Prospective Cohort Study of Hospitalized Adults With Advanced Cancer: Associations Between Complications, Comorbidity, and Utilization

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BACKGROUND: Inpatient hospital stays account for more than a third of direct medical cancer care costs. Evidence on factors driving these costs can inform planning of services, as well as consideration of equity in access.

OBJECTIVE: To measure the association between hospital costs, and demographic, clinical, and system factors, for a cohort of adults with advanced cancer.

DESIGN: Prospective multisite cohort study.

SETTING: Four medical and cancer centers.

PATIENTS: Adults with advanced cancer admitted to a participating hospital between 2007 and 2011, excluding those with dementia. Final analytic sample included 1020 patients.

METHODS: With receipt of palliative care controlled for, the associations between hospital cost and patient factors were estimated. Factors covered the domains of demographics (age, sex, race), socioeconomics and systems (education, insurance, living will, proxy), clinical care (diagnoses, complications deemed to pose a threat to life or bodily functions,

Of the major chronic conditions that affect adult patients in the United States, cancer accounts for the highest levels of per capita spending.¹ Cost growth for cancer treatment has been substantial and persistent, from \$72 billion in 2004 to \$125 billion in 2010, and is projected to increase to \$173 billion by 2020.² Thirty-five percent of US direct medical cancer costs are attributable to inpatient hospital stays.³ Policy responses that can provide financially sustainable, high-quality models of care for patients with advanced cancer and other serious illness are urgently sought.⁴⁻⁷

Patterns and levels of resource utilization in providing healthcare to patients with serious illness reflect not only treatment choices but a complex set of relationships among demographic, clinical, and system factors.⁸⁻¹⁰ Patient-level

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comorbidities, symptom burden, activities of daily living), and prior healthcare utilization (home help, analgesic prescribing).

OUTCOME MEASURE: Direct hospital costs.

RESULTS: A major (markedly abnormal) complication (+\$8267; P < 0.01), a minor but not a major complication (+\$5289; P < 0.01), and number of comorbidities (+\$852; P < 0.01) were associated with higher cost, and admitting diagnosis of electrolyte disorders (-\$4759; P = 0.01) and increased age (-\$53; P = 0.03) were associated with lower cost.

CONCLUSIONS: Complications and comorbidity burden drive inhospital utilization for adults with advanced cancer. There is little evidence of sociodemographic associations and no apparent impact of advance directives. Attempts to control growth of hospital cancer costs require consideration of how the most resource-intensive patients are identified promptly and prioritized for cost-effective care. *Journal of Hospital Medicine* 2017;12:407-413. © 2017 Society of Hospital Medicine

factors previously identified as potentially significant drivers of resource utilization among cancer populations specifically include age,¹¹ sex,¹² primary diagnosis,¹³ and comorbidities.¹¹ Among end-of-life populations, significant associations have been found between cost and ethnicity,¹⁴ socioeconomic status,¹⁵ advance directive status,¹⁶ insurance status,¹⁶ and functional status.¹⁷

Evidence on factors strongly associated with cost of hospital admission for patients with advanced cancer can therefore inform provision and planning of healthcare. For example, when a specific diagnosis or clinical condition is found to be associated with high cost, then improving coordination and provision of care for this patient group may reduce avoidable utilization. Determining associations between sociodemographics and hospital care cost can help in identifying possible disparities in care, such as those that might occur when care differs by race, class, or insurance status.

