CARE DELIVERY

original contributions

Predictors of Unplanned Hospitalizations Among Older Adults Receiving Cancer Chemotherapy

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abstract

PURPOSE Hospitalizations during cancer treatment are costly, can impair quality of life, and negatively affect therapy completion. Our objective was to identify risk factors for unplanned hospitalization among older adults receiving chemotherapy.

METHODS This is a secondary analysis of a multisite cohort study (N = 750) of patients ≥ 65 years of age evaluated with a geriatric assessment (GA) to predict chemotherapy toxicity. The primary outcome of this analysis was unplanned hospitalizations during treatment; the secondary outcome was length of stay (LOS) of the first hospitalization. Independent variables included pretreatment GA measures, laboratory values, cancer type and stage, and treatment intensity characteristics. We used logistic regression to estimate the odds of hospitalization and generalized linear models for LOS in multivariable analyses.

RESULTS The sample median age was 72 years (range, 65-94 years); 59% had stage IV disease. At least one unplanned hospitalization occurred in 193 patients (25.7%) during receipt of chemotherapy. In multivariable analyses controlling for cancer type, the following baseline characteristics were significantly associated with increased odds of hospitalization: needing help bathing or dressing (odds ratio [OR], 1.8; 95% CI, 1.0 to 3.1), polypharmacy (≥ 5 meds) (OR, 1.6; 95% CI, 1.1 to 2.4), more comorbid conditions (OR, 1.1; 95% CI, 1.0 to 1.3), availability of someone to take them to the doctor (OR, 2.0; 95% CI, 1.0 to 4.1), CrCl < 60 mL/min (OR, 1.7; 95% CI, 1.1 to 2.4), and albumin < 3.5 g/dL (OR, 1.8; 95% CI, 1.2 to 2.8). In multivariable analyses, older age, self-reported presence of liver or kidney disease, living alone and depressive symptoms were associated with longer LOS.

CONCLUSION Readily available GA variables and laboratory data, but not age, were associated with unplanned hospitalizations among older adults receiving chemotherapy. If validated, these data can inform prediction models and the design of interventions to decrease unplanned hospitalizations.

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INTRODUCTION

Older patients with cancer are at risk for high healthcare utilization after a cancer diagnosis and during cancer treatment.[1,2] Unplanned hospitalizations are a major concern for patients, practitioners, and the healthcare system. Hospitalizations are costly, impair quality of life, increase the risk of disability, and can negatively affect completion of therapy.[3-5] Identification of factors associated with unplanned hospitalizations during chemotherapy can inform the design of preventative interventions and avoid their subsequent negative effects on treatment and survivorship.

Compared to younger patients, older adults are more likely to have vulnerabilities such as comorbidity, impaired physical function, social support constraints, and cognitive dysfunction. These geriatric impairments may increase risk of hospitalization independent of tumor or treatment-related factors.[6-8] However, few studies have addressed risk factors for hospitalization among older adults during chemotherapy. Several large cohort studies that investigated geriatric assessment (GA) as a predictor of chemotherapy toxicity have captured hospitalization as a secondary outcome.[9,10] These studies have shown that a GA-derived toxicity score or a frailty assessment can identify patients at higher risk for both chemotherapy toxicity and hospitalizations. Understanding which vulnerabilities increase the odds

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of hospitalization is a next step that could inform interventions to minimize risk.

The primary goal of this analysis was to identify factors associated with unplanned hospitalizations among older patients receiving chemotherapy for cancer. We hypothesized that pretreatment GA impairments inclusive of physical function and comorbidity would be associated with unplanned hospitalization. A secondary objective was to evaluate factors associated with length of hospitalization.

METHODS

Analysis Cohort

This is a secondary analysis of data from an institutional review board–approved, prospective cohort study, which aimed to develop and validate a predictive model of severe chemotherapy toxicity in older adults.[9,11] The City of Hope institutional review board provided approval for conduct of this analysis; the parent study was approved by all site institutional review boards. Eligible patients were 65 years of age or older starting a new course of chemotherapy for a solid tumor diagnosis. Between 2006 and 2009, 500 patients enrolled in the development cohort, and between 2008 and 2012, 250 enrolled in the validation cohort. Eligibility criteria were identical for both cohorts. The development cohort included seven accruing academic institutions across the United States.[9] Participants included in the validation cohort were recruited from eight institutions in the United States, six had participated in the development cohort and two new sites were added.[11] The two cohorts were combined to maximize the number of events observed.

