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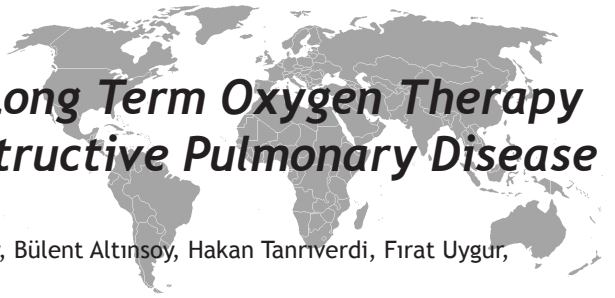

Evaluating the Efficiency of Long Term Oxygen Therapy and Mortality in Chronic Obstructive Pulmonary Disease

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ABSTRACT

It has been shown that Long Term Oxygen Therapy (LTOT) improves polycythemia secondary to hypoxemia and right heart failure, decreases pulmonary hypertension, improves quality of life and increases life expectancy in COPD patients. In our study we aimed to evaluate clinical data, mortality, patient's adherence and efficiency of the therapy in COPD patients receiving LTOT. Mean age was 70.5%±9.7 and 57% of the participiants were male. It was shown that one year hospital admission count after LTOT (0.56±0.79) was decreased according to one year hospital admission count before LTOT (1.14±1.64). When arterial blood gas values after LTOT compared to the values at the time prescription PaO_2 was increased (47.9±4, 53.4±9) and $PaCO_2$ was decreased (56.1±11, 50.5±11). Although there was no significant difference in pulmonary artery pressure after LTOT, a significant increase was determined in hematocrit (38.37±6, 40.14±6). 41.1% of the patients had at least once device maintanence, and after LTOT only 38.4% had a clinical control due to COPD. The most common reason for irregular use was lack of necessity. Mean daily oxygen usage was 13.88±4.35 hours/day and 68.8% of the patients were using 15 hours or more. Mean follow-up of the patients were 17.85±14.53 (1-55) months and mortality rate in this period was 67%. Mortality was higher in LTOT with 15hours/day or more compared to less than 15 hours (respectively 54.6%, 12.5%). In conclusion, all patients with an indication for LTOT should be followed by national registry system and monitored in terms of technical services. Patients adherence and routine controls should be provided.

Key words: *COPD, mortality, concentrator, oxygen, LTOT*

Kronik Obstrüktif Akciğer Hastalığında Uzun Süreli Oksijen Tedavisi Etkinliğinin ve Mortalitenin Değerlendirilmesi

ÖZET

Kronik Obstrüktif Akciğer Hastalığı (KOAH) olan hastalarda uzun süreli oksijen tedavisi (USOT) hipoksemiye sekonder polisitemiyi ve sağ kalp yetmezliğini düzelttiği, pulmoner hipertansiyonu düşürdüğü, yaşam kalitesini ve yaşam süresini uzattığı gösterilmiştir. Çalışmamızda oksijen konsantratörü ile USOT alan KOAH'lı hastaların klinik verilerini ve mortaliteyi değerlendirmeyi ve bu hastalarda tedavi uyumunu ve USOT'un KOAH'lı hastalar üzerindeki tedavi yararlılığını değerlendirmeyi amaçladık. Çalışmaya alınan hastaların yaş ortalaması %70.5±9.7 olup %57'si erkek idi. USOT sonrası bir yıllık hastane yatış sayısının (0.56±0.79), USOT öncesi bir yıllık hastane yatış sayısına (1.14±1.64) göre azaldığı bulundu. USOT sonrası kan gazlarının, oksijen konsantratörü verildiği dönemdeki kan gazlarıyla kıyaslandığında PaO_2'nin (47.9±4, 53.4±9) arttığı, $PaCO_2$'nin (56.1±11, 50.5±11) azaldığı tespit edildi. USOT sonrası pulmoner arter basıncı ve hemoglobinde belirgin bir değişiklik olmazken hematokrit'de (38.37±6, 40.14±6) artış tespit edildi. Çalışmaya katılan hastaların %41.1'i oksijen konsantratörüne en az bir kere bakım yaptırdığı ve USOT sonrası hastaların sadece %38.4'ü (n:43) KOAH nedeniyle en az bir kere poliklinik kontrolüne geldiği tespit edildi. En sık düzensiz USOT kullanma nedeni ise ihtiyaç duymama idi. Çalışmaya alınan hastaların günlük USOT kullanım süresi 13.88±4.35 saat/gün olup, hastaların %68.8'i oksijeni günlük ortalama 15 saat ve üzeri kullanıyordu. Çalışmaya alınan hastaların takip süresi 17.85±14.53 (1-55) ay olup takip süresi içinde mortalite oranı %67 idi. USOT'ni 15 saat/gün ve üzeri kullanan hastaların mortalitesi kullanmayanlara göre daha yüksekti (%54.6, %12.5). Sonuç olarak USOT endikasyonu olan tüm olgular ulusal kayıt sistemi ile takip edilmeli ve teknik hizmetler yönünden de izlenmelidir. USOT verilen hastaların tedaviye uyumu incelenmeli ve hastaların düzenli kontrole gelmeleri sağlanmalıdır.

