Original Paper

Intensive care in cases with thoracic and extrathoracic malignant solid tumours:
Indications and survival

Aybuke Kekecoglu[1], Levent Dalar[2], Derya Ozden Omaygenc[1], Burcu Arpinar Yigitbas, Ecder Ozenc[3], Filiz Kosar[1]

[1]Department Respiratory Intensive Care Unit, Yedikule Chest Disease and Surgery Training and Research Hospital, Istanbul, Turkey
[2]Department of Pulmonary Medicine, School of Medicine, Istanbul Bilim University, Istanbul, Turkey
[3]Department of Anesthesia and Reanimation, Haseki Training and Research Hospital, Istanbul, Turkey

Key words:
- Extrathoracic malignant tumours
- Lung cancer
- Prognosis
- Survival

Correspondence:
Levent Dalar, MD,
Department of Pulmonary Medicine, School of Medicine, Istanbul Bilim University, Istanbul, Turkey;
Tel.: +905052607170, Fax: +902122403132,
E-mail: leventdalar@gmail.com

ABSTRACT. AIM: The patients with thoracic and extra-thoracic solid organ tumours hospitalized in the intensive care unit (ICU) were retrospectively analyzed and the effects of their ICU stays on survival rates were investigated. **METHODS:** Medical files of the patients hospitalized in the adult ICUs between January 2010 and September 2013 were retrospectively investigated. ICU stays of the cases with solid organ tumours were evaluated and survival related factors were analyzed. The correlation between available parametres and survival rates was analyzed. **RESULTS:** A total of 87 patients (74 males) with a mean age of 64.07 ± 11.90 years were included in the study. The cases were divided into 2 groups as those with thoracic (n = 52; 59.8%) and extrathoracic (n = 35; 40.2%) malignancies. Thoracic malignancies were divided within themselves into two subgroups as SCLC (n = 11; 21.2%) and NSCLC (n = 41; 78.8%) and their survival rates were compared. Respiratory failure (n = 35; 40.2%), respiratory failure and additional indications (n = 37; 42.5%) and other indications (n = 15; 17.2%) were main indications. Mean duration of ICU stays was 12.95 ± 16.48 days (range 1-105). Fifty (57.5%) cases died, 6 (6.9%) patients transferred to another center and 31 cases (35.6%) were discharged. Hospitalization times of the cases with respect to mortality rates were significantly different (p = 0.014). Mean survival was 6.78 ± 1.81 months and six month-survival rate was 29.7%. **CONCLUSION:** Treatment of patients with thoracic and extra-thoracic solid organ tumours in the ICU increases their survivals; however, admission of cancer patients into an ICU should be based on certain objective criteria. ***Pneumon 2015, 28(3):222-229.***

INTRODUCTION

Based on recent estimates, patients with newly diagnosed cancers and cancer-related deaths have increased relative to previous estimates. Based on GLOBOCAN 2012 data, in the year 2012, a total of 14.1 million

newly developed cases and 8.2 million cancer-related deaths occurred in the world. As reports have indicated, globally, most frequently diagnosed cases with cancer include lung (13.0%), breast (11.9%) and colon (9.7%) cancers, while cancer-specific deaths were mostly due to lung (19.4%), liver (9.1%) and gastric (8.9%) cancers[1]. The incidence rates of lung cancer in male and female population in Turkey have been reported as 75.2/100000 and 9.3/100000, respectively. It is the most fatal cancer type, in men in the whole world and in women in the United States of America and Northern Europe[2,3].