We conducted the Palliative Care for Cancer (PC4C) study, a prospective multisite cohort study of the palliative care consultation team intervention for hospitalized adults with advanced cancer.^{18,19} In our primary analysis, we controlled for receipt of palliative care and analyzed a rich patient-reported dataset to examine associations between hospital care cost, and sociodemographic factors, clinical variables,

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TABLE 1. Baseline Covariates for Analytic Sample (N = 1020)

	Contir	Continuous		Binary	
	Mean	SD	N	%	
Age, y	60.4	12.1			
Female sex			562	55	
Race					
White			680	67	
Black			272	27	
Education					
Elementary ^a			72	7	
College ^a			504	49	
Insurance					
Medicare only			191	19	
Medicaid and Medicare			173	17	
Advance directive					
Living will			443	43	
Healthcare proxy			541	53	
Primary diagnosis					
Solid tumor			683	67	
Hematologic (leukemia or multiple myeloma)			25	2	
Gynecologic			114	11	
Central nervous system			17	2	
Lymphoma			54	5	
Admitting diagnosis					
Cancer			331	32	
Electrolyte disorder			31	3	
Infection			51	5	
Symptom			385	38	
Hematologic			27	3	
Respiratory failure			22	2	
Intestinal obstruction			24	2	
Renal failure			15	1	
Complication					
Major			53	5	
Minor			169	17	
Comorbidities: Elixhauser index	3.7	1.9			
Activities of daily living, total	10.4	2.4			
Symptom burden					
Number	7.9	3.5			
Severity	12.3	9.8			
Visiting nurse services, yes ^b			115	11	
Home health aide, yes ^b			77	8	
Prior analgesic use, yes ^c			529	52	
*Highest level attained.					

^bWithin 2 weeks before hospitalization.

°In morphine sulfate equivalents within week before hospitalization.

NOTE: References cases: Race: Neither white nor black; Insurance: Neither Medicare nor Medicaid; Education: High School; Primary diagnosis: Other cancer diagnosis; Admitting diagnosis: Other diagnosis; Complication: None. Clinical interviewers observed each patient daily and reviewed the medical record to identify complications occurring prior to consultation day (palilative care) or reference day (usual care), where reference day is the day they had the most similar symptom severity to PC patients. Complications that were identified were reviewed by two physicians and categorized as described below; where there was disagreement, a third physician reviewed the complication and the majority decision was used. Complications were defined as medical events that occurred during hospitalization but were not present as comorbid conditions prior to admission. We included only complications that were deemed to pose a threat to life or bodily functions, and that were typically treated with parenteral medications, procedures, or intensive monitoring. Examples of complications include: (1) pneumonia if both respiratory symptoms and/or hypoxia were documented; and (2) arrhythmias if their occurrence increased the risk of ischemia or hemodynamic compromise (eg, atrial fibrillation with rapid ventricular response). Complications were further categorized as major (markedly abnormal) or minor (mild) abnormal) (25).

Comorbidities: The Elixhauser index includes three cancer diagnoses: lymphoma, metastatic cancer, and solid tumor without metastasis. It was therefore possible for a patient to have an Elixhauser total of 0 (with a different advanced cancer diagnosis, eg, myeloma), or to have more than one cancer type counted in their Elixhauser total (if they had more than one of the counted cancers). Cancer diagnoses were therefore kept in the Elixhauser index to capture this variability.

Severity: The Condensed Memorial Symptom Assessment Scale (CMSAS) is a 14-item inventory on a 5 point scale of acuteness; 'Number' is an additive count of presence of 14 conditions (YesINo), 'Severity' is the total of acuteness scale for all 14 conditions.

and prior healthcare utilization. The results provide evidence regarding the factors most associated with the cost of hospital-based cancer care.

METHODS

Design, Setting, Participants, Data Sources

The PC4C study has been described in detail by authors who

estimated the impact of specialist palliative care consultation teams on hospitalization cost.¹⁹⁻²¹ We prospectively collected sociodemographic, clinical, prior utilization, and cost data for adult patients with a primary diagnosis of advanced cancer admitted to 4 large US hospitals between 2007 and 2011.

All 4 of these high-volume tertiary-care medical centers were selected for their high patient volume (to facilitate sample size) and research capacity (to facilitate proficient recruitment and data collection). Before the study was initiated, it was approved by the institutional review board of each facility. In addition, approval was sought from each attending physician at each hospital site; patients whose physician did not grant approval were not considered for enrollment. More than 95% of physicians gave their approval.