Predictor Variables

Clinical data, abstracted from the medical record, included routinely collected laboratory values (albumin, white cell count, blood urea nitrogen, creatinine, and hepatic function tests), cancer type, stage, treatment (single-agent *v* multi-agent; standard dose versus dose reduction at first cycle), use of growth factor, and receipt of prior chemotherapy. Creatinine clearance was calculated using the Jelliffe formula with ideal body weight. Participants completed a GA before starting chemotherapy. The GA tool includes a healthcare provider-administered assessment and a self-administered patient questionnaire.[9,11] The healthcare provider-administered questionnaire included the following assessments: (1) Karnofsky Performance Scale (KPS); (2) timed up and go (TUG) (a performance-based measure of physical function; time assessed in seconds for those who could complete the test or recorded as unable to perform)[12]; (3) Blessed Orientation Memory Concentration test (score $\geq$ 11 indicating impairment)[13]; (4) recording of height and weight (current and 6 months prior) to evaluate nutritional status including calculation of body mass index.

The self-administered patient questionnaire included the following surveys: self-reported measures of physical function and activities (activities of daily living [ADL] subscale of Medical Outcomes Study physical health survey and the instrumental activities of daily living subscale of the Older Americans Resources and Services survey),[14,15] a patient-rated KPS,[16] self-reported falls in the past 6 months, self-reported comorbid conditions and a rating of the degree to which each causes interference in activities (Physical Health Section Subscale of the Older Americans Resources and Services survey),[14] number and type of medications, assessment of psychologic state (symptoms of anxiety and depression using the Mental Health Inventory-17),[17] social activity, and social support (Medical Outcomes Study social activity and social support surveys).[15]

Outcomes

The primary outcome of this secondary analysis was incident unplanned hospitalization(s) during chemotherapy treatment, excluding any planned or scheduled admissions. The secondary outcome was the length of stay (LOS) of the first hospitalization. Data on hospitalization were abstracted from the medical records at each site and underwent review by two physicians. This process included review of notes, discharge summaries, phone notes, and scanned media to capture hospitalizations that happened within or outside of the institutions' electronic medical records system. The treating physician was queried to resolve any uncertainty. Reasons for hospitalization were recorded and adjudicated by two-physician review. If more than one reason was listed, the highest-grade toxicity resulting in hospitalization was reported.

Statistical Approach

We calculated descriptive statistics summarizing patient demographic, clinical characteristics, and GA domains. Univariate logistic regression models were used to obtain odds ratios (ORs), corresponding 95% CIs, and *P* values for each variable associated with hospitalization. These variables included demographic or disease characteristics, GA measures of function, comorbidity, cognition, nutrition, and psychosocial status, and laboratory values including albumin, hemoglobin, creatinine, white cell count, and liver function tests.

Variables with univariate *P* value $< .1$ were included in the multivariable logistic regression for stepwise selection. Forward selection and backward elimination was used to select the final set of variables independently associated with hospitalization. Collinearity among predictors was evaluated and they were not highly correlated (data not shown). Of note, the Cancer and Aging Research Group toxicity score, previously developed to predict grade 3-5 toxicity,[9] was not included as a variable in this analysis because (1) the objective was to identify individual characteristics associated with hospitalization, and (2) the Cancer and Aging Research Group toxicity score includes some of the variables identified in the regression analysis

(ie, creatinine clearance and cancer type). We evaluated the discrimination ability of the final set of variables by calculating the model's area under the curve. We also conducted an exploratory analysis among those with advanced-stage disease only (N = 436).

Next, we created an index indicating the number of risk factors for each patient from those identified in multivariate analyses (number of comorbid conditions, albumin, creatinine clearance, GI cancer, polypharmacy, requiring assistance with dressing or bathing, and having someone available to take them to the doctor most or all of the time). For this purpose, we dichotomized the continuous variables using Youden's index to determine the best cutoff point for each. The cutoff points for number of comorbidities, albumin, and creatinine clearance were three conditions, 3.5 g/dL, and 60 mL/min, respectively.

Similarly, a generalized linear model was used to examine risk factors associated with LOS among those who were hospitalized. LOS was unavailable for a small number of patients (N = 12). Baseline characteristics were similar between those with missing LOS (N = 12) and those with available LOS (N = 181) (Appendix Table A1, online only). We also conducted sensitivity analyses by assigning patients with missing LOS of 1 day or 4 (median) days of stay as well as multiple imputations using a fully conditional specification method to assess the impact of missing values on the final findings; the results were similar (Appendix Tables A2 and A3 [online only]) and complete case analysis results were presented.

All statistical tests were two-sided, and *P* values $< .05$ were considered statistically significant. Data were analyzed using SAS 9.4 analytic software (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the study population are described in Table 1. Among the 750 study participants, 193 (25.7%) experienced at least one unplanned hospitalization. Overall, their median age was 72 years (range, 65-94 years); more than half (55.9%) were female; the majority were White (84.3%) with college or higher education (61.5%), married (60.7%), and living with someone (77.5%). The most common four types of cancer were lung (27.6%), GI (27.1%), breast (15.5%), and gynecologic (14.0%), and the majority were stage IV at enrollment (58.1%). Most were receiving first-line chemotherapy (70%), were on a combination treatment (70.3%), and started with a standard dose regimen (73.1%). Their median KPS was 90 (range, 40-100), they had a median of two comorbidities (range, 0-12), and about half were taking five or more medications. About 19% of the patients reported a fall in the prior 6 months and about half had unintentional weight loss (49.2%). Few screened positive for cognitive impairment (6.1%).