As an outcome of studies targeted at early diagnosis of lung cancer and developments in nonsurgical treatment modalities, hospitalizations secondary to lung cancer to the intensive care unit (ICU) have increased. This topic has been debated largely and it has been indicated that most of the patients with solid cancers and hematological malignancies died at the ICU and very costly bills paid for the treatment in the ICU. It has been also stated that before hospitalization in the ICU, this issue should be discussed with the patients and their intimates[4]. However intensive care support has been evolved within years with conceivably favourable effects on survival rates. In many studies, the most frequent cause of ICU stays in patients with underlying malignancies has been associated with respiratory failure. Among these etiological factors massive malignant pleural effusion, obstruction of the common airway with tumoral infiltration, massive hemoptysis or treatment-related pneumonitis have been indicated. Pneumonia, acute exacerbation of COPD or pulmonary embolism can result in admission into the ICU: When ages and comorbidities of lung cancer patients are taken into consideration, they can be hospitalized in ICU, because of medical problems such as severe sepsis, cardiac and/or neurological problems[5,6]. However, to what extents will these patients benefit from ICU has not been fully determined yet. For cancer patients treated in the ICU, worsening of the general health state of the patient within 72 hours has been cited among factors effecting patients' survival. However, two or three organ-failures together with vasopressor use have been demonstrated among factors influential on the long-term prognosis[7,8]. Hemoptysis and acute respiratory failure at admission into ICU have been also reported among survival-related factors. Mechanical ventilation and performance status ≥2 are independent factors demonstrating worse prognosis[9].

In the present study, patients with thoracic and extra-thoracic solid organ tumours hospitalized in the ICU of two tertiary centers were retrospectively analyzed and the effects of their ICU stays on survival rates were investigated.

SUBJECTS AND METHODS

Medical files of the patients hospitalized in the adult ICUs between January 2010 and September 2013, namely, in the Respiratory ICU of Yedikule Chest Diseases and Thoracic Surgery Teaching and Research Hospital and General ICU of Haseki Teaching and Research Hospital were retrospectively analyzed. ICU stays of the cases with thoracic and extra-thoracic solid organ tumours were evaluated and survival and related factors were analyzed. In all cases tumours were non-resectable. Cases admitted into the postoperative ICUs were excluded from the study. Approval of the study was obtained from the ethics committee.

Study population was divided into 2 groups as thoracic and extra-thoracic malignancies. Thoracic malignancies were divided among themselves into subgroups as small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). ICU stays, intubation times, ventilatory support, indications for hospitalizations, stages of tumour based on TNM staging and results of routine laboratory tests were analyzed and APACHE II scores were calculated. The correlation between available parametres and survival rates was also analyzed.

Statistical Analyses

Data were analyzed using NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). Comparisons were made with parametric (Student's t test) and nonparametric (Mann-Whitney) tests. The distribution of categorical variables in both groups was compared using Pearson chi-square, Yates Continuity Correction, and Fisher's exact tests. All differences associated with a chance probability of <0.05 and <0.01 were considered statistically significant.

RESULTS

A total of 87 patients with diagnosis of solid cancers admitted into the ICUs were included in the study. Ages of the study patients changed between 31 and 88 years, with a mean age of 64.07±11.90 years. Study population consisted of 74 (85.1%) male and 13 (14.9%) female patients. ICU stays changed between 1 and 105 days with a mean duration of 12.95±16.48 days. Their intubation

times varied between 0 and 105 (mean: 11.73±17.49) days. APACHE II scores changed between 11 and 49 points (mean: 24.35±7.48 pts) (Table 1).

The cases were divided into 2 groups as those with thoracic (n=52; 59.8%) and extrathoracic (n=35; 40.2%) malignancies. Thoracic malignancies were divided within themselves into two subgroups as SCLC (n=11; 21.2%) and NSCLC (n=41; 78.8%) and their survival rates were compared.

Disease stages of 79 patients could be disclosed (stage 2; n=6, 7.6%; stage 3; n=22, 27.8% and stage 4; n=51; 64.6%). As indications of hospitalization, acute respiratory failure (n=35; 40.2%), acute respiratory failure and additional indications (n=37; 42.5%) and other indications (n=15; 17.2%) were detected.