Patients were at least 18 years old and had a primary diagnosis of metastatic solid tumor; central nervous system malignancy; locally advanced head, neck, or pancreas cancer; metastatic melanoma; or transplant-ineligible lymphoma or multiple myeloma. Patients were excluded if they did not speak English, had a diagnosis of dementia, were unresponsive or nonverbal, had been admitted for routine chemotherapy, died or were discharged within 48 hours of admission, or had had a previous palliative care consultation.

Eligible patients were identified through daily review of admissions records and administrative databases. For each potential study patient identified, that patient's bedside nurse inquired about willingness to participate in the study. Then, for each willing patient, a trained clinical interviewer approached to explain the study and obtain informed consent. With the patient's consent, family members were also approached and enrolled with written informed consent.

Quantitative Variables

Independent variables. In the dataset, we identified 17 patient-level variables we hypothesized could be significantly associated with hospitalization cost. These variables covered 4 domains:

- Demographics: age, sex, race.
- Socioeconomics/systems: education level, insurance status, presence of advance directive (living will or healthcare proxy).
- Clinical care: primary cancer diagnosis, admitting diagnosis, comorbidities (Elixhauser index²²), symptom burden and severity (Condensed Memorial Symptom Assessment Scale [CMSAS]²³), and activities of daily living²⁴ or presence of a hospital-acquired condition or complication.²⁵
- Prior utilization: visiting homecare nurse and home health aide within 2 weeks before admission, and analgesic use in morphine sulfate equivalents within week before admission.

Data were collected through a combination of medical record review (age, sex, diagnoses, comorbidities, complications), patient interview (race, education, advance directive, CMSAS, activities of daily living, prior utilization), and hospital administrative databases (insurance). For use

TABLE 2. Summ	ry of Utilization	for Analytic Sample
(N = 1020)		

	Mean	25th/50th/75th Percentiles
Direct cost of hospital stay, \$	10,364	4950/7525/12,325
Hospital length of stay, d	8.5	5/7/9
Intensive care unit admission	12.1%	—
Palliative care consultation within 2 days	20%	—

in regression, variables were divided into categories when appropriate. Table 1 lists these predictors and their prevalence in the analytic sample.

Dependent variable. The outcome of interest in this analysis was total direct cost of hospital stay. Direct costs are those attributable to the care of a specific patient, as distinct from indirect costs, the shared overhead costs of running a hospital.²⁶ Cost data were extracted from hospital accounting databases and therefore reflect actual costs, the US dollar cost to the hospitals of care provided, also known as direct measurement.²⁷ Costs were standardized for geographical region using the Medicare Wage Index²⁸ and year using the Consumer Price Index²⁹ and are presented here in US dollars for 2011, the final year of data collection.

Statistical Methods

Primary analyses. We regressed total direct hospital costs against all predictors listed in Table 1. To control for receipt of palliative care, we used additional independent variables—a fixed-effects variable for each of 3 hospitals (the fourth hospital was used as the reference case) and a binary treatment variable (whether or not the patient was seen by a palliative care consultation team within 2 days of hospital admission).^{19,20}

Associations between cost and patient-level covariates were derived with use of a generalized linear model with a γ distribution and a log link, 30 selected after comparative evaluation of performance for multiple linear and nonlinear modeling options. 31

For each patient-level covariate, we estimated average marginal effects. For continuous variables, we estimated the marginal increase in cost associated with a 1-unit increase in the variable. For binary variables, we estimated the average incremental effect, the increase in cost associated with a move from the reference group, holding all other covariates to their original values. All analyses were performed with Stata Version 12.³²

Secondary analyses. Primary analyses showed that number of patient comorbidities (Elixhauser index) was strongly associated with complications and comorbidity count. Prior analyses with these data have shown that palliative care had a larger cost-saving effect for patients with a larger number of comorbidities.²⁰ Additional analyses were therefore performed to examine associations between complications, utilization, and palliative care. First, we cross-tabulated the

