



Association of the Hospitalization and in-hospital Mortality Rates with Aspartate Aminotransferase, Alanine Aminotransferase, Lactate Dehydrogenase, C-Reactive Protein, and Prothrombin Time Levels in Cancer Patients Admitted to the Emergency Department

Sedat BİLGE, Yahya Ayhan ACAR

Department of Emergency Medicine, University of Health Sciences, Gülhane School of Medicine, Ankara-Turkey

OBJECTIVE

This study determined predictive risk factors for hospitalization and in-hospital mortality (IHM) in cancer patients presenting to the emergency department (ED).

METHODS

Patients diagnosed with cancer who visited the general ED were reviewed retrospectively for the period from October 01, 2016, to April 01, 2019. We recorded age, sex, triage category, and vital signs at ED admission and laboratory results of blood samples collected in the ED. Data were analyzed to evaluate the association of the abovementioned parameters with rates of hospitalization and IHM.

RESULTS

We enrolled 493 patients (males 283 [57.4%], females 210 [42.6%]; mean age \pm SD [range] 59.58 \pm 17.07 [18–96] years). The overall hospitalization rate was 26.4%; IHM occurred in 90 (18.3%) patients. Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and C-reactive protein (CRP), as well as the prothrombin time (PTT) differed significantly between hospitalized and non-hospitalized ($p=0.001, 0.003, 0.011, 0.020, \text{ and } 0.031$; respectively) patient groups and the survivor and non-survivor ($p<0.001, 0.015, <0.001, <0.001, \text{ and } 0.005$; respectively) hospitalized patient groups.

CONCLUSION

Vital signs, liver function tests, and coagulation parameters at ED admission could predict IHM of cancer patients. These parameters must be evaluated in oncology patients admitted to the ED.

Keywords: Cancer; coagulation; emergency department; hospitalization; mortality.

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Introduction

Cancer is the second most prevalent cause of mortality across all leading causes of death.[1] There is an increasing incidence of malignant tumors worldwide,

and a progressively higher frequency of emergency department (ED) visits by cancer patients due to various reasons.[2] Oncology patients constitute a risk group across ED patients.[3] The incidence of ED visits ranges from 7% to 12% in cancer patients, and some

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Dr. Yahya Ayhan ACAR,
Gülhane Tıp Fakültesi,
Sağlık Bilimleri Üniversitesi,
Acil Tıp Anabilim Dalı,
Ankara-Turkey
E-mail: yahyaacar@gmail.com

risk factors for ED visits, such as the black race, male gender, advanced age, medication non-adherence, and living alone, have been previously reported.[4] Most cancer patients need hospitalization in the last months of their lives and their frequency of ED visits increases due to inadequate provision of palliative care.[4] However, ED crowding is increasingly a problem, and cancer patients often experience longer ED waiting times due to their possible multisystem pathologies.[5] In addition to the systemic effects of malignancy, the potential for metastatic organ involvement may result in excessive use of hospital resources, such as laboratory procedures and various imaging tools, during the ED stay of cancer patients.[5]

Most ED admissions or visits of cancer patients are not due to cancer-related problems; instead, are attributable to pain, nausea, vomiting, infection, local mass effect, pleural effusion, ascites, chemotherapy/radiotherapy side effects, and hematologic or metabolic disorders.[6-8] Because patients admitted to the ED need a multidisciplinary approach and as the oncology, palliative care, and intensive care units are similarly overburdened as the ED, it is crucial for the emergency physician to be aware of the characteristics and risk factors of cancer patients for effective resource management and swiftly making a precise diagnosis.

This study was conducted to determine the risk factors for hospitalization and in-hospital mortality (IHM) in adult ED patients with cancer.

Materials and Methods

This retrospective observational study was approved by the Non-Interventional Research Ethics Committee, Gülhane School of Medicine, University of Health Sciences (approval no. 19/253, June 11, 2019). We reviewed the patient charts and records in the Hospital Data Management System to identify patients who presented to the general ED of the hospital in the period from October 1, 2016, to April 1, 2019. Patients with a diagnosis of any type of cancer were eligible for study inclusion. We excluded patients younger than 18 years, with missing data, of patients referred to an external treatment center (Fig. 1).

