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TANAFFOS

Comparison of Morbidity, Mortality, and Costs of VAP Patients with Non-VAP Patients in the Tertiary Referral Hospital of Kerman, Iran

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Background: Ventilator-associated pneumonia is the most common type of nosocomial infection in ICUs. Hence, this study shall focus on the morbidity, mortality, and costs associated with this infection among ICU patients.

Materials and Methods: The current research is a prospective descriptive-analytical study. The study population included patients admitted to the Tertiary Referral Hospital of Kerman University of Medical Sciences who were enrolled in the study according to inclusion criteria and demographic characteristics data, length of stay in ICU and general wards, and direct and indirect medical expenses such as unemployment and rehabilitation cost, etc.

Results: Nine of the 144 patients studied died. (4 in the Ventilator-Associated Pneumonia (VAP) group and 5 in the non-VAP group). Among them, the prevalence of *Acinetobacter Baumannii* was significantly higher than other bacteria (P-Value=0.001). The duration of hospitalization in the ICU (18±9 vs. 9.5±6 days) and recovery time (21.6±9 9.6 vs. 13.2±7 days) were higher in the VAP group (P-Value<0.05). Moreover, the duration of hospitalization in the general ward was 15.4±8 days in the VAP group and 10.6±6 days in the non-VAP group (P-Value<0.05). The cost of treatment in the VAP group ($7952.28) was significantly higher than in the non-infected group ($4400.98). The average rehabilitation cost in the VAP group was $2571.42 and in the non-affected group was $1530.88. The financial loss due to the delay in work starting was $482 in the non-VAP group which was significantly less than the VAP group ($792).

Conclusion: Having VAP can significantly increase mortality, length of stay in the ICU as well as increase direct and indirect costs for patients.

Keywords: Cost Analysis; Intensive Care Units; Morbidity; Mortality; Ventilator-Associated Pneumonia

INTRODUCTION

Nosocomial infections occur 48-72 hours after hospitalization or within a specified period (10-30 days) after discharge (1). The prevalence of nosocomial infections in the Intensive Care Unit (ICU) is 5-7 times higher than in other hospital units (2). Respiratory tract infections are a frequently occurring type of hospital-acquired infection that can prolong hospital stays and lead to higher expenses (3).

Ventilator-Associated Pneumonia (VAP) is the most common ICU infection (4) that patients under mechanical ventilation are susceptible to (5). In previous studies, it was discovered that infection occurs between 2%-40% of

patients who have been under mechanical ventilation for more than 48 hours (6).

VAP diagnosis is confirmed via at least two of the following: Fever/temperature above 38° C, white blood cell counts above 12,000/mm3 or below 4,000/mm3, or purulent respiratory discharge, plus new or progressive consolidation on chest X-ray. For definitive confirmation and diagnosis of VAP, a quantitative culture of TBAS (Tracheal and Bronchoalveolar Secretions) with colony count ≥105 CFU/ml2, bronchoalveolar lavage (BAL) ≥104 CFU /ml or mini-BAL with ≥ 103 CFU /ml has been defined (7).

VAP is classified into two types: early-onset and late-onset. Early-onset pneumonia occurs in less than 4 days from initiation of invasive mechanical ventilation while the late-onset occurs after 4 days (8).

The microbial strains of ventilator-associated pneumonia are often multidrug-resistant bacteria. Their relative abundance in different hospitals may vary significantly from one hospital to the next and even between various intensive care units in a single hospital (9).

Nosocomial infections are a common cause of death, disability, increased length of hospital stay, increased hospital costs, and other health problems (10).

Health systems are one of the largest economic sectors in the world (11). Due to the increasing costs of the health sector, a lot of effort has been made to find practical solutions to reduce costs. Among these, medical services in hospitals are one of the main factors in the growth of health costs in each country (12).

In Iran, hospital care accounts for about 40% of government health expenditures. Hence, action needs to be taken to control these costs (13).