TABLE 3. Associations Between Patient-Level Baseline Factors and Hospitalization Costs (N = 1020)

	Average Marginal	0	95 Confi	5% dence
	Effect, \$	P		ervai
	-03	0.03	-99	-0
Female sex	-470	0.39	-1535	596
Race			1007	0400
White	81	0.94	-1967	2128
	-103	0.69	-2392	2000
Education	1107	0.01	0005	071
Elementary ^a	-1197	0.21	-3065	1292
	211	0.03	-041	1302
Insurance Madiaara aplu	120	0.05	1000	1501
Medicale Univ	-795	0.65	-1302	621
	-135	0.27	-2210	021
Advance directive	252	0.72	1640	1127
Healthcare proxy	-623	0.39	-2034	789
Drimony diagoogle	020	0.00	2001	100
Solid tumor	-1102	0.18	-2704	499
Hematologic (leukemia or multiple myeloma)	1437	0.48	-2524	5398
Gynecologic	-881	0.39	-2870	1108
Central nervous system	3425	0.22	-1994	8843
Lymphoma	-117	0.93	-2708	2475
Admitting diagnosis				
Cancer	698	0.39	-891	2287
Electrolyte disorder	-4759	<0.01	-7928	-1590
Infection	-880	0.51	-3473	1712
Symptom	-1446	0.07	-3021	128
Hematologic	-2051	0.23	-5386	1285
Respiratory failure	-506	0.78	-4126	3114
Benal failure	-4160	0.04	-8461	141
		0.00	0101	
Maior	8267	~0.01	4509	12 025
Minor	5289	< 0.01	3480	7097
Comorbidities: Elixhauser index	852	<0.01	550	1153
Activities of daily living, total	-68	0.52	-277	141
Symptom burden				
Number	207	0.18	-92	507
Severity	-32	0.56	-142	77
Visiting nurse services, yes ^b	-591	0.50	-2300	1118
Home health aide, yes ^b	-696	0.51	-2752	1359
Prior analgesic use, yes ^c	370	0.48	-664	1405

^aHighest level attained.

bWithin 2 weeks before hospitalization.

°In morphine sulfate equivalents within week before hospitalization.

NOTE: See Table 1 footnote. Statistical model used was a generalized linear model with a γ distribution and a log link. For continuous variables, average marginal effect is the estimated marginal increase in cost associated with a 1-unit increase in the variable; for binary variables, it is the increase in cost associated with a move from the reference group, holding all other covariates to their original values

sample by complications status (none; minor or major) and receipt of timely palliative care, and we present their summary utilization data. Second, we estimated the effect for each complications stratum (none; minor or major) of receiving timely palliative care on cost. These estimates are calculated consistent with prior work with these data: We used propensity scores to balance patients who received the treatment (palliative care) with patients who did not (usual care only),^{33,34} and we used a generalized linear model with a γ distribution and a log link to regress the direct hospital care cost on the binary treatment variable and all predictors listed in Table 1.¹⁹⁻²¹

RESULTS

Participants

We have previously detailed that in our study there were 1023 patients eligible for cost analysis,¹⁹ of whom three were missing data in a field in Table 1 and excluded from this paper. The final analytic sample (N = 1020) is presented according to base-line covariates in Table 1 and according to summary utilization measures in Table 2.

Main Results

The results of the primary analysis, estimating the association between patient-level factors and cost of hospitalization, are presented in Table 3.

These results show the evidence of an association with cost is strongest for 3 clinical factors: a major complication (+\$8267; 95% confidence interval [CI], \$4509-\$12,025), a minor but not a major complication (+\$5289; CI, \$3480-\$7097), and number of comorbidities (+\$852; CI, \$550-\$1153). In addition, there is evidence of associations between lower cost and admitting diagnosis of electrolyte disorders (-\$4759; CI, -\$7928 to -\$1590) and older age (-\$53; CI, -\$99 to -\$6). There is no significant association between primary diagnosis, symptom burden or other clinical factors, sociodemographic factors or healthcare utilization prior to admission and direct hospitalization costs.

