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Incidence of Neutropenia in Veterans Receiving Lung Cancer Chemotherapy: A Comparison of Administrative Coding and Electronic Laboratory Data

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Abstract

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Methods: Retrospective cohort study of 718 veterans receiving their first course of chemotherapy for non-small cell lung cancer. Incidence of neutropenia was assessed using electronic laboratory results and ICD-9 codes captured in the Department of Veterans Affairs (VA) electronic medical records (EMR).

Results: A total of 118 of 718 patients (16.4 percent) were identified with an absolute neutrophil count (ANC) less than 1,000 cells/mm^3, while only 49 of 718 patients (6.8 percent) had ICD-9 codes for neutropenia. Using the combination of laboratory results and diagnosis codes, 136 of 718 patients (18.9 percent) experienced a neutropenic event. Compared to laboratory results as a gold standard, diagnosis codes were specific (not present for individuals without a laboratory-documented low ANC), but not sensitive (missing for many individuals with a low ANC documented in their laboratory test results).

Conclusion: Relying on ICD codes to identify neutropenia in administrative data likely results in under-reporting. The emerging availability of electronic laboratory results provides an opportunity to more accurately quantify patterns of neutropenia, identify individual risk factors, and assess clinical management practices—including use of colony-stimulating factor prophylaxis—in large community cohorts.

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Keywords

non-small cell lung cancer, neutropenia, laboratory data, administrative data, electronic health record

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Introduction

Neutropenia is a common toxicity resulting from myelosuppressive chemotherapy that leads to dose delays and reductions (i.e., deviations from recommended drug dose intensity and timing), which can compromise treatment efficacy and survival.[1] Neutropenia-associated complications, namely fever and infection, generate hospitalizations and increase costs and mortality during chemotherapy.[2] Myeloid colony-stimulating factors (CSFs) can be used to decrease the risk of neutropenia, but defining appropriate application of such drugs has been controversial as they are expensive and not likely to improve outcomes in low risk patients.[3,4] Understanding the frequency of neutropenia so that clinicians can more effectively manage chemotherapy, including the administration of prophylactic CSF drugs, is critical for improving patient outcomes and controlling health care spending.

Current data on chemotherapy-associated toxicities come primarily from clinical trials. Trial participants tend to be highly selected and do not represent the majority of patients receiving chemotherapy in the community.[5,6] Additionally, reporting of hematologic toxicities within clinical trials is inconsistent.[7] Prospective cohort studies can produce generalizable high-quality data on chemotherapy toxicities, but are expensive and time-consuming to conduct.[8] Administrative data containing diagnosis codes for neutropenia and other toxicities provide better patient representation than do clinical trial populations and are relatively inexpensive to obtain, but likely underestimate the occurrence of adverse events as toxicities are only captured when a clinical intervention generates a billing claim.[9,10] The lack of reliable data documenting neutropenia events in real-world settings makes it difficult to provide patients with information on both efficacy and toxicity of various drug regimens, to identify key risk factors, and to create clinically useful predictive modes with which to guide CSF administration.[7,11] Advances in health information technology, including detailed electronic records of laboratory test orders and results, may be capable of fulfilling the need for accurate clinical information on chemotherapy toxicities to improve patient care.

The Department of Veterans Affairs (VA) electronic medical record (EMR) includes diagnosis codes from inpatient and outpatient visits as well as the results of all laboratory tests performed on a given patient, allowing instances of neutropenia to be identified from the results of laboratory tests measuring neutrophil and white blood cell (WBC) count. To explore the ability of electronic laboratory results to better quantify the burden of neutropenia in a broad population of veterans receiving chemotherapy for lung cancer, this study compared algorithms based on electronic test results with more common approaches relying on claims data.[12,13] Specifically, we calculated the incidence of neutropenia in the first cycle of chemotherapy using laboratory results, diagnosis codes, and the combination of these two approaches, and we described variation in these algorithms by patient treatment characteristics. As a secondary aim we determined the accuracy of administrative coding of neutropenia compared to absolute neutrophil counts (ANC) derived from laboratory test results.