Of the hospitalized patients, the majority (N = 162, 83.9%) were hospitalized once, and 31 (16.1%) experienced at least two hospitalizations during chemotherapy. Median LOS for the first incident hospitalization was 4 days (range, 1-66 days) with data available on 181 (93.8%) of the hospitalized patients. Reasons for hospitalization were available for 191 of the hospitalized patients and are reported in Appendix Table A4 (online only). The most common reasons for hospitalization were infection (51%) followed by GI symptoms (14.5%).

Compared to nonhospitalized patients, in univariate analyses, those who were hospitalized were older and more likely to have GI cancer, self-reported limitation in physical function (specific items were self-reported mobility limitation, difficulty walking several blocks, and requiring assistance with bathing or dressing), polypharmacy (≥ 5 daily medications), higher number of comorbid conditions, available social support (having someone to take them to the doctor most or all of the time), lower MD-rated KPS, lower creatinine clearance, and lower albumin (Table 2).

In multivariable analyses, the following characteristics remained independently associated with hospitalization: GI cancer type (OR, 1.5; 95% CI, 1.0 to 2.2), requiring assistance with bathing or dressing (OR, 2.1; 95% CI, 1.0 to 4.1), higher number of daily medications (OR, 1.8; 95% CI, 1.0 to 3.1 for ≥ 5 $v < 5$), greater number of comorbid conditions (OR, 1.1; CI, 1.0 to 1.3 per additional comorbid condition), availability of someone to take them to the doctor most or all of the time (OR, 2.0; 95% CI, 1.0 to 4.1), lower creatinine clearance per 10 mL/min reduction (OR, 1.1; 95% CI, 1.0 to 1.3), and lower albumin per 1 g/dL reduction (OR, 2.1; 95% CI, 1.5 to 3.0) (Table 2). Chronologic age was no longer significant and did not change results when forced into the model (both area under the curve = 0.68). When restricting the analysis to only those with advanced-stage disease, the effect sizes were similar (Appendix Table A5 [online only]).

To ease interpretation, we dichotomized albumin, creatinine clearance, and number of comorbidities and created an index of number of risk factors that each patient had (0-7). The proportions of hospitalized patients among those with 0-2, 3, or 4-7 risk factors were 14.3%, 23.6%, and 41.2% ($P < .001$) respectively (Fig 1). The association between number of risk factors and hospitalization is detailed in Appendix Table A6 (online only).

In addition, we also examined risk factors associated with LOS among hospitalized patients. In univariate analyses, LOS was associated with older age, living alone, less social support, use of single-agent chemotherapy versus polychemotherapy, worse self-reported physical function, fall in the past 6 months, self-reported comorbidity (specifically, presence of liver or kidney disease), anxiety or depression, lower KPS, lower creatinine clearance, and lower albumin. In multivariable analyses, baseline characteristics independently associated with longer hospitalization were older age, self-reported presence of liver or kidney disease, living

TABLE 1. Baseline Patient Demographic, Disease, and Treatment Characteristics in Relation to Hospitalization

		Unplanned Hospitalization During Chemotherapy		
Patient Characteristics	**Total (N = 750)**	**No (n = 557)**	**Yes (n = 193)**	***P***
Age, years				.007
Mean (SD)	73.1 (6.04)	72.7 (6.00)	74.0 (6.07)	
Median (range)	72 (65-94)	72 (65-94)	74 (65-89)	
Sex, n (%)				.25
Female	419 (55.9)	318 (57.1)	101 (52.3)	
Male	331 (44.1)	239 (42.9)	92 (47.7)	
Race or ethnicity, n (%)				.94
White	632 (84.3)	469 (84.2)	163 (84.5)	
Black	62 (8.3)	46 (8.3)	16 (8.3)	
Asian	36 (4.8)	26 (4.7)	10 (5.2)	
Others	20 (2.7)	16 (2.9)	4 (2.1)	
Education, n (%)				.20
High school or less	289 (38.5)	205 (36.9)	84 (43.5)	
College graduate	311 (41.5)	234 (42.1)	77 (39.9)	
Advanced degree	149 (19.9)	117 (21)	32 (16.6)	
Missing	1	1		
Marital status, n (%)				.42
Married	455 (60.7)	333 (59.8)	122 (63.2)	
Widowed	167 (22.3)	123 (22.1)	44 (22.8)	
Single, separated, or divorced	128 (17.1)	101 (18.1)	27 (14.0)	
Household composition, n (%)				.84
Alone	157 (20.9)	118 (21.5)	39 (20.7)	
With someone	581 (77.5)	432 (78.5)	149 (79.3)	
Missing	12	7	5	
Employment, n (%)				.52
Employed	112 (14.9)	88 (15.9)	24 (12.5)	
Retired, homemaker, unemployed	603 (80.4)	444 (80)	159 (82.8)	
Disabled or medical leave	32 (4.3)	23 (4.1)	9 (4.7)	
Missing	3	2	1	
Body mass index				.29
N	748	556	192	
Median (range)	25.34 (14.94-51.65)	25.27 (14.94-51.65)	25.56 (17.81-42.36)	
Cancer type, n (%)				.03
Lung	207 (27.6)	160 (28.7)	47 (24.4)	
GI	203 (27.1)	137 (24.6)	66 (34.2)	
Breast	116 (15.5)	80 (14.4)	36 (18.7)	
GYN	105 (14)	84 (15.1)	21 (10.9)	
GU	80 (10.7)	66 (11.8)	14 (7.3)	
Others	39 (5.2)	30 (5.4)	9 (4.7)	