For the eligible cancer patients included in this study, we identified and recorded the following information: age, gender, triage category, and vital signs at admission; test results of complete blood count, routine biochemistry, coagulation panels, cardiac panels, and blood gas parameters obtained at ED visit; and whether the patients arrived at the ED by ambulance

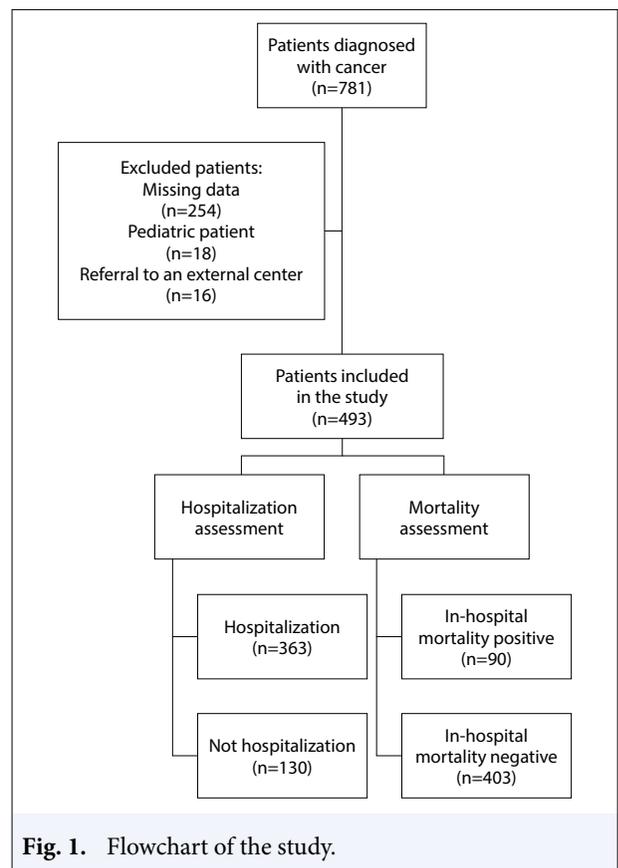


Fig. 1. Flowchart of the study.

or underwent cardiopulmonary resuscitation (CPR) in ED. Triage categories were classified according to the Turkish Ministry of Health triage system, which comprises different codes to specify priority to ED patients: a black code indicates patients with the cardiopulmonary arrest at the admission; a red code indicates patients who need emergent resuscitative efforts for survival; a yellow code specifies patients who require close observation, multiple resources (e.g., laboratory, radiological, intravenous intervention), having a high-risk medical history (e.g., diabetes, pregnancy, prior heart attack), or admitted with a critical complaint (e.g., chest pain, severe abdominal pain), as they may be stable but at the risk of immediate danger; and the green code is for patients with stable vital signs (such as pulse rate, respiratory rate, body temperature, oxygen saturation, arterial blood pressure), without any critical complaints, and are not expected to develop a dangerous medical condition during their ED stay.[9]

We stratified our study participants into hospitalized and non-hospitalized patient subgroups, as well as a survivor (no-IHM) and non-survivor hospitalized patient (IHM) groups, based on mortality from the time of hospitalization until discharge.

Statistical Analysis: Demographic data were presented as frequencies and percentages. Normally distributed continuous variables are presented as mean and standard deviation, whereas non-normally distributed variables were presented as the median and interquartile range (IQR). The chi-square test was used for the comparison of two groups concerning categorical variables. The Mann–Whitney U test and Student’s t-test were used for pairwise comparisons of continuous data that did not or did conform to a normal distribution, respectively. All statistical analyses were conducted in SPSS 18.0 software. A p-value of <0.05 was considered statistically significant.

Power Analysis: For an alpha value of 0.05, 80% power, enrollment ratio of 1, and an expected hospitalization rate of 50%, we calculated that this study should include 338 patients.

Results

We identified 781 patients, excluded 288 patients, and included 493 patients (males 283 [57.4%], females 210 [42.6%]; mean age±SD [range] 59.58±17.07 [18–96] years) in this study, a study flowchart presents patient disposition (Fig. 1). There were no significant between-group differences in age and sex between the hospitalized and non-hospitalized patient groups and the no-IHM and IHM groups (Table 1). The mean length of ED stay was 189.50 (IQR: 91–321.25) minutes.

