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Article

An Ignored Population in Emergency Department: Cardio—Oncology Patients

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Abstract: Background:The aim of this study is to analyze cancer patients who were admitted to the emergency department with cardiac symptoms and hospitalized in the cardiology service or cardiology intensive care unit. Methods:One hundred thirty-one patients cancer patients who were hospitalized in the period of 5 years were included in the study. Age, sex, type of cancer, treatment, emergency department diagnosis, laboratory parameters, and in-hospital outcomes were evaluated. Results: The most common hospitalization diagnosis was acute coronary syndromes (69.5%, n=91). The mortality rate was 14.5%(n=19). NTproBNP levels were found to be higher in all patients, and especially high in patients with LVEF <40%. Conclusion: Cancer patients with low LVEF and elevated NTproBNP levels and increased HEART and TIMI scores have increased risk for cardiac toxicity and mortality. This patient group should be treated and followed up with great care.

Keywords: cardiology; emergency; oncology

1. Introduction

Cardiovascular diseases are the leading cause of death in our country, as in the whole world, and cancer-related deaths took the second place [1,2]. In addition, the survival rates of these patients increase in parallel with developments in cancer treatment [3]. Chest pain is the one of the most common complaint of admission to emergency department [4]. Another important sustained cardiac problem is arrhythmia, especially atrial fibrillation and flutter [5,6]. But it could be different in the patient population on cancer treatment due to the nature of chemotherapeutics. There is also an interesting role of emergency departments in the diagnosis of cancer. But it is generally late-stage cancers [7]. There are different biomarkers and scoring systems in the diagnosis and risk assessment of cardiac pathologies. But most commonly used are; hs Troponin, NTproBNP, HEART (history, ECG, age, risk factors, and troponin level) and TIMI (Thrombolysis in Myocardial Infarction) scores [4]. Another problem for these patients is overcrowded emergency departments. Overcrowded emergency departments may result in this patient population not receiving adequate service. Overcrowded emergency departments may result in this patient population not receiving adequate service [8]. Patients receiving cancer treatment are at increased risk in terms of cardiovascular complications compared with other oncologic patients because of the adverse effects of chemotherapeutic agents and radiotherapy used in the treatment [9,10]. In view of all these factors, there is a need for a subspecialty formation called cardio-oncology to reduce the cardiac risks of patients undergoing cancer treatment [11]. These clinics mainly serve on the following parameters: determination of the patient's cardiac status before cancer treatment, minimization of cardiotoxic effects during therapy, development of personalized cardiac protection programs, and establishment

of appropriate follow-up strategies [12]. The first cardio-oncology clinic of our country was put into service in May 2016, for the purpose of cardiac follow-up of patients receiving cancer treatment. In this clinic, pre-treatment cardiovascular risk assessment of patients, as well as preventive treatment regimens, cardiovascular risk reduction of patients, and support treatments with medium and long-term follow-up are performed. The aim of this study was to analyze patients who were admitted to the emergency department with cardiac symptoms and determine the cardiac markers and scoring systems for the diagnosis in the period of five years, and hospitalized in the cardiology service or cardiology intensive care unit.

2. Materials and Methods

Following the approval of the ethics committee (Scientific Researches Ethical Committee, Reference Number: TUTF-BAEK 2018/221) a total of 302 patients who were admitted to ED with cardiac symptoms and transferred to the cardiology units were detected in the study period. But 171 of them were excluded from the study because of having previously history of cardiac disease, comorbid diseases such as diabetes mellitus, chronical kidney failure, chronic obstructive pulmonary disease etc, or having no echocardiographic evaluation and NTproBNP levels before cancer treatment.