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TABLE 1. Baseline Patient Demographic, Disease, and Treatment Characteristics in Relation to Hospitalization (continued)

		Unplanned Hospitalization During Chemotherapy		
Patient Characteristics	**Total (N = 750)**	**No (n = 557)**	**Yes (n = 193)**	***P***
Cancer stage, n (%)				.11
I	33 (4.4)	29 (5.3)	4 (2.1)	
II	99(13.2)	67 (12.2)	32 (16.7)	
III	175 (23.3)	134 (24.3)	41 (21.4)	
IV	436 (58.1)	321 (58.3)	115 (59.9)	
Missing	7	6	1	
Line of chemotherapy, n (%)				.54
First line	531 (70.8)	391 (70.2)	140 (72.5)	
> First line	219 (29.2)	166 (29.8)	53 (27.5)	
Number of chemotherapy agents, n (%)				.24
Single	223 (29.7)	172 (30.9)	51 (26.4)	
Poly	527 (70.3)	385 (69.1)	142 (73.6)	
Standard dose, n (%)				.36
No	177 (23.6)	126 (23.6)	51 (26.8)	
Yes	548 (73.1)	409 (76.4)	139 (73.2)	
Missing	25	22	3	
Use of granulocyte colony stimulating factor				
No	438 (58.4%)	333 (59.8%)	105 (54.4%)	.19
Yes	312 (41.6%)	224 (40.2%)	88 (45.6%)	
Low hemoglobin, n (%)				.21
No (≥ 10 [female], ≥ 11 [male])	646 (86.1)	485 (87.1)	161 (83.4)	
Yes (< 10 [female], < 11 [male])	104 (13.9)	72 (12.9)	32 (16.6)	
Creatinine clearance (mL/min)				.002
Median (range)	58.1 (12.3-122.9)	59.2 (12.3-122.9)	53.8 (16.0-110.9)	
Missing	16	9	7	
Albumin (g/dL)				< .001
Median (range)	3.9 (1.0-5.0)	3.9 (2.1-5.0)	3.7 (1.0-4.9)	
Missing	28	17	11	
Physician rated KPS				.003
Median (range)	90 (40-100)	90 (50-100)	80 (40-100)	
Missing	12	7	5	
Number of daily medications, n (%)				< .001
0-4	384 (52.2)	308 (56.4)	76 (40)	
5+	352 (47.8)	238 (43.6)	114 (60)	
Missing	14	11	3	
Number of comorbidities				.008
Median (range)	2 (0-12)	2 (0-12)	3 (0-9)	
Missing	23	14	9	
Falls in the past 6 months				.74
No	603 (80.6%)	449 (80.9%)	154 (79.8%)	
Yes	145 (19.4%)	106 (19.1%)	39 (20.2%)	
Missing	2	2	0	

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TABLE 1. Baseline Patient Demographic, Disease, and Treatment Characteristics in Relation to Hospitalization (continued)