The intensive care units of Shahid Bahonar Hospital in Kerman are considered as tertiary-level referral centers in Southeastern Iran. Due to the importance of controlling costs of intensive care units, especially for preventable diseases such as ventilator-associated pneumonia, this study has been undertaken to compare the morbidity, mortality, and treatment costs of patients with ventilator-induced pneumonia in the intensive care unit of Shahid Bahonar Hospital in Kerman.

MATERIALS AND METHODS

The present study is descriptive-analytical in a prospective manner and was performed on patients admitted to the Tertiary Referral Hospital ICU (Shahid Bahonar Hospital) of Kerman University of Medical Sciences in 2019. In this study, adult patients under invasive mechanical ventilation in the intensive care unit of Shahid Bahonar Hospital in Kerman were enrolled in the study by census. This study was approved by the ethic committee of Kerman University of Medical Sciences (IR.KMU.AH.REC. 1398.168).

Exclusion criteria were immunocompromised and massive transfusion, APACHE II score> 25, history of cardiovascular and lung disease, diabetes mellitus, and any organ failure.

Data were collected on various factors such as age, gender, type of organism, and hospitalization in both ICU and non-ICU wards. Additionally, the duration of unemployment and costs associated with antibiotics, procedures, and hospitalization were assessed. Indirect costs such as rehabilitation expenses and duration of unemployment were also taken into consideration. VAP diagnosis was compliant with CPIS criteria, and a Broncho Alveolar Lavage (BAL) sample was sent to determine the bacterial strains.

Data Analysis

To compare cost differences within groups, the Man-Whitney Test (Natural Logarithm Transformation) was utilized to normalize cost distribution, the x2 test was used to compare class (qualitative) variables, and the independent T-Test was utilized to compare the length of stay in wards including mean and standard deviations. A P-Value less than 0.05 was considered statistically significant.

After completing the checklist, the data were entered into SPSS software (version 20) and analyzed through statistical tests.

RESULTS

A total number of 144 patients under invasive mechanical ventilation in the ICU of Shahid Bahonar Hospital were enrolled in the study. Among the patients, 104 (71.9%) were male and 40 (28.1%) were females. Nine (6.2%) patients including 4 (11.4%) patients of VAP and 5 (4.8%) patients of non-VAP group died during the study. The difference in mortality between the two groups was significant (p= 0.01). The mean age of patients participating in the study was 44.6±14 years. 31(22.9%) of our patients developed VAP including 8 (25.8%) females and 23 (74.2%) males. In the 104 non-VAP groups, 30 (28.8%) were females and 74 (71.2%) were male. There was not a significant difference between the two groups in terms of gender (P >0.05) (Table 1).

Table 1. Demographic characteristics of patients

variable		NO		P
		VAP	Non-VAP	
Gender	Male	23	74	0.23
	Female	8	30	
	Total	31	104	
Average age of patients		46.2±16	44.1±14	0.42
	Total	44.6±14		

Most common side effects observed in all studied patients include: 88(65%) feeding and GI disorders, 83(61%) sleep disorders, 58(42.9%) muscular weakness, 14(10%) PTSD, 8(5.9%) drop foot, 5 (3.7%) pressure ulcer, and 1 (0.7%) DVT. All complications were significantly higher in the group with VAP (p=0.007) (Table 2).

The mean length of ICU stay was 15.3±7 days. In the VAP group, it was18±9 days and in the non-VAP group it was 9.5±6 days. ICU stay was significantly longer in the VAP group (p=0.02). However, the mean duration of non-ICU ward stays was 12.1±6 days. In the VAP group it was 15.4±8 days vs 10.6±6 days in the non-VAP group, with no meaningful difference (p=0.06). Even though the same rehabilitation program was prescribed for both groups, patients in the VAP group returned to their job after 21.6±9 days while in the non-VAP group, this time was 13.2±7 days, meaningfully less than the VAP group (p=0.04) (Table 3).

