



Emergency Department Utilization Among Cancer Patients Receiving Immune Checkpoint Inhibitors: Patterns, Clinical Characteristics, and Associated Factors

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have become an integral component of cancer treatment across multiple solid and hematologic malignancies. Although these agents can produce durable clinical responses, they are also associated with immune-related adverse events (irAEs) that may lead to emergency department (ED) visits. However, real-world data describing ED utilization among patients receiving ICIs in Saudi Arabia remain limited.

Objectives: This study aimed to describe all-cause ED utilization among patients with cancer receiving immune checkpoint inhibitors, characterize immune-related and non-immune-related ED presentations, and explore factors associated with ED use.

Methods: This retrospective observational cohort study included adult patients with cancer who received at least one immune checkpoint inhibitor at King Abdullah Medical City, Makkah, Saudi Arabia, between January 2019 and December 2023. Patients were followed for a predefined 24-week period after the first documented administration of an ICI. The primary outcome was the occurrence of at least one all-cause ED visit. Secondary outcomes included ED visits attributed to irAEs, documented toxicity patterns, management, hospitalization, and exploratory factors associated with ED utilization. Logistic regression analyses were exploratory and not intended to establish causal associations.

Results: A total of 288 patients were included. The mean age was 58.4 ± 13.69 years, and most patients were male. The most common cancer types were non-small cell lung cancer, renal cell carcinoma, and urothelial carcinoma. Pembrolizumab was the most frequently used immune checkpoint inhibitor. During the 24-week observation period, 162 patients (56.3%) had at least one ED visit, whereas 25 patients (8.7% of the total cohort) had an ED visit attributed to an irAE. Gastrointestinal, dermatologic, and endocrine toxicities were the most frequently documented irAE categories. Most toxicities were graded as grade 1 or 2. In exploratory regression analyses of all-cause ED utilization, treatment-cycle count, alanine aminotransferase (ALT), and total bilirubin were statistically associated with ED visits. These associations should be interpreted cautiously because treatment-cycle count was not a fixed baseline exposure, laboratory timing could not be fully standardized retrospectively, and residual confounding may remain.

Conclusions: ED utilization was common among patients receiving ICIs, whereas only a minority of patients had ED visits attributed to irAEs. These findings primarily characterize real-world acute healthcare utilization in a Saudi tertiary oncology setting. Associations identified in exploratory analyses should not be interpreted as causal or as specific predictors of immune-mediated toxicity. Further prospective studies are needed to evaluate structured approaches for assessing acute presentations in patients receiving ICIs.

Keywords: Immune Checkpoint Inhibitors, Emergency Department, Immune-related Adverse Events, Saudi Arabia

1. Background

Immune checkpoint inhibitors (ICIs) are an established component of modern cancer treatment across a wide range of malignancies. By targeting inhibitory immune pathways, including programmed cell death protein 1 (PD-

1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), these agents enhance antitumor immune activity and can produce durable clinical responses in selected patients. The clinical value of immune checkpoint blockade was first clearly demonstrated in advanced melanoma, in which

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ipilimumab improved overall survival, and the subsequent development of PD-1 and PD-L1 inhibitors expanded the use of immunotherapy to lung cancer, renal cell carcinoma, urothelial carcinoma, head and neck cancer, and other tumor types (1-4). Despite their therapeutic benefit, ICIs are associated with a distinct toxicity profile known as immune-related adverse events (irAEs). These events result from nonspecific immune activation and may affect nearly any organ system, including the skin, gastrointestinal tract, endocrine glands, liver, lungs, kidneys, nervous system, and hematologic system. The clinical course of irAEs is variable: some events are mild and self-limited, whereas others may progress rapidly and require treatment interruption, corticosteroids, additional immunosuppression, hospitalization, or permanent discontinuation of immunotherapy (5-7).

Recognition of irAEs is particularly important in the emergency department (ED), where patients receiving ICIs may present with nonspecific symptoms, such as fever, diarrhea, abdominal pain, dyspnea, fatigue, rash, nausea, vomiting, or abnormal laboratory values. These presentations can overlap with infection, cancer progression, chemotherapy-related toxicity, metabolic disturbances, or complications of advanced malignancy. Consequently, attributing symptoms to immune-related toxicity in the acute care setting can be challenging, particularly when immunotherapy exposure is not clearly documented or recognized at triage (8-11).

