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BRIEF RESEARCH REPORT

Infectious Disease

Emergency department disposition of non-neutropenic febrile patients with cancer

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Abstract

Objectives: National data reveal that 60% of the 4.5 million annual emergency department (ED) visits by patients with cancer result in admission. Many of these visits are due to a febrile illness. Current literature provides limited guidance on how to treat non-neutropenic febrile ED patients. This study characterizes clinical outcomes of non-neutropenic febrile patients with cancer presenting to an academic, Comprehensive Cancer Center affiliated ED.

Methods: Retrospective chart review of 101 randomly selected adult patients with active cancer presenting with a chief complaint of fever or a documented fever in the ED and an absolute neutrophil count above 1000 between October 2015 and September 2016. Descriptive statistics were calculated.

Results: The primary malignancies represented were hematologic (24%), gastrointestinal (13%), head and neck (13%), and genitourinary (8%). Sixty-two percent were on chemotherapy, 15% on radiation therapy, and 12% were on targeted therapy. Severe illness outcomes occurred in 39% and 83% were admitted with a median length of stay of 4 days. Among admitted patients, 24% experienced a length of stay ≤2 days. A return visit to the ED or an in-system hospitalization within 7 days of the index visit occurred in 10% and death occurred within 7 days of the index visit in 4%.

Conclusion: A majority of patients presenting to the ED with non-neutropenic fever are admitted (83%), of whom nearly a quarter experience a length of stay of ≤2 days with infrequent serious illness outcomes. Future efforts should focus on the development of risk stratification tools in this population to avoid potentially unnecessary hospitalizations.

KEYWORDS
acute oncology, ambulatory care, cancer, fever, non-neutropenic fever, risk stratification

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1 | INTRODUCTION

1.1 | Background

The American Cancer Society estimates that there were >16.9 million Americans with a history of cancer alive on January 1, 2019 and an additional 1.8 million were expected to be diagnosed in 2020.[1] Cancer is the second-leading cause of death in the United States.[1] In 2020, there were an estimated 606,520 cancer deaths in the United States. Cancer prevalence is increasing because of the aging population and the increasing success of cancer therapies, thus contributing to the growing number of cancer survivors. Of the >136 million patient visits to US emergency departments each year,[2] 3 million or more have cancer.[3] Almost two-thirds of these visits result in hospital admission.[4]

The number of patients with cancer seeking acute care in the ED is steadily increasing. These patients seek acute care for a variety of reasons,[5] including but not limited to new infection, chemotherapy side effects, acute or chronic pain related to their cancer or cancer treatment, and non-oncologic acute pathologies.[6] It is important to further characterize this population in order to more effectively risk-stratify and treat these patients.

1.2 | Goals of this investigation

Fever is a leading ED presenting symptom (14.4%) in patients with cancer.[6] Current research relating to the population of infected patients with cancer is focused on risk stratification for mortality and morbidity, predominantly in a neutropenic population.[7–9] Several risk stratification scores,[10,11] such as the Multinational Association of Supportive Care of Cancer (MASCC) risk index score[12] or the Clinical Index of Stable Febrile Neutropenia[13] have been developed to help physicians appropriately identify need for admission in a neutropenic cancer patient. However, febrile neutropenia represents a small and limited subset of the potentially infected population of patients with cancer seeking care in EDs. The majority of febrile ED patients with cancer are not neutropenic, yet in this population no risk stratification tool exists to assist the treating physician. In the absence of clinical decision support, we hypothesize that a significant portion of these patients are unnecessarily admitted for further specialty evaluation.

To improve the care of this high-risk patient population, we conducted a retrospective chart review to further characterize the non-neutropenic population of patients with active cancer presenting to an ED. Our primary objective was to describe the admission rate in this important population and to quantify the proportion that may not require admission per the Centers for Medicare and Medicaid Services (CMS) Two-Midnight Rule,[14] demonstrated by a length of stay of ≤2 days.

The Bottom Line

In a retrospective review of 101 adult patients with active cancer and fever presenting to the emergency department, a majority (83%) were admitted, and nearly a quarter (24%) had a length of stay ≤2 days, suggesting an opportunity for risk stratifying patients with cancer and fever in the ED to prevent potentially unnecessary hospitalizations.