The commonest presenting complaints were pain (n=187, 37.9%), fever (n=71, 14.4%), nausea/vomiting (n=56, 11.4%), and dyspnea (n=55, 11.2%). The presenting complaints were not significantly different in the hospitalization and IHM groups (Table 2). Moreover, 327 (66.3%) arrived at the ED by ambulance and 166 (33.7%) by their vehicles. Stratification of triage codes indicated 138 (28.0%) red triage, 350 (71.0%) yellow triage, and 5 (1.0%) black triage code patients; no cancer patients were assigned a green triage code. We detected a statistically significant relationship between the triage codes and hospitalization rates (p=0.001, chi-square test), but this was not related to IHM (p=0.431, chi-square test).

Among the patients who visited the ER, 130 (26.4%) were hospitalized and 363 (73.6%) were discharged; moreover, 16 (3.2%) patients were transferred from the ED to another hospital. The hospitalized patients were further stratified by hospitalization in the medical oncology clinic (n=182, 36.9%), intensive care unit (n=18, 3.7%), palliative care clinic (n=2, 0.4%), and other clinical departments (n=202, 59.0%). Sixteen (3.2%) patients underwent cardiopulmonary resuscitation

Table 1 Comparison of the demographic data and vital signs at presentation by the hospitalization and in-hospital mortality status

Parameter	Hospitalization				In-Hospital Mortality			
	n	Mean±SD	95% CI	p	n	Mean±SD	95% CI	p
Age	130 Hospitalized	61.56±16.32	-0.87-5.98	0.261*	403 IHM negative	59.20±17.37	-6.57-1.25	0.257*
Gender (Male/Female)	363 Discharged	59.01±17.29	N/A	0.05**	90 IHM positive	61.86±15.56	N/A	0.480**
	65/65 Hospitalized	N/A	N/A	0.885*	228/175 IHM negative	N/A	N/A	<0.001*
Pulse	218/145 Discharged	95.27±26.49	-8.11-12.73	0.593***	55/35 IHM positive	90.57±18.47	-14.41-(-4.85)	0.032***
	15 Hospitalized	92.96±19.75	-7.31-12.78	0.850*	253 IHM negative	100.20±22.64	0.45-9.79	0.009*
Mean arterial pressure	326 Discharged	110.84±26.02	-2.59-2.80	0.850*	80 IHM positive	109.55±16.62	1.12-3.62	0.009*
	15 Hospitalized	108.11±19.00	94.18±5.03		254 IHM negative	104.43±25.30		
Oxygen saturation	327 Discharged	94.29±4.43			88 IHM positive	94.81±3.40		
	14 Hospitalized	94.18±5.03			224 IHM negative	92.44±7.63		

*: Mann-Whitney U test; **: Chi-Square test; ***: Student’s t-test; IHM: In-hospital mortality; SD: Standard deviation

Table 2 Distribution of the patients' complaints

Symptoms	n (%)	Hospitalized/ not hospitalized	p*	With IHM/ without IHM	p*
Fever	71 (14.4)	52/19	0.582	12/59	0.067
Nausea and vomiting	56 (11.4)	37/19		8/48	
Shortness of breath	55 (11.2)	41/14		20/35	
Weakness, fatigue	18 (3.7)	13/5		2/16	
Epilepsy, hemiplegia, neurological	15 (3.0)	12/3		4/11	
Bleeding	13 (2.6)	11/2		1/12	
Syncope	13 (2.6)	12/1		3/10	
Renal insufficiency	10 (2.0)	5/5		1/9	
Palpitations, hypotension	10 (2.0)	6/4		2/8	
Diarrhea, constipation	6 (1.2)	5/1		2/4	
Other	39 (7.9)	29/10		4/35	
Pain	187 (37.9)	140/47		31/156	
Total	493 (100)	363/130		90/403	
• Acute pain	120 (24.3)	87/33	0.087	20/100	0.252
• Abdominal pain	41 (8.3)	36/5		9/32	
• Chest pain	15 (3.0)	8/7		0/15	
• Low back/musculoskeletal pain	7 (1.4)	6/1		2/5	
• Headache	4 (0.8)	3/1		0/4	

*: Chi-square test; IHM: In-hospital mortality

during the ED stay, and IHM occurred in 90 (18.3%) patients. The identified infections were pneumonia (n=22, 4.5%), urinary tract infections (n=16, 3.2%), upper respiratory tract infections (n=6, 1.2%), cellulitis (n=6, 1.2%), biliary tract infections (cholecystitis; n=1, 0.2%), and pancreatitis (n=1, 0.2%).