Methods

Setting and Study Population

After institutional review board approval, we accessed data for the VA Northwest Health Network, which comprises 8 medical centers and 30 Community Based Outpatient Clinics (CBOCs) across a multistate area that includes Washington, Alaska, Oregon, Idaho, one county in western Montana, and one county in northern California. Veterans newly diagnosed with non-small cell lung cancer (NSCLC) in these areas between January

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1, 2000 and December 31, 2009 were identified through the VA's cancer registry program.[14,15] Once identified, we extracted detailed demographic and medical history information for each patient along with specific treatment, care delivery, and outcome information from the first year after their diagnosis from the VA Northwest Health Network's Data Warehouse. Compiled data included all laboratory tests ordered by providers and their results, as well as linked pharmacy records detailing all administered chemotherapy agents. Laboratory tests and results have been included in the VA EMR since January 2000. The final patient cohort was restricted to individuals receiving a chemotherapy agent related to lung cancer (VA drug class AN900) within 11 months of diagnosis and surviving 28 days after their initial chemotherapy administration, similar to the criteria described by Hosmer et al.[16]

Electronic Laboratory Result for Identifying Neutropenia

All laboratory records from the 28 days following initiation of chemotherapy were reviewed to identify measures associated with WBC count. A 28-day window was used to ensure that observed neutropenic events were associated with the first cycle of chemotherapy, when risk of neutropenia is greatest and most patients still receive full-dose chemotherapy, as opposed to subsequent cycles.[17] This time frame was also used for predictive modeling of neutropenia risk to inform CSF prophylaxis.[16] Two approaches were used to determine ANC on a given day. Laboratory results directly reporting neutrophil count or number were cleaned and standardized to give ANC in cells/mm^3. Additionally, laboratory results reporting WBC count and percentage of "segs" (i.e., segmental mature) and "bands" (i.e., rod-shaped immature) neutrophils were used to indirectly calculate ANC by multiplying WBC count by the sum of percent segs and bands. Our primary measure of neutropenia was defined as having an ANC of < 1,000 cells/mm^3 calculated by either approach on any day within the 28-day window. We also identified patients whose ANC fell below 500 cells/mm^3 and 100 cells/mm^3 during this period.

ICD-9 Assessment of Neutropenia

Inpatient and outpatient records from the 28 days following chemotherapy initiation were queried to identify International Classification of Diseases, Ninth Edition (ICD-9) codes for neutropenia or an associated disorder of the white blood cell. Based on consultation with clinical colleagues, receipt of any of the following six codes was considered an occurrence of neutropenia: 288.0 (agranulocytosis), 288.00 (neutropenia), 288.03 (drug induced neutropenia), 288.5 (leukocytopenia), 288.8 (specified disease of WBC), 288.9 (unspecified disease of WBC).

Patient Characteristics and Chemotherapy Treatment Variables

Data on cancer stage and treatment extracted from the EMR included receipt of surgery or radiation therapy and the American Joint Committee on Cancer (AJCC) stage as recorded by the cancer registrar. Using the linked pharmacy data, time to initial chemotherapy administration was calculated based on the date the first chemotherapy claim for VA drug class AN900 appeared in pharmacy data post diagnosis. Extracted patient demographics included the following: date of birth, body mass index (BMI) at diagnosis, and gender. Finally, pre-existing comorbidity was categorized based on the Charlson comorbidity index using inpatient and outpatient records from the same period. The Charlson comorbidity index predicts one-year mortality in patients with a range of comorbid conditions. Conditions are scored based on mortality risk and summed to give a total score, with higher scores indicating greater mortality risk.[18]