Anahtar kelimeler: *KOAH, mortalite, konsantratör, oksijen, USOT*

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease that is often characterized by progressive persistent airflow obstruction. The condition is associated with increased chronic inflammatory response in the lungs and airways caused by toxic gases and particles (1). The disease ranks fourth among the other causes of death in the world, and it is expected to rank in the third place in 2020 in connection with increased smoking rates. Parallel to other countries, COPD appears to be an important health concern also in Turkey (2). An oxygen concentrator is the most commonly used oxygen supply system. Patients with COPD constitute the largest group among patients receiving long-term oxygen therapy (LTOT), and the data on the effectiveness of LTOT has mostly been derived from studies conducted on this patient group. It is estimated that 1,500-2,000 concentrators are prescribed each year in Turkey, and 10,000-15,000 patients receive LTOT (3).

The effect of oxygen therapy on survival is considered to be related to improvement in pulmonary hemodynamic parameters. Patients with polycythemia, pulmonary hypertension, or hypercapnia benefit most from oxygen therapy (4). In patients with COPD, LTOT corrects polycythemia secondary to hypoxemia, reduces pulmonary hypertension, improves right heart failure, and strengthens cardiac functions. This therapy also increases exercise capacity, improves the quality of life, and prolongs survival (5).

Our aim in the present study was to evaluate clinical and mortality data of patients with COPD receiving LTOT, and to further evaluate adherence to treatment and the effectiveness of LTOT in patients with COPD.

MATERIALS AND METHODS

The patients with COPD, who were followed in the pulmonology clinic between July 2008 and June 2012, and who were discharged with the prescribed oxygen concentrator for LTOT, were included in the study. The patients who were prescribed an oxygen concentrator were identified by the review of archived committee reports of the department of pulmonology. The study consisted of two parts: retrospective and prospective. Data including socio-demographic features, clinical characteristics, and laboratory results of the patients were retrieved from the electronic hospital charts. The results of the arterial blood gases analysis, pulmonary function test (PFT), echocardiography and complete blood count (CBC), which were obtained during the hospitalization after which LTOT was prescribed, and other hospital admissions within the last year before discharge were recorded.

In the prospective section of the study, the patients were contacted by phone and invited to attend a visit in the hospital. Arterial blood gases analysis, PFT, echocardiography, and CBC were obtained from the patients who agreed to attend a visit in the hospital. Hospital admissions within one year after discharge, the yearly number of outpatient control visits due to COPD, and oxygen concentrator device usage characteristics were questioned. If the patient was dead, these data and the date of death were obtained from the patient's relatives. A total of 169 patients who were prescribed LTOT for COPD were identified. Of these patients, 66.3% (n:112) were contacted and these patients were included in the study group. Among the contacted patients, control tests could not be obtained from 75 patients who were dead and from six patients who did not attend the control visit (Figure 1). Arterial blood gases analysis, PFT, echocardiography, and CBC were obtained from the remaining 31 patients. By comparing the test results obtained before the prescription of an oxygen concentrator with the control test results, whether and to what extent the patient benefited from LTOT and the oxygen concentrator device usage characteristics were determined.

The study protocol was approved by the University Ethics Committee during the assembly dated 13.11.2012, numbered 2012/23-4.