Fifty (57.5%) cases died, 6 (6.9%) patients transferred to another center and 31 cases (35.6%) were discharged. Life supportive measures used in the ICU were detected to be invasive mechanical ventilation (IMV) (n=52; 59.8%), IMV plus noninvasive mechanical ventilation (NIMV) (n=26; 29.9%) and only NIMV (n=9; 10.3%), respectively.

Distribution of ages and genders did not demonstrate statistically significant difference with respect to mortality rates (P >0.05) (Table 2).

Hospitalization times of the cases with respect to mortality rates were statistically significantly different (P=0.014). Hospitalization times of the cases with mortality were significantly longer than those survived.

A statistically significant difference was found between intubation times of the cases and mortality rates (P=0.001). Mortality rates in cases with longer intubation times were comparatively higher.

A statistically significant and greater difference was found between stages of malignancy and mortality rates. Mortality rates in cases with stage 2 malignancies did not differ (P >0.05). Mortality rates in stage 3 cases were lower than those who survived. (P=0.012). However, mortality rates in stage 4 cases were significantly higher than those who survived (P=0.002) (Figure 1). Mortality rates in cases with various types of malignancies did not demonstrate

TABLE 1. The main characteristics of the patients.

		Mean ± SD (min-max)
Age		64.07 ± 11.90 (31-88)
Sex (F/M), n (%)		13 (14.9%) / 74 (85.1%)
Duration of hospitalisation (days)		12.95 ± 16.48 (1-105)
Duration of intubation (days)		11.73 ± 17.49 (0-105)
APACHE II		24.35 ± 7.48 (11-49)
		n (%)
Malignancy type (n=87)	Thoracic	52 (59.8%)
	Extrathoracic	35 (40.2%)
Thoracic malignancy type (n=52)	Small-cell lung cancer	11 (21.2%)
	Non-small cell lung cancer	41 (78.8%)
Malignancy stage (n=79)	Stage 2	6 (7.6%)
	Stage 3	22 (27.8%)
	Stage 4	51 (64.6%)
Indication of hospitalization	Respiratory failure	35 (40.2%)
	Respiratory failure + additional indications	37 (42.5%)
	Others	15 (17.2%)
Prognosis	Non-survived	50 (57.5%)
	Transferred to another center	6 (6.9%)
	Discharged	31 (35.6%)
ICU support	Mechanical ventilation	52 (59.8%)
	Mechanical ventilation + noninvasive mechanical ventilation	26 (29.9%)
	Noninvasive mechanical ventilation	9 (10.3%)

ICU= Intensive care unit

TABLE 2. Factors affecting prognosis.

		Prognosis		P *Value*
		Non-survivors	Survivors	
		mean±SD	mean±SD	
Age (years)		63.52 ± 13.55	64.81 ± 9.34	[a]0.601
Duration of hospitalisation (days) *(Median)*		15.26±17.55 (10.5)	9.84±14.57 (6.0)	[b]0.014*
Duration of intubation (days) *(Median)*		14.18 ± 17.75 (10.5)	7.52 ± 16.48 (4.0)	[b]0.001**
		n (%)	n (%)	
Gender	Male	42 (84.0%)	32 (86.5%)	[c]0.986
	Female	8 (16.0%)	5 (13.5%)	
Malignancy stage (n=79)	Stage 2	2 (4.2%)	4 (12.9%)	[d]0.204
	Stage 3	8 (16.6%)	14 (45.2%)	[c]0.012*
	Stage 4	38 (79.2%)	13 (41.9%)	[c]0.002**
Malignancy type (n=87)	Thoracic	24 (64.9%)	28 (56.0%)	[c]0.404
	Extrathoracic	13 (35.1%)	22 (44.0%)	
Thoracic malignancy type (n=52)	Small-cell lung cancer	6 (25.0%)	5 (17.9%)	[d]0.530
	Non-small cell lung cancer	18 (75.0%)	23 (82.1%)	
ICU support	Mechanical ventilation	38 (76.0%)	14 (37.8%)	[c]0.001**
	Mechanical ventilation + noninvasive mechanical ventilation	11 (22.0%)	15 (40.5%)	[c]0.103
	Noninvasive mechanical ventilation	1 (2.0%)	8 (21.7%)	[d]0.004**
Indication of hospitalization	Acute Respiratory failure	25 (50.0%)	10 (27.0%)	[e]0.031*
	Respiratory failure + additional indications	20 (40.0%)	17 (46.0%)	[c]0.737
	Others	5 (10.0%)	10 (27.0%)	[c]0.073

