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Evaluation of the Prognosis of Cancer Patients Treated in Intensive Care Units

Yoğun Bakımda Tedavi Edilen Kanser Hastalarının Prognozunun Değerlendirilmesi

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ABSTRACT *Objective:* The number of cancer cases and mean life expectancy are increasing with improvements in diagnosis and treatment options. This increase creates the need for intensive care units (ICUs) for cancer patients. This study aimed to determine the risk factors associated with admission of cancer patients to the ICU, intensive care prognosis, and mortality rates and cost per patient.

Materials and Methods: In this study, we analyzed the data of cancer patients who were followed up in Pamukkale University Faculty of Medicine, Anesthesiology ICU. The variables that were analyzed included intensive care prognosis, mortality rates, risk factors affecting mortality, and cost per patient. ICU patient's folders, epicrisis reports, and follow-up documents of 251 patients with solid or systemic malignancies who were admitted to the ICU of Pamukkale University Faculty of Medicine, Anesthesiology Department for a period of two-years were analyzed.

Results: The most common reason for admission to ICU for patients with solid or systemic malignancies was respiratory failure 63.34% (n=159) followed by sepsis 16.33% (n=41) and cardiac arrest 5.17% (n=13). According to the cancer staging of the patients, 58.5% (n=147) were classified as stage 4 and 16.3% (n=41) as stage 3. The cost per patient per day in the ICU ranged from 186.86 Turkish Liras (TL) to 4407.39 TL and the mean cost was 1628.49±524.12 TL. The mortality rate among these cancer patients was 89.2%.

Conclusion: Most of the cancer patients died in the ICU with high medical expenses. When patients are evaluated for admission to the ICU, the patient's primary physician and ICU physician should reach a consensus as to whether the patient is in a terminal condition or not and whether palliative care should be administered to them.

Keywords: Cancer, intensive care unit, prognosis

ÖZ *Amaç:* Tanı ve tedavi seçeneklerinin artmasıyla kanser olgularının sayısı ve ortalama yaşam beklentisi artmaktadır. Bu artış kanser hastaları için yoğun bakım ünitesine (YBÜ) duyulan ihtiyacı beraberinde getirmektedir. Bu çalışmada kanser hastalarının YBÜ'ye yatış risk faktörleri, yoğun bakım prognozu, ölüm oranları, mortaliteyi etkileyen risk faktörleri ve hasta başına maliyeti araştırmak amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada Pamukkale Üniversitesi Tıp Fakültesi, Anesteziyoloji YBÜ'de izlenen kanser hastaları ile ilgili değişkenler analiz edildi. Yoğun bakım prognozu, mortalite oranları, mortaliteyi etkileyen risk faktörleri ve hasta başına maliyet gibi değişkenler analiz edildi. Pamukkale Üniversitesi Tıp Fakültesi, Anestezi ve Reanimasyon Anabilim Dalı'na iki yıl süre ile başvuran katı veya sistemik malignitesi olan 251 hastanın YBÜ hasta dosyaları, epikriz raporları ve takip belgeleri incelendi.

Bulgular: En sık başvuru nedeni solunum yetersizliği %63,34 (n=159) idi, bunu sepsis %16,33 (n=41) ve kalp durması %5,17 (n=13) izledi. Hastaların kanser evrelemesine göre %58,5'i (n=147) evre 4, %16,3'ü (n=41) evre 3 olarak sınıflandırıldı. YBÜ'de hasta başına günlük maliyet 186,86 Türk Lirası (TL)-4407,39 TL ve ortalama maliyet 1628,49±524,12 TL'dir. Bu kanser hastalarının mortalite oranı %89,2 idi.

Sonuç: Kanser hastasının çoğu yüksek YBÜ giderleri ile yoğun bakımda eks oldu. Hastalar YBÜ'ye kabul için değerlendirildiğinde, hastanın birincil hekimi ve YBÜ doktoru, terminal olup olmadıkları ve onlara palyatif bakım verilmesi gerekip gerekmediği konusunda fikir birliğine varmalıdır.

Anahtar Kelimeler: Kanser, yoğun bakım ünitesi, prognoz

Introduction

Intensive care units (ICUs) have become important for the oncology patients. 15% of all ICU admissions is cancer patients (1). There are several reason for admission to ICU such as severe acute illnesses, postoperative care after major surgical resections, severe cancer, chemotherapy-radiation related complications. However, there is still a lot of debate, which medical interventions performed in patients with terminal oncologic illness benefit the patient around the world. Many countries have different approaches in the management of these groups depending on their medical, legal, ethical, cultural and economic structures. Scientific and ethical perspectives continue to be debated whether the purpose of treatment should focus on the patient's life span or whether it is aimed at quality of life, termination of treatment, withdrawal of life support and indications for resuscitation (2,3).