2 | MATERIALS AND METHODS

2.1 | Study setting and patient selection

All patients presenting to the ED of an urban, academic tertiary care center over the study period of October 1, 2015 through September 30, 2016 were potentially eligible. Of note, the ED physician is responsible for admission decisions at this facility and contacting the primary oncology team at time of disposition is at the discretion of the emergency physician. Inclusion criteria included age ≥18 years, fever ≥38.0°C in the 24 hours before or 6 hours after ED presentation and active cancer. Patients who were neutropenic (absolute neutrophil count <1000 cells/μL), pregnant, incarcerated or seen as a trauma response were excluded from the study. Patients were enrolled only once, at their first identified eligible visit during the study period. Patients meeting inclusion were identified by querying the electronic medical record (Epic, Epic Systems Corporation, Verona, WI). A random subset of ≈10% of eligible patients was chosen for chart review using the runinformint command in STATA v12 (StataCorp LLC, College Station, TX).

2.2 | Study design

This was a retrospective chart review of patients meeting inclusion criteria. Trained chart reviewers confirmed inclusion and exclusion criteria before completion of full chart reviews. All chart abstractors used a codebook, received directed training in chart review, and completed the same 3 standardized chart reviews as training. Patient outcomes of interest were abstracted from the chart and included severe illness. This project was approved by the local institutional review board.

2.3 | Outcomes

Severe illness outcomes were adapted for ED use from the list of severe illness categories used in previously published risk stratification of patients with febrile neutropenia per the MASCC risk index score.[12]

TABLE 1 Demographic summary

Variable		Discharge (n = 16)	Admit (n = 85)	Total (n = 101)
Gender	Female	10 (63%)	40 (47%)	50 (50%)
Age	Median [interquartile range] (min, max)	58.5 [47, 69.5] (21, 85)	59 [53, 68] (26, 85)	59 [51, 68] (21, 85)
Hispanic or Latino	Hispanic or Latino	0 (0%)	2 (2%)	2 (2%)
	Not Hispanic or Latino	15 (94%)	70 (82%)	85 (84%)
	Not reported/Unknown	1 (6%)	13 (15%)	14 (14%)
Current living situation	Home/apartment	15 (94%)	74 (87%)	89 (88%)
	Skilled nursing facility/extended care facility/rehabilitation facility	0 (0%)	6 (7%)	6 (6%)
	Unknown	1 (6%)	5 (6%)	6 (6%)
Current primary active cancer	Breast	0 (0%)	5 (6%)	5 (5%)
	Dermatologic	2 (13%)	2 (2%)	4 (4%)
	Endocrine	0 (0%)	1 (1%)	1 (1%)
	Gastrointestinal	2 (13%)	11 (13%)	13 (13%)
	Genitourinary	0 (0%)	8 (9%)	8 (8%)
	Gynecologic	0 (0%)	6 (7%)	6 (6%)
	Head and neck	2 (13%)	11 (13%)	13 (13%)
	Hematologic	6 (38%)	20 (24%)	26 (26%)
	Other	4 (25%)	21 (25%)	25 (25%)
Chemotherapy in preceding 30 days		12 (75%)	50 (59%)	62 (61%)
Targeted drug therapy in preceding 30 days		2 (13%)	11 (13%)	13 (13%)
Systemic steroids in preceding 30 days		3 (19%)	2 (2%)	5 (5%)
Radiation therapy in preceding 30 days		4 (25%)	11 (13%)	15 (15%)
Surgical intervention in preceding 30 days		0 (0%)	3 (4%)	3 (3%)
History of stem cell or bone marrow transplant		1 (6%)	5 (6%)	6 (6%)
Presence of indwelling line or tunneled catheter		5 (31%)	39 (34%)	34 (34%)
Prior hospice care		0 (0%)	0 (0%)	0 (0%)
Prior palliative care services		1 (6%)	9 (11%)	10 (10%)
Emergency Severity Index	1	9(56%)	37 (44%)	46 (46%)
	2	4(25%)	46 (54%)	50 (50%)
	3	3 (19%)	2 (2%)	5 (5%)
	4/5	0 (0%)	0 (0%)	0 (0%)

These were defined as any ED systolic blood pressure <100 mmHg, need for mechanically assisted ventilation in the ED, need for intensive care admission from the ED, ED documented patient confusion, ED or hospital readmission within 7 days of index ED visit, and mortality within 7 days of index ED visit. Basic demographics, ED vital signs, medical history, oncology history, and infection diagnoses were obtained from the electronic medical record by chart review.

