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Clinical, Demographic Characteristics and Short-Term Prognosis of Cancer Patients Presenting to the Emergency Department

Acil Servise Başvuran Kanser Hastalarının Klinik, Demografik Özellikleri ve Kısa Dönem Prognozu

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ABSTRACT

Aim: *The aim of this study was to determine the demographic findings, clinical features, short-term mortality/ factors affecting mortality in cancer patients admitted to the emergency department.*

Material and Method*: This is a cross-sectional and retrospective study. This study was carried out with 204 patients with a diagnosis of cancer who presented to the emergency department. Clinical and demographic characteristics and short-term mortality status of the patients were analysed.*

Results: *The study was conducted with a total of 204 patients, 111 (54.4%) males and 93 (45.6%) females, with a mean age of 62.63 ± 14.16 years. Six patients presented with hematologic malignancy and 198 patients (97.1%) presented with solid malignancy. The number of patients with ≥3 comorbidities was 28 (13.7%) and the most common presenting complaint was gastrointestinal problems (26%). The most common performance score was 3 in 85 (41.7%) patients, while only 20 patients with a performance score of 4 were identified. Eighty-five (41.7%) of the patients were hospitalized. Mortality was observed in 9 patients (4.4%) in the emergency department, 22 patients (10.8%) within 1 week and 33 patients (16.2%) within 28 days. In cancer patients with a performance score of 4, the mortality rate was 75% at the end of week 1 and 90% at the end of 28 days. Multiple admissions, performance score 4, ≥3 comorbidities and metastasis were found to be significant predictors of 1-week and 28-day survival.*

Conclusion: *Mortality of cancer patients is high, and factors affecting mortality have been identified. These conclusions may provide significant pieces of information regarding the development of algorithms designed to determine the care needs of cancer patients in the Emergency Department.*

Keywords: *Cancer, Emergency department, Prognosis*

ÖZET

Amaç: *Bu çalışmanın amacı, acil servise başvuran kanser hastalarının demografik bulgularını, klinik özelliklerini, kısa dönem mortalite/ mortaliteyi etkileyen faktörleri belirlemektir.*

Gereç ve Yöntem: *Bu çalışma kesitsel ve retrospektif bir araştırmadır. Bu çalışma kanser tanısı olup, acil servise başvuran 204 hasta ile gerçekleştirildi. Hastaların, klinik, demografik özellikleri, kısa dönem mortalite durumları incelendi.*

Bulgular*: Çalışma, yaş ortalaması 62.63 ± 14.16 yıl olan, 111'i (%54.4) erkek ve 93'ü (%45.6) kadın olmak üzere toplam 204 hasta ile gerçekleştirilmiştir. Altı hasta hematolojik malignite ve 198 hasta (%97.1) solid malignite ile başvurmuştur. ≥3 komorbiditesi olan hasta sayısı 28 (%13.7) hasta iken, en yaygın başvuru şikayeti gastrointestinal problemler (%26) olmuştur. En sık görülen performans skoru 85 (%41.7) hasta ile 3 iken, performans skoru 4 olan sadece 20 hasta tespit edilmiştir. Hastaların 85'i (%41.7) hastaneye yatırılmıştır. Acil serviste 9 (%4.4) hastada, 1 hafta içinde 22 hastada (%10.8) ve 28 gün içinde ise 33 hastada (%16.2) mortalite gözlenmiştir. Performans skoru 4 olan kanser hastalarında mortalite oranı 1. hafta sonunda %75, 28 gün sonunda ise %90 olarak bulunmuştur. Birden fazla başvuru, performans skorunun 4, ≥3 sayıda komorbidite ve metastaz olması 1 hafta ve 28 günlük sağkalımın anlamlı belirleyicileri olarak bulunmuştur.*

Sonuç: *Kanser hastalarının mortalitesi yüksek olup, mortaliteyi etkileyen faktörler tespit edilmiştir. Bu sonuçlar, acil serviste kanserli hastaların bakım ihtiyaçlarını belirlemeyi amaçlayan algoritmaların geliştirilmesi için önemli bilgiler sağlayabilir.*