Table 2. Complications related to the hospitalization in ICU in two groups

Variables		Total	VAP	Non-VAP	P
Disorders	Drop foot	8(5.9%)	4(12.9%)	4(3.8%)	0.007
	Muscular weakness	58(42.9%)	20(64.5%)	38(36.5%)	
	Sleep disorders	83(61%)	22(70%)	61(58%)	
	Feeding and GI	88(65%)	25(80%)	63(60%)	
	PTSD*	14(10%)	6(19%)	8(7.6%)	
	Pressure ulcer	5(3.7%)	2(6.4%)	3(2.8%)	
	DVT**	1(0.7%)	1(3.2%)	0	

*Post-traumatic stress disorder

**Deep vein thrombosis

Table 3. Mortality, length of stay in ICU/general ward, and time/delay in returning to work in both groups

Variable		NO		Extra Length of Stay	P
		VAP	Non-VAP		
ICU Stay (day)	Total	18 ±9	9.5±6	8.5	0.02
		15.3±7			
Non- ICU Stay (day)	Total	15.4±8	10.6±6	4.8	0.06
		12.1±6			
Time to return to the job(day)	Total	21.6±9	13.2±7	8.4	0.04
		15.1±8			
Mortality Rate	Total	4(11.4%)	5(4.8%)	-	0.01
		9			

The average total cost of the patient was $5989.31 (1877-14845). In the VAP group [$7952.28 (4073-15744)] and the non-VAP group [$4400.98 (1877-6673)], demonstrating a meaningful difference (p=0.005).

Regarding direct costs, including daily charges and the cost of prescribed drugs and procedures, the findings revealed the mean cost of ICU daily charges was $3086.59 total (in the VAP group $3631.28 and in the non-VAP group $1916.51). The findings demonstrate higher costs in the VAP group (p=0.004). Also, the mean cost of medications and procedures in total was $551.96

(meaningfully higher in the VAP group [$957.58] than the non-VAP group [$431.05]) (p=0.03).

Indirect costs assessment showed the average rehabilitation costs including physiotherapy, occupational therapy, and psychotherapy were $1797.61(1100-3943). In the VAP group it was $2571.42 and $1530.88 in non-VAP group indicating a meaningful increase in rehabilitation costs of VAP patients (p=0.003).

According to the 2019 Iranian income average, patients who experienced unemployment faced an average economic loss of $553.18. The loss was higher in VAP patients at $792 and lower in non-VAP patients at $482. The difference between the two groups was significant (p=0.01) as shown in Table 4.

Table 4. Direct and indirect costs and their total in both groups

Variable			Cost		P
			VAP	Non-VAP	
Direct Cost	Mean Cost of ICU Bed		3631.28 (1895-7690)	1916.51 (322-2201)	0.004
		Total	3086.59 (322-7690)		
	Cost of drugs and procedures		957.58 (406-2012)	431.05 (121-780)	0.003
		Total	551.96 (121-2012)		
Indirect Cost	Cost of rehabilitation		2571.42 (1244-4842)	1530.88 (1100-2822)	0.003
		Total	1797.61 (1100-3943)		
	Cost of unemployment		792 (528-1200)	482 (334-870)	0.01
		Total	553.18 (334-1200)		
The average additional cost in the VAP group		Total	3551.3 (2196-9061)		0.0001
The mean cost of prevention		Total	409.66		0.0001
Mean total cost			7952.28 (4073-15744)	4400.98 (1877-6673)	0.005
		Total	5989.31 (1877-14845)		

Overall, the average total cost for men with VAP was $5882.01(1877-1396) and $6255.42(1922-14845) for women indicating the relatively equal cost of VAP treatment in both genders (p=0.5) (Table 5).

The additional cost imposed on the VAP patients was 3551.3 $ ($2196-$9061) which was significantly more than the mean prevention costs ($409.66) (including training class and VAP bundle formation and materials and consumables such as mouthwash and endotracheal tube with subglottic suction port) (p=0.003).