Previous studies have shown that ED utilization among patients receiving ICIs is not uncommon, but the proportion of visits directly related to irAEs varies across settings. El Majzoub et al. described the spectrum of immune checkpoint therapy-related adverse effects among patients with cancer presenting to the ED at a comprehensive cancer center. Holstead et al. similarly reported that only a subset of ED visits among patients treated with ICIs were directly attributed to irAEs, whereas Guven et al. found that many ED visits were related to disease burden or non-immune-related causes rather than immunotherapy toxicity itself (10, 12, 13). International guidelines, including those from the American Society of Clinical Oncology and the Society for Immunotherapy of Cancer, emphasize early recognition, severity grading, and organ-specific management of irAEs. Most grade 1 toxicities can be managed with close monitoring, whereas moderate to severe toxicities often require holding ICI therapy and initiating systemic corticosteroids or additional immunosuppressive therapy when indicated (6, 7).

Although ED utilization among patients receiving immune checkpoint inhibitors has been described internationally, evidence from Saudi Arabia and the Gulf region remains limited. Differences in cancer populations, treatment delivery, emergency care pathways, and healthcare utilization may influence patterns of acute presentation. Characterizing ED utilization in this setting may support local service planning and improve recognition and management of immune-related and non-immune-related acute presentations.

2. Objectives

This study aimed to evaluate the frequency, clinical characteristics, management, and factors associated with ED visits among patients with cancer receiving immune checkpoint inhibitors at a tertiary oncology center in Saudi Arabia.

3. Methods

3.1. Study Design and Setting

This retrospective observational cohort study was conducted at King Abdullah Medical City, Makkah, Saudi Arabia. The study included adult oncology patients who received at least one immune checkpoint inhibitor between January 2019 and December 2023.

3.2. Study Population

Patients were eligible if they were aged 18 years or older, had a confirmed cancer diagnosis, and received at least one immune checkpoint inhibitor during the study period. Immune checkpoint inhibitors included pembrolizumab, nivolumab, ipilimumab, atezolizumab, and avelumab. Patients younger than 18 years were excluded. The index date was defined as the date of the first immune checkpoint inhibitor administration during the study period. Each patient was followed for 24 weeks from the index date to identify emergency department visits and related clinical outcomes. The 24-week period was selected as a standardized observation window to characterize early acute healthcare utilization following ICI initiation while allowing a consistent nominal follow-up period across the cohort. This observation window was not intended to capture all late-onset irAEs, which may occur after prolonged exposure or after treatment discontinuation. Only ED visits recorded within the institutional electronic medical record were available for assessment; ED visits

occurring at outside institutions could not be captured systematically. Patients were identified retrospectively from available institutional oncology and pharmacy records. The analytic cohort consisted of 288 patients who met the documented eligibility criteria. Because this was a retrospective database review and a formal screening log was not maintained, the exact number of potentially eligible records initially identified and the number of exclusions before the final cohort was established could not be reconstructed reliably.

3.3. Data Collection

Patients were identified through institutional oncology and pharmacy records. Data were extracted retrospectively from electronic medical records, including demographics, cancer type, disease stage, metastatic status, Eastern Cooperative Oncology Group (ECOG) performance status, type of immune checkpoint inhibitor, line of therapy, number of treatment cycles, laboratory values, ED visits, presenting complaints, suspected or confirmed immune-related adverse events, management strategies, corticosteroid use, hospital admission, and length of stay. The number of treatment cycles represented the total number of documented ICI treatment cycles available in the medical record. Because the cycle count could accumulate during the same period in which ED outcomes were ascertained, it was not considered a fixed baseline exposure and was interpreted only as an exploratory treatment-exposure variable. Concomitant antineoplastic therapies documented during ICI treatment were also recorded. Because treatment combinations varied substantially across cancer types and treatment lines, these therapies are presented descriptively in the Supplementary File and were not incorporated into the primary regression model.

3.4. Outcomes

The primary outcome was the occurrence of at least one ED visit during the 24-week observation period. Secondary outcomes included irAE-related ED visits, the type and grade of irAEs, irAE management, corticosteroid use, ICI interruption or discontinuation, hospital admission, length of stay, and factors associated with ED visits.

3.5. Definition of Immune-Related Adverse Events

Immune-related adverse events were identified retrospectively based on documented clinical diagnoses,

laboratory findings, imaging findings, specialist assessments, and treatment decisions recorded in the electronic medical record. Attribution primarily reflected the treating team's documented clinical assessment rather than prospective independent adjudication. Alternative explanations, including infection, malignancy progression, toxicity from concomitant anticancer therapy, and other medical conditions, were considered when documented in the medical record. Because a formal independent toxicity-adjudication committee and a standardized prospective assessment process were not used, cases were classified according to the best available clinical documentation. Toxicities were categorized by organ system and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, when sufficient information was available to assign a grade.