Anahtar Kelimeler: *Kanser, Acil Servis, Prognoz*

INTRODUCTION

Cancer is an international public health issue. The International Cancer Research Agency reported 18 million new cancer cases and 9.6 million deaths tied to cancer in the year 2018 (Fauvel et al., 2023). Cancer patients apply to the emergency department more often than the general public and the emergency services play a significant role in the management and care of these patients (Lash et al., 2017). Cancer treatments aim to increase survival and improve patients' quality of life. However, cancer patients demonstrate morbidity and mortality at significant rates. Thus, extremely defenseless, insecure, and fragile cancer patients seeking the care of the emergency services often send their applications (de Santis et al., 2022).

As the prevalence of cancer increases alongside the survival rates of cancer patients, the rates of their visits to the emergency department may also increase (Lee et al., 2021). This increase in cancer cases reflects the increased number of visits made to the emergency department globally. In the USA, over 4.5 million cancer patients apply to the emergency department each year (Caterino et al., 2019).

Approximately two thirds of cancer patients' applications to the emergency services result in hospitalization (Caterino et al., 2019; Vandyk et al., 2012). This circumstance confirms that the emergency department is a critical unit handling patients' acute problems and the continuity of cancer management. Moreover, when the busy clinical atmospheres of emergency departments are considered, these patients lead to the formation of circumstances that are difficult to manage for emergency service personnel and there are not enough studies regarding the properties of these patients (Lash et al., 2017). The acquisition of knowledge regarding the clinical and demographical properties of cancer patients who apply to emergency services holds critical importance in the management of symptoms, the improvement of patients' quality of lives, and the reduction of morbidity.

Cancer patients may apply to the emergency services for various complaints unrelated to the development of the stage of the tumor, complications regarding their treatments, or cancer. Thus, some ontological emergency situations may have an atypical appearance and, if not diagnosed correctly, may lead to increased morbidity and mortality. In this regard, The aim of this study was to determine the demographic findings, clinical features, short-term mortality/ factors affecting mortality in cancer patients admitted to the emergency department.

MATERIAL AND METHOD

Research Type

This study is a cross-sectional and retrospective research.