131 patients who were admitted to the emergency department with cardiac symptoms or diagnosed as having a cardiac pathology and then transferred to the cardiology service or cardiology intensive care in the period of 5 years were included in the study. All of the patients were previously healthy and had no comorbid disease. They were all examined in terms of cardiac pathologies and had echocardiographic evaluation, hsTroponin, NTpro BNP levels, HEART and TIMI scores before the chemotherapy. Throughout the study, echocardiographic evaluations of all patients were performed by the same cardio-oncologist who is an expert in this field. In this way, it was aimed to make the follow-ups more reliable. Echocardiographic examination was performed in accordance with EACVI/American Society of Echocardiography (ASE) recommendations. The age, sex, type of cancer, treatment, emergency department diagnosis, laboratory parameters, and in-hospital outcomes of the patients were recorded on study forms that were prepared previously. Among patients who had repeated emergency department visits during the study period, only those whose admissions were their first hospital stay were included in the study. The data were recorded using the SPSS statistical program and statistical analysis was performed. Statistical evaluation was performed by using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY. USA, IBM Corp.). The Shapiro-Wilk test was used for the assessment of normal distribution. For quantitative variables that did not conform to normal distribution, group comparisons were performed using the Mann-Whitney U test. The relationships between qualitative variables were investigated using Pearson's Chi-square test and Fisher's exact test (if the expected value of at least one of the eyes in the 2x2 tables was below 5 and the expected value of at least 20% of the eyes in the multi-eyed tables was below 5). For descriptive statistics, quantitative variables are given as median, smallest and the maximum value, and qualitative variables are given as number and percentage. The significance level was determined as 0.05 in all statistical analyses.

3. Results

Of the patients included in the study, 27.5% (n=36) were female and 72.5% (n=95) were male. The mean age was 68.4±11.5 years. Demographic characteristics, final diagnoses, and cancer type of the patients are shown in Table 1.

Table 1. Demographic characteristics, service diagnoses, and comorbid diseases of the patients.

Age (mean±SD)	68.4±11.5	<i>p</i>
Sex	n (%)	
Male	95 (72.5)	0.024

Female	36 (27.5)	0.087
Metastasis	48 (36.6)	0.064
Oncologic surgery	43 (32.8)	0.058
Hospitalized Department		
Cardiology Ward	107 (81.7)	0.011
Cardiology ICU**	24 (18.3)	0.092
Outcome		
Exitus	19 (14.5)	0.086
Discharged	112 (85.5)	0.009

CAD: Coronary Artery Disease, **ICU: Intensive Care Unit.

Left ventricular ejection fraction (LVEF) rate of all of the patients were higher than 40% (51±6.3% (mean±SD)), and they had normal NTproBNP levels (<125 pg/mL) (74±21.8 pg/mL (mean±SD) before the cancer treatment. While the HEART score of all patients was below 3 before the start of treatment, the HEART scores calculated at the time of emergency service admission were 5 and above. A statistically significant difference was detected in this respect (p < 0.01). Similarly, while the TIMI scores of the patients calculated before oncological treatment were all below 3, the TIMI scores calculated at the emergency department admissions were 4 and above. In this respect, a statistically significant difference was found between the TIMI scores at the beginning of treatment and at the emergency department admissions (p < 0.01). However, when the patients' HEART and TIMI scores were compared with each other in terms of diagnostic value, no statistically significant difference was detected (p:0.42).

The most common admission complaints of the patients were not to feel well 42.7% (n:56), shortness of breath 24.4 % (n: 32), palpitation 13% (n:17). Other complaints of admission were shown in Table 2.

Table 2. Oncologic diagnoses of the patients.