Results of the secondary analyses of associations between complications, utilization, and palliative care are listed in Table 4. Patients are stratified by complication (none; major | minor) and their direct cost of hospital care and hospital length of stay (LOS) presented by treatment group (palliative care; usual care only). The data show that within each strata patients who received palliative care had lower costs and LOS than those who received usual care only. Estimated effects of palliative care on utilization is found to be statistically significant in all four quadrants, with a larger cost-effect in the complications stratum than the non-complications stratum.

Sensitivity Analysis

Fifty-one patients died during admission. After removing these cases, because of concerns about possible unobserved heterogeneity,³⁵ we checked our primary (Table 3) and secondary (Table 4) results. Patients discharged alive had results substantively similar to those of the entire sample.

	No Co	No Complication		Minor or Major Complication	
	(N	(N = 798)		(N = 222)	
	Palliative Care	Usual Care Only	Palliative Care	Usual Care Only	
	(n = 184)	(n = 684)	(n = 25)	(n = 197)	
Mean cost of hospital care, \$	8572	10,597	15,706	18,734	
Estimated effect of palliative care	–\$150€	-\$1506 (<i>P</i> = 0.01)		-\$5617 (<i>P</i> = 0.02)	
	95% Cl, −\$	95% Cl, -\$2647 to -\$366		95% Cl, -\$10,134 to -\$1101	
Mean hospital length of stay, d	7.2	7.9	11.6	14.6	
Estimated effect of palliative care	-0.8 (-0.8 (P = 0.03)		-3.6 (<i>P</i> <0.01)	
	95% Cl.	95% Cl1.5 to -0.8		95% Cl6.1 to -1.1	

TABLE 4 Utilization Stratified by Complication Status and Palliative Care Receipt, Weighted Samples (N = 1020)

NOTE: Patients with a major complication (n = 53) and patients with a minor complication (n = 169) were merged for this analysis to provide sufficient sample size for matching and estimating effects of palliative care. Estimated effects were derived in a fashion consistent with previous methods used with these data: Within each stratum (no complication; minor or major complication), the palliative care and usual care only groups were matched using propensity scores for all variables listed in Table 1 (except admitting diagnosis). Estimated effect of palliative care represents the average treatment effect (estimated effect on outcome of moving a patient from the usual care only group to the palliative care group, holding all other values constant) and was calculated with a generalized linear model with all propensity scores variables as predictors in regression. Abbreviation: Cl, confidence interval.

DISCUSSION

Results from our primary analysis (Table 3) suggest that complications and number of comorbidities are the key drivers of hospitalization cost for adults with advanced cancer. Hospitalization for electrolyte disorders and age are both negatively associated with cost.

The association found between higher cost and hospital-acquired complications (HACs) is consistent with other studies' finding that HACs often result in higher cost, longer LOS, and increased inhospital mortality.³⁶ Since those studies were reported, policy attention has been increasingly focused on HACs.³⁷ Our findings are notable in that, though prior evidence has also suggested high hospital cost is multifactorial, driven by a diversity of demographic, socioeconomic, and clinical factors, this rich patient-reported dataset suggests that, compared with other variables, HACs are emphatically the largest driver of cost. Moreover, cancer patients typically are a vulnerable population, more prone to complications and thus also to potentially avoidable treatments and higher cost. Our prior work suggested earlier palliative care consultation can reduce cost, in part by shortening LOS and reducing the opportunity for HACs to develop^{19,20}; our secondary analysis (Table 4) suggested a palliative care team's involvement in HAC treatment can significantly reduce cost of care as well. These associations possibly derive from changed treatment choices and shorter LOS. Further work is needed to better elucidate the role of palliative care in the prevention of HACs in seriously ill patients.