Statistical Analysis

The data were analyzed using Statistical Packages for the Social Sciences (SPSS) 16.0 (Chicago, USA) software package. Descriptive statistics for numeric variables were expressed as mean ± standard deviation and categorical variables were expressed as number and percentage. The distribution of the groups was evaluated by the Kolmogorov-Smirnov test. The mean values of the dependent groups were compared using the Wilcoxon signed test in cases where the data were not distributed normally between the groups, and the paired samples t-test (student’s t-test) was used where the data showed normal distribution. The mean values of the independent groups were compared using the Mann-Whitney U-test in cases where the data were not distributed normally, and the paired samples t-test (student’s t-test) was used

***Table 1**. Demographic characteristics of the study patients.*

Age- mean	*70.52±9.75*
Gender	
Male- n(%)	*64 (57.1)*
*Smoking**	
Current smoker (%)	*10 (8.9)*
Ex-smoker n(%)	*71 (63.4)*
Nonsmoker n(%)	*31 (27.7)*
Occupation	
Housewife n(%)	*47 (42.0)*
Miner n(%)	*37 (43.0)*
Worker n(%)	*15 (13.4)*
Other n(%)	*13 (11.6)*

**Smoking status before the oxygen concentrator was given. Three patients among 10 smokers was determined as curent smokers after LTOT.*

where the data showed normal distribution. Categorical variables were compared using the chi square and Fisher's exact test, where appropriate. Survival analysis was performed using the Kaplan-Meier method. The results were assessed within a 95% confidence interval and p values <0.05 were considered significant.

RESULTS

The mean age of the study participants (n:112) was 70.52±9.75 (43-87) years, and 57.1% were male. The patients' history was not remarkable for smoking in 27.7% of the patients (Table 1). Ten patients (8.9%) reported that they did not regularly use the oxygen concentrator. The most common reason for irregular use of the device was the lack of need (4.5%) (Table 2). It was found that 41.4% of the patients (n:46) performed maintenance to the oxygen concentrator device at least once. Patients performing maintenance to their devices performed an average of 1.22±0.42 maintenances per year. After initiating LTOT, only 38.4% of the patients (n:43) were admitted to the outpatient clinics at least once due to COPD. The mean number of control visits per year was 2.86±2.97 among patients who attended control visits.

***Table 2**. Reasons of irregular use of LTOT.*

Does not need- n (%)	5 (4,5)
Noise- n (%)	2 (1,8)
Believes of no benefit- n (%)	2 (1,8)
Uncomfortable- n (%)	1 (0,9)

The study participants used an average of 13.88±4.35 (2-24) hours LTOT per day. The mean duration of oxygen use was significantly shorter among patients who attended control visits (p<0.01). The mean duration of oxygen use was significantly higher in patients who did not survive compared to survivors (p<0.001) (Table 3). In the study group, the mean number of hospital admissions was 1.14±1.64 one year before the initiation of LTOT and became 0.56±0.79 one year after the initiation of LTOT (p<0.001). The mean duration of follow-up was 17.85±14.53 (1-55) months among patients receiving LTOT (n:112) and 30.77±11.13 (12-55) months among patients who were invited to and attended their control visit at the hospital (n:31). The one-year mortality rate was 43.7% in patients receiving LTOT, and the mortality rate within the follow-up period was 67% (Table 4). The mortality rate was 79.2% (n:61) among patients (n:77) who effectively used oxygen therapy (daily mean 15 hours and above) and 40% (n:14) among patients (n:35) who did not effectively use oxygen therapy (p<0.001). Figure 2 shows the survival analysis of patients who effectively used oxygen therapy versus those who did not use. There

***Table 3**. Some of the factors that impact on daily LTOT usage duration (hours).*

Variable	*Daily LTOT usage duration*	*p value*
Reexamination by pulmonologist (n:43)	*12.70±4.55*	
No reexamination by pulmonologist (n:69)	*14.71±4.03*	*0.010*
Exitus (n:75)	*14.96±3.23*	
Survivor (n:37)	*11.70±5.44*	*0.001*
Patients with concentrator maintenance (n:46)	*14.57±4.37*	
Patients without concentrator maintenance (n:66)	*13.41±4.30*	*0.167*
Smoking history (n:81)	*13.72±4.61*	
Nonsmokers (n:31)	*14.32±3.62*	*0.511*
Male (n:64)	*14.20±4.18*	
Female (n:48)	*13.46±4.57*	*0.660*
Intensive care admission (n:34)	*13.47±5.04*	
No intensive care admission (n:78)	*14.06±4.03*	*0.509*

***Table 4**. Mortality of the study patients*

Duration	*Mortality*	*n/total*
1 year	*43.7%*	*49/112*
2 year	*59.8%*	*67/112*
3 year	*66.1%*	*74/112*
4 year	*67%*	*75/112*
During the follow-up period	*67%*	*75/112*

was no difference between patients who effectively used or did not use oxygen therapy in terms of the number of hospitalizations in one year (0.51+0.82 versus 0.69+0.72, p=0.269).