Oncologic Diagnosis	n %	p
Lung cancer	47 (35.9)	0.028
Prostate cancer	25 (19.1)	0.054
Breast cancer	20 (15.3)	0.062
Gastric cancer	16 (12.2)	0.088
Rectum cancer	8 (6.1)	0.14
Colon cancer	4 (3.1)	0.26
Liver cancer	3 (2.3)	0.38
Pancreatic cancer	2 (1.5)	0.42
Endometrial cancer	2 (1.5)	0.42
Hematologic malignancy	2 (1.5)	0.42
Bladder cancer	1 (0.8)	0.94
Skin cancer	1 (0.8)	0.94

When the admission electrocardiograms (ECGs) of the patients were evaluated, it was seen that,49 (37.4%) were ST segment elevated myocardial infarction (STEMI), 47 (35.9%) atrial fibrillation,19 (9.9%) normal sinus rhytm 12 (9.2%) had sinus tachycardia, 7 (5.3%) left bundle branch block, 3 (2.3%) had right bundle branch block, and 2 (1.5%) patients ventricular fibrillation. These two patients were defibrillated and ventricular fibrillation terminated with return of spontaneous circulation (ROSC). Electrocardiogram rhythms were evaluated statistically among themselves, STEMI and atrial fibrillation were found to be significantly more frequent than other rhythms (p=0.024 and p=0.028, respectively).

When the hospitalization diagnoses of the patients were examined, 49 (37.4%) patients had acute ST elevated myocardial infarction, 30 (22.9%) had decompensated heart failure, 30 (22.9%) had non-

ST-elevation myocardial infarction (NSTEMI), 12 (9.2%) had unstable angina pectoris, 6 (4.6%) had pericardial effusion without pericardial tamponade, 3 (2.3%) had symptomatic bradycardia, and 1 (0.8%) patients had treatment-resistant supraventricular tachycardia. When the patients were evaluated statistically in terms of their hospitalization diagnoses, it was seen that the number of patients who were hospitalized with diagnoses of acute myocardial infarction was significantly higher than the other patient types ($p=0.042$).

When the patients were evaluated in terms of the type of chemotherapeutic agent they received, it was found that alkylating agents were used most frequently ($n=23$, 27.7%), followed by monoclonal antibodies ($n=16$, 19.2%). There was a statistically significant difference in the frequency of alkylating agent use compared with other treatments ($p=0.036$). Patients receiving chemotherapeutic treatment and their treatment regimens are shown in Table 3.

Table 3. Treatment regimens of patients receiving chemotherapy.

Type of chemotherapeutic	n (%)	p
Alkylating agent	23 (27.7)	0.036
Monoclonal antibody	16 (19.2)	0.058
Antimicrotubule agent	10 (12.1)	0.066
Aromatase inhibitor	9 (10.8)	0.074
Immunomodulatory agent	8 (9.6)	0.086
Kinase inhibitor	8 (9.6)	0.086
Fluoropyrimidine	5 (5.5)	0.12
Anthracycline	5 (5.5)	0.12

The mean left ventricular ejection fraction of the hospitalized patients was $43.82 \pm 4.34\%$ (mean $\pm$ SD). The mean N-terminal pro B-type natriuretic peptide (NTproBNP) values were 3570.93 ± 1062.01 and these values were much higher than the upper limit of normal values. The mean high-sensitivity cardiac troponin assay (hsTroponin I) levels of patients were 160.21 ± 129.22 . When the serum electrolyte parameters of the patients were examined, no major electrolyte disturbance was found. These values are shown in Table 4.

Table 4. The mean serum electrolyte level of the patients.

Electrolyte	Serum level (mean $\pm$ SD)
Sodium (mEq/L)	136.09 ± 4.76
Potassium (mEq/L)	4.37 ± 0.62
Chloride (mEq/L)	103.23 ± 5.44
Calcium (mEq/L)	8.81 ± 0.69
Magnesium (mEq/L)	1.94 ± 0.31