		Unplanned Hospitalization During Chemotherapy		
Patient Characteristics	**Total (N = 750)**	**No (n = 557)**	**Yes (n = 193)**	***P***
OARS-IADL survey				.02
Median (range)	14 (2-14)	14 (4-14)	14 (2-14)	
Missing	6	5	1	
MOS physical survey				.002
Median (range)	72 (0-100)	75 (0-100)	65 (0-100)	
Missing	1	1		
TUG (seconds)				.38
Median (range)	11 (4-79)	11 (4-79)	12 (4-54)	
Missing	145	111	34	
BOMC cognition test score, n (%)				.94
< 11	703 (93.9)	523 (93.9)	180 (93.8)	
≥ 11	46 (6.1)	34 (6.1)	12 (6.3)	
Missing	1	0	1	
Social support				.7336
Median (range)	96 (0-100)	96 (0-100)	96 (0-100)	
Missing	6	5	1	
Social activity				.21
Median (range)	62.50 (0-100)	62.50 (0-100)	56.25 (0-100)	
Missing	2	2	0	
HADS anxiety				.65
Median (range)	4 (0-20)	4 (0-20)	4 (0-18)	
Missing	6	3	3	
HADS depression				.32
Median (range)	3 (0-17)	3 (0-17)	3 (0-14)	
Missing	6	3	3	
Unintentional weight loss, n (%)				.38
No	375 (50)	283 (51.4)	92 (47.7)	
Yes	369 (49.2)	268 (48.6)	101 (52.3)	
Missing	6	6	0	

Abbreviations: BOMC, blessed orientation memory concentration test; HADS, hospital anxiety and depression scale; IADL, instrumental activities of daily living; KPS, Karnofsky Performance Scale; MOS, Medical Outcomes Study; OARS, older adults retirement survey; SD, standard deviation; TUG, timed up and go.

alone, and depressive symptoms (Hospital Anxiety Depression Scale depression subscale score ≥ 6). After adjusting for age, patients with liver or kidney disease had a least square mean hospitalization duration of 11.6 (95% CI, 7.3 to 15.7) days compared with 5.9 (95% CI, 4.7 to 7.0) days for those without this comorbidity ($P = .01$); living alone versus living with someone resulted in a nearly 3-day longer hospitalization (8.6 [95% CI, 6.1 to 11.1] *v* 5.5 days [95% CI, 4.2 to 6.7], $P = .03$); patients with depressive symptoms (Hospital Anxiety Depression Scale ≥ 6) had a nearly double LOS compared with those without depressive symptoms (9.5 [95% CI, 7.2 to 11.8] *v* 5.1 [95% CI, 3.8 to 6.4] days, $P = .001$).

DISCUSSION

Among older adults starting a new chemotherapy regimen, characteristics derived from a GA are associated with risk of hospitalization and length of hospitalization. Risk of incident hospitalization was not associated with age or performance status but rather with the type of cancer, dependence in ADL, polypharmacy, below normal creatinine clearance and albumin levels, and availability of social support. Once hospitalized, risk factors for longer LOS differed and included older age, comorbid liver or kidney disease, depressive symptoms, and living alone. These results have implications for using readily available information to identify older adults at higher risk for

TABLE 2. Univariate and Multivariable Results for Risk Factors Associated With Hospitalization

	Univariate		Multivariable	
Risk Factor	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age (per year increase)	1.04 (1.01 to 1.06)	.01	Not selected	
Physician rated KPS (per unit decrease)	1.02 (1.01 to 1.04)	.001	Not selected	
Number of comorbidities (per unit increase)	1.20 (1.09 to 1.31)	< .001	1.13 (1.02 to 1.26)	.03
Albumin (per unit reduction)	1.99 (1.45 to 2.74)	< .001	2.09 (1.45 to 3.00)	< .001
Creatinine clearance (per 10 unit reduction)	1.14 (1.04 to 1.26)	.007	1.12 (1.02 to 1.25)	.02
GI *v* other cancer	1.59 (1.12 to 2.27)	.01	1.49 (1.00 to 2.24)	.05
Daily medications ≥ 5	1.94 (1.39 to 2.72)	< .001	1.59 (1.09 to 2.34)	.02
Need help get to places out of walking distance	1.78 (1.19 to 2.68)	.005	Not selected	
Need help with bathing or dressing	2.28 (1.39 to 3.74)	.001	1.76 (1.00 to 3.11)	.05
Limited in walking several blocks	1.63 (1.17 to 2.27)	.004	Not selected	
Have someone to take them to the doctor most or all of the time	1.96 (1.03 to 3.71)	.04	2.01 (1.00 to 4.06)	.05

Abbreviations: KPS, Karnofsky Performance Scale; OR, odds ratio.

hospitalization and for interventions designed to decrease hospitalization risk and LOS.

Older age is a known risk factor for hospitalization among patients diagnosed with cancer.[8] Receipt of chemotherapy further increases the risk of hospitalization.[1] In an analysis of older adults with advanced cancer using Surveillance Epidemiology End Results or Medicare data, the majority were hospitalized during follow-up and more than half were hospitalized for likely chemotherapy toxicity.[1] However, it remains challenging to identify those at highest risk for hospitalization among older adults who are planned to receive chemotherapy treatment. There is an unmet clinical need to facilitate proactive management strategies designed to avoid costly and often complicated hospitalizations. Previously published studies have shown an association between GA-derived chemotherapy toxicity prediction tools and hospitalization risk.[9,18] Similarly, frailty measures derived from an accumulation of deficits are also predictive of risk of hospitalization.[10,19] Our study adds to this literature by identifying specific vulnerabilities at the time of chemotherapy initiation that increase the risk of hospitalization.

