The influence of multimorbidity on hospital, intensive care, and emergency department use at the end of life for patients with chronic conditions

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Abstract

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Abstract

Background: Multimorbidity, defined as 3 or more co-existing conditions, poses unique challenges for patients, providers, and the health care system overall. These challenges include accurate prediction of prognosis, delivery of appropriate care and provision of coordinated care. An understanding of the impact of multimorbidity on health care utilization at the end of life may provide insights into interventions that improve the quality of health care provided to patients with multimorbidity.

Objective: To determine differences in hospital utilization at the end of life for patients with multimorbidity compared with patients with one or two chronic diseases.

Research Design: Mortality follow-back analysis using Washington State death records and electronic health records of patients at UW Medicine.

Population: Patients in the UW Medicine system who had at least one chronic condition and died between 2011 and 2015.

Measures: Healthcare use in the last 30 days of life including hospitalization, emergency department use, intensive care unit admission, as well as 30-day hospital readmission in the last 90 days of life and death in hospital.

Results: Patients with multimorbidity had significantly higher utilization in the last 30 days of life for each category than those with a single diagnosis (inpatient admission 0.33 vs 0.22, $p<0.001$; ED admission 0.04 vs 0.03, $p<0.001$; and ICU admission 0.26 vs 0.15, $p<0.001$.) In addition, patients with multimorbidity were more likely to have a 30-day readmission in the last 90 days of life (0.12 vs 0.08) and death in hospital (0.45 vs 0.36, $p<0.01$.) Specific combinations of diseases were associated with utilization that was not simply additive. Cancer and COPD particularly had significant and contrasting impacts on hospital utilization, with cancer generally lessening and COPD increasing the effects.

Conclusion: Multimorbidity is associated with increased healthcare utilization at the end of life. However, individual combinations of chronic conditions result in unpredictable interactions. Providers must consider the multimorbidity and specific combinations of disease when determining a patient's treatment plan. Further research will add understanding to these complex relationships.

Keywords: multimorbidity, utilization, end-of-life care

Introduction

Over one in four Americans are diagnosed with more than one chronic condition[i] and this population is growing,[ii] creating increased demands on the health care system. Treating patients with multimorbidity as a result of multiple, co-occurring chronic conditions poses many challenges. Coordinating treatment regimens necessary to manage multiple conditions can lead to increased patient stress, medical error, and adverse effects.[iii] Patients with multimorbidity can live for long periods in poor health, and the absence of validated predictive models for survival with multimorbidity makes it difficult for providers to determine a patient's expected course of disease and plan for future care.[iv] Furthermore, patients with multimorbidity are more likely to have multiple providers, often creating a lack of clarity as to which provider should take responsibility for global aspects of patient care, such as advance care planning. Characterizing these demands and identifying optimal ways to address them are healthcare and research priorities.[v]

Care coordination for patients with multimorbidity can be even more challenging as a patient's diseases progress, and poor care coordination can lead to unnecessary hospital utilization.[vi] Patients with multimorbidity have a much higher rate of hospitalization than patients with none or one chronic condition,[vii] and this is magnified when a patient's health is deteriorating. Even though most patients indicate that they would prefer to die at home, research shows that more than half of patients die in a healthcare institution.[viii]

This study explores end of life care for patients with multimorbidity and whether they experience differences in healthcare utilization as compared to those with only one or two chronic conditions. I compared admissions to the hospital, the emergency department (ED), or intensive care unit (ICU) in the last 30 days of life among patients with one chronic condition compared to patients with two, or three or more chronic conditions. I also examined 30-day hospital readmissions in the last 90 days of life and the proportion of patients dying in the hospital.

Methods

Setting and study population

UW Medicine is an integrated healthcare system that incorporates four diverse hospitals and a large clinic network. Patient volume exceeds 64,000 hospital admissions and 1.6 million outpatient and emergency department visits. The University of Washington Medical Center (UWMC) is an academic medical center providing tertiary care for the region. It has a 450-bed hospital with 50 ICU beds. Harborview Medical Center (HMC) operates a 330-bed hospital owned by King County and operated by the University of Washington. It is the only Level 1 Trauma Center serving five states, and its mission population includes inner-city poor, recent immigrants to the US, and persons with HIV/AIDS. It has 350 acute care beds and 94 ICU beds. Valley Medical Center (VMC) is a non-profit acute care hospital and clinic network in South Seattle serving over 600,000 residents and operates a 303-bed acute care hospital with 30 ICU beds. Northwest Hospital and Medical Center (NHMC) is a non-profit community hospital located in North Seattle with 281 acute care beds and 15 ICU beds.