3.6. Statistical Analysis

Categorical variables were summarized as frequencies and percentages. Continuous variables were reported as means with standard deviations or medians with interquartile ranges, according to their distributions. The Shapiro-Wilk test was used to assess normality. Chi-square or Fisher's exact tests were used for categorical comparisons, and the Mann-Whitney U or Kruskal-Wallis tests were used for non-normally distributed continuous variables. Logistic regression was used as an exploratory analysis of factors associated with the occurrence of at least one all-cause ED visit during the 24-week observation period. Variables demonstrating statistical significance in univariate analyses were included in the multivariable model. Because variable selection was data-driven and several clinically relevant variables had missing observations, the adjusted estimates should be interpreted as exploratory associations rather than causal or predictive effects. Missing data were not imputed, and regression analyses were based on complete cases for the variables included in each model. Odds ratios with 95% confidence intervals were reported. No formal causal inference was intended. The analysis did not specifically model irAE-related ED visits because the number of such events was limited. Similarly, recurrent ED visits were summarized descriptively rather than modeled as repeated events. A P value < 0.05 was considered statistically significant. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Table 1. Baseline Demographic and Clinical Characteristics of the Included Patients ^a

Characteristic	Overall Cohort, n = 288
Age, y	
Mean $\pm$ SD	58.4 $\pm$ 13.69
Range, y	19 - 95
18 - 30	9 (3.1)
31 - 40	24 (8.3)
41 - 50	44 (15.3)
51 - 60	70 (24.3)
> 60	141 (49.0)
Sex	
Male	173 (60.1)
Female	115 (39.9)
Anthropometric measurements, median (IQR)	
Weight, kg	63.0 (53.0 - 75.0)
Height, cm	161.0 (155.0 - 168.0)
BSA, m ²	1.67 (1.52 - 1.81)
BMI, kg/m ²	23.88 (20.17 - 28.72)
Smoking status	
Smoker	67 (23.3)
Non-smoker	209 (72.6)
Missing	12 (4.2)
Drug allergy	
Yes	21 (7.3)
No	267 (92.7)
Comorbidities ^b	
Hypertension	112 (38.9)
Diabetes mellitus	86 (29.9)
Cardiovascular disease	23 (8.0)
Hyperthyroidism	23 (8.0)
Chronic kidney disease	10 (3.5)
Respiratory disease/asthma	11 (3.8)
Benign prostatic hyperplasia	7 (2.4)
Dyslipidemia	5 (1.7)
Liver disease	3 (1.0)
No comorbidity documented	111 (38.5)

^a Values are expressed as No. (%) unless otherwise indicated. Abbreviations: BMI, Body Mass Index; BSA, body surface area; IQR, interquartile range; SD, standard deviation.

^b Patients may have had more than one comorbidity; therefore, percentages may not total 100%.

3.7. Supplementary Material

Additional detailed tables, including documented drug allergies, concomitant antineoplastic medications, less frequent ED presenting complaints, detailed irAE/adverse drug reaction (ADR) diagnoses, and supplementary figures, are provided in the Supplementary File.

3.8. Ethical Approval

This study was approved by the Institutional Review Board of King Abdullah Medical City under approval number 24 - 1220. The requirement for informed consent was waived due to the retrospective nature of the study and the use of de-identified data.

4. Results

A total of 288 patients who met the documented eligibility criteria constituted the final analytic cohort. The mean age was 58.4 $\pm$ 13.69 years (range, 19 - 95 years). Nearly half of the cohort was older than 60 years. Most patients were male (60.1%). Hypertension and diabetes mellitus were the most frequently documented comorbidities. Table 1 summarizes the baseline demographic and clinical characteristics of the included patients. Non-small cell lung cancer was the most common malignancy, followed by renal cell carcinoma and urothelial carcinoma. Most patients (71.9%) had advanced disease, with stage IV disease documented in 207 patients. The median ECOG performance status was 1; however, ECOG data were missing for 21 patients. Pembrolizumab was the most frequently used ICI, followed by nivolumab. The median number of treatment cycles was 5, and the largest group