[a]Student-t Test; [b]Mann-Whitney U Test; [c]Yates' Continuity Correction Test; [d]Fisher's Exact Test; [e]Pearson Ki-square Test; *P<0.05; **P<0.01.

statistically significant differences (P >0.05). Mortality rates according to the ICU support were analyzed and mortality rates in cases who received IMV support were found to be significantly higher (P=0.001). While any significant difference was not detected between cases who received IMV or NIMV support (P >0.05), mortality rates were found to be significantly lower in our cases reinforced with NIMV support (P=0.004). Statistically significant differences were found between indications for hospitalization and mortality rates (Figure 2). In cases who were hospitalized with the diagnosis of respiratory failure, mortality rates were significantly higher (P=0.031). In cases who were hospitalized with the diagnosis of respiratory failure and an additional indication mortality rates did not comparatively demonstrate statistically significant differences (P >0.05). However in patients hospitalized in ICUs for other indications, mortality rates were found to be significantly lower (P=0.073) (Table 3).

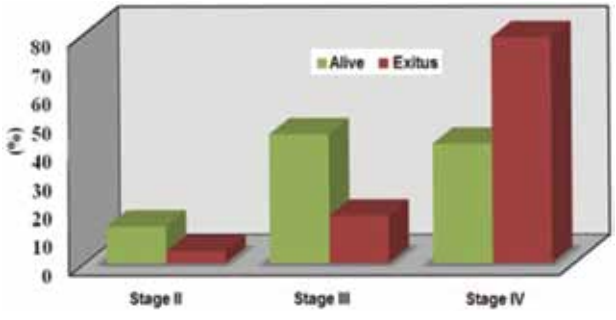

FIGURE 1. Mortality rates according to the stages.

In our study where a total of 87 cases were analyzed, 37 (42.5%) patients survived. Mean and median survival times were 21.73±3.83 and 15 days, respectively. In a total of 87 cases, 37 (42.5%) patients survived, while 50 cases of death were observed. Mean and median survival times were 6.78±1.81 months and 16.8 days, respectively. Six and

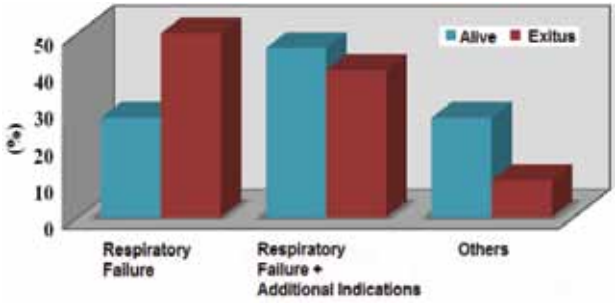

FIGURE 2. Mortality rates according to the indications for hospitalization.