There was no significant relationship between smoking, gender, number of hospitalizations due to COPD within the last year before the initiation of LTOT, pulmonary artery pressure at times the oxygen concentrator was prescribed, hemoglobin, hematocrit, blood gases, respiratory function tests, admissions to intensive care unit, and mortality (Table 5). Accompanying diseases did not have influence on the mortality (Table 6). When the clinical and laboratory data before and after the use of the oxygen concentrator among patients who were invited to and attended control visit at the hospital (n:31) were evaluated, hematocrit, PaO_2, SaO_2, and maximal mid-expiratory flow (MMEF) values showed significant increase, and pH, $PaCO_2$ and HCO_3 values showed a significant decrease after the initiation of LTOT (Table 7).

DISCUSSION

The first study on LTOT was conducted by Levin et al. in 1967 (6). This small-scaled and uncontrolled study reported improvement in the clinical condition and exercise tolerance and the reduction in pulmonary vascular resistance in patients with hypoxemic chronic airway obstruction. Skwarski et al. (7) reported that LTOT had a significant positive impact on survival in 179 patients

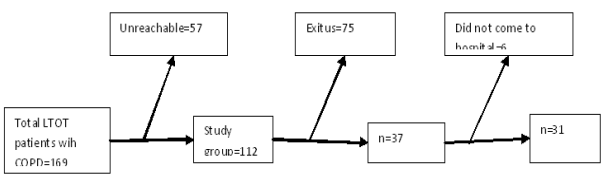

***Figure 1**. Flow chart describes the denouement of patients included in the study.*

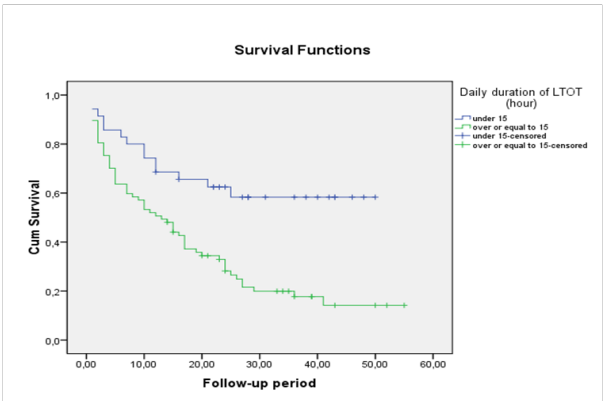

***Figure 2**. Survival analysis of LTOT patients using over or equal to 15 hours (n:77) and under 15 hours (n:45).*

with COPD and receiving LTOT. The Nocturnal Oxygen Therapy Trial (NOTT) and the British Medical Research Council Domiciliary (BMRCD) studies observed decreased morbidity and mortality with the use of LTOT >15 hours/day, survival increased parallel to the duration of LTOT, and 15 hours/day was determined as the cutoff for the optimal effective therapy duration (8, 9). The European Respiratory Society (ERS) indicates that the cessation of smoking is one of the criteria for the initiation of LTOT (10). Smoking during LTOT may result in life-threatening accidents (11). In the present study, three patients continued smoking while on LTOT. Ten patients (8.9%) were active smokers the time the oxygen concentrators were prescribed, and the researchers observed that the smoking cessation condition of ERS for LTOT was not satisfied.

LTOT is a discomforting therapy restricting daily activities, and the adherence to therapy is often low. Adherence to therapy ranged between 17% and 70% depending on the features, size of the study groups, and patient follow-up (12-15). Pepin et al. (16) evaluated adherence to therapy in 930 patients with COPD and reported effective use in 45% of the patients. In the present study, 68.8% of the patients used LTOT 15 hours per day or above. All patients used the oxygen concentrator. In the study by Akçay et al. (17), device noise, disturbed sleep, increased energy consumption, discomfort related with nasal cannula, limitation of movements, headache, and the concerns that the treatment would lead to an addiction were reported as factors influencing adherence to LTOT. Kurtar et al. (18) defined the lack of need, energy consumption and