Based on the culture results, the most prevalent strains that cause VAP were, in order: *Acinetobacter baumannii* (53.9%), *Klebsiella pneumoniae* (17.7%), *Staphylococcus aureus* (11.8%), *Pseudomonas aeruginosa* (9.6%), Enterobacteriaceae (6) % and *Candida albicans* (3%). The prevalence of *Acinetobacter baumannii* was meaningfully higher than the other bacteria (p=0.001). The average cost according to different VAP strains was as follows: *Acinetobacter baumannii* ($559.04), *Klebsiella pneumoniae* ($545.9), *Staphylococcus aureus* ($549.16), *Pseudomonas aeruginosa* ($550.43), Enterobacteriaceae ($560.2) and *Candida albicans* ($630). The findings revealed no significant relationship between the type of organism and treatment costs of patients (p=0.085) (Table 6).

Table 5. Average cost of VAP patients by gender

Gender	Mean total Cost	P-Value
Male	5882.01 (1877-1396)	
Female	6255.42 (1922-14845)	0.5
Total	5989.31 (1877-14845)	

Table 6. Relationship between organisms causing VAP and treatment cost

BAL culture	Variable	Value	P-value
Acinetobacter baumanii	No (percent)	70 (53.9%)	0.001
	The mean cost of treatments (range)	559.04 (138-1822)	0.2
Klebsiella pneumoniae	No (percent)	24 (17.7%)	0.001
	The mean cost of treatments (range)	545.9 (200-1665)	0.2
Staphylococcus aureus	No (percent)	16 (11.8%)	0.001
	The mean cost of treatments (range)	549.16 (121-1782)	0.2
Pseudomonas aeruginosa	No (percent)	13 (9.6%)	0.001
	The mean cost of treatments (range)	550. 43 (332-2012)	0.2
Enterobacteriaceae	No (percent)	8 (6%)	0.001
	The mean cost of treatments (range)	560.2 (408-1990)	0.2
Candida albicans	No (percent)	4 (3%)	0.001
	The mean cost of treatments (range)	630 (345-1660)	0.2

Based on the results of this study, it was found that out of 135 patients who were admitted to the ICU with VAP, 93.3% of them were able to recover and were discharged, while 6.7% of the patients unfortunately expired.

DISCUSSION

Due to the high prevalence of pneumonia in critical patients (14) and several reports of increased morbidity and mortality in ICU patients following VAP infection (15), the present descriptive-analytical study was conducted to investigate the prevalence of VAP and its effect on mortality, morbidity, and treatment costs in patients admitted to a tertiary referral medical center of Kerman University of Medical Sciences in 2019.

Our research is one of the first studies investigating the imposition of additional costs due to VAP to patients hospitalized in ICU in Iran. One of the highlights of this research is the investigation of direct expenses related to the duration of hospitalization, costs of antimicrobial therapy, the diagnostic measures and procedures costs during ICU stay, and the indirect costs related to the delay in returning to the previous job and the expenses related to rehabilitation programs and treatments of complications due to ICU stay.

In previous studies, different values of VAP prevalence between 10% to 65% among adults hospitalized in ICU have been reported while our results showed a prevalence of 24.3%. Previously, incidence of VAP was reported from 10% (16) to 65% (17); it was 24.3% in our patients.

The results of some studies have shown a higher prevalence of VAP among males; in the study of Khan et al., VAP was equally prevalent among women and men (16). We also did not observe a significant relationship between the gender and the prevalence of VAP, but in the study of Sharp et al., men were more susceptible to VAP than women (17).

It is demonstrated that VAP will lead to an increase in the length of ICU stay. For example, in the study of Mathai et al., the length of hospitalization (21 days vs. 11 days) and ICU stay (13 days vs. 6 days) were significantly longer in VAP patients (18).