TABLE 3. Other indications of hospitalization.

	n (%)
Cardiac arrest	5 (5.7%)
Acute renal failure	3 (3.4%)
Sepsis	3 (3.4%)
Myocardial infarction	3 (3.4%)
Haemoptysis	1 (1.1%)

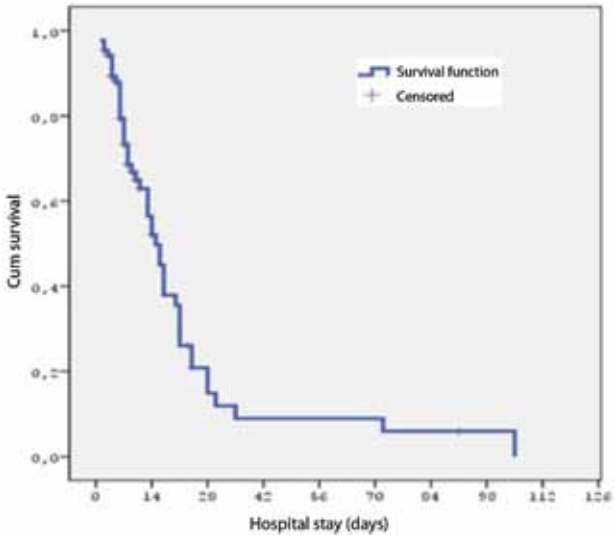

FIGURE 3. Kaplan-Meier survival graph of study group.

12 month-survival rates were similar (29.7±5.4%) (Figure 3). In thoracic group, 24 (46.2%) cases survived, while 24 patients died with a mean survival time of 19.916±4.423 days. While in extrathoracic cancers 13 (37.1%) cases survived and 22 patients died with a mean survival time of 23.308±5.973 days (Table 4). Survival rates were evaluated according to malignancies using Log Rank test and any statistically significant difference was not found between survival rates (P=0.730; P >0.05). Fourteen (26.9%) cases survived and 38 patients died in the IMV support group with a mean survival time of 20.910±3.977 days. While in the IMV+NIMV support group, 15 (57.7%) cases survived and 11 patients died with a mean survival time of 15.395±2.017 days. In the NIMV group, 8 (88.9%) patients survived and one patient died with a mean survival time of 8.286±0.661 days (Table 5). Survival rates were evaluated based on ventilation support using Log Rank test and any statistically significant difference was not found between survival rates (P=0.796; P >0.05). In the group with SCLC, 6 (54.5%) patients survived, while 5 cases died with a mean survival time of 29.575±11.882 days. Among NSCLC cases, 18 (43.9%) cases survived, while 23 patients died with a mean survival time of 15.172±2.033 days (Table 4). Survival rates were evaluated based on types of malignancies using Log Rank test and a statistically significant difference was not detected between survival rates (P=0.168; P >0.05).

TABLE 5. Survival analysis according to ventilation support type.

	N		NS	S	Survival rate	Survival time (days)
					Mean±SE	Median
IMV	52	38	14	26.9%	20.910±3.977	14.00
IMV+NIMV	26	11	15	57.7%	15.395±2.017	16.00
NIMV	9	1	8	88.9%	8.286±0.661	-

Abbreviations: NS: Non-survivors, S: Survivors, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation.

TABLE 4. Survival analysis according to thoracic malignancy type.

	n	Exitus	Survivor	Survival rate	Duration of survival (days)	
					Mean ± SD	Median
Small-cell lung cancer	11	5	6	54.5%	29.575±11.882	21.00
Non-small cell lung cancer	41	23	18	43.9%	15.172±2.033	14.00

Kaplan-Meier Analysis

DISCUSSION

The cancer-related deaths have been increasing world wide. If incidence rates of cancer patients persist, dependent on the increased world population and aging of the people, a total of 19.3 million newly developed cases with cancer will be observed in the year 2025. It has been demonstrated that more than half of the cancer cases (56.8%) and cancer-specific deaths (64.9%) occurred in underdeveloped countries[1]. Lung cancer is most frequent type among cancer-related deaths. Mortality rates are gradually increasing in stage 3 and 4 cancers[3,10].

