed high non significent mortality rate among patients with respiratory failure typeII (94,3%). However, **Fouda *et al.*** [20] reported that type II respiratory failure was significantly more frequent in non-survivors than survivors. Also **Guy *et al.*** [36] showed that respiratory failure is a common reason for admission and death of patients with TB in ICU. The most common and significant cause of death in ICU. In the present study ventilator causes including respiratory failure and mechanical ventilation related complications were representing 80% of mortality causes, like a previous study of **Sandrine *et al.*** [18].

APACHE II score were found to be significantly higher in non-survivor patients versus survivor patients 21.4±6.2 with mortality of 81,45% in the current study ,the same result was reported by **Fouda *et al.*** [20] who stated that APACHE II score was 20.5± 5.9 and mortality rate of 74% and also **Sandrine *et al.*** [18] reported higher APACHE II score in non survivors than survivors. **Raquel *et al.*** [24] noticed that the median APACHE II score was 26.0

The leading cause of ICU admission was respiratory failure and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ranged from 13 to 23 [3]. In the present study, part of the information was obtained retrospectively from patient records and probably was not as complete and accurate as when data collection was done in the prospective part of study. Single center study with relatively small sample size may have lacked sufficient statistical power to reveal an association with some of the factors. Despite these limitations, the present results provide important implications for similar demographic areas and clinical settings.

REFERENCES

1. World Health Organization (2009): Global health risks: mortality and burden of disease attributable to selected major risks. Geneva, World Health Organization.www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks

2. Lönnroth K, Williams BG *et al.* (2008): Alcohol use as a risk factor for tuberculosis - a systematic review.BMC Public Health, 8: 288-299.

3. Lin HH, Ezzati M and Murray M (2007): Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and metaanalysis. PLoS Med ., 4: 20-29.

4. Wang H, Yu M, Ochani M *et al.* (2003): Nicotinic acetylcholine receptor α7 subunit is an essential regulator of inflammation. Nature International Weakly Journal of Science, 421: 384–388.

5. Guler M, Unsal E, Dursun B *et al.*(2007): Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. Int.J. Clin. Pract., 61: 231–235.

6. Dooley KE and Chaisson RE (2009): Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect. Dis., 9: 737–746.

7. Maalej S, Belhaoui N, Bourguiba M *et al.* (2009): Pulmonary tuberculosis and diabetes.A retrospective study of 60 patients, in Tunisia. Presse Med., 38: 20–24.

8. Rees D and Murray J (2007): Silica, silicosis and tuberculosis. Int.J.Tuberc.Lung Dis., 11: 474–484.

9. Murray J, Sonnenberg P, Shearer S *et al*.(2000): Drug resistant pulmonary tuberculosis in a cohort of southern African gold miners with a high prevalence of HIV infection. S.Afr.Med.J., 90: 381–386.

10. Khan A, Sterling TR, Reves R *et al.*(2006): Lack of weight gain and relapse risk in a large tuberculosis treatment trial. Am.J. Respir.Crit.Care Med., 174: 344–348.

11. Jeon CY and Murray MB (2008): Diabetes mellitus increases the risk of active tuberculosis: a

systematic review of 13 observational studies. PLoS Medicine, 5: 150-160.

12. Programmatic Management Guidelines (2009): Guide lines for management of drug resistant tuberculosis. National Tuberculosis Program, Egypt.whqlibdoc.who.int/publications/2011/9789241501583_eng.

13. Penner C, Roberts D, Kunimoto D *et al.* (1995): Tuberculosis as a primary cause of respiratory failure requiring mechanical ventilation. Am. J. Respir. Crit. Care Med., 151: 867-872

14. Frame RN, Johnson MC, Eichenhorn MS *et al.* (1997): Active tuberculosis in the medical intensive care unit: a 15-year retrospective analysis.Crit.Care. Med.,15(11):1012-1014.

15. Erbes R, Oettel K, Raffenberg M *et al.* (2006): Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. Eur. Respir. J., 27(6):1223-1228.

16. Silva D. R., D. M. Menegotto, L. F. Schulz *etal.* (2010): Mortality among patients with tuberculosis requiring intensive care: a retrospective cohort study. BMC. Infectious Diseases, 10:54 60.