Table 2. Tumor and Treatment Characteristics ^a

Characteristic	Overall Cohort, n = 288
Cancer type	
Non-small cell lung cancer	78 (27.1)
Renal cell carcinoma	38 (13.2)
Urothelial carcinoma	34 (11.8)
Breast cancer	24 (8.3)
Endometrial cancer	23 (8.0)
Head and neck cancer	20 (6.9)
Squamous cell carcinoma	13 (4.5)
Colorectal cancer	12 (4.2)
Melanoma	10 (3.5)
Gastric cancer	9 (3.1)
Small cell lung cancer	7 (2.4)
Hodgkin lymphoma	6 (2.1)
Hepatocellular carcinoma	2 (0.7)
Ovarian cancer	2 (0.7)
Cervical cancer	2 (0.7)
Other cancers	8 (2.8)
Disease stage	
Stage 0	2 (0.7)
Stage I	15 (5.2)
Stage II	16 (5.6)
Stage III	37 (12.8)
Stage IV	207 (71.9)
Missing	11 (3.8)
Metastatic disease	
Yes	207 (71.9)
No	81 (28.1)
ECOG performance status	
Median (IQR)	1 (0 - 2)
Range	0 - 4
ECOG 0: asymptomatic	85 (29.5)
ECOG 1: symptomatic but ambulatory	60 (20.8)
ECOG 2: < 50% in bed during the day	61 (21.2)
ECOG 3: > 50% in bed, not bedbound	40 (13.9)
ECOG 4: bedbound	21 (7.3)
Missing	21 (7.3)
Type of ICI received ^b	
Pembrolizumab	183 (63.5)
Nivolumab	100 (34.7)
Ipilimumab	8 (2.8)
Avelumab	3 (1.0)
Atezolizumab	3 (1.0)
Number of treatment cycles	
Median (IQR)	5 (2 - 10)
Range	1 - 59
Line of therapy	
First line	36 (12.5)
Second line	126 (43.8)
Third line	38 (13.2)
Fourth line	8 (2.8)
Fifth line	2 (0.7)
Missing	78 (27.1)

^a Values are expressed as No. (%) unless otherwise indicated. Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IQR, interquartile range.

^b Patients may have received more than one ICI during the study period; therefore, ICI categories are not mutually exclusive.

(43.8%) received ICIs as second-line therapy. Table 2 summarizes tumor and treatment characteristics.

During the 24-week observation period, 162 of 288 patients (56.3%) had at least one all-cause ED visit. In the overall cohort, 25 patients (8.7%) had an ED visit attributed

Table 3. Emergency Department Utilization, Documented irAEs, and Management^a

Variables	Summary
A. Overall emergency department utilization, n = 288	
Any ED visit within 24 weeks	
Yes	162 (56.3)
No	126 (43.8)
Type of ED visit	
irAE-related ED visit	25 (8.7)
Another ED visit	137 (47.6)
B. Characteristics among patients with ≥ 1 ED visit, n = 162	
Number of ED visits, median (IQR)	2 (1 - 4)
Range	1 - 15
Most common ED presenting complaints^b	
Body aches/pain	52 (32.1)
Fever	51 (31.5)
Abdominal pain	42 (25.9)
Nausea/vomiting	37 (22.8)
Shortness of breath	26 (16.0)
Diarrhea	25 (15.4)
Cough	22 (13.6)
Chest pain	19 (11.7)
Dizziness	16 (9.9)
Headache	14 (8.6)
Fatigue	11 (6.8)
Symptoms related to underlying disease	10 (6.2)
Generalized weakness	10 (6.2)
C. Documented irAE/ADR diagnoses	
Diarrhea	13
Hypothyroidism	12
Skin reaction	8
Pruritus	5
Nausea/vomiting	4
Pneumonitis	4
Skin rash	2
Thrombocytopenia	1
Fatigue	1
Hyperthyroidism	1
D. Documented irAE toxicity categories	
Gastrointestinal toxicity	15
Dermatologic toxicity	13
Endocrine toxicity	13
Pulmonary toxicity	4
Hematologic toxicity	1
E. Toxicity grade among cases with sufficient documentation, n = 23	
Grade 1	12
Grade 2	8
Grade 3	3
F. ICI management^b	
Continued ICI with close monitoring	22
Temporarily held ICI	15
Permanently discontinued ICI	9
G. Corticosteroid exposure in the overall cohort, n = 288	
Documented corticosteroid use	106 (36.8)
Steroid dose, median (IQR)	10 (10 - 20)
Steroid dose range	10 - 30
Supportive/related medications	
Levothyroxine	13
Prednisone	7

^a Values are expressed as No. (%) unless otherwise indicated. Percentages for overall ED utilization were calculated using the total cohort (N = 288). Percentages for ED presenting complaints were calculated among patients with at least one ED visit (n = 162). Patients may have had more than one presenting complaint, diagnosis, or toxicity category; therefore, these categories are not mutually exclusive. Corticosteroid use was documented in 106 patients; however, the exact indication for corticosteroid therapy could not be confirmed in all cases because of the retrospective design. Abbreviations: ADR, adverse drug reaction; ED, emergency department; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IQR, interquartile range.