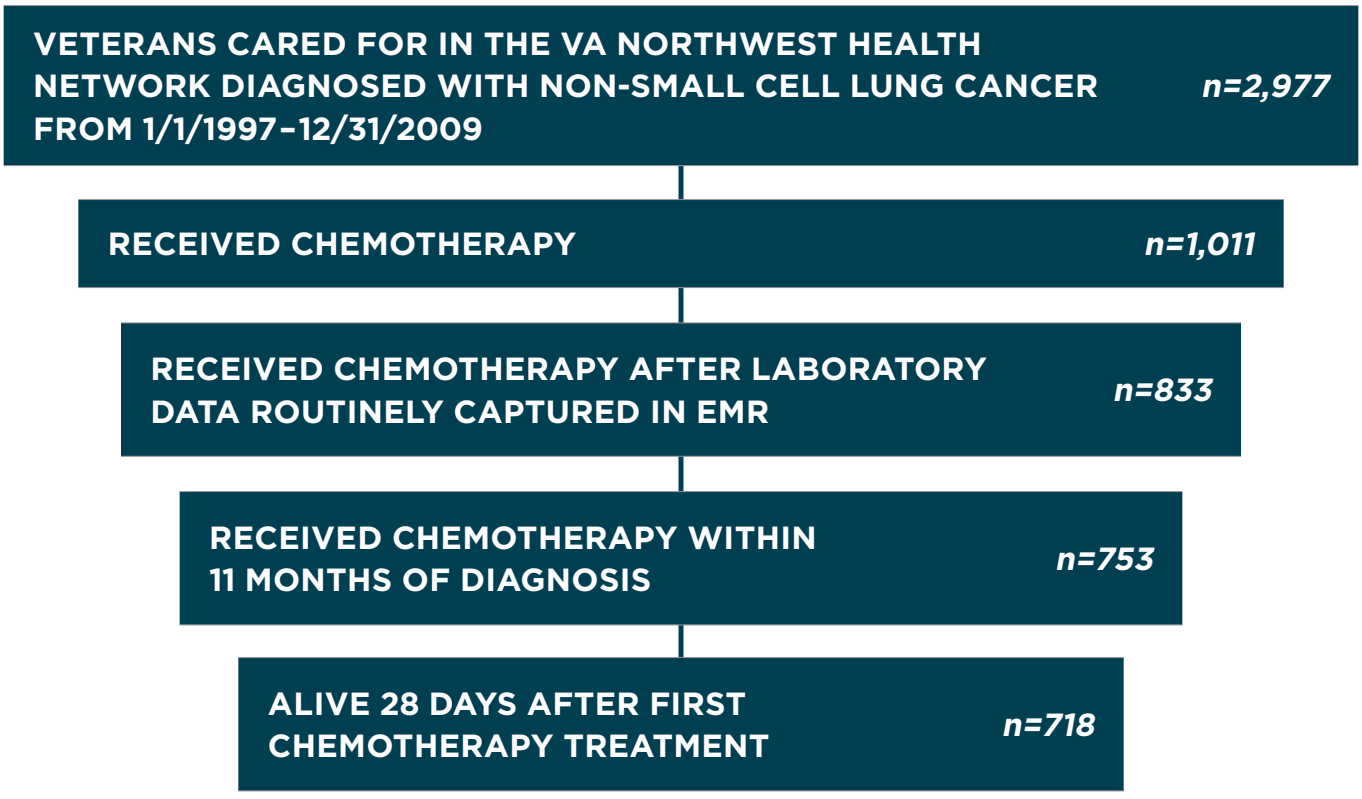
Statistical Analysis

Patient clinical and demographic characteristics were examined overall and by neutropenia outcomes. Descriptive statistics including Chi-square tests were compared to identify variation in frequency of neutropenia events by algorithm. Accuracy of the ICD-9 diagnosis codes for neutropenia was assessed by calculating sensitivity (percentage of patients with a laboratory result indicating low ANC who had an ICD-9 code for neutropenia) and specificity (percentage of patients without a laboratory result indicating low ANC who had no ICD-9 codes for neutropenia) of diagnostic codes using the laboratory-derived outcome measures of neutropenia as a gold standard. We also calculated positive predictive value (PPV) (the percentage of patients with an ICD-9 code for neutropenia who had a laboratory result indicating low ANC) and negative predicative value (NPV) (the percentage of patients without an ICD-9 code for neutropenia who had no laboratory results indicating low ANC). All analyses were conducted in STATA 11.[19]