***Table 5**. Evaluation of factors that may effect the mortality*

Variable	*Survivor (n=37)*	*Exitus (n=75)*	*p value*
Smoking history- n (%)	*27 (73)*	*54 (72)*	*0.877*
Male- n (%)	*17 (45.9)*	*47 (62.7)*	*0.139*
Number of hospitalization previous year- mean	*1.16±1.83*	*1.13±1.55*	*0.852*
Intensive care unit admission- n (%)	*14 (37.8)*	*20 (26.7)*	*0.322*
Pulmonary artery pressure mmHg- mean	*43.49±14.06*	*46.57±17.81*	*0.405*
Hemoglobin gr/dl- mean	*12.49±1.85*	*12.23±2.02*	*0.368*
Hematocrit %- mean	*38.55±6.11*	*37.28±6.30*	*0.240*
Arterial blood gases- mean			
pH	*7.39±0.04*	*7.40±0.04*	*0.523*
$PaCO_2$	*55.67±10.32*	*52.40±11.71*	*0.134*
PaO_2	*47.80±4.27*	*47.97±6.04*	*0.868*
HCO_3	*34.20±4.94*	*32.06±5.97*	*0.062*
SO_2	*83.38±5.70*	*84.21±6.07*	*0.423*
Pulmonary function tests- mean			
FEV_1	*35.47±11.0*	*39.19±12.04*	*0.323*
FVC	*49.42±15.16*	*54.44±14.91*	*0.302*
FEV_1/FVC	*57.37±6.67*	*56.85±6.97*	*0.813*
MMEF	*15.12±4.74*	*16.74±6.85*	*0.411*

noise as the three most common reasons leading to irregular use of LTOT. In the present study, 8.9% of the patients reported irregular use of the oxygen concentrator. The lack of need was the most common reason for irregular use. Our findings were parallel to the findings of Kurtar et al. in terms of the reasons for irregular use of the oxygen concentrator.

Oxygen concentrators require periodic maintenance performed by the technical service. Ideally, oxygen concentrators should undergo monthly maintenance for the control of flow rate and oxygen concentration. There patients are recorded in the national registration system in countries such as the United States, Switzerland, and France (19). A national registration system is not available to record patients on LTOT in Turkey, and furthermore, technical services for the maintenance of oxygen concentrations are not sufficiently provided. Atış et al. (3) reported that 11% of the devices did not operate properly, and technical services were regularly provided in 75% of the patients; however, in the present study, the rate of maintenance by the company was 41%. While oxygen concentrators require maintenance ideally once in a month, maintained devices in the present study underwent maintenance 1.22±0.42 times a year on average. The low rate of maintenance in the present study and even the insufficient frequency of maintenance among the maintained devices indicate the need to establish a monitoring system for oxygen concentrators and other similar devices in Turkey. Block et al. (20) found that regular control visits increased adherence to treatment by 3.8 fold. In contrast, daily duration of LTOT use was longer in patients who did not attend control visits compared to patients who did (Table 3). Although there are no clear findings that would explain this unexpected result, this may suggest that patients who did not participate in the control visit had severe COPD and therefore had a higher need for an oxygen concentrator, and may have had difficulty with

***Table 6**. Effect of comorbidities on mortality*

Comorbidity	*Survivor*	*Exitus*	*p value*
Congestive Heart Failure n(%)	*10 (27.0)*	*12 (16.0)*	*0.167*
Chronic Renal Failure n (%)	*3 (8.1)*	*2 (2.7)*	*0.330*
Hypertension n(%)	*9 (24.3)*	*25 (33.3)*	*0.329*
Diabetes Mellitus n(%)	*8 (21.6)*	*15 (20.0)*	*0.842*
Cerebrovascular event n(%)	*0*	*4 (5.3)*	*0.300*
Sleep apnea n(%)	*2 (5.4)*	*2 (2.7)*	*0.598*
Obesity n(%)	*4 (10.8)*	*2 (2.7)*	*0.091*
Pulmonary embolism n(%)	*4 (10.8)*	*9 (12.0)*	*1.0*
Pneumoconiosis n(%)	*1 (2.7)*	*10 (13.3)*	*0.097*

Table 7. *The laboratory and clnical values of LTOT patients (n:31) after and before oxygen concentrator.*