^b ICI management categories were not mutually exclusive and may represent management decisions occurring at different points during the clinical course. Toxicity grading was available for 23 cases with sufficient documentation.

to an irAE, whereas 137 patients (47.6%) had ED visits attributed to other causes. Thus, the primary outcome largely reflected overall acute healthcare utilization rather than immune-mediated toxicity specifically. The most common presenting complaints were body aches or pain, fever, abdominal pain, nausea or vomiting, shortness of breath, diarrhea, cough, and chest pain. Gastrointestinal,

dermatologic, and endocrine toxicities were the most frequently documented irAE categories. Among 23 irAE cases with sufficient documentation for CTCAE grading, 12 were grade 1, 8 were grade 2, and 3 were grade 3. No inference regarding the frequency of severe toxicity was made for cases in which complete grading information was

Table 4. Available Laboratory Characteristics of the Study Cohort ^a

Laboratory parameter	N	Mean ± SD	Median	IQR	Range
Serum creatinine, mg/dL	282	1.00 ± 0.48	0.88	0.69 - 1.21	0.32 - 4.31
BUN, mg/dL	280	15.81 ± 8.61	14.00	10.33 - 19.41	2.03 - 65.0
AST, U/L	263	24.19 ± 16.37	21.0	15.0 - 26.0	0.37 - 155.0
ALT, U/L	281	24.16 ± 21.31	18.0	13.0 - 26.0	0.86 - 169.0
Total bilirubin, mg/dL	277	0.41 ± 0.26	0.37	0.25 - 0.50	0.05 - 2.20
HbA1c, %	27	6.39 ± 1.64	6.0	5.5 - 6.6	4.2 - 13.0
Glucose, mg/dL	8	234.37 ± 190.87	124.0	102.0 - 363.0	91.0 - 606.0
Sodium, mEq/L	278	137.10 ± 3.81	137.5	136.0 - 139.0	121.0 - 147.0
WBC, ×10 ³ /μL	285	8.39 ± 4.98	7.36	5.37 - 9.42	2.13 - 37.0
Platelet count, ×10 ³ /μL	285	332.07 ± 144.95	313.0	227.0 - 393.0	80.0 - 981.0
Hemoglobin, g/dL	285	11.10 ± 2.10	11.00	9.70 - 12.40	4.84 - 17.0
TSH, μIU/mL	99	2.34 ± 2.34	1.70	0.87 - 3.08	0.25 - 16.0

^a Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HbA1c, glycated hemoglobin; IQR, interquartile range; SD, standard deviation; TSH, thyroid-stimulating hormone; WBC, white blood cell count.

unavailable. Table 3 summarizes ED visits, presenting complaints, irAE categories, and management.

Immune checkpoint inhibitor therapy was continued with close monitoring in 22 patients, temporarily held in 15 patients, and permanently discontinued in 9 patients. Corticosteroid exposure was documented in 106 patients (36.8%) in the overall cohort. Because corticosteroids may have been prescribed for irAEs, cancer-related symptoms, antiemetic regimens, respiratory symptoms, or other indications, corticosteroid use could not be reliably attributed to immune-mediated toxicity in all cases. Hospital admission was documented in 27 patients; however, the retrospective dataset did not permit reliable attribution of all admissions specifically to confirmed irAEs.

Available laboratory findings are summarized in Table 4. Liver function tests showed a median aspartate aminotransferase (AST) level of 21 U/L, a median alanine aminotransferase (ALT) level of 18 U/L, and a median total bilirubin of 0.37 mg/dL. The median serum creatinine was 0.88 mg/dL. The median hemoglobin level was 11.0 g/dL, the median white blood cell count was $7.36 \times 10^3/\mu\text{L}$, and the median platelet count was $313 \times 10^3/\mu\text{L}$.

In exploratory univariate analyses, treatment-cycle count, ALT, total bilirubin, and platelet count were statistically associated with all-cause ED utilization. In the original multivariable model, treatment-cycle count, ALT, and total bilirubin remained statistically associated with ED visits. These results should be interpreted cautiously.