That the number of comorbidities was found to be a key driver of hospitalization cost is consistent with recent findings that high spending on seriously ill patients is associated with having multiple chronic conditions rather than any specific primary diagnosis.^{38,39} It is important to note that, unlike impending complications, serious chronic conditions generally are known at admission and can be addressed prospectively through provision and policy. A prior analysis with these data found that palliative care consultation was more cost-effective for patients with a larger number of comorbidities.²⁰ Our 2 studies together suggest that, notwithstanding the preferable alternative of avoiding hospitalization entirely, palliative care and other skilled coordination of care services ought to be prioritized for inpatients with multiple serious illnesses and the highest medical complexity. This patient group has both the highest costs and the greatest amenability to skilled transdisciplinary intervention, possibly because multiple chronic conditions affect patients interactively, complicating identification of appropriate polypharmacy responses and prioritization of treatments.

Our findings also may help direct appropriate use of palliative care services. The recently published American Society of Clinical Oncology palliative care guidelines note that all patients with advanced cancer (eg, those enrolled in our study) should receive dedicated palliative care services, early in the disease course, concurrent with active treatment.40 Workforce estimates suggest that the current and future numbers of palliative care practitioners will be unable to meet the ASCO recommendations alone never mind patients with other serious illnesses (eg, advanced heart failure, COPD, CKD).⁴¹ As such, specialized palliative care services will need to be targeted to the patient populations that can benefit most from these services. Whereas cost should not be the principle driver specialized palliative care provision, it will likely be an important component due to both the necessity of allocating scarce resources in the most effective way and the evidence that in care of the seriously-ill lower costs are often a proxy for improved patient experience.

These findings also have implications for research: Different conditions and presumably different combinations of conditions have very different implications for hospital care costs for a cohort of adults with advanced cancer. Given the increasing number of co-occurring conditions among seriously ill patients, and the increasing costs of cancer care and of treating multimorbidity cases, it is essential to further our understanding of the relationship between comorbidities and costs in order to plan and finance care for advanced cancer patients.

Limitations and Generalizability

In this observational study, reported associations may be attributable to unobserved confounding that our analyses failed to control. Our results reflect associations in a prospective multisite study of advanced cancer patients hospitalized in the United States. It is not clear how generalizable our findings are to patients without cancer, to patients in nonhospital settings, and to patients in other health systems and countries. Analyzing cost from the hospital perspective does not take into account that the most impactful way to reduce cost is to avoid hospitalization entirely.

Results of our secondary analysis will not necessarily be robust to patient groups, as specific weights likely will vary by sample. The idea that costs vary by condition, however, is important nevertheless. Elixhauser total was derived with use of the enhanced *ICD-9-CM* (*International Classification* of *Diseases*, *Ninth Revision*, *Clinical Modification*) algorithm from Quan et al.⁴² and does not include subsequent Elixhauser Comorbidity Software updates recommended by the Healthcare Cost and Utilization Project (HCUP; Agency for Healthcare Research and Quality).⁴³ The Elixhauser index is recommended over Charlson and other comorbidity indices by both HCUP⁴⁵ and a recent systematic review.⁴⁴

One possible unobserved factor is prior chemotherapy, which is associated with increased hospitalization risk. Related factors that are somewhat controlled for in the study include cancer stage (advanced cancer was an eligibility criterion) and receipt of analgesics within the week before admission (patients admitted for routine chemotherapy were excluded from analyses at the outset).

CONCLUSION

Other studies have identified a wide range of sociodemographic, clinical, and health system factors associated with healthcare utilization. Our results suggest that, for cost of hospital admission among adults with advanced cancer, the most important drivers of utilization are complications and comorbidities. Hospital costs for patients with advanced cancer constitute a major part of US healthcare spending, and these results suggest the need to prioritize high-quality, cost-effective care for patients with multiple serious illnesses.

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