The patients were divided into two groups, the LVEF $\geq 40\%$ group ($n=105$, 80.2%) and the LVEF $<40\%$ group ($n=26$, 19.8%). During the follow-up period, 19 (14.5%) patients died. The mortality rate was 26.9% ($n=7$) in the LVEF $<40\%$ group, and 11.4% ($n=12$) in the LVEF $\geq 40\%$ group. There was a statistically significant difference found between these two groups in terms of mortality ($p=0.045$). It was also found that hsTroponin I and NTproBNP levels were significantly higher in the LVEF $<40\%$ group compared with the LVEF $\geq 40\%$ group ($p=0.024$, $p=0.015$, respectively). However, there was no statistically significant difference between the two groups in terms of serum electrolyte levels ($p>0.05$). When the relationship between the types of treatment and mortality was evaluated, no significant relationship was found ($p>0.05$). When the relationship between comorbid diseases and mortality was evaluated, it was found that the mortality rate was significantly higher in patients with a history of heart failure than in the other patients ($p=0.036$). When the relationship between the type of chemotherapeutic treatment and mortality was evaluated, the highest mortality rate was 50% ($n=5$).

in the group receiving antimicrotubule agent. This rate was significantly higher than in the other groups ($p=0.018$).

4. Discussion

In parallel with the increase in the number of cancer cases in the world, the number of patients with cancer in our country is increasing day by day. These patients have an increased risk of cardiotoxicity as well as suppression of their immune system. Therefore, cardiac follow-up of these patients is vital. For this purpose, the number of cardio-oncology clinics is increasing. The first of these clinics in our country was established in our university and has been conducting cardiac follow-up and treatment of oncology patients for more than two years. Many risk factors have been defined for the development of treatment-induced cardiotoxicity in these patients. One of the risk factors for cardiotoxicity in patients with cancer has been reported as female sex [13]. However, in our study, only one-quarter of the patients were female patients. We think that higher number of male patients in our study is accounted for by the high frequency of lung and prostate cancers in our region. As another risk factor, hypertension was found in 75.6% ($n=99$) of our patients and such a high rate indicates the importance of hypertension control in these patients.

Another important result of our study was that the in-hospital mortality rate of the patients was 14.5% ($n=19$), and the diagnoses of all of these patients were acute myocardial infarction and ventricular fibrillation. The in-hospital mortality rate is reported to be below 7% in the normal population with acute myocardial infarction [14,15]. We assume that both treatment-related complications and comorbid conditions are effective in the oncologic patient population, and this ratio is twice as high. From this point of view, we emphasize the importance of cardiac evaluation and follow-up in this patient population once again.

Previous studies have shown that the most important parameter in cardiac follow-up of oncology patients is the protection of LVEF [16]. In the study of Albini et al, it was reported that; there is reduction between 5-20% in LVEF of the patients who were on chemotherapy. These drugs could effect the cardiovascular system directly or indirectly via thrombogenic status and blood-flow alterations. In our study, the most effective factor on in-hospital mortality was found to be low LVEF in the cancer patient population. Accordingly, it is evident that very close follow-up of systolic functions of patients who have myocardial toxicity due to cancer treatment is very important in terms of patient's health.

Pareek et al. [12] reported that BNP levels were an early indicator of cardiotoxicity in patients receiving cancer treatment. In our study, NTproBNP levels were found to be higher in all patients, especially so in patients with LVEF <40%. Moreover, these levels were measured during the emergency service admissions of all patients. This was also true for patients who died during hospitalization. Therefore, we think that NTproBNP levels could be useful as a predictor of in-hospital mortality risk in these patients. In many studies investigating the risk of coronary artery disease in patients receiving chemotherapy [16,17], it has been shown that these patients have an increased risk of coronary artery disease. In our study, 67.2% ($n=88$) of patients had a previous history of coronary artery disease and only 6 patients had newly developed coronary artery disease. No statistical evaluation could be made for the chemotherapeutic drugs they received because of the insufficient number of these patients. In this respect, we think that future studies with more patients will be beneficial.

In a study conducted among patients presenting to the emergency department with chest pain, it was reported that both HEART and TIMI scores had high predictive value, but the HEART score had a higher predictive value compared to the TIMI score [4]. In our study, both scoring systems were found to have high predictive value. However, no statistically significant superiority of one scoring system was found over the other. We think that the presence of comorbid diseases in the patients included in the study by Kagansky et al. [4] may have been effective in this situation. Because the patients included in our study did not have any comorbid conditions before the treatment.