In line with increases in cancer diagnoses and related mortality rates, the number of referrals to hospitals has increased and admissions into ICUs have also proportionally increased. Cases with lung cancers constitute 16% of all cancer patients admitted into ICUs[11]. In 1993, 18% of cancer patients were hospitalized in the ICUs and in 2003 its rate increased to 25 percent[12]. With usage of invasive and noninvasive support in the ICUs, increase in survival times has been targeted. Treatment in ICUs is costly which requires due responsibility and also incurs burden on ICU physicians, patients and their intimates. Overall treatment cost of the ambulatory patients and those hospitalized in ICU was calculated as $27.160 and $40.929, respectively (P <0.001)[12,13]. Advances within years should not be underestimated. When increases in actual survival rates in cancer patients relative to past incidence rates and enhanced levels of knowledge and experience in the field of intensive care are considered, health care of these patients in the ICUs should be managed very carefully. Patients who will need aggressive treatments and more or less support should be carefully discriminated. We think that multidisciplinary approaches are needed which will develop objective criteria in the patient selection targeting at decreased mortality, morbidity and improved quality of life in cancer patients in the ICU. This approach will invalidate the term "cemetery" used for ICUs. These approaches can be realized only with the collaboration of ICU specialists, oncologists and other specialists who will be needed during care and treatment of these patients.

A total of 87 cancer patients were monitored in authors' respiratory ICU. These patients were statistically analyzed using Kaplan – Meier analysis and mortality rates in lung and extrathoracic cancer patients were observed to be 50 and 63%, respectively. Among lung cancer patients, any statistically significant difference was not detected between survival rates of small-cell and non-small cell lung cancers, This lack of difference was associated with relatively small number of small-cell lung cancers (SCLC n=11, NSCLC n=41) . In their study, Bonomi et al reported mortality rate in patients with only stage IIIB and IV non-small cell lung cancer as 33%, while they indicated 90-day and 1-year mortality rates as 71 and 90%, respectively[14]. Chou KT et al reported 30-day mortality rate as 58.6% in stage III and IV lung cancer patients who had been hospitalized in the ICU with the indication of sepsis-related acute respiratory failure[15]. In a study by Slatore et al the authors detected 6-month mortality rate as 64 percent[16]. Toffart et al reported ICU and in-patient mortality rates as 69 and 52%, respectively, while the corresponding 90-day and 1-year survival rates were 37 and 12%, respectively[8].

Indications for hospitalizations included acute respiratory failure (n=35), acute respiratory failure plus an additional indication (n=37; pneumonia, hemoptysis, malignant effusion, empyema, pulmonary embolism, acute coronary syndrome, mediastinitis, febrile neutropenia, gastrointestinal bleeding) and other indications (n=15; encephalitis, post-CPR myocardial infarction, acute renal failure, ileus, gaseous gangrene, sepsis). A total of 87 patients enrolled into the study were hospitalized in the ICU with the diagnosis of lung (n=52; 60%) and extrathoracic cancer (n=35; 40%). Acute respiratory failure was the most frequently encountered symptom in lung cancer patients and also the most frequently observed indication for the hospitalization of extrathoracic cancer patients in the ICU. Toffart et al reported indications for hospitalization in the ICU as acute respiratory failure (n=58), shock (n=27), neurological complications (n=7) and other indications (n=11). They detected etiological factors which led to respiratory failure as infection (n=18), airway obstruction (n=9), tumoral obstruction of the airway (n=7), vena cava superior syndrome (n=2), pneumothorax (n=7), pulmonary embolism (n=4), pleural effusion (n=4), hemoptysis (n=4), aacut pulmonary edema (n=4) and other indications (n=6). In current series, the most frequent causes of acute respiratory failure was infection (n=13) and airway obstruction (n=11).

Factors effective on survival rates were analyzed and Adam et al[7] indicated these factors as vasopressor use and two or more organ failure. In a study by Roques et al prognostic factors were determined as mechanical ventilation, performance scores ≥2 and acute respiratory failure[9]. In our study, distribution of ages and genders did not demonstrate statistically significant differences (P >0.05). However, ICU stays differed significantly. Mean ICU stay and intubation times were 12.95±16.48 and 11.73±17.49 days, respectively. Mortality rates increased

in paralel with ICU hospitalization and intubation times. In compliance with the general literature, mortality rates increase in line with the stage of the lung cancer of the patients[10,17].