Treatment-cycle count was not a fixed baseline exposure and may reflect treatment duration, survival, tolerance, and time at risk. Similarly, laboratory abnormalities are nonspecific in oncology patients and should not be interpreted as specific indicators of immune-mediated toxicity. The analyses evaluated all-cause ED utilization and not irAE-related ED visits specifically. Tables 5 and 6 summarize the univariate and multivariable logistic regression analyses. Additional detailed data are provided in the Supplementary File, including drug allergy details, antineoplastic medications, less frequent ED complaints, detailed irAE/ADR diagnoses, and supplementary figures.

5. Discussion

This retrospective cohort study primarily describes all-cause ED utilization among patients receiving ICIs in a Saudi tertiary oncology setting. More than half of the cohort had at least one ED visit during the predefined 24-week observation period, whereas only 25 of 288 patients had an ED presentation attributed to an irAE. This distinction is important because acute presentations in patients receiving ICIs may result from infection, cancer progression, concomitant anticancer treatments, comorbid illness, or complications of advanced malignancy rather than immune-mediated toxicity alone.

The high rate of ED utilization observed in this study is consistent with previous real-world evidence. Guven et al. reported that almost 40% of patients receiving ICIs had ED visits and emphasized that collaboration between oncology and emergency medicine is essential in this

Table 5. Univariate Logistic Regression Analysis for Factors Associated with ED Visits ^a

Variables	ED visit, n = 162	No ED visit, n = 126	P Value	OR	95% CI
Male sex	97 (59.9)	76 (60.3)	0.982	0.982	0.610 - 1.579
Age, y	58.90 ± 12.88	57.75 ± 14.70	0.483	0.994	0.977 - 1.011
Weight, kg	63 (51 - 73)	64 (54 - 76)	0.121	1.012	0.997 - 1.026
Height, cm	160 (155 - 167)	163 (154 - 169)	0.935	1.001	0.980 - 1.022
BSA, m ²	1.65 (1.50 - 1.79)	1.71 (1.57 - 1.82)	0.988	0.999	0.907 - 1.101
BMI, kg/m ²	23.76 (19.98 - 28.70)	24.51 (20.57 - 29.05)	0.140	1.027	0.991 - 1.064
Drug allergy	14 (8.6)	7 (5.6)	0.330	1.595	0.624 - 4.078
Smoker	40 (24.7)	27 (21.4)	0.641	1.142	0.653 - 1.999
Comorbidities	93 (57.4)	72 (57.1)	0.978	1.007	0.627 - 1.615
ECOG score	1 (0 - 3)	1 (0 - 2)	0.275	0.899	0.743 - 1.088
Number of treatment cycles	7 (3 - 13)	3 (2 - 7)	0.002	1.044	1.015 - 1.074
Serum creatinine, mg/dL	0.8 (0.7 - 1.2)	0.9 (0.7 - 1.2)	0.316	1.287	0.786 - 2.110
BUN, mg/dL	12.6 (10 - 18)	14.6 (11 - 19.4)	0.076	1.026	0.997 - 1.055
AST, U/L	21.0 (14 - 26)	22.0 (16 - 26)	0.417	1.006	0.991 - 1.021
ALT, U/L	17.0 (13 - 24)	20.0 (13 - 29)	0.006	1.019	1.006 - 1.033
Total bilirubin, mg/dL	0.3 (0.2 - 0.4)	0.4 (0.3 - 0.6)	0.005	4.136	1.530 - 11.179
HbA1c, %	6.0 (5.5 - 7.5)	6.0 (6.0 - 7.0)	0.857	1.044	0.657 - 1.658
Sodium, mEq/L	137 (136 - 139)	138 (136 - 139)	0.441	1.025	0.962 - 1.092
Potassium, mEq/L	4.1 (3.8 - 4.5)	4.1 (3.9 - 4.5)	0.418	1.099	0.875 - 1.381
Chloride, mEq/L	101 (96 - 106)	101.5 (99 - 105)	0.240	1.045	0.971 - 1.125
WBC, ×10 ³ /μL	7.3 (5.4 - 9.9)	7.4 (5.3 - 9.0)	0.757	0.993	0.946 - 1.041
Platelet count, ×10 ³ /μL	343 (258 - 402)	284 (190 - 367)	0.016	0.998	0.996 - 1.000
Hemoglobin, g/dL	11.1 (9.6 - 12.2)	11.0 (9.8 - 12.6)	0.193	1.077	0.963 - 1.205
TSH, μIU/mL	1.7 (0.9 - 3.1)	1.9 (1.0 - 2.8)	0.760	1.027	0.866 - 1.217