2.4 | Analysis

Abstracted data were directly entered into REDCap.[15,16] Descriptive statistics including medians and interquartile values, minimum and maximum for continuous variables, and proportions for categorical variables were calculated overall and by ED hospital admittance. Ninety-five percent confidence intervals were calculated for outcomes. All analyses were performed with SAS v9.4 (SAS Institute Inc., Cary, NC), STATA v12 and v15 (StataCorp LLC, College Station, TX).

3 | RESULTS

3.1 | Characteristics of study subjects

A sample of 1038 potentially eligible patients were identified from the initial electronic medical record query and 101 patients were randomly selected for manual chart abstraction. Patient demographic and disease characteristics are reported in Table 1. The study population included a heterogeneous group of malignancies with the following

TABLE 2 Severe illness outcomes – modified from Klastersky et al.[12]

Variable	Discharge (n = 16) (%, 95% CI)	Admit (n = 85) (%, 95% CI)	Total (n = 101) (%, 95% CI)
Any emergency department systolic blood pressure reading <100 mmHg	2 (13, 2–38)	21 (25, 16–35)	23 (23, 15–32)
ED mechanical ventilation	0 (0, 0–21)	3 (4, 1–10)	3 (3, 1–8)
ICU admission	0 (0, 0–21)	7 (8, 3–16)	7 (7, 3–14)
Confusion noted in ED	0 (0, 0–21)	6 (7, 3–15)	6 (6%, 2–12)
ED or hospital readmission within 7 days of index visit	4 (25, 7–52)	6 (7, 3–15)	10 (10, 5–17)
Mortality within 7 days of index visit	0 (0, 0–21)*	4 (5, 1–12)	4 (4, 1–10)
Severe illness outcome			
≥1	6 (38, 15–65)	33 (39, 28–50)	39 (39, 29–49)

*One-sided 97.5% confidence interval (CI).

primary tumor types being the most predominant: hematologic (26%), gastrointestinal (13%), head and neck (13%), and genitourinary (8%). In the previous 30 days, 61% of patients had received chemotherapy, 15% radiation therapy, and 12% targeted therapy. Approximately a third of patients had an indwelling line or tunneled catheter and nearly all patients were classified as level 1 or 2 on the emergency severity index at time of nursing triage (96%).

3.2 | Main results

Severe illness outcomes occurred in 39% of all patients, most commonly because of systolic hypotension <100 mmHg in the admitted group (25%) and repeat ED visits or hospitalization within 7 days of the index ED visit in the discharged group (25%) (Table 2). No deaths within 7 days of the index ED visit were recorded in the discharged group and 4 deaths occurred in the admitted group (5%).

A significant proportion of patients with non-neutropenic fever were admitted from the ED (n = 85, 83%). The median length of stay for admitted patients was 4 days [interquartile range 3–7]. Among hospitalized patients, 20 (24%, 95% confidence interval [CI]: 15%–34%) had a length of stay ≤ 2 days and only 2 of this subset of patients experienced 1 or more serious illness outcomes. For patients hospitalized >2 days, 48% (31/65, 95% CI: 35%–61%) had 1 or more serious illness outcome in the ED. An infectious etiology was suspected by the ED in 38% (95% CI: 15%–65%) of discharged patients and 76% (95% CI : 60%–80%) of admitted patients (Table 3). Further analysis of hospitalization records for the presence of infectious diagnoses among the admitted group reveals no significant different exists between the proportions of patients discharged in ≤2 days (90.0%, 95% CI: 68.3%–98.8%) versus those admitted for >2 days (90.8%, 95% CI: 81.0%–95.5%).

TABLE 3 Emergency department suspected presence of infection

Type of infection	Discharge (n = 16) (%, 95% CI)	Admit (n = 85) (%, 95% CI)
Diagnosed infection	6 (38%, 15%–65%)	60 (76%, 60%–80%)
Lower respiratory	2 (13%, 2%–38%)	35 (41%, 31%–52%)
Urinary tract	4 (25%, 7%–52%)	16 (19%, 11%–29%)
Soft tissue	0 (0%, 0%–21%)*	11 (13%, 7%–22%)
Gastrointestinal	0 (0%, 0%–21%)*	3 (4%, 1%–12%)

*One-sided 97.5% confidence interval (CI); Coinfection may be suspected.