Also in a meta-analysis conducted by Papazian et al., it was shown that one of the most common causes of prolonged mechanical ventilation and ICU stays is VAP (19). Our results also demonstrated a significant prolonged ICU stay in the VAP group (18±9 vs 9.5±6)

On the other hand, although the duration of hospitalization of VEP patients in general wards was longer than that of the non-VEP group, this difference was not statistically significant (15.4 ± 8 days vs. 10.6 ± 6 days).

In a study by Luchraz et al., patients were evaluated after open heart surgery. It was observed that the duration of mechanical ventilation, length of ICU stay (8 vs. 3), and total hospitalization period (16 vs. 9) were meaningfully longer in VAP patients (20).

The results of most of the studies are consistent with our results which show the effect of VAP on the length of ICU stay. The main treatment of VAP is based on the prescription of appropriate antibiotics in most guidelines and articles

A duration of 8-day antimicrobial treatment is recommended for VAP treatment (21). This treatment can be quite expensive due to the costs of drugs, procedures, and hospital beds. In our study, the cost of drugs, diagnostic measures, and procedures in the VAP group was $957.58 and in the non-VAP group was $431.05; it was significantly higher in the first group (p=0.003). Additionally, the expense for hospitalization in the VAP group amounted to $3,631.28, while it was $1,916.51 in the non-VAP group. This indicates a notable increase in expenses for the former group.

In another study in UK, the cost of each patient with VAP was 6000-22000 pounds (14). VAP is associated with approximately a four-day increase in the length of ICU stay which imposes $1000 per patient in a year on the health care system (15). In the study of Mathai et al., 95 patients who suffered from VAP, experienced longer hospitalization and incurred higher hospital costs (18).

Our results showed that the ICU stay was 18 ± 9 days in the VAP group and 9.5 ± 6 days in the non-VAP group which was significantly different. As a result, the cost of hospitalization in the VAP group was $3631.28 and in the non-VAP group was $1916.51 which was significantly higher in the former group.

In the Kalil et al. study, VAP patients had longer hospitalizations and higher treatment costs than similar non-VAP patients. However, in this study, unlike ours, the direct and indirect costs were not separately analyzed (22).

Even in developed countries, VAP imposes a significant economic burden on the health care system. As evidenced in a study in United States in 2013 by Zimlichman et al., the cost of VAP infections was reported to be $40144 (CI 95% 36.286-44.220) which is consistent with our findings (5).

In the Luchraz et al. study, the cost of open heart surgery was significantly higher in patients who were involved with pneumonia after the operation which was consistent with our findings (20).

The Dat et al. study in Vietnam found that the average additional cost per patient with VAP was $174.90 including additional ICU hospitalization expenses and antimicrobial treatment costs. An amount of $1.86 million could be saved annually by reducing VAP by just 1% (23).

Sosa-Hernández et al. found that VAP caused by MDR bacteria confers 9 times the risk of increasing the costs of care above the expected average (24).

The most common VAP strains are Gram-negative organisms. In Huang et al. showed that the most common microorganisms were *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, Acinetobacter, and *Staphylococcus aureus* species (25). In a four-year study in North Carolina including 327 patients with VAP, the most common strains were Methicillin-susceptible *S. aureus* (9%), MRSA (18%), *P. aeruginosa* (18%), *Stenotrophomonas maltophilia* (7%), *Acinetobacter baumannii* (8%), and other species (9%), respectively (26).

Moreover, Sadigov et al. showed the most common VAP strains were *Acinotebacter baumannii*, *Pseudomonas aerigunosa*, MRSA, *Escherichia coli*, and *Klebsiella pneumonia* in Azerbaijan (27). In line with their study, the most common strains in our study were *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Enterobacteriaceae, and *Candida albicans*, respectively. It could be due to the geographical proximity and genetic affinity of our patients (27). However, there was no relationship between the VAP strains and costs. In other similar studies, no relationship was found between microbial strain and treatment costs (19).