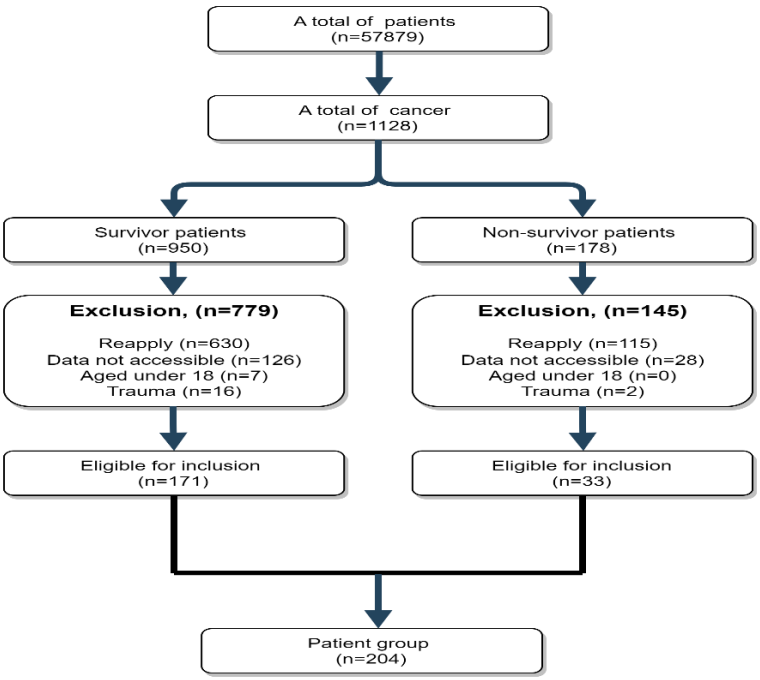

Figure 1. Flowchart for inclusion in the study

Study Population and Sample

The electronic database of the hospital was scanned for all patients who met the inclusion criteria. In the working year of 2021, a total of 57879 visits to the emergency department was recorded, with 1128 of them being by cancer patients (Figure 1). Patients who were under the age of 18, whose medical information could not be accessed through the hospital automation, and those applying to the emergency department due to trauma were excluded from the study. Repeated hospital applications occurred, varying from 1 to 9 time(s). A total of 204 cancer patients who applied to tertiary emergency departments were included in the study (Figure 1).

Data Collection

This study was conducted in a tertiary university hospital emergency department between January 1, 2021 and December 31, 2021. Comorbidity [hypertension, the coroner artery disease, congestive cardiac failure, diabetes mellitus, the chronic obstructive respiratory disease, dementia, cerebrovascular diseases, other (gastrointestinal diseases, kidney diseases, rheumatic diseases)], their demographical properties (age, gender), the number of visits to the emergency department, the duration of stay in the emergency department, the primary location of the cancer [gastrointestinal (pancreas, stomach, colon, rectum, pancreas), respiratory system, skin/musculoskeletal, urogenital system, central nervous system, breast, hematologic cancers, head and neck cancers], their original application complaints, the stage of the cancer, their treatment statuses, and their final statuses in the emergency department were retrospectively evaluated. ICD-10 was used for diagnostic evaluation. The classification of cancer patients was made as early stage, regional and metastatic. Patients' performance status was determined according to the Eastern Cooperative Oncology Group (ECOG) Scale (Table 1) (Bozdemir et al. 2009). In addition, it was determined by obtaining permission from the relevant institution and examining 7-day and 28-day death data from the "Death Report System". This study was conducted in the form of a retrospective scan through accessing patient files from the hospital information system and the hospital archive. Patients' age, gender, length of stay in the emergency department, hospitalisations and fatalities within 7-day or 28 days were analysed according to the performance score.

Ethics Consideration

This study was a cross-sectional and retrospective study and approval was obtained from the scientific research ethics committee of the university before the study (Date: 19.10.2022 and Approval Number: 2022-10/31). The necessary permission for the study was obtained from the institution where the study took place.

Data analysis

Data obtained from our study was evaluated through the use of IBM SPSS Statistics 22 (IBM Statistical Package for Social Sciences Corp., Armonk, NY, ABD). For descriptive statistics regarding continuous data, mean averages, standard deviation, medians, interquartile ranges (IQR), discrete data, numbers, and percentages were provided. Suitability for normal distribution was determined with the Kolmogorov-Smirnov test. The inter-group evaluations of non-parametric variables [Length of stay, hospitalization, mortality (within 7-day), mortality (within 28-day)] were analyzed through Kruskal Wallis multi-comparisons. In the logistic regression model, our dependent variables were death (survival) in 7-day and 28-day after ED admission. For logistic regression analyses, respiration (shortness of breath > 20 breath/min), pulse rate (tachycardia > 100 beat/min), systolic blood pressure (>140 mmHg), diastolic blood pressure (>90 mmHg), body temperature (fever >36.5 °C), and stage of the disease (patients with early stage, regional or metastatic disease) were evaluated. $P<0.05$ was accepted to be statistically significant.

Table 1. Performance Score of Cancer Patients

	Performance score
Fully active, able to carry on all pre-disease activities without restriction	0
Restricted physically strenuous activity but ambulatory and able to carry out activities of a light or sedentary nature	1
Ambulatory, capable of a self-core but unable to carry out any work activities; up and about more than 50% of waking hours	2
Capable of only limited self-core; confined to bed or chair 50% or more of waking hours	3
Completely disabled, cannot carry on any self core; totally confined to bed or chair	4

Kaynak: Bozdemir et al. 2009

RESULTS

The study was conducted with a total of 204 patients whose age average was 62.63 ± 14.16 years, with 111 of them (54.4%) of them being male and 93 of them (45.6%) being female. The patients' original complaints at the time of their applications to the health department have been depicted in detail (Table 2).