Results

A total of 2,977 patients diagnosed with NSCLC were identified from the cancer registry during the study period. Figure 1 provides an overview of patient selection. We included 753 patients who received chemotherapy for lung cancer within 11 months of diagnosis. We excluded 35 patients who died within 28 days of initial chemotherapy administration, resulting in a final sample of 718 individuals. Patient characteristics and treatment variables for the final cohort are reported in Table 1.

Figure 1. Flow Diagram of Cohort Selection



Note: Abbreviations - Veterans Affairs (VA); electronic medical record (EMR)

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Table 1. Characteristics of Veterans Receiving Lung Cancer Chemotherapy

		% (N)
Overall		718
Time to initial chemotherapy administration from diagnosis date	<1 month	21.7 (156)
	1–3 months	54.3 (390)
	>3 months	24.0 (172)
Disease stage	I and II	21.4 (154)
	III	39.8 (286)
	IV	36.2 (260)
	Unknown	2.5 (18)
Surgery and radiation	Surgery	13.4 (96)
	Radiation	46.2 (332)
	Both	16.2 (116)
	Neither	24.1 (173)
	Missing	(1)
Charlson comorbidity score	0	40.0 (287)
	1	37.2 (267)
	≥2	22.8 (164)
BMI (kg/m^2)	Underweight (<18.50)	2.9 (21)
	Normal (18.50-24.99)	40.3 (289)
	Overweight (≥25.00)	32.3 (232)
	Obese (≥30.00)	22.8 (164)
	Missing	(12)
Year of diagnosis	2000–2002	26.3 (189)
	2003–2005	33.4 (240)
	2006–2009	40.3 (289)
Age at diagnosis	59 or younger	32.6 (234)
	60–64	20.9 (150)
	65–69	18.5 (133)
	70 or older	28.0 (201)
Gender	Male	97.5 (700)
	Female	2.5 (18)

Note: Abbreviations – body mass index (BM).

Incidence of Neutropenia from Electronic Laboratory Results

Based on electronic laboratory data, 118 individuals (16.4 percent) were identified as having an ANC <1000 cells/mm^3 within 28 days of their initial dose of chemotherapy (Table 2). Additionally, 61 individuals had an ANC <500 cells/mm^3 (8.5 percent) and 13 had an ANC <100 cells/mm^3 at least once during their first treatment cycle (1.8 percent). Of the 718 patients, 90.3 percent had at least one electronic laboratory test result to quantify ANC level available in their EMR in the 28 days following chemotherapy initiation. The average number of ANC measurements for each individual was 4.85 and ranged from zero to 18. In instances where there were multiple measures of ANC available for a given day, which occurred 1,018 times (41.5 percent of all available ANC measures were from a day where more than one assessment of ANC was available), they were consistently similar. Calculating ANC from laboratory tests reporting WBC count and percent of mature and immature neutrophils identified more individuals who experienced neutropenia than direct measures of neutrophil count. Of the 118 individuals whose ANC fell below 1,000 cells/mm^3 during their first cycle of chemotherapy, 56 were identified based on a direct measure of neutrophil count while the 62 remaining individuals were identified using calculations based on test results reporting WBC count, segs, and bands.

Incidence of Neutropenia from ICD-9 Codes

We identified ICD-9 codes for neutropenia in the 28 days following chemotherapy initiation among 49 individuals (6.8 percent) (Table 2). Of these individuals, 33 had at least one outpatient code identifying a neutropenic event, 23 had at least one inpatient code, and 7 had both. The ICD-9 code for agranulocytosis (288.0) appeared most frequently (63.3 percent of patients with a neutropenia event received this code) (Table 3).