4 | LIMITATIONS

This manuscript reports the experience of a single site ED affiliated with a Comprehensive Cancer Center. As a result the experience in non-academic settings may differ; however, it can be postulated that the rate of admission would be even higher in settings without an affiliated cancer center and its associated outpatient resources. Further characterization of this population is required but was limited in this analysis because of the retrospective nature and chart review study design employed. Additionally, owing to the chart review study design, repeat ED visits, repeat hospitalizations, and mortality were limited to in hospital system occurrences and may be underrepresented in our study population. In order to limit bias, key variables and outcomes were limited to easily identifiable and consistently recorded variables in the electronic medical record. Because of the study time period immunotherapy was not recorded; however, the rapid adoption of these novel therapies is likely to increase the population of non-neutropenic fever and should be assessed in future studies. Also, admission decisions are complex and some patients may have been admitted for other, non-fever-related considerations. Lastly, there is a lack of published ED based literature in this population to which to compare our findings.

5 | DISCUSSION

Much of the unscheduled care for patients with cancer and non-neutropenic fevers occurs in EDs across the country. An analysis of the US Nationwide Emergency Department Sample from 2006–2012 revealed that 4.2% of all ED visits were by patients with cancer.[17] As a result, additional attention is warranted on the ED management of this population for key presentations, such as fever (14.4% of ED visits by patients with cancer).[6] Although neutropenia is a particularly high-risk

clinical scenario, it represents a minority of fever cases (3.4% of all ED visits).[6] Little attention has been devoted to the larger proportion of patients with non-neutropenic fever warranting this pilot study.

Serious illness outcomes were observed in both the discharged and admitted groups (Table 2). Of note, a quarter of these outcomes in the discharge group were repeat ED visits or hospitalization within 7 days of the index ED visit. This emphasizes the need for close outpatient follow-up when discharging this patient population. The most common serious illness outcome noted in the admitted group was hypotension (25%), which is indicative of potential sepsis in a febrile population and consistent with a likely need for admission. The data indicate the admitted patients were more commonly diagnosed with infectious etiologies in the ED (76%) compared to the discharged group (38%). The ED diagnosis of infections likely contributes to admission decisions; however, among those admitted no significant difference was noted in the proportion of diagnosed infections between the group discharged in ≤2 days versus the group with a length of stay >2 days. Further investigation of ED clinical decision making relating to admitting this patient population is warranted to avoid potentially unnecessary hospitalizations.

In this pilot study of a non-neutropenic ED population, we note that the admission proportion (83%) exceeds the average admission proportion for patients with cancer presenting to the ED (~60%) reported from a national dataset of ED visits and a multicenter observational trial of patients with active cancer.[6,17] The majority of admitted patients met inpatient care criteria as defined by the CMS Two-Midnight rule.[14] Importantly nearly a quarter of these patients are discharged within 48 hours with only 2 individuals experiencing a serious illness outcome (any ED systolic blood pressure reading <100 mmHg), suggesting that a portion of admissions may be appropriate for outpatient or observation care as defined by the CMS Two-Midnight rule. Risk stratification for hospital admission of patients with febrile neutropenia has been developed; however, no such decision aid currently exists in the non-neutropenic setting. The data from this study reflect a potential opportunity for the development of decision tools for this population. Additionally, the transition from cytotoxic chemotherapy to novel immunotherapy approaches in the treatment of cancer is likely to increase the number of non-neutropenic fever presentations. Appropriate risk stratification is important across all practice settings to avoid iatrogenic complications and additional health care spending associated with potentially unnecessary hospitalizations and transfers to referral centers. Such tools are of particular relevance for community and rural EDs with limited resources and not affiliated with a Cancer Center. Our pilot data demonstrate an opportunity for practice improvement for patients with non-neutropenic, febrile presentations to EDs.

6 | CONCLUSION

A majority of patients presenting to the ED with non-neutropenic fever are admitted (83%), of which nearly a quarter experience a length of stay ≤2 days with infrequent serious illness outcomes. These data suggest an opportunity for practice improvement and future efforts should focus on the development of risk stratification tools to aid in the admission decision for this patient population to avoid potentially unnecessary admissions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JJB, CH, and JMC developed the study protocol. PJS, JAF, BH, and JG performed data acquisition. JJB, JMC, and JAS performed data analysis. All authors contributed to manuscript development and revision.

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