^a Values are expressed as No. (%), mean ± SD or median (IQR) unless otherwise indicated. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ED, emergency department; HbA1c, glycated hemoglobin; ICI, immune checkpoint inhibitor; IQR, interquartile range; OR, odds ratio; SD, standard deviation; TSH, thyroid-stimulating hormone; WBC, white blood cell count. Note: P < 0.05 was considered statistically significant.

population (13). Holstead et al. also found that ED visits among ICI-treated patients were frequent, but only a proportion were directly related to irAEs (12). Similarly, El Majzoub et al. showed that patients receiving checkpoint inhibitor therapy may present to the ED with a wide range of adverse effects, requiring clinicians to maintain a high index of suspicion while also evaluating alternative causes (10). Collectively, these findings support the interpretation that ED visits are common among ICI-treated patients, but immune-mediated toxicity accounts for only part of the acute care burden.

The most common ED presentations included pain, fever, gastrointestinal symptoms, dyspnea, cough, and chest pain. These symptoms are nonspecific and may reflect irAEs, infection, treatment toxicity, disease progression, or other acute medical conditions. Accordingly, recognition of ICI exposure should be

accompanied by systematic evaluation for competing diagnoses.

An additional consideration is concomitant anticancer treatment. A proportion of patients received cytotoxic chemotherapy, targeted therapy, or other antineoplastic agents during the study period. Such therapies may independently contribute to fever, gastrointestinal symptoms, cytopenias, infection, fatigue, and other causes of ED presentation. Because these exposures were heterogeneous and were not incorporated comprehensively into the multivariable model, residual confounding by concomitant anticancer therapy cannot be excluded.

The irAE profile in this cohort was mainly gastrointestinal, dermatologic, and endocrine. This pattern is consistent with the recognized toxicity spectrum of ICIs. Reviews and guidelines consistently identify dermatologic reactions, diarrhea or colitis, thyroid dysfunction,

Table 6. Exploratory Multivariable Logistic Regression Analysis of Factors Associated with All-Cause ED Utilization ^a

Variables	P Value	Adjusted OR	95% CI
Number of treatment cycles	0.018	1.037	1.006 - 1.069
ALT, U/L	0.025	1.016	1.002 - 1.031
Total bilirubin, mg/dL	0.033	3.036	1.095 - 8.422
Platelet count, $\times 10^3/\mu\text{L}$	0.130	0.999	0.997 - 1.000

^a This analysis was exploratory. Treatment-cycle count was based on documented treatment exposure and was not a fixed baseline variable. Estimates should therefore not be interpreted causally. The outcome was occurrence of ≥ 1 all-cause ED visit rather than an irAE-related ED visit. Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; ED, emergency department; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; OR, odds ratio.

hepatitis, and pneumonitis as some of the clinically important irAEs associated with these agents (5-9, 14). In the present study, gastrointestinal toxicity was the most common irAE category, followed by dermatologic and endocrine toxicities. Among cases with available grading information, most documented toxicities were grade 1 or 2, whereas grade 3 events were uncommon. This finding may explain why many cases were managed with monitoring, supportive care, temporary treatment interruption, or limited pharmacologic therapy rather than prolonged hospitalization.

Management was broadly consistent with guideline-based approaches, including monitoring for mild toxicity, temporary treatment interruption, permanent discontinuation in selected cases, corticosteroid therapy when clinically indicated, and organ-specific supportive treatment (6, 7, 9).

Corticosteroid use requires careful interpretation in this retrospective dataset. Although corticosteroids are a cornerstone of treatment for many moderate to severe irAEs, chart review may not fully capture the exact indication, initial dose, duration, tapering schedule, response, or recurrence after discontinuation. Some corticosteroid prescriptions may also have been used for non-irAE indications, including cancer-related symptoms, antiemetic regimens, airway symptoms, or other inflammatory conditions. Therefore, corticosteroid use should be presented descriptively rather than as a direct marker of confirmed immune-mediated toxicity unless cases were individually adjudicated.

The relatively low proportion of irAE-related ED visits should not be interpreted as evidence that irAEs are clinically minor. Some irAEs, including pneumonitis, myocarditis, neurologic toxicity, severe colitis, hepatitis, adrenal insufficiency, and insulin-dependent diabetes, can progress rapidly and become life-threatening if diagnosis

and treatment are delayed (5-9, 14). Rather, the present findings highlight the complexity of acute care in this population. ED clinicians must balance two risks: missing a serious irAE that requires urgent immunosuppression or incorrectly treating a non-irAE condition with corticosteroids when infection or another diagnosis is responsible.