Patient-Level Variation in Neutropenia Events by Algorithm

The proportion of individuals with neutropenia identified by laboratory data was significantly higher than the proportion of patients with neutropenia identified by ICD-9 codes in all patient subgroups except those who did not receive surgery or radiation (Table 2). In bivariate analysis, additional treatment and age at diagnosis were associated with having a neutropenia event identified by laboratory values, with those receiving both surgery and radiation and individuals diagnosed between 65 and 69 having the highest rate of identified neutropenic events using this algorithm. None of the patient or treatment variables were associated with having a neutropenia event identified by ICD-9 codes. When a combination of ICD-9 codes and laboratory-determined ANC was used, only receipt of radiation was associated with identification of neutropenic events (Table 2).

Accuracy of Administrative Coding Compared to Electronic Laboratory Results

Of the 49 patients who had an ICD-9 code for neutropenia during their first cycle of chemotherapy, 31 were also identified with an ANC level <1000 cells/mm^3 during this period (Table 4). Of the remaining individuals, 16 had only normal laboratory results and 2 had no laboratory results from which to calculate ANC during that time. Conversely, of the 669 patients without codes for neutropenia during the 28 days after beginning chemotherapy, 87 had laboratory results indicating their ANC had fallen below 1000 cells/mm^3 in their EMR. Compared to the available laboratory data, ICD-9 codes for neutropenia had a sensitivity of 26.3 percent and specificity of 97.0 percent. The diagnostic performance characteristics of ICD-9 codes for an ANC <500 cells/mm^3 and an ANC <100 cells/mm^3 are given in Table 2. Overall, sensitivity and NPV of diagnostic codes increased while specificity and PPV decreased with increasing levels of myelotoxicity.

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Table 2. Characteristics of Veterans Receiving Chemotherapy by Neutropenia Outcomes

		NEUTROPENIA OUTCOMES[a]			
		ICD-9 ROW % (N)	ANC < 1,000 ROW % (N)	P-VALUE[b]	COMBINED[c] ROW % (N)
Overall, n=718		6.8 (49)	16.4 (118)	0.0000	18.9 (136)
Time to initial administration from diagnosis	<1 month	9.6 (15)	16.0 (25)	0.0064	20.5 (32)
	1–3 months	6.9 (27)	17.2 (67)	0.0000	19.5 (76)
	>3 months	4.1 (7)	15.1 (26)	0.0000	16.3 (28)
Disease stage	I and II	5.2 (8)	17.5 (27)	0.0000	18.2 (28)
	III	7.7 (22)	18.5 (53)	0.0000	21.7 (62)
	IV	6.5 (17)	12.7 (33)	0.0001	15.4 (40)
	Unknown	11.1 (2)	27.8 (5)	0.0243	33.3 (6)
Surgery and radiation	Surgery	4.2 (4)	11.5 (11)[d]	0.0004	11.5 (11)[d]
	Radiation	7.2 (24)	19.9 (66)	0.0000	23.2 (77)
	Both	6.9 (8)	20.7 (24)	0.0000	21.6 (25)
	Neither	7.5 (13)	9.8 (17)	0.2453	13.3 (23)
Charlson comorbidity score	0	7.3 (21)	16.0 (46)	0.0000	18.8 (54)
	1	6.0 (16)	16.5 (44)	0.0000	18.7 (50)
	≥2	7.3 (12)	17.1 (28)	0.0000	19.5 (32)
BMI (kg/m^2)	Under/normal weight (<24.99)	7.1 (22)	15.5 (48)	0.0000	18.7 (58)
	Overweight (≥25.00)	5.2 (12)	15.1 (35)	0.0000	16.4 (38)
	Obese (≥30.00)	9.1 (15)	20.1 (33)	0.0000	23.2 (38)
Year of diagnosis	2000–2002	7.9 (15)	20.1 (38)	0.0000	23.3 (44)
	2003–2005	7.9 (19)	17.9 (43)	0.0000	19.6 (47)
	2006–2009	5.2 (15)	12.8 (37)	0.0000	15.6 (45)
Age at diagnosis	≥ 59	7.7 (18)	11.5 (27)[e]	0.0276	15.0 (35)
	60–64	8.7 (13)	17.3 (26)	0.0002	20.0 (30)
	65–69	7.5 (10)	23.3 (31)	0.0000	25.6 (34)
	70 or older	4.0 (8)	16.9 (34)	0.0000	18.4 (37)