Table 2. Chief Complaints and Symptoms for Emergency Departments Visits Among People with Cancer

Chief complaint	Symptoms
Pain	Back pain, headache, limb pain, other pain
Respiratory	Respiratory distress, shortness of breath, cough, hemoptysis, pneumonia, acute bronchitis
Fever	Chills, fever, febrile neutropenia
Gastrointestinal	Bloating, gastroenteritis, anorexia, nausea, vomiting, diarrhea, food poisoning, abdominal pain, gastrointestinal bleeding
Neurologic	Altered mental status, dizziness, drowsiness, encephalitis, seizures
Malaise/fatigue	Weakness, fatigue, eating/drinking disorder
Urological	Hematuria, dysuria
Cardiovascular	Chest pain, hypertension, palpitations
Other	Psychiatric problems, dermatological problems
	Penetrating sharps injuries, trauma patients (such as traffic accidents and falls), burns, intravenous drug therapy, prescription writing.

During the study period, the hospital's electronic database was retrospectively searched for all patients who met the inclusion criteria, and 1128 admissions belonging to 204 cancer patients were identified and evaluated from 57879 patients presenting to the emergency department. The patient flow chart is presented in Figure 1.

In the working year of 2021, 57879 visits were made to the emergency department, with 1128 of them being made by patients with cancer diagnoses. When repeated applications are considered, the rate of the patients applying to the emergency department was 1128/57879 (≈ %2).

Six patients presented with hematological malignancy and 198 (97.1%) with solid malignancy. 23 patients were in early stage, 65 had localised tumours and 116 had metastases at the time of emergency department presentation. 61 patients presented to the emergency department for the first time, 28 patients presented twice, and 115 (56.4%) patients presented ≥3 times. Comorbidity status of cancer patients in the study was analysed and no comorbidity was found in 51 patients. While 68 patients had one comorbidity, 57 patients had two comorbidities, the number of patients with ≥3 comorbidities was 28 (13.7%). The most frequent performance score was 3 with 85 (41.7%) patients and there were only 20 (9.8%) patients with a performance score of 4 (Table 3). 85 of the patients were hospitalised and 9 (4.4%) patients died in the emergency department. The 7-day and 28-day mortality rates of the patients were analysed and mortality was observed in 22 (10.8%) patients within 7-day and in 33 (16.2%) patients within 28 days (Table 3).

The most common complaints were gastrointestinal problems (26%), followed by pain (25.5%) and lung problems (19.1%). Gastrointestinal, lung and breast cancers were the most common types. The most common comorbidities were COPD 56 (27.5%), hypertension 47 (23%), coronary artery disease 46 (22.5%) and diabetes mellitus 45 (22.1%) (Table 4).

The distribution of performance score results is shown in Table 5. Age (P<0.001), waiting time in the emergency department (P=0.012), hospitalization (P=0.004), mortality within 7-day and 28-day (P<0.001) were found to be significant in terms of performance score. In cancer patients with a performance score of 4, the mortality rate was 75% at the end of the 7-day and 90% at the end of 28 day (Table 5).

In multivariate analysis to determine the independent predictors of 7-day mortality, more than 1 application (OR:1.17, 95% CI:1.16-3.26, P<0.001), performance score 4 (OR:28.3, 95% CI: 5.2-152.2, P<0.001), ≥3 number of comorbidities (OR:1.61, 95% CI: 0.65-3.98, P<0.001), tachycardia (OR:2.43, 95% CI: 1.18-6.12, P=0.021) and stage of cancer (metastasis) (OR:14, 95% CI: 2.1-136.5, P=0.005) were significant (Table 6).