Acute respiratory failure is the major cause of ICU admissions in critical cancer patients. Hospital mortality in critical cancer patients 60-80% in those undergone mechanical ventilation (4). Factors potentially affects patients' outcomes should be known to make appropriate management decisions. The patient's age, organ failure status, diagnosis, functional status, illness severity index and the need of vasopressors were shown to inşuence the ICU admission (2,4). In this study, it was aimed to study the risk factors for admission to ICU of cancer patients, intensive care prognosis, mortality rates, risk factors that affecting mortality and cost of per patient.

Materials and Methods

After the Local Ethics Committee of the Pamukkale University, Medical School approval (decision no: 60116787-020/3413, date: 10.01.2017), solid or systemic malignancy patients admitted to ICU were evaluated for two years. Postoperative malignancy patients were excluded from the study. This study were done retrospectively. Patient files and bills were examined.

The demographic data of the patients, type of malignancy, location and duration of malignancy were recorded. In intensive care follow-up forms, hemodynamic parameters of the patient, laboratory value and clinical data are recorded. From twenty-four hours after admission data, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score is calculated. Patients ventilation parameters such as orotracheal intubation and taken to support mechanical ventilation. Non-invasive or invasive mechanical ventilation times were recorded as days. The presence of organ failure was checked and recorded. Non-invasive or invasive mechanical ventilation support was accepted as respiratory failure; initiation of vasopressor was accepted as circulation failure; renal replacement therapy was accepted as renal insufficiency. Hospital cost per patient were recorded. Length of stay in ICU and hospital were also determined.

Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis. Student's t-test was used for comparison of normal distribution parameters and Mann-Whitney U test was used for abnormal distribution parameters. Pearson chi-square test was used to compare qualitative data. Pearson correlation analysis was used in evaluating the relationships between the parameters and mortality. Kaplan-Meier Survival Analysis was used to assess survival. Statistical significance was accepted at $p<0.01$ and $p<0.05$ levels.

Results

Two hundred and fifty one cases were included to the study; 37.1% (n=93) were female and 62.9% (n=158) were male. Patients' ages ranged from 29 to 84 years with an average of 61.91±12.09 years.

When the causes of intensive care and admission are examined; the most common is acute respiratory failure (n=159), of which 143 are exitus and 13 are discharge. This is followed by sepsis (n=41), of which 38 are exitus and 3 are discharge.

Distribution of malignancy type and its location is examined; 8,94% of patients is (n=22) acute myeloid leukemia, 8.13% of patients is (n=20) small cell lung cancer and 8.13% of patients is (n=20) lung squamous cell carcinoma. The other malignancy type and location are shown in Table 1. Because of no pathological diagnosis, five of 251 cases were accepted as new diagnoses.

Systolic blood pressure and heart rate data of the patients ranged from 40 to 220, with mean ± standard deviation (SD) 130.03±39.17 and ranging from 54 to 160, with with mean ± SD 101.70±20.15. Patients' clinical parameters related intensive care and hospital periods are shown in Table 2.

The length of stay in the ICU ranged from 1 to 51 days, with an mean ± SD of 4.69±5.51 days. Of the cases, 10.8% (n=27) survived and 89.2% (n=224) were exitus (Table 3).

Table 1. Malignancy type and location (n=246)					
Malignancy type and location	**n**	**%**		**n**	**%**
Lung adeno Ca	11	4.47	Breast invasive ductal carcinoma	4	1.63
Lung small cell	20	8.13	Breast carcinoma	1	0.41
Lung squamous cell	20	8.13	Breast malign epithelial TM	1	0.41
ALL	8	3.25	Breast squamous cell	3	1.21
ALL and B-cell lymphoma	1	0.41	Bladder urothelial carcinoma	5	2.04
AML	22	8.94	Gastric adeno Ca	8	3.25
Ampulla vateri TM	1	0.41	Stomach cohesive carcinoma	3	1.21
Brain lymphoma	3	1.21	Gastric GIST	2	0.82
Renal cell Ca	10	4.06	Gastric carcinoma	1	0.41
Caecum adeno Ca	2	0.82	Gastric signet ring cell	1	0.41
Endometrium adeno Ca	2	0.82	Multiple myeloma	3	1.21
Endometrium sarcoma	1	0.41	Nasal cavity malign melanoma	1	0.41
Undifferentiated endometrium Ca	3	1.21	Nasopharynx Carcinoma	8	3.25
Epithelial TM	1	0.41	Non-Hodgkin	6	2.43
Kaposi sarcoma	1	0.41	Over adeno Ca	4	1.63
CLL	6	2.43	Over squamous cell	1	0.41
Cholangiocellular carcinoma	2	0.81	Esophagus adeno Ca	3	1.21
Colon adeno Ca	11	4.47	Pancreas adeno Ca	9	3.66
Colon squamous cell Ca	2	0.82	Pancreas carcinoma	3	1.21
Laryngeal carcinoma	3	1.21	Prostate adeno Ca	11	4.47
Lymphoma	1	0.41	Rectum adeno Ca	11	4.47
Leukemia	1	0.41	Renal cell	1	0.41
Malign epithelial TM	1	0.41	Klatskin tumor	2	0.82
Mantle cell lymphoma	2	0.82	Squamous cell	2	0.82
Breast adeno Ca	12	4.88	CNS lymphoma	1	0.41
Breast ductal carcinoma	1	0.41	T-cell leukemia-lymphoma	3	1.21