Notes: Abbreviations – International Classification of Diseases, Ninth Edition (ICD-9); absolute neutrophil count (ANC); body mass index (BMI). [a]Categories with small cell sizes were combined. [b]For Z-test of proportions, relative to proportion with ICD-9 codes for neutropenia. [c]Either ICD-9 or ANC. [d]Chi-squared test of heterogeneity significant at p<0.01. eChi-squared test of heterogeneity significant at p<0.05.

Table 3. Distribution of ICD-9 Codes Identifying Neutropenia Events in Administrative Data

		% (N)
OVERALL, N=49		
Agranulocytosis	288.0	63.3 (31)
Neutropenia	288.00	6.1 (3)
Drug inducted neutropenia	288.03	10.2 (5)
Leukocytopenia, unspecified	288.5	4.1 (2)
Specified disease of WBC	288.8	16.3 (8)
Unspecified disease of WBC	288.9	2.0 (1)

Notes: Abbreviations – International Classification of Disease, Ninth Edition (ICD-9); white blood cell (WBC).

Table 4. Concordance of Administrative Codes and Laboratory Data Identifying Neutropenia in First Chemotherapy Cycle (n=718).

	LABORATORY RESULTS					
	ANC <1,000 CELLS/MM^3		ANC <500 CELLS/MM^3		ANC <100 CELLS/MM^3	
	YES	NO	YES	NO	YES	NO
ICD-9 code for neutropenia	31	18	20	29	6	43
No ICD-9 code for neutropenia	87	582	41	628	7	662
Sensitivity	26.3%		37.8%		46.2%	
Specificity	97.0%		95.6%		93.9%	
PPV	63.3%		40.8%		14.0%	
NPV	86.9%		93.8%		98.9%	

Notes: Abbreviations – International Classification of Diseases, Ninth Edition (ICD-9); absolute neutrophil count (ANC); positive predictive value (PPV); negative predictive value (NPV).

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Discussion

This study utilized administrative data collected in the VA EMR to compare diagnostic coding for neutropenia with laboratory-determined ANC measurements in lung cancer patients treated within the VA Northwest Health Network. The prevalence of neutropenia during the first cycle of chemotherapy was 6.8 percent based on administrative diagnostic coding, 16.4 percent based on laboratory data, and 18.9 percent using either indicator. Additionally, 8.5 percent of patients experienced severe neutropenia (ANC <500 cells/mm^3). These estimates fall within the range of incidence rates reported in previous studies of NSCLC patients undergoing chemotherapy. For example, Hardy et al. observed neutropenia during the first three months of chemotherapy in 9.2–22.5 percent of NSCLC patients identified in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, depending on their chemotherapy regimen.[11] In a prospective cohort study, Lyman et al. identified severe or febrile neutropenia in 9.3 percent of one NSCLC sample and 11.1 percent of a second sample.[20] Comparing rates of neutropenia between studies is difficult because of variation in its definition and measurement, but our results indicate that using a combination of ICD-9 codes and laboratory results identified more patients who experienced neutropenia than either method alone, suggesting that the burden of neutropenia in NSCLC patients undergoing chemotherapy may be greater than previously estimated.