We detected significant between-group differences in the levels of hemoglobin (Hb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), lactate, and prothrombin time (PTT) (Tables 1-4) in the hospitalized and non-hospitalized groups. Moreover, we found significant between-group differences in the pulse rate, diastolic blood pressure, oxygen saturation (SaO₂), white blood cell count (WBC), PTT, and international normalized ratio (INR), and the levels of glucose, urea, AST, ALT, LDH, CRP, PTT, troponin, and lactate (Tables 1-4) in the IHM and no-IHM groups.

Discussion

The results of the present study show that emergency physicians can predict the IHM of cancer patients via a detailed examination of the vital signs, liver function tests, and coagulation parameters at the time of ED admission.

The age and sex distribution of cancer patients admitted to the ED were consistent with the reports in the

literature.[5-8] Given that cancer is commonest at the advanced age (fifth and sixth decades), our study had a distribution of cancer patients who visited the ED that was in agreement with this information. As cancer patients constitute a risk group among other patients with ED, they are hospitalized more commonly compared to the non-cancer patients.[1,5-7] Moreover, the IHM rate among cancer patients in our study was consistent with reports in the available literature [7,8,10,11], which supports the more frequent observation of high-risk triage categories and more frequent hospitalizations in our study.

Conventional cancer treatment includes chemotherapy and radiotherapy. Cancer staging determines the treatment modality and mortality in these patients but has limited value for the emergency physician.[12] This is because acute and life-threatening conditions, such as hematological disorders (e.g., neutropenia, bleeding diathesis), symptoms due to compression by primary or metastatic mass, acute pain, predisposition to thromboembolic events, as well as radiotherapy- and chemotherapy-induced immunosuppression, are primarily evaluated during ED procedures.[12] In the present study, these conditions are indicated by an increase in infective parameters, such as WBC, CRP, bleeding diathesis (caused by INR elevation), and increased levels of liver enzymes. Therefore, we recom-

Table 3 Comparison of the laboratory parameters by the hospitalization and in-hospital mortality status

Parameter	Hospitalization					In-hospital Mortality				
	n	Mean±SD	95% CI	p	IHM status	n	Mean±SD	95% CI	p	
White blood cell count	Discharged	113	9.86±10.06	-8.02-1.26	0.358*	IHM negative	362	10.40±12.07	-15.61 -(-5.45)	<0.001*
	Hospitalized	333	13.24±24.38			IHM positive	84	20.93±42.45		
Hemoglobin	Discharged	113	11.43±2.42	0.09-1.15	0.023**	IHM negative	364	11.02±2.51	-0.29-0.89	0.330**
	Hospitalized	335	10.81±2.51			IHM positive	84	10.73±2.45		
Hematocrite	Discharged	113	33.77±7.21	-0.21-2.87	0.090**	IHM negative	363	32.92±7.18	-0.98-2.45	0.398**
	Hospitalized	334	32.44±7.12			IHM positive	84	32.18±7.34		
Glucose	Discharged	108	154.79±93.66	-14.85-29.39	0.243*	IHM negative	355	153.07±103.31	-4.45-44.09	0.031*
	Hospitalized	330	147.52±103.97			IHM positive	83	133.25±92.04		
Urea	Discharged	110	71.20±65.29	-17.05-11.75	0.476*	IHM negative	361	71.88±67.49	-22.96-8.91	0.023*
	Hospitalized	334	73.85±67.08			IHM positive	83	78.90±62.51		
Creatinine	Discharged	110	1.65±1.52	-0.21-0.44	0.961*	IHM negative	361	1.57±1.54	-0.33-0.38	0.835*
	Hospitalized	334	1.53±1.49			IHM positive	83	1.54±1.29		
Sodium	Discharged	110	134.85±5.92	-1.69-1.58	0.582*	IHM negative	358	134.89±7.27	-1.78-1.88	0.255*
	Hospitalized	329	134.92±8.03			IHM positive	81	134.85±8.75		
Potassium	Discharged	108	4.22±0.81	-0.16-0.21	0.546*	IHM negative	353	4.18±0.82	-0.32-0.09	0.179*
	Hospitalized	325	4.19±0.84			IHM positive	80	4.30±0.88		
AST	Discharged	110	37.95±57.79	-48.29-1.08	0.001*	IHM negative	361	43.43±63.03	-93.15(-39.42)	<0.001*
	Hospitalized	333	61.56±127.39			IHM positive	82	109.72±224.29		
ALT	Discharged	110	35.47±60.05	-20.99-6.86	0.003*	IHM negative	361	37.17±54.39	-34.94(-4.14)	0.015*
	Hospitalized	333	42.54±65.81			IHM positive	82	56.7195.88±		
LDH	Discharged	86	391.77±525.06	-406.47-27.62	0.011*	IHM negative	298	467.50±889.60	-578.70(-124.08)	<0.001*
	Hospitalized	286	581.19±981.59			IHM positive	74	818.89±891.71		
CRP	Discharged	88	94.02±103.52	-41.90-4.56	0.020*	IHM negative	274	100.50±97.71	-63.92(-12.64)	<0.001*
	Hospitalized	251	112.69±92.30			IHM positive	65	138.78±79.22		