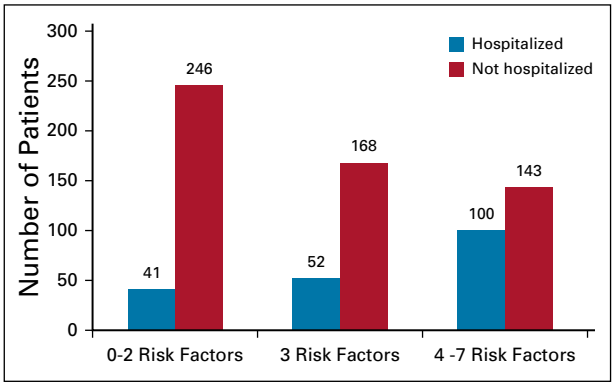

FIG 1. Number of older adults hospitalized during chemotherapy by presence of number of identified risk factors. Risk factors included ≥ 3 self-reported comorbid conditions, albumin < 3.5 g/dL, creatinine clearance ≤ 60 mL/min, GI cancer, polypharmacy (≥ 5 medications), requiring assistance with dressing or bathing, and having someone available to take them to the doctor most or all of the time.

Our findings highlight specific risk factors independently associated with risk of hospitalization in this cohort of older adults initiating chemotherapy. Importantly, these risk factors are readily available (ie, routine labs and medication list) and/or require minimal effort to ascertain (ie, self-reported function). First, dependence in ADLs highlights the importance of functional disability that is not captured by routine oncology performance status assessment.[20] ADL impairment has previously been associated with hospital readmission risk among older adults with cancer.[21] Other measures of impaired physical function (dependence on instrumental activities of daily livings and slow gait speed) have been associated with hospitalization risk among older adults diagnosed with solid tumors and those with hematologic malignancies.[7,22-24] Our study suggests that asking brief questions about need for assistance with two basic ADLs (bathing and dressing) may be high yield screening questions to help identify those older adults at higher risk for hospitalization.

Second, consistent with other reports, our study highlights the importance of recognizing polypharmacy as a potentially modifiable risk factor for hospitalization.[25] Polypharmacy may increase risk of hospitalization during chemotherapy because of increased risk of drug-drug interaction or as a surrogate measure for the burden of multiple chronic conditions. For example, Beinse et al[26] evaluated the association between potential drug-drug

interactions and risk of unplanned hospitalization among 442 older adults with cancer. In this study, the median number of daily medications was six (consistent with other reports in the literature)[27] and almost 77% had a potential drug interaction recorded. Recognition of the relevance of polypharmacy can prompt intervention including medication review by a pharmacist and active consideration of deprescribing.[28]

Two lab-based risk factors for hospitalization were identified, lower than normal creatinine clearance and albumin. Impaired creatinine clearance has been previously identified as a risk factor for chemotherapy toxicity[29-31] and was associated with hospitalization risk in a large cohort of adults receiving chemotherapy in the community setting.[8] Increased risk of toxicity related to impaired clearance of chemotherapeutic agents may be contributing to the association observed and could potentially be mitigated in some patients by appropriate dosing adjustments.[32] Low albumin can be a marker of poor nutritional status and is a biomarker correlated with physical frailty in older adults.[33] Poor nutritional status is a risk factor for treatment toxicity among older adults with cancer and is associated with shorter survival.[29,34,35] Both of these measures are routinely available to oncology providers and provide rapid opportunity to screen for those at risk for toxicity and hospitalization.

Interestingly, we had not hypothesized that availability of social support, specifically someone available to take you to the doctor, would be a risk factor for hospitalization. However, a prior publication from this cohort has described a relationship between less social support and lower nonhematologic chemotherapy toxicity.[36] Our results build on that observation and may reflect an effect of engaged or proactive caregivers on healthcare utilization. Another possibility is that patients who had more vulnerabilities at start of treatment had already engaged with caregivers for assistance. This observed association between available support and hospitalization suggests a potential value to engage caregivers in interventions designed to decrease hospitalization risk.

Finally, comorbidity burden was associated with risk of hospitalization when considered as a continuous variable. Some prior studies have shown a relationship between increased comorbidity and hospitalization risk[8] during receipt of chemotherapy, although not all.[37,38] Comorbidity in this analysis was self-reported, and although this correlates with other comorbidity scales,[39,40] it may be a less sensitive measure of compensated versus uncompensated conditions. Availability of functional measures and polypharmacy, which are correlated with comorbidity, may better reflect vulnerability in this setting. Importantly, our exploratory analysis confirms the importance of multiple concurrent vulnerabilities on risk of hospitalization with the risk increasing from 14% for those with two or fewer risk factors to 40% for those with >3 concurrent risk factors. Identifying those at highest risk with simple screening measures can inform clinical management and provides an opportunity to develop care delivery interventions for those most likely to benefit.