The most common disorders that cause a delay in returning to work and often require therapeutic intervention include: drop foot, sleep disorder, muscle weakness, eating and digestive disorders (such as swallowing disorder and anorexia, nausea and vomiting, constipation), PTSD, DVT, pressure ulcer. These disorders were significantly more common in the group of VAP sufferers which caused an increase in the indirect costs of patients due to the delay in returning to work.

Patients with VAP often require multiple sessions of physical therapy, occupational therapy, speech therapy, and psychotherapy consultations to address issues like foot drops, muscle weakness, sleep disorders, and PTSD. As a result, treatment costs have been increasing significantly.

In the study of García-Martínez et al., the prevalence of drop foot in patients hospitalized in the ICU was estimated at 10% which is often observed in patients hospitalized for more than 15 days. Our study found that patients with VAP have a higher prevalence of foot drop compared to non-infected patients due to the longer period of mechanical ventilation required (28).

According to Granja et al., over half of ICU patients experienced sleep disorders after being discharged, with a higher prevalence among those who stayed for more than 12 days. The main causes were nursing procedures and excessive light and noise at night. Our research indicates that patients with VAP were found to have a higher incidence of sleep disorders, likely due to their extended stays in the ICU (29).

According to the report by Adike and Quigley, gastrointestinal disorders are prevalent in 50-80% of patients after being discharged from the ICU. These disorders include the inability to feed through the digestive system, ileus, diarrhea, and bacterial translocation. Our study found that patients with sepsis, inflammatory conditions, certain drugs, and metabolic disturbances have a significantly higher prevalence of these disorders, especially in the VAP group (30).

PTSD symptoms can affect 20% of adult critical care survivors, with a high likelihood of prevalence 12 months after discharge. Patients who were under mechanical ventilation and were critically ill and conscious tend to suffer from post-traumatic stress disorder (PTSD) after being discharged from the ICU. Our study found that 10% of patients experienced PTSD, with the highest percentage in the VAP group (19% vs. 7.6%) (31).

It has been observed that 56-74% of patients in the ICU exhibit signs of muscle weakness. Factors such as sepsis, hyperglycemia, prolonged use of mechanical ventilation, being bedridden, and the use of drugs like glucocorticoids, neuromuscular blocking agents, and vasoactive drugs increase the risk of ICU-induced muscle weakness (32). Regarding this matter, it was found that 42.5% of our patients experienced muscle weakness. Specifically, the VAP group had a higher incidence of 64.9%, while the non-VAP group had a lower incidence of 36.5%.

With effective preventive measures and the use of modern medical tools, the prevalence of DVT and pressure ulcers has decreased significantly in recent years (33, 34). In our study, it was 0.7% and 3.7% in VAP and non-VAP groups, respectively, which was significantly higher in the VAP group.

After analyzing the expenses involved in preventing VAP and treating it, we found that the cost of preventing pneumonia ($409.66) was significantly lower than the direct and indirect costs incurred by patients ($3551.3, with a range of $2196 to $9061).

In the Branch-Elliman et al. study, preventive methods such as the use of probiotics and endotracheal tubes with subglottic suction are shown to be cost-effective (35).

The study conducted by Møller et al. revealed that using the VAP bundle can reduce treatment costs by 31.6% and lower the risk of VAP-related deaths by 85.9% (36). Our own findings align with this, indicating that treating VAP is expensive and prevention is more cost-effective than treatment.

The presence of VAP in critically ill patients can result in a mortality increase of up to 50%. (37, 38). In the Dogru et al. study, it was 66.7% (39), but in the Melsen et al. study, the VAP mortality rate was 13% (40). The mortality rate of our VAP patients was 11.4%.

CONCLUSION

Patients who develop VAP tend to have longer stays in the ICU, as well as longer recovery periods and higher rates of unemployment compared to those who don't have VAP. This translates to higher direct and indirect costs, which can be a burden for patients, insurance companies, and the government. Therefore, it is important to implement effective and practical measures to prevent VAP, given the limited financial resources available.

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Conflict of interest

The authors declare no conflict of interest.

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