*, Mann-Whitney U test; **, Student's t-test; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; IHM: In-hospital mortality; LDH: Lactate dehydrogenase; SD: Standard deviation

Table 4 Comparison of the parameters of coagulation, cardiac functions, and blood gases by the hospitalization and in-hospital mortality status in cancer patients admitted to the emergency department

Parameter	Hospitalization				In-hospital Mortality					
	n	Mean rank	Z-score	p*	n	Mean rank	Z-score	p*		
INR	Discharged	63	126.13	-1.698	0.089	IHM negative	219	132.24	-3.556	<0.001
	Hospitalized	219	145.92			IHM positive	63	173.69		
PTT	Discharged	63	121.93	-2.162	0.031	IHM negative	218	134.17	-2.786	0.005
	Hospitalized	219	147.13			IHM positive	64	166.47		
aPTT	Discharged	29	61.83	-1.293	0.196	IHM negative	113	68.08	-1.445	0.149
	Hospitalized	111	72.77			IHM positive	27	80.63		
Troponin	Discharged	67	100.21	-0.221	0.825	IHM negative	163	96.80	-2.337	0.019
	Hospitalized	135	102.14			IHM positive	39	121.15		
CK	Discharged	57	114.57	-0.489	0.625	IHM negative	175	108.67	-1.059	0.290
	Hospitalized	164	109.76			IHM positive	46	119.88		
CK-MB	Discharged	67	105.41	-0.493	0.622	IHM negative	165	102.52	-0.012	0.990
	Hospitalized	137	101.08			IHM positive	39	102.40		
proBNP	Discharged	12	38.75	-1.830	0.067	IHM negative	43	31.12	-0.435	0.664
	Hospitalized	48	28.44			IHM positive	17	28.94		
pH	Discharged	79	164.08	-0.925	0.355	IHM negative	242	157.76	-0.646	0.518
	Hospitalized	232	153.25			IHM positive	69	149.83		
pCO ₂	Discharged	79	170.31	-1.638	0.101	IHM negative	242	160.92	-1.808	0.071
	Hospitalized	232	151.13			IHM positive	69	138.73		
HCO ₃	Discharged	79	166.35	-1.185	0.236	IHM negative	242	160.68	-1.720	0.086
	Hospitalized	232	152.47			IHM positive	69	139.58		
Lactate	Discharged	79	137.78	-2.036	0.042	IHM negative	241	145.66	-3.613	<0.001
	Hospitalized	231	161.56			IHM positive	69	189.86		

*: Mann-Whitney U test; aPTT: Activated partial thromboplastin time; BNP: Brain natriuretic peptide; CK: Creatine kinase; IHM: in-hospital mortality; INR: International normalized ratio; PTT: Prothrombin time; SD: Standard deviation

mend that emergency physicians and other clinicians should evaluate laboratory findings together with the patients' vital signs (hypotension, tachycardia and hypoxemia).

Cancer patients visited the ED mostly between 12 p.m. and 3 a.m., similar to non-cancer patients, and experienced significantly longer ED wait times than non-cancer patients.[5,6,8,10] Yates et al. reported no association between the cause of hospitalization and length of stay.[8] In the present study, we found that the mean length of ED stay of cancer patients was shorter than the time reported in the literature.[8,10] Notably, ED practices in Turkey are regulated by local legislation, which requires strict compliance. A decree of the Emergency Department Legislation, issued by the Republic of Turkey's Ministry of Health, stipulates patients with a defined diagnosis should be hospitalized or discharged from the ED within four hours, whereas patients without any defined diagnoses must be hospitalized or discharged from the ED within eight hours. Therefore, the short ED waiting period identified in the present study is attributable to the implementation of regulatory requirements, undertaken to reduce ER wait time in the respective hospital to prevent non-compliance to legislation and future potential sanctions.