Type of the the ventilation support has been also detected as another factor effective on mortality rates. In cases who received IMV support mortality rates were significantly higher than those who had only NIMV support. A significant difference in mortality rates was not observed between only NIMV users and successive usage of NIMV and IMV supports. The data obtained resemble to those reported by Slatore et al in 2012[16]. In the study by Slatore et al only less than 20% of the patients who received MV were discharged and 6 months later only 15% of the patients could survive.

Still, in a study where mechanical ventilation was correlated (75.4%) with increased mortality rates, predictive factors were determined as invasive aspergillosis, undiagnosed cases, vasopressor use, delayed onset of mechanical ventilation and failed noninvasive mechanical ventilation[17,18]. In a study performed on stage III-IV NSCLC patients aged >65 years, sepsis, respiratory, cardiac, neurological and renal failures were recorded and old age (>65) was detected as a major prognostic factor[14].

In a study by Toffart et al., any correlation between 90-day mortality and referral hospital, indication for ICU stay, NIMV use or length of ICU stay was not detected[8]. However, a correlation was detected between mortality rates and presence of ECOG-PS >2, metastatic disease at admission into the ICU, use of vasoactive drug within 72 hours following hospitalization in the ICU or worse LOD score or SAPS II. Three-month survival rates were similar in patients with or without NIMV support, but they were lower in patients who received IMV support. This finding was comparable to our outcomes.

Highest mortality rates were detected in cancer patients admitted into ICUs with the indication of only respiratory failure, while as a striking finding, relatively lower, though not statistically significant rates were found in cancer patients hospitalized in the ICU.

Detection of statistically significantly higher levels of hemoglobin and hematocrit in cases with lung cancer is thought to be related to pre-existing COPD and hypoxia developed secondary to lung cancer. Counts of white blood cells, platelets and other biochemical analytes did not demonstrate differences dependent on types of malignancies. However, CRP levels were found to be significantly higher in patients with lung cancer. APACHE II scores of the patients did not demonstrate significant differences among different types of malignancies. Mean APACHE II score was calculated as 12.7 in a study conducted by Medarov et al and in oıur study they were 6.98 and 8.09 in patients with lung and extrathoracic cancers, respectively[19]. Anisoglou S et al declared that their data shown improving outcome of lung cancer patients in medical intensive care unit. They also stated that further studies of patients selected to ICU admission are needed to assess long-term mortality, quality of life, ability to continue chemotherapy and economic cost[20].

In the present study, factors effective on the outcomes of our study were determined as[1] prolonged hospitalization period[2], longer intubation times[3], stage IV NSCLC[4], application of invasive mechanical ventilation and[5] acute respiratory failure.

CONCLUSION

In conclusion, the factors affecting on mortality are considered, admission of cancer patients into an ICU should be based on certain objective criteria. Besides, ICUs should not be units treating agony and they should provide health care services for more active patients whose life will be prolonged and become more qualified with treatment. ICUs should be reserved for the maintenance therapy of cancer patients. Establishment of ICUs should be considered with the expectation of improvement of respiratory system and recovery of the respiratory capacity of the patients. The patient with the diagnosis of advanced cancer, should be informed and interviewed before decision to hospitalize him/her in the ICU. Especially the decision of intubation and ventilatory support should be given by exact criteria. The patients and their intimates should be informed about potential complications and treatments. Since any guidelines for the admission of cancer patients into ICUs and their management in ICU have not been established yet, decisions including admission of these patients into ICUs should be based on multidisciplinary consensus. We think that guidelines formulated based on the outcomes of multi-centered, larger-scale studies performed in the future, will facilitate the management and decision-making process related to these patients.

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