Ca: Cancer, CLL: chronic lymphocytic leukaemia, GIST: gastrointestinal stromal tumors, CNS: central nervous system, AML: acute myelocytic leukemia, ALL: acute lymphoblastic leukemia

There was no statistically significant difference between the ICU mortality and the mean age and sex of the cases (p>0.05). There was a statistically weak correlation between systolic blood pressures at admission and mortality [exitus: 100.67±20.38 and survive: 110.30±16.17 (r =0.14, p=0.019)]. There was no statistically significant relationship between intensive care mortality and presence of infection (r=0.04, p>0.05), receiving of chemotherapy (r=0.08, p>0.05) and type of feeding (r=0.10, p>0.05).

There was no statistically significant correlation between length of malignancy diagnosis and intensive care mortality (r=0.05, p>0.05) while it was found statistically weak significant correlation between mortality and APACHE-II levels (r=0.18, p<0.01) and PaO_2/FiO_2 ratio (r=0.17, p<0.01). There was no statistically significant correlation between mortality and organ failure (p=0.078, r=-0.15) and vasopressor requirement (p=0.087, r=0.13). It was found statistically significant correlation between mortality and metabolic acidosis (r=0.36, p<0.01) and mechanical ventilation (r=0.53, p<0.01) (Table 4). According to the cancer staging of the patients, 58.5% (n=147) of the patients were classified as stage 4 and 16.3% (n=41) as stage 3.

Mortality and length of ICU stay (r=0.23, p<0.05) and hospital stay (r=0.17, p<0.01) significantly correlated. Of the 251 patients in ICU; while there were 27 cases survive (10.8%); 224 (89.2) mortality were observed. The median survival time is 3±0.24 days.

Table 2. Patients' clinical parameters (n=251)		
	Min-max	**Mean ± SD**
Duration of malignancy diagnosis (month)	0.25-170	20.83±25.22
APACHE-II	17-50	31.92±5.94
PaO_2/FiO_2 rate	68-473	195.93±87.71
Mechanical ventilation duration (day)	0.25-41	4,32±4,68
	n	**%**
Metabolic acidosis (no/yes)	176/75	29.9%/70.1%
Mechanical ventilation (IMV/NIMV)	241/10	96%/4%
Organ failure (no/yes)	135/113	54.4%/46.6%
Organ failure (1)	82	72.5%
Organ failure (2)	31	27.5%
Vasopressor (no/yes)	166/85	66.1%/33.9%
Renal replacement therapy (no/yes)	176/75	70.1%/29.9%

SD: Standard deviation, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, min: minimum, max: maximum

Table 3. Patients' length of stay in ICU/hospital and mortality		
	Min-max	**Mean ± SD**
Length of stay in ICU (day)	1-51	4.69±5.51
Length of stay in hospital (day)	1-61	13.10±11.82
	n	**%**
Discharge status (ex/survive)	224/27	89.2/10.8
Discharge (ward/home)	14/13	5.6/5.2

ICU: Intensive care unit, SD: standard deviation, min: minimum, max: maximum

Average cost of the patients was 8103.79±8189.17 Turkish Liras (TL). The daily cost of 251 patients in ICU was between 186.86TL-4407,39 TL and mean was 1628,4-49±524,12 TL. Total cost of the patients was 1,912,900 TL for 1,175 hospital days. Total cost of dead patients was 1,465,200 TL for 900 days of hospitalization.