Inflammatory processes play a role in the development and progression of cancer and infections and are reported as the commonest cause (19.4%) of hospitalization across all identified etiological factors.[1, 8] Wulaningsih et al. reported that high levels of CRP were associated with mortality in cancer patients, and are potentially related to chronic inflammation.[13] We found increased levels of inflammatory markers (WBC counts, CRP levels) in hospitalized patients and in the IHM group. Thus, infections possibly prolong the length of hospital stay and increase the risk of mortality, and infectious processes are simultaneously involved in tumor progression.

Cancer affects the management of diabetes adversely in association with increased mortality in cancer patients.[14] In contrast, Boursi et al. reported that high blood glucose levels are associated with better prognosis in cancer patients.[15] We found low glucose levels in the IHM group, which is consistent with the findings of Boursi et al. However, the information in the literature on the value of glucose levels in predicting mortality in cancer patients is controversial, and the exact mechanism underlying these findings has not been clarified yet.

Yang et al. reported that high levels of BUN and creatinine were risk factors for mortality in septic can-

cer patients.[16] We found higher urea levels of IHM patients, indicating that the association between increased urea levels and death might be secondary to the evolution of multiorgan failure. Oh et al. reported that increased ALT and GGT levels were associated with mortality in patients younger than 60 years.[17] Wulaningsih et al. reported that higher LDH levels might be associated with mortality in cancer patients due to chronic hypoxia with excessive energy use in rapidly proliferating cancer cells.[18] In concordance with these reports, we found higher levels of AST, ALT, and LDH in both hospitalized and IHM groups than non-hospitalized and non-IHM subgroups. However, there are no proposed mechanisms in the literature to precisely explain this observation. Castle et al. reported that prolonged PTT or INR values in pancreatectomy patients were associated with increased 30-day mortality rates.[19] Fischer et al. reported a close relationship between inflammation and several coagulation parameters, including INR and PTT levels, and platelet counts in predicting mortality in patients with ED with suspected infections.[20] These findings may have arise from dysregulation of anticoagulant and procoagulant protein release from hepatocytes, endothelium, and circulating cells.[21] Furthermore, the homeostasis of these systems purportedly shifts to a procoagulant state during inflammatory processes.[22] Our study results are in alignment with the literature, as prolonged PTT and INR values potentially are risk factors for hospitalization and IHM.

Yang et al. reported that lactate levels over >4 mmol/L were predictive of mortality in septic cancer patients.[16] Similarly, we found a high lactate levels may indicate high risk and can be a predictor for hospitalization and IHM. Yang et al. reported that cardiac troponin I and CK-MB are independent risk factors for mortality in cancer patients, and CK and CK-MB levels, but not brain natriuretic peptide, were associated with mortality.[16] Therefore, we recommend the use of troponin levels as a marker for IHM in cancer patients, provided emergency physicians carefully evaluate the differential diagnoses of the acute coronary syndrome in patients with high troponin levels.

Limitations of the Study

This study is retrospective, which is subject to the inherent risks of bias associated with this research design, and we could neither evaluate the time between the end of treatment and ED admission nor the patient prognosis post-discharge.

Conclusion

Cancer patients undertake a higher number of ED visits. Despite the chronic disease process and relative rarity of oncological emergencies, such as superior vena cava syndrome, emergency physicians should remain updated on the management of cancer patients. The pain was one of the commonest reasons for ED visits; emergency physicians should conduct a thorough differential diagnosis to identify the pain source and provide appropriate pain-control strategies for the patient. Hospitalization and IHM rates are higher in cancer patients compared to non-cancer patients. Therefore, complete blood counts, liver and kidney function tests, coagulation parameters, and lactate levels should be evaluated in these patients concomitantly.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethics Committee Approval: This retrospective observational study was approved by the Non-Interventional Research Ethics Committee, Gülhane School of Medicine, University of Health Sciences (Approval no. 19/253, June 11, 2019).

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