It should be noted that the effect sizes for most predictors identified were modest, which supports the premise that risk of hospitalization will be better predicted by a comprehensive evaluation typical in a GA rather than focusing on one or two characteristics alone. The more risk factors patients have, the higher odds they will be hospitalized.

Our study also identified patient-specific characteristics associated with LOS among those who were hospitalized. Importantly, risk factors for longer LOS differed from those that predisposed to hospitalization. There is limited information in the literature examining factors associated with LOS among older adults with cancer receiving chemotherapy. One study investigating the relationship of functional impairment and symptom burden with clinical outcomes among hospitalized patients with advanced cancer found an association between ADL impairment and LOS.[41] Our study did not show this association, although our cohort had a lower prevalence of functional impairment with all patients receiving active chemotherapy. Regarding our observed risk factors, depressive symptoms are highlighted as a potentially modifiable risk factor and warrant screening in the inpatient setting. Patients with depressive symptom may require more posthospitalization services or may be less proactively engaged in discharge planning resulting in longer LOS. Not surprisingly, once hospitalized, patients with limited social support are likely to experience a longer hospitalization potentially because of challenges related to discharge planning. Understanding both risk factors for hospitalization and those associated with longer LOS can inform cancer care delivery and supportive care interventions designed to mitigate risk and attenuate the negative consequences of unplanned hospitalization. Conduct of GA for hospitalized older patients with cancer may identify these deficits and facilitate personalized care plans.[42]

This study has limitations. The analysis cohort represents a heterogeneous US-based population with varied solid tumor cancer types and stages included. We do not have data on the impact of hospitalization on subsequent treatments nor on quality of life or functional independence. Findings may not reflect risk factors for hospitalization with noncytotoxic therapies such as immunotherapy or biologics. We did not evaluate timing of hospitalization during the treatment course in this analysis. We also note a high proportion of missing data for the TUG physical performance test. We observed that in many cases, the GA was performed on the date of chemotherapy initiation and participants were no longer able to perform the TUG once chemotherapy pretreatment was started. Future studies should sequence performance testing before surveys to minimize this limitation. Strengths of this study include the large sample size of older adults derived from a multisite

study and detailed characterization of patients and hospitalizations. All patients were starting a new chemotherapy regimen.

In conclusion, we identify risk factors for hospitalization among older adults starting chemotherapy, which are largely readily available in routine care. A next step is to validate these risk factors in an external data set. These risk factors, if validated, can help to screen older adults and guide interventions. Interventions to decrease hospitalization could target specific GA-identified vulnerabilities such as addressing physical limitations and polypharmacy proactively as well as care delivery interventions to navigate high-risk patients and their caregivers through their treatment. Interventions designed to minimize the negative impact of hospitalizations on patients should address the unique factors associated with increased LOS.

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DISCLAIMER

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APPENDIX

TABLE A1. Comparison of Baseline Characteristics Among Hospitalized Patients With and Without Available LOS

Characteristic	With LOS (n = 181)	Missing LOS (n = 12)	P
Age, years			.21
Mean (SD)	73.9 (6.14)	75.8 (4.81)	
Median (range)	73.0 (65.0-89.0)	76.5 (67.0-84.0)	
Sex			.87
Female	95 (52.5%)	6 (50.0%)	
Male	86 (47.5%)	6 (50.0%)	
Race			.17
White	155 (85.6%)	8 (66.7%)	
Black	14 (7.7%)	2 (16.7%)	
Asian	8 (4.4%)	2 (16.7%)	
Others	4 (2.2%)	0 (0%)	
Education			.11
≤ High school	82 (45.3%)	2 (16.7%)	
College	69 (38.1%)	8 (66.7%)	
Graduate school	30 (16.6%)	2 (16.7%)	
Marital status			.86
Married	114 (63%)	8 (66.7%)	
Widowed	42 (23.2%)	2 (16.7%)	
Others	25 (13.8%)	2 (16.7%)	
Living condition			.83
Alone	37 (20.9%)	2 (18.2%)	
With someone	140 (79.1%)	9 (81.8%)	
Employment			.93
Retired	149 (82.3%)	10 (83.3%)	
Work	32 (17.7%)	2 (16.7%)	
Cancer type			.22
Lung, breast, gynecologic, or other	108 (59.7%)	5 (41.7%)	
GI or genitourinary	73 (40.3%)	7 (58.3%)	
Stage			.94
I or II	34 (18.9%)	2 (16.7%)	
III	38 (21.1%)	3 (25.0%)	
IV	108 (60.0%)	7 (58.3%)	
Growth factor use			.78
No	98 (54.1%)	7 (58.3%)	
Yes	83 (45.9%)	5 (41.7%)	
Polychemotherapy			.22
No	46 (25.4%)	5 (41.7%)	
Yes	135 (74.6%)	7 (58.3%)	

Abbreviations: LOS, length of stay; SD, standard deviation.