17. Alshimemeri AA, Arabi YM, Al-Jahdali H *et al.* (2011): Clinical presentation and outcome of patients diagnosed with active pulmonary tuberculosis in a large critical care unit. Crit. Care shock org., 14: 1-6.

18. Sandrine V R, Laurent A, Mounir A *et al.* (2012): Tuberculosis in the intensive care unit: a retrospective descriptive cohort study with determination of a predictive fatality score . Can. J.Infect.Dis.Med.Microbiol., 23(4): 173–178.

19. Zahar JR, Azoulay E, Klement E *et al.* (2001): Delayed treatment contributes to mortality in ICU patients with severe active pulmonary tuberculosis and acute respiratory failure. Intensive Care Med.,27(3):513-20.

20. Fouda M, Madkor A, and Mansour M (2014): Clinical presentation and outcome of active pulmonary TB patients in respiratory ICU Chest Department, Master Thesis.Faculty of Medicine Ain Shams University. pp: 120-135.

21. Fremond CM, Yeremeev V *et al.* (2004): Fatal Mycobacterium tuberculosis infection despite adaptive immune response in the absence of MyD88. J.Clin. Invest.,114:1790-1800.

22. Leung CC, Lam TH *et al.(*2010): Passive smoking and tuberculosis. Arch. Intern. Med., 170:287.

23. Bates MN, Khalakdina A, Pai M *et al.* (2007): Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Arch. Intern. Med., 167: 335-342.

24. Raquel P, Paulo F D , Alcina A, Ferreira *et al.* (2017): Sever tuberculosis requiring intensive care. Critical Care Research and Practice.https://www.hindawi.com/journals/ccrp/2017/9535463/

25. **Lin HH, Ezzati M *et al.* (2009):** Association between tobacco smoking and active tuberculosis in Taiwan prospective cohort study. Am.J.Respir.Crit.Care.Med., 180:475-483.

26. Wu JY, Ku SC, Shu CC *et al.* (2009): The role of chest radiography in the suspicion for and diagnosis of pulmonary tuberculosis in intensive care units. Int.J. Tuberc. Lung Dis., 13(11):1380-1386.

27. Valade S L, Raskine M *et al.*, (2012): Tuberculosis in the intensive care unit: a retrospective descriptive cohort study with determination of a predictive fatality score. Canadian Journal of Infectious Diseases and Medical Microbiology, 23(4): 173–178.

28. Lee PL, Jemg JS, Chang YL *et al.* (2003): Patient mortality of active pulmonary tuberculosis requiring mechanical ventilation. Eur. Respir. J., 22(1):141-147.

29. Levy H, Kallenbach JM, Feldman C *et al.* (1987): Acute respiratory failure in active tuberculosis. Crit.Care Med., 15(3):221-225.

30. Rajesh U,Singh D (2012): Tuberculosis in liver cirrhosis. Medicine Update, 22 :476-478.

31. Stoneburner R, Laroche E, Prevots R *et al.* (1992): Survival in a cohort of human immunodeficiency virus-infected tuberculous patients in New York City. Arch. Intern. Med., 152:2033-2037

32. **Hui C, Wu CL, Chan MC *et al.* (2003):** Features of severe pneumonia in patients with undiagnosed pulmonary tuberculosis in an intensive care unit. J.Formos.Med. Assoc., 102(8):563-572.

33. Tsai TC, Hung M, Chen C *et al.*(2008):Delayed diagnosis of active pulmonary tuberculosis in emergency department.The American Journal of Emergency Medicine, 26(8): 888–892.

34. Lanoix J, Gaudry P, Flicoteaux R *et al.* (2014): Burden country. International Journal of Tuberculosis and Lung Disease, 18(5): 581–587.

35. **Keim LW, Schuldt S and Bedell GN (1977):** Tuberculosis in the intensive care unit.J. Heart Lung, 6: 624–634.

36. Guy H and Nazim N (2013): Tuberculosis on the intensive care unit. Biomed.Central Critical care ,17(5): 240