Table 3. Demographic Data of the Study Population

Variable	N	%
Age	62.63±14.16	
ED length of stay (hours) median (IQR)	4 (2-8)	
Gender		
Female	93	45.6
Male	111	54.4
Cancer type		
Solid	198	97.1
Hematological	6	2.9
Number of visit ED		
1	61	29.9
2	28	13.7
≥3	115	56.4
Number of comorbidities		
0	51	25.0
1	68	33.3
2	57	27.9
≥3	28	13.7
Performance score		
PS0	28	13.7
PS1	37	18.1
PS2	34	16.7
PS3	85	41.7
PS4	20	9.8
Stage of canser		
Early-stage	23	11.3
Locoregional	65	31.9
Metastasis	116	56.9
Receiving treatment		
Yes	182	89.2
No	22	10.8
ED outcome status		
Hospitalization	85	41.7
Discharged	110	53.9
Exitus	9	4.4
Mortality (within 7-day)		
Yes	22	10.8
No	182	89.2
Mortality (within 28-day)		
Yes	33	16.2
No	171	83.8

ED: emergency department, IQR: Inter Quantile Range.

Table 4. Patients' Complaints, Localization of Malignancies and Comorbidities

Complaints	**N**	**%**
Gastrointestinal problems	53	26.0
Pain anywhere	52	25.5
Lung problems	39	19.1
General condition disorder	28	13.7
Fever	12	5.9
Neurological problems	7	3.4
Urological problems	7	3.4
Cardiovascular system problems	4	2.0
Other*	2	1.0
All (visits)	204	100
Malignancy		
Gastrointestinal	76	37.3
Respiratory system	51	25.0
Breast	25	12.3
Urogenital system	25	12.3
Central nervous system	9	4.4
Skin, musculoskeletal	8	3.9
Hematologic cancers	6	2.9
Head and neck cancers	4	2.0
Comorbidity		
COPD	56	27.5
Hypertension	47	23
Coronary Artery Disease	46	22.5
Diabetes Mellitus	45	22.1
Cerebrovascular Disease	31	15.2
Congestive Heart Failure	22	10.8
Dementia	18	8.8
Other**	19	9.3

Other*: psychiatric problems, dermatologic problems, sharps injuries, trauma patients (such as traffic accidents and falls), burns, intravenous drug treatment, prescription writing, Other**: gastrointestinal diseases, renal diseases, rheumatologic diseases, COPD: Chronic obstructive pulmonary disease.

Table 5. Outcomes of Cancer Patients According to Performance Score

	Performance score						**p**
	All (n=204)	**0** (n=28)	**1** (n=37)	**2** (n=34)	**3** (n=85)	**4** (n=20)	
Age, median [years] (IQR)	64.5 (24-90)	38.5 (24-76)	55 (32-66)	59.5 42-73)	72 (55-90)	76 (61-90)	<0.001
Female sex, n (%)	93 (45.6)	16 (57.1)	17 (45.9)	17 (50)	35 (41.2)	8 (40)	0.612
Length of stay (hours)	4 (2-8)	4 (2-6)	4 (2-6)	4 (2-8)	5 (2-8)	5 (2-8)	0.012
Hospitalization, n (%)	85 (41.7)	6 (21.4)	15 (40.5)	9 (26.5)	46 (54.1)	9 (45.0)	0.004
Mortality (within 7-day), n (%)	22 (10.8)	0 (0)	0 (0)	0 (0)	7 (8.2)	15 (75)	<0.001
Mortality (within 28-day), n (%)	33 (16.2)	0(0)	0 (0)	0 (0)	15 (17.6)	18 (90)	<0.001

IQR: Inter Quantile Range

In multivariate analyses of the factors predicting mortality within 28 days, more than 1 application (OR:1.79, 95% CI: 1.17-2.75, P<0.001), performance score of 4 (OR:50.22, 95% CI: 6.90-365.19, P<0.001), ≥3 comorbidities (OR:1.30, 95% CI: 0.59-2.85, P<0.001), long ED wait (OR:0.91, 95% CI: 0.57-1.44, P=0.040), cancer stage (metastasis) (OR:32.2, 95% CI: 7.1-192.3, P<0.001) were found significant (Table 6).