Life-threatening cardiac rhythm disorders can be seen in 16-36% of patients under oncologic treatment [17,18]. However, a low number (5-10%) of these patients is admitted with severe arrhythmias with a need for treatment as inpatients [19]. In our study, pathologic ECG findings were found in 54.2% (n: 71) of the patients at the time of admission to the emergency department. However, since we didn't have all of the patients' ECG data before starting the treatment, it was not possible to evaluate exactly how much of these pathological rhythms were related to treatment. When the ECG findings of the patients who died were evaluated, supraventricular tachycardia was found statistically significantly more frequently at 50.4% (n=12) than other pathologic rhythms (p=0.024). In the literature, it was stated that this situation might be related to previous comorbid conditions, left ventricular dysfunction, direct tumor effect or the toxic effects of cancer treatment [19,20]. When this situation is evaluated from this perspective, it can be seen that; patients who have cancer treatment and are admitted with supraventricular tachyarrhythmia have an increased risk of mortality compared with other patients.

In the study of Bossaer et al. [21], it was reported that the most common types of cancer related to cardiotoxicity were multiple myeloma, lung cancer, non-Hodgkin lymphoma, and breast cancer. However, in our study, the frequency ranking was found as lung, prostate, breast, and stomach cancer, respectively. We think that the type and frequency of cancer in our country was effective in this result. According to cancer data of 2015, the most common types of cancer in our country were lung, prostate, colon, and bladder, respectively [2]. And we think that; it could also be related to the chemotherapy and radiotherapy treatment. It is well known that there is strong relationship between cardiotoxicity and chemotherapeutic agents such as; anthracyclines, antimetabolites, vinca alkaloids and tyrosine-kinase inhibitors [21]. In our study we have found that; the most commonly used chemotherapeutic agents were; alkylating agents, monoclonal antibodies and antimicrotubule agents.

Liquid-electrolyte disturbance is another condition that causes cardiac effects in patients undergoing cancer treatment. This may be associated with the underlying malignancy itself or may be associated with the treatment [22]. The most common types of these electrolyte disorders are hyponatremia, hypercalcemia, hypokalemia, and hypomagnesemia [23]. In a study, it was found that 47% of patients who received cancer treatment and were hospitalized for any reason had hyponatremia [24]. In our study, none of the patients had a major electrolyte disorder at admission. Regular assessment of the blood parameters of these patients has great importance in the prevention of electrolyte disorders that may occur during treatment.

One of the most important factors limiting our study is the small number of patients. However, we only included patients with cancer who were admitted to the emergency department and then transferred to the cardiology unit, and the relatively new cardio-oncology unit in this study. Although there are a large amount of cardio-oncology patients, we have only included the patients who were previously healthy in terms of cardiac condition and have no comorbid disease. This situation has limited the number of patients. We have also excluded the patients who were treated with radiotherapy. Because radiotherapy near the cardiac region effects directly the myocardium and LVEF. We think that it can be studied separately in another study.

5. Conclusions

We believe that this study may be a guide for emergency department applications of this patient group, especially since the number of studies conducted in the field of cardio-oncology is limited. This descriptive study shows the importance of cardiotoxicity in patients receiving cancer treatment. As a result of this study, it was seen that oncology patients with low LVEF, elevated NTproBNP levels and increased HEART and TIMI scores have increased risk for cardiac toxicity and mortality. Since this patient population has a high risk of cardiac effects due to the treatments they receive, they need to be evaluated in more detail than the normal population. From this perspective, the importance of cardiac evaluation in this patient group appears once more. We believe that this study will play a guiding role in future studies.

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Conflicts of Interest: The authors declare that they have no conflict of interest. The authors declare no competing interests.

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