Discussion

In this study it was found the most common reason for admission was respiratory failure, followed by sepsis and cardiac arrest. Cost of the per patient per day in ICU was between 186,86 TL-4407,39 TL and mean cost was 1628,49±524,12 TL. Mortality rate of these cancer patients was 89.2%.

Patients with malignancy are serious patient groups that result in higher ICU and hospital mortality rates than patients without malignancy. In recent years, a number of studies have been conducted to identify the causes associated with reduced mortality in cancer patients and to reduce mortality with early intervention. Many clinicians are able to avoid aggressive treatment in patients with high mortality. Health providers often discuss the necessity of treatments such as mechanical ventilation, vasoactive agents, and renal replacement therapy in end-stage cancer patients (5,6).

The cause of hospital admission is also effect on mortality. There are variety of reasons for intensive care in malignant patients in different studies. In the most studies sepsis, acute respiratory failure, shock, renal failure are common causes of admission (7,8). Kress et al. (8) found that respiratory failure was the most common cause of hospitalization in malignancy patients. In another study, it was reported that life-threatening organ failure and infection had the most frequent admission criteria patients with cancer. There is a strong correlation between the number of organ failure and high mortality (9). In malignancy patients, respiratory failure and sepsis were shown as the most common cause of intensive admission (10). In our study in accordance with many studies in the literature, we found that the most common cause of admission to ICU was respiratory failure (63.34%, n=159), followed by sepsis (16.33%, n=41) and cardiac arrest (5.17%, n=13).

Different mortality ratios have been reported in studies that involving a large number of case series for patients followed up in ICUs. Andréjak et al. (11) shown that mortality rates were 46% in advanced lung cancer patients whereas Kress et al. (8) found that intensive care mortality was 41% in cancer patients. Adam and Soubani (12) reported 22% mortality rate in the study. They pointed out that this resulted from patient selection. Intensive care mortality rate ranged from 30% to 100% in many studies (4,8,11,12). These conflicting results are due to the reasons such as differences in the type of cancer, the patients' comorbidities, the effectiveness of treatment of the underlying cancer, intensive care admission criteria, whether or not the admitted patients are in terminal period, and differences in end-of-life care. The mortality of postoperative cancer patients is lower than that of medical patients (13). In our study, mortality rate reported 89.2% (n=224) of patients with malignancy. Our mortality rates were higher than most of the studies due to the fact that 58.5% (n=147) of the patients were classified as stage 4 and 16.3% (n=41) as stage 3 for disease staging.

Different studies have shown various independent risk factors for mortality in cancer patients. Patients with

Table 4. Relationship intensive care mortality and clinical parameters				
	Ex (n=224)	Survive (n=27)	p	r
[b]Length of diagnosis	20.37±25.51	24.52±22.47 (3)	0.397	0.05
[a]APACHE-II	32.31±5.77	28.70±6.48	0.001	0.18
[b]PaO_2/FiO_2	190.54±87.72	240.70±75.09	0.003	0.17
[b]Length of stay ICU	7.46±6.00	4.71±5.42	0.020	0.23
[b]Length of stay hospital	14.56±14.74 (10)	25.24±23.23 (19)	0.002	0.17
[c]Metabolic acidosis (-)	153 (53.7%)	25 (64.3%)	0.007	0.36
Metabolic acidosis (+)	73 (46.3%)	2 (35.7%)	-	-
[c]IMV	222 (95.1%)	19 (48.6%)	0.001	0.53
NIMV	2 (4.9%)	8 (51.4%)	-	-
[c]Organ failure (-)	115 (29.3%)	20 (94.3%)	0.078	-0.15
Organ failure (+)	106 (70.7%)	7 (5.7%)	-	-
[c]Vasopressor (-)	144 (43.9%)	22 (95.7%)	0.087	0.13
Vasopressor (+)	80 (56.1%)	5 (4.3%)	-	-
[a]Student's t-test, [b]Mann-Whitney U test, [c]Pearson chi-square, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, ICU: intensive care unit				

hematological malignancies, had stem cell transplantation, presence of organ failure, presence of infection, need for mechanical ventilation, vasopressor requirement, poor performance status and low PaO_2/FiO_2 ratio was found to be associated with increased mortality in ICU (7,9,14,15). Correlation between the number of organ failure and high mortality rates was reported in cancer patients in ICU. Necessity of mechanical ventilation was shown to be the strongest factor affecting survival (7). In our study, low systolic blood pressure measurements, APACHE-II, PaO_2/FiO_2 ratio, the presence of metabolic acidosis, invasive mechanical ventilation requirement, length of stay in ICU were significantly correlated with mortality.