Table 6. Independent Factors Predicting 7-Day and 28-Day Mortality

Variable	OR	95% CI	p
7-Day Mortality			
More than 1 application	1.17	1.16-3.26	<0.001
Performance score of 4	28.3	5.2-152.2	<0.001
≥3 Number of comorbidities	1.61	0.65-3.98	<0.001
Tachycardia	2.43	1.18-6.12	0.021
Stage of canser (metastasis)	14	2.1-136.5	0.005
28-Day Mortality			
More than 1 application	1.79	1.17-2.75	<0.001
Performance score of 4	50.22	6.90-365.19	<0.001
≥3 Number of comorbidities	1.30	0.59-2.85	<0.001
ED long residence time (hours)	0.91	0.57-1.44	0.040
Stage of canser (metastasis)	32.2	7.1-192.3	<0.001

OR: Odds ratio

DISCUSSION

In the study, the emergency department leanings of oncology patients, their epidemiological properties, and their 7 day/28 day survival was researched. The conclusions of the study could be utilized in order to guide recommended applications designed to increase the coordination of patient care and the appropriate management of symptoms, to ensure that palliative or supportive care is managed in time, and to further develop care giving models.

This study showed that emergency physicians deal with at least 3 cancer patients a day during routine clinical practice. This number highlights the importance of cancer patient care in the ED and why emergency physicians need to know how to manage a patient with cancer. In the study, it was determined that ≈2% of individuals who applied to the emergency department were oncology patients. Previous results reported from the United States of America have stated that from 1.4% to 4.2% of adult emergency department visits were regarding cancer (Rivere et al. 2017; Hsu et al. 2018; Scholer et al. 2017), and a country-wide study conducted in France reported that 2.8% of emergency department visits were regarding cancer (Peyrony et al. 2020). These pieces of data support the findings of this study.

In our study, 7-day and 28-day mortality was found to be significantly higher in patients with metastases. Consistent with our data, many studies have reported that it may be a clinically important indicator of distant stage or worse survival in cancer patients presenting to the emergency department, gastrointestinal and lung cancers (Bozdemir et al. 2009; Polednak 2000; McArdle et al.).

The hospitalization rate in our study was 41.7%. In previous studies, hospitalization rates were different, ranging from 28.9% to 57.2% (Lee et al 2021; Caterino et al. 2019; Kim et al. 2021). Literature data regarding hospitalization numbers and data belonging to our study depict close numbers.

In this study, the most commonly observed comorbidities were, in order; the chronic obtrusive lung disease (COPD), hypertension, the coroner arteries disease (CAD), and diabetes mellitus. The number of patients with at least one comorbidity was 153 (75%). Previous studies have reported that cancer patients have comorbidities at significant rates, which is consistent with our study (Panigrahi et al. 2021; Fowler et al. 2020; Carrillo-Estrada et al. 2021). Some circumstances leading to comorbidity also play a role in the formation of cancer. Comorbidity may hide symptoms, cause confusions and difficulties in diagnoses, and increases morbidity/mortality (Sarfati et al. 2016). The existence of one or more comorbidities in cancer patients may also impact their prognoses. Thus, we believe that doctors providing care to patients applying to the emergency department must be extremely mindful in this regard.