TABLE A2. Sensitivity Analyses Results for Factors Associated With LOS

Variable	Category	LSM (95% CI)	P
Missing LOS values assigned to 1 day			
Liver or kidney disease			.006
	No	5.6 (4.4 to 6.7)	
	Yes	11.6 (7.5 to 15.7)	
Living alone			.03
	No	5.2 (4.0 to 6.4)	
	Yes	8.2 (5.8 to 10.7)	
Depression			.002
	No	4.9 (3.6 to 6.1)	
	Yes	8.9 (6.7 to 11.1)	
Missing LOS values assigned to 4 days (median value for cohort)			
Liver or kidney disease			.007
	No	5.7 (4.6 to 6.9)	
	Yes	11.6 (7.5 to 15.7)	
Living alone			.03
	No	5.4 (4.2 to 6.6)	
	Yes	8.4 (6.0 to 10.8)	
Depression			.002
	No	5.1 (3.8 to 6.3)	
	Yes	9.1 (7.0 to 11.3)	

Abbreviations: LOS, length of stay; LSM, least square means.

TABLE A3. Comparison of Parameter Estimates for Factors Associated With Length of Stay Using Complete Case Versus Multiple Imputations Analysis

	Complete Case		Multiple Imputations	
Factor	Estimate (SE)	P	Estimate (SE)	P
Liver or kidney disease	5.6 (2.2)	.01	5.8 (2.2)	.01
Living alone	3.2 (1.4)	.03	3.2 (1.4)	.03
Depression	4.5 (1.3)	.001	4.2 (1.4)	.003
Age (per year)	0.3 (0.1)	.005	0.3 (0.1)	.005

Abbreviation: SE, standard error.

TABLE A4. Primary Reason for Incident Hospitalization (N = 191)

Reason	N (%)
Infection with or without neutropenia	94 (49.2)
Infection with neutropenia	22 (23.4)
Infection plus bleeding	1 (0.5)
Infection plus thrombosis	2 (1)
Infection plus GI disorder	1 (0.5)
GI disorders	26 (14)
Diarrhea	10 (5.2)
Nausea or emesis	6 (3.1)
Constipation	4 (2.1)
GI disorder plus thrombosis	1 (0.5)
Cardiovascular	17 (9)
Arrhythmia	8 (4.2)
Myocardial infarction	2 (1)
Cardiomyopathy or congestive heart failure	2 (1)
Cardiopulmonary arrest	1 (0.5)
Dehydration	12 (6)
Thrombosis	8 (4)
Respiratory	7 (4)
Bleeding	5 (3)
Neurologic	5 (3)
Confusion	3 (1.6)
Pain	4 (2)
Other (edema, syncope, fatigue, electrolyte abnormality, and renal)	8 (4)

TABLE A5. Factors Associated With Hospitalization in Multivariable Analysis Among Advanced-Stage Patients (N = 436)

Baseline Characteristic	OR (95% CI)	*P*
Number of comorbidities (per unit increase)	1.18 (1.02 to 1.36)	.02
Albumin (per unit reduction)	2.16 (1.35 to 3.47)	.002
Creatinine clearance (per 10 unit reduction)	1.15 (1.01 to 1.32)	.03
GI *v* other cancer	2.22 (1.31 to 3.76)	.003
Daily medications ≥ 5	1.65 (0.98 to 2.77)	.06
Need help with bathing or dressing	1.85 (0.93 to 3.65)	.08
Have someone to take them to the doctor most or all of the time	2.28 (0.87 to 5.96)	.09

Abbreviation: OR, odds ratio.

TABLE A6. Association Between Number of Risk Factors and Hospitalization

	Hospitalization		
	No (n = 557)	Yes (n = 193)	*P*
Number of risk factors			< .0001
0	5 (83.3%)	1 (16.7%)	
1	82 (86.3%)	13 (13.7%)	
2	159 (85.5%)	27 (14.5%)	
3	168 (76.4%)	52 (23.6%)	
4	99 (61.1%)	63 (38.9%)	
5	39(57.4%)	29 (42.6%)	
6	5 (45.5%)	6 (54.5%)	
7	0 (0%)	2 (100%)	
Grouped number of risk factors			< .0001
0-2	246 (85.7%)	41 (14.3%)	
3	168 (76.4%)	52 (23.6%)	
4-7	143 (58.8%)	100 (41.2%)	