Infection is an important competing diagnosis because it may mimic or coexist with irAEs. This overlap is particularly relevant when corticosteroid therapy is considered, reinforcing the need for careful evaluation before attributing acute symptoms solely to immune-mediated toxicity.

Alanine aminotransferase and total bilirubin were associated with all-cause ED utilization in the exploratory regression analysis. These findings should be interpreted cautiously because abnormal liver function tests in patients receiving ICIs may reflect immune-mediated hepatitis, hepatic metastases, biliary obstruction, infection, drug-induced liver injury, sepsis, disease progression, or overall clinical vulnerability rather than immune-related toxicity alone.

The observed association between treatment-cycle count and ED utilization requires particularly cautious interpretation. Cycle count was not a fixed baseline characteristic and may have accumulated during the same observation period during which ED visits occurred. Patients receiving more cycles may also have longer survival, greater treatment exposure, and more opportunity to experience an ED visit, whereas fewer cycles may reflect early progression, toxicity, treatment discontinuation, or death. Therefore, this association may reflect treatment duration and time at risk rather than an independent effect of cycle number itself, and no causal or predictive interpretation should be made.

These findings suggest that structured approaches to assessing patients receiving ICIs in the ED may warrant prospective evaluation. Potential components could include early identification of ICI exposure, assessment for competing diagnoses such as infection and disease progression, CTCAE-based toxicity grading when an irAE is suspected, medication review, and early oncology consultation. The effectiveness of such a pathway was not evaluated in the present study. CTCAE-based grading is particularly important because management decisions, including whether to continue, hold, or discontinue ICIs, depend heavily on toxicity grade (15).

Oncology pharmacists may support this process by verifying ICI exposure, reviewing concomitant therapies, assisting with corticosteroid management, and contributing to medication reconciliation and discharge counseling.

This study has several strengths. It included a real-world cohort of 288 patients treated with ICIs over a five-year period and evaluated ED visits, presenting symptoms, irAE categories, management strategies, hospital admission, and outcomes. It also provides regional data from Saudi Arabia, where published evidence on ED utilization among patients receiving ICIs remains limited. The findings are directly relevant to tertiary oncology practice, where patients often have advanced disease, multiple comorbidities, concomitant medications, and complex acute presentations.

5.1. Study Limitations

Several limitations should be acknowledged. First, the retrospective design made the study dependent on the completeness and accuracy of routine clinical documentation. Attribution of irAEs relied primarily on the treating team's documented assessment rather than prospective independent adjudication; therefore, some events may have been underrecognized, incompletely graded, or misclassified. Second, the study was conducted at a single tertiary center, which may limit generalizability. Third, a formal screening log was not available, preventing complete reconstruction of the number of potentially eligible patients initially identified and excluded. Fourth, several clinical and laboratory variables had missing observations, and missing data were not imputed. Fifth, the multivariable analysis was exploratory and used variables selected according to univariate statistical significance; consequently, clinically relevant confounding

by factors such as cancer type, disease severity, treatment regimen, concomitant systemic therapy, and treatment line may remain. Treatment intent, including adjuvant versus treatment of advanced or metastatic disease, was not consistently captured as a separate variable in the retrospective dataset. Sixth, treatment-cycle count was not a fixed baseline exposure and may partly reflect survival, treatment duration, treatment tolerance, and time at risk, creating potential temporal ambiguity. Seventh, laboratory measurements could not be standardized to a uniform prespecified collection window for every patient and should not be interpreted as specific predictors of immune-mediated toxicity. Eighth, the fixed 24-week observation period may have missed late-onset irAEs, while death, treatment discontinuation, transfer of care, or loss of institutional follow-up may have reduced observable time at risk. ED visits occurring at outside institutions could not be systematically captured. Finally, corticosteroid indication, dose, duration, tapering schedule, and relationship to confirmed irAEs could not be reliably established in all cases. These limitations preclude causal interpretation of the observed associations.

5.2. Conclusions

ED utilization was common among cancer patients receiving ICIs during the predefined 24-week observation period, whereas only a minority of patients had ED visits attributed to irAEs. Documented irAEs most commonly involved gastrointestinal, dermatologic, and endocrine manifestations and were predominantly low grade among cases with available grading information. This study primarily provides descriptive real-world evidence regarding acute healthcare utilization in a Saudi tertiary oncology setting. Associations identified in exploratory regression analyses should be interpreted cautiously and should not be considered causal or specific predictors of immune-mediated toxicity. Larger multicenter prospective studies are warranted to confirm these findings and evaluate structured approaches to the assessment of acute presentations among patients receiving ICIs.

Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

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