Variable	*Before LTOT*	*After LTOT*	*p value*
Hemoglobin gr/dl- mean	*12.41±1.9*	*12.80±1.9*	*0.164*
Hematocrit %- mean	*38.37±6.5*	*40.14±5.9*	*0.049*
Pulmonary artery presuure mmHg- mean	*43.32±14*	*38.68±12*	*0.196*
Arterial blood gases- mean			
pH	*7.39±0.41*	*7.37±0.40*	*0.024*
$PaCO_2$	*56.15±11*	*50.50±11*	*0.006*
PaO_2	*47.94±3.9*	*53.41±9.4*	*0.003*
HCO_3	*34.44±5.3*	*28.74±5*	*<0.001*
SO_2	*83.60±5.3*	*86.58±9.7*	*0.006*
Pulmonary function tests- mean			
FEV_1	*34.15±9.5*	*38.47±11*	*0.053*
FVC	*48.92±12*	*51.92±16*	*0.334*
FEV_1/FVC	*56.57±6.9*	*55.68±8.25*	*0.516*
MMEF	*15.18±4.8*	*19.45±10*	*0.033*

transportation to the hospital.

In the NOTT study, hematocrit levels showed a decrease in patients receiving continuous oxygen therapy compared to those receiving oxygen at night at the end of six months, and the decrease in hematocrit levels at 12 and 18 months reached statistical significance (8). However, there are studies that did not report a significant decrease in hematocrit levels (21, 22). In the present study, no significant change was observed in the hemoglobin levels of patients on LTOT, although we found an increase in hematocrit levels in contrast to the studies in the literature. The mean duration of follow-up for patients who attended the control visit and underwent control blood test was 30.77±11.13 (12-55) months. This finding suggests that LTOT may cause a decrease in hematocrit levels in the short term and an increase in hematocrit levels together with disease progression in the long term. The studies conducted in Turkey revealed that the rate of hospitalizations declined with LTOT (23-25). In the present study, the mean number of hospitalizations was 1.14±1.64 before LTOT and declined to 0.56±0.79 after LTOT (p=0.001). Although these findings suggest that LTOT may decrease the number of hospitalizations, the lack of control groups comprising patients in whom LTOT was indicated and who never used LTOT reduces the reliability of the current data.

There was no significant difference between FEV1 percentage before LTOT and control FEV1 percentage; however, MMEF percentage values showed a significant increase. Tutluoğlu et al. (24) reported lower yearly loss in FEV1 percentage in patients receiving LTOT compared to those who were not on LTOT. Our data are not comparable with the findings of this study due to methodological differences and the use of a different control group in the present study. Some studies have found a significant relationship between survival and FEV_1 in patients receiving LTOT (26-27). In the present study, there was no significant difference between FEV_1 values of patients who survived compared to non-survivors (p= 0.323). We consider that this finding may be related to the high mortality rate (67%) during the follow-up period.

Taskar et al. (22) employed oxygen therapy for at least 18 hours a day over three weeks in patients with COPD and reported a significant increase in PaO_2 and a significant decrease in $PaCO_2$. In line with other studies, we found a significant decrease in PCO_2 and a significant increase in PaO2 with the use of LTOT. In the present study, we were unable to explain the significant decrease in pH levels measured in blood gas analysis after LTOT compared to blood gas analysis obtained before the prescription of the oxygen concentrator. There are also studies that failed to demonstrate the effectiveness of LTOT on hypoxemia. Veale (28) and Gorecka (29) could not demonstrate the benefit of oxygen therapy in patients with moderate hypoxemia. Kurtar et al. (18) found greater survival rates in patients receiving LTOT <15 hours per day in comparison to patients receiving ≥15 hours/day. Similarly in the present study, 79.2% of the patients (≥ 15 hours/day) who effectively used oxygen therapy died, and only 12.5% of the patients who did not effectively (<15 hours/day) use oxygen therapy were non-survivors (p< 0.001). In addition, the mean duration of daily oxygen use was higher among

non-survivors (14.96±3.23 hours/day) compared to survivors (11.70± 5.44) (p= 0.001). This unexpected effect and longer daily duration of LTOT among non-survivors suggests that these patients had severe COPD and a higher need for LTOT.

In conclusion, the patients need to be carefully evaluated for their eligibility for LTOT due to low rates of effective use and high costs, patients requiring LTOT should be scrutinized for their compliance, and the decision to initiate LTOT should be re-assessed in cases with possible incompliance. Patients' adherence to medical therapy should be evaluated, and patients should be encouraged to attend regular visits and quit smoking. The coordination of health care facilities, social security institutions and device providers would be appropriate due to high cost of the devices. All cases found eligible for LTOT should be monitored over a national registration system, and the status of technical services should be followed. All candidates for LTOT should be thoroughly informed of the therapy. The patients should attend regular controls, and the devices must undergo regular maintenance.

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