Some studies shown that there is a relationship between prolonged ICU stay and high mortality, while some studies suggest that there is no relationship between those. Soares et al. (16) examined the length of stay in ICU cancer patients. They accepted 21 days as prolonged length of stay in ICU, and found that 15% of the patient were prolonged ICU stay. The mean of the stay in ICU was 11.2 days. Sepsis and acute respiratory failure has been reported 48% of total intensive care bed days with prolonged stay. There was a relationship between ICU stay and intensive care infections and mechanical ventilation. In another study, the prolonged ICU stay was associated with increased mortality (17). Multiple organ failure and necessity of mechanical ventilation has led to the longer stay of ICU. In our study, the ICU stay was 4.69±5.51 days (range: 1-51 days) and hospital stay was 13.10±11.82 days (range: 1-127 days). There was a statistically significant correlation between intensive care mortality and length of stay in ICU and in the hospital.

Acute respiratory failure is common in critical cancer patients and usually requires mechanical ventilation support. Azoulay et al. (18) found that the use of noninvasive mechanical ventilation reduced the 30-day mortality, but emphasized that the use of high FiO_2 in noninvasive mechanical ventilation also increased mortality. In a multicenteric European study of cancer patients and non-cancer intensive care patients, mortality was higher in mechanically ventilated cancer patients than in mechanically ventilated non-cancer patients (19). In our study, 96% (n=241) of the cases required invasive mechanical ventilation and 4% (n=10) of non-invasive mechanical ventilation. In agreement with the European study, there was a statistically significant correlation between intensive care mortality and invasive mechanical ventilation requirement ($r=0.53$, $p<0.01$).

Renal replacement therapy ranges from 8% to 13% in solid tumors, ranging from 10% to 34% in hematologic malignancies (15,19). In our study, 70.1% (n=176) of the patients was not required renal replacement therapy while 29.9% (n=75) was.

Thirty percent of the total health expenditure of the United States is spent in terminal illness whereas 80% of this money was spent in the last month of the life for

aggressive life support treatments in the hospital and especially in the ICU (20,21). Aygencel and Türkoğlu (22) reported that the total number of invoices for terminal cancer patients in the ICU was 581352,2 TL with mean 677.6 TL/day of hospitalization. With the transfer of the intensive care patient ($3,500/day) to the palliative care unit ($1,500/day), health spending is reduced by $ 2,000 per day (44). In our study, the mean cost of patients in ICU is 8103,79±8189,17 TL (range of 223,4 TL-431956,22 TL. Total cost of dead patients was 1,465,200 TL for 900 days of hospitalization.

Death with dignity or euthanasia includes allowing certain adult patients to request a medication that will end their lives, should they choose to take it. Since death with dignity is not legal nationwide, including government healthcare systems, cannot be used for physician-assisted dying services. Additionally, patients must find a physician who is willing to participate, and many are against the act for either personal or religious reasons. In the future, the right to die for advanced cancer patients will be discussed among the patient, their family and their primary physician, and the patients in this situation will be followed up in separate departments instead of intensive care.

Our study has several limitations. First, it was included the small number of patients from a single center. Second, it was conducted retrospectively. In addition, do not resuscitate, do not intubate, the withholding and withdrawal of life support could not be applied actively to our patients because of the legal reservations.

Conclusion

The patient who does not have anything to do medically and expects to die must have the peace and certain comforts. It is obvious that the search for and desired peaceful environment can not be provided in a hospital bed, especially in an ICU. The tests, practices and care that are made in this unit for the patient have little impact on their life span or quality of life. Money is being spent in very high amounts for end of life cancer patients. In the ICUs, there are many problems related to inadequate team and equipment, limited resources and the distribution of services. These units must be triaged for reasons such as lack of improvement in the treatment and care of the ICUs, inadequacy of the budget and health worker, and low number of ICU beds.

The decision as to whether or not to admit a critically ill cancer patient to the ICU is difficult. Their medical problems along with their cancer disease underscore a need for an individual approach to this patient population. The decision to apply life-sustaining treatment in these patients involves weighing the potential benefit against a futility. Identification of factors associated with outcomes would help physicians, patients and families in determining the goals of treatment. In the meantime, cooperation of the ICU team with palliative care specialists that is the most appropriate way to make decisions in the context of uncertainty.

Ethics

Ethics Committee Approval: The study was approved by the Pamukkale University Non-Invasive Clinical Research Ethics Committee (decision no: 60116787-020/3413, date: 10.01.2017).

Informed Consent: This study were done retrospectively. Patient files and bills were examined.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Data Collection and Process: G.K., Analysis or Interpretation: H.S., Literature Search: S.K., Writing: H.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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