In this study, it was determined that the visits of individuals with cancer occurred most commonly due to gastrointestinal system (37.3%), lung (25.0%), breast (12.3%), and urogenital system (12.3%) cancers. Studies conducted in the USA and Korea reported that the most common admissions of people with cancer to the emergency department were gastrointestinal cancers, and the second most frequent was lung cancer (Lee et al. 2021; Gallaway et al. 2021; Min et al. 2022). Other studies in the literature have handled gastrointestinal cancers (colon, rectum, pancreas, and liver) individually. Our study, on

the other hand, evaluated these aforementioned cancer variations as gastrointestinal cancers, and our data has been presented accordingly. When this circumstance is considered, our data and the data of the literature is consistent in terms of the observation frequencies of these cancer types. However, our data differ from the Global Cancer Obervatory data in terms of incidence. The first reason for this difference is that our data do not reflect the whole population since they are limited to the emergency department. Secondly, we think that regional factors may be effective, and lastly, considering the most common complaints, we think that patients in these cancer groups may face more complaints that will present to the emergency department.

The most frequent application complaints of the patients were gastrointestinal problems, pain, lung problems, and general condition disorders. Similarly to other studies, our conclusions have demonstrated that aching, gastrointestinal complaints, and lung problems, the most commonly observed primary complaints, are similar (Chen et al. 2020; Koch et al. 2022; Kim et al. 2021). Our data is consistent with other studies. However, high incidence of nausea and vomiting and pain can be also interpreted as a result of insufficient supportive care at outpatient clinics and this may cause more ED admissions. Probably, advanced adjunctive therapeutic approaches including effective pain management and anti-emetics at outpatient clinics may decrease ED presentations of cancer patients.

Of the patients in our study, mortality occurred in the emergency department in 4.4%, within 7-day in 10.8%, and within 28 days in 16.2%. According to other study data in the literature, the mortality rates of patients within 30 days after applying to the emergency department vary between 5.8% and 30.7% (Caterino et al. 2019; Lee et al. 2021; Kim et al. 2021; de Santis et al. 2022). Our data are consistent with other studies.

One of the important aspects of this study is the use of the ECOG performance score (Bozdemir et al. 2009). This scoring system is used by oncologists to evaluate cancer patients in follow-up clinics. Since the performance score contains practical and easily evaluable parameters, we think that it is also useful, simple and applicable for emergency physicians. In multivariate analysis, multiple admissions, poor ECOG performance status, ≥3 Number of comorbidities, and metastatic disease stage were highly predictive of both 7-day and 28-day short-term mortality. Additionally, ED long residence time (hours) has a significant predictive value for 28-day mortality. In the study conducted by Bozdemir et al., more than 1 presentation, tachycardia and performance score of 4 parameters were found to be highly predictive for 1-month mortality (Bozdemir et al. 2009). These factors may help in decision making for more aggressive treatment and hospitalization.

Our study includes some limitations, the first of which is the fact that the study was conducted retrospectively. Retrospective study design may lead to some biases. The study was conducted in a single center, tertiary care emergency department. Thus, more studies in different regions must be conducted in order to corroborate our findings. Thus, these limitations of our study may have impacted our conclusions.

CONCLUSION

In conclusion, this study reports that cancer patients account for ≈ 2% of admissions to emergency departments, that a significant portion of them (41.7%) are hospitalised, that 75% of the patients demonstrated at least one comorbidity, and that 16.2% of patients demonstrated mortality within 28 days. Aching and gastrointestinal complaints were the leading reason behind cancer patients' applications to the emergency department. Gastrointestinal cancers were the most commonly observed. This study showed that the ECOG performance score has a very high power in determining the short-term prognosis of cancer patients presenting to the emergency department. We believe that our study provides valuable information about the emergency department visits of cancer patients and the outcomes of these visits.

Ethics Committe Approval

Ethics committee approval was received for this study from the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (Date: 19.10.2022, and Aproval Number: 2022-10/31).

Author Contributions

Idea/Concept: Ş.Ç., P.Ç.; Design: Ş.Ç., P.Ç.; Supervision/Consulting: Ş.Ç. P.Ç.; Analysis and/or Interpretation: Ş.Ç.; Literature Search: Ş.Ç., P.Ç. Writing the Article: Ş.Ç.; Critical Review: Ş.Ç., P.Ç

Peer-review

Externally peer-reviewed.

Conflict of Interest

The authors have no conflict of interest to declare.

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