When comparing diagnosis codes and laboratory results, inpatient and outpatient ICD-9 codes have a low sensitivity (26.3–46.2 percent) for identifying individuals with neutropenia as determined by laboratory tests, even using a liberal outcome definition combining multiple ICD 9 codes. Specificity (93.9–97.0 percent) was higher. These results are similar to a recent study that evaluated the accuracy of claims-based definitions of febrile neutropenia in patients receiving chemotherapy in a large health care system, where diagnostic codes had relatively poor sensitivity compared to definitions that relied on EMR data including ANC, body temperature, and administration of antibiotic or antiviral therapy.[10] The mechanisms explaining the discordance between ANC measures and ICD-9 codes in our study are unknown, but it did not appear that those with low ANC measurements were receiving other neutropenia-associated codes. For example, of the 7 individuals who had an ANC <100 cells/mm^3 during the first cycle of chemotherapy, but no corresponding ICD-9 codes in their EMR, only one had a code for fever, infection, or symptoms of neutropenia in their chart (an outpatient code for fever).

None of the patient-level variables were associated with the likelihood of having a neutropenia event identified by ICD-9 codes, while the likelihood of having a neutropenia event identified in laboratory data varied by both age and treatment type. Thus, it is possible that the results of previous studies of patient-specific risk factors that relied on diagnostic codes may be biased. Older age is a known risk factor for neutropenia, but our algorithms identified the most neutropenia events in those patients ages 60–69 years.[20] Higher rates of adverse events have been previously observed in this age group and may reflect more aggressive treatment of patients under age 70, potentially explaining these findings.[21] Similarly, the higher rates of neutropenia events identified in patients who underwent surgery and radiation in addition to chemotherapy may also be due to treatment intensity, though these findings should be interpreted with caution as this study was not designed to identify patient-level neutropenia risk factors. Overall, our results highlight the limitations of diagnosis codes for answering key question about chemotherapy treatment and speak to the need for additional clinical data on toxicities

to supplement their use.[10] Electronic records of laboratory test ordering and results appear well suited to fulfill this need.

This study is limited by its potential lack of generalizability outside the VA.[22] The patient population receiving care at the VA is primarily male and has a different comorbidity profile than the general population of NSCL patients receiving chemotherapy. The VA is a separate entity within the broader U.S. health care system with its own unique practices and norms. Thus, concordance between diagnosis codes and laboratory data may be different in other settings, particularly those with more recent EMR implementation or where coding is linked to reimbursement. Another limitation is our use of ANC as a gold standard for assessing neutropenia, as opposed to more clinically relevant outcomes such as low ANC with presence of a fever or duration of neutropenia. There is no ICD-9 code for febrile neutropenia and clinicians may not code for neutropenia unless the patient has an infection that requires intervention or is at extremely high risk for infection based on other factors. Neutropenia or low ANC alone also may not be the ideal outcome for future patient-centered research using laboratory data. Finally, laboratory data with which to measure ANC (i.e., a direct measure or results reporting WBC count, segs, and bands) were available for only 90.3 percent of the sample, possibly limiting our ability to identify all individuals who experienced neutropenic events during the period of interest. This data source should not be interpreted as a true gold standard for neutropenia events as it has similar limitations as other types of EMR-derived data. Despite these limitations, this study addresses a key methodological challenge to generating evidence about treatment-related toxicities by presenting a novel comparison of administrative and more granular laboratory data in a large population of veterans receiving care across six western states.

Conclusion

Diagnostic codes in administrative data identified only a portion of the patients who experienced neutropenia during the first cycle of chemotherapy and do not fully capture the burden of this adverse event in NSCLC patients treated within the VA. In addition to more expensive prospective studies, laboratory tests results contained in the EMR are a feasible source of clinical data on chemotherapy toxicities. Such data will be essential for future research aimed at predicting, preventing, and treating neutropenia in patients receiving myelosuppressive chemotherapy. With the increasing availability of systems that capture computerized administrative and medical data, it will be possible to develop algorithms that identify patients at risk of neutropenia and to guide their treatment with CSF drugs, further personalizing chemotherapy care and controlling health care cost.[11,23]

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Conflict of interest

The authors have no conflicts of interest to disclose. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

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