The study population was selected from patients cared for in the UW Medicine healthcare system who died in Washington State between 2011 and 2014. Dates of death were obtained either from Washington State Death Certificates or, if missing, from UW Medicine electronic health record (EHR). In order for a patient to be attributed to UW Medicine, he/she must have had at least one non-surgical inpatient visit at a UW Medicine hospital in the two years prior to death or two outpatient visits at a UW Medicine facility in the 32 months prior to death, with the more recent visit occurring in the last two years of life. Participants were those with at least one of the nine chronic conditions used by the Dartmouth Atlas in their over 20 years of studying health care quality in the US: non-hematologic cancer, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), congestive heart failure (CHF), chronic liver disease, chronic renal disease, dementia, diabetes, and peripheral vascular disease (PVD.) These diseases were chosen because they cause nine out of ten deaths in the Medicare population.[ix]

Outcomes

The outcomes of interest were hospital utilization at the end of life. Hospital utilization included the proportion of patients experiencing the following: 1) acute care hospitalization in the last 30 days of life; 2) emergency department (ED) visits in the last 30 days of life; 3) ICU stay in the last 30 days of life; 4) 30-day readmissions to the hospital in the last 90 days of life; and 5) death in the hospital. For death in the hospital, I was able to use death certificate data to determine deaths at all hospitals in Washington State. For the other four outcomes, I examined data from EHR.

Predictor

The predictor of interest was multimorbidity defined as the number of patients' chronic conditions, categorized into one, two, or three or more.

Confounders

I considered the following variables as possible confounders: age, gender, race, education, insurance status (insured, under-insured, insured but type unknown, no documented insurance), and UW Medicine location at which the patient was treated (UWMC, HMC, Valley, Northwest). Age, gender, insurance status, and location at which patient was treated were identified from the UW Medicine EHR; race and level of education were identified from Washington State Death Certificates.

Statistical analysis

I used adjusted, multi-predictor probit regression models to examine the association between multimorbidity and the five specified outcomes; multimorbidity was defined as a three-category measure (1, 2, 3 or more diagnoses) with two dummy indicators. Confounders were included in a model if their addition to the unadjusted model changed the coefficient for the predictor by 10% or more. If the p-value for the predictor was >0.50 in the unadjusted model, no testing for confounders was done.

Similarly, to further examine the effect of multimorbidity on the outcomes of interest, I looked at specific combinations of disease. Because the combined effect of each individual disease did not account for the whole of the difference in the outcomes, I wanted to explore the effect of the various combinations. I ran a series of probit regression models using a weighted least squares estimator to create a model that included all nine individual diagnoses and all possible two-way interactions. I then sequentially removed the interaction terms with the highest p-values until only interactions with p<0.05 remained. I then re-checked the

Table 1a. Decedent Demographics[a]				
Characteristic	Total	1 Diagnosis	2 Diagnoses	3+ Diagnoses
Diagnosis, n (%)				
Cancer	9,762 (52.0)	5,700 (59.4)	2,478 (50.1)	1,584 (37.4)
COPD	4,855 (25.9)	906 (9.4)	1,669 (33.7)	2,280 (53.8)
CAD	4,744 (25.3)	516 (5.4)	1,406 (28.4)	2,822 (66.6)
CHF	4,237 (22.6)	493 (5.1)	1,157 (23.4)	2,587 (61.1)
Chronic Liver Disease	2,209 (11.8)	613 (6.4)	859 (17.4)	737 (17.4)
Chronic Renal Disease	3,562 (19.0)	346 (3.6)	978 (19.8)	2,238 (52.8)
Dementia	1,743 (9.3)	615 (6.4)	487 (9.8)	641 (15.1)
Peripheral Vascular Disease	2,353 (12.5)	242 (2.5)	540 (10.9)	1,571 (37.1)
Diabetes	1,529 (8.1)	157 (1.6)	328 (6.6)	1,044 (24.6)
Insurance Status, n (%)				
Insured	13,426 (71.5)	6,907 (72.0)	3,536 (71.4)	2,983 (70.4)
Under-insured	4,493 (23.9)	2,059 (21.5)	1,256 (25.4)	1,178 (27.8)
Insured, but Type Unknown	37 (0.2)	21 (0.2)	11 (0.2)	5 (0.1)
No Documented Insurance	820 (4.4)	601(6.3)	148 (3.0)	71 (1.7)
Male, n (%)	10,725 (57.1)	5,038 (52.5)	2,937 (59.3)	2,750 (64.9)
Race, n (%)				
White	14,077 (82.7)	7,274 (84.8)	3,706 (82.1)	3,097 (78.7)
Black	1,020 (6.0)	386 (4.5)	286 (6.3)	348 (8.8)
Hispanic	311 (1.8)	158 (1.8)	84 (1.9)	69 (1.8)
Asian	1,110 (6.5)	537 (6.3)	293 (6.5)	280 (7.1)
Native Hawaiian / Other Pacific Islander	108 (0.6)	44 (0.5)	31 (0.7)	33 (0.8)
Native American / Alaska Native	403 (2.4)	179 (2.1)	116 (2.6)	108 (2.7)
Age, mean (SD)	66.2 (15.0)	63.9 (15.5)	67.3 (14.7)	70.1 (13.1)
Education, n (%)				
8th Grade or Less	775 (4.6)	323 (3.8)	211 (4.8)	241 (6.3)
9-12 Years, No Diploma	1,175 (7.0)	509 (6.0)	319 (7.2)	347 (9.1)
High School Graduate or Equivalent	5,542 (33.2)	2,617 (31.0)	1,557 (35.3)	1,368 (35.8)
Some College, No Degree	3,331 (20.0)	1,739 (20.6)	876 (19.8)	716 (18.8)
Associate's Degree	1,352 (8.1)	741 (8.8)	347 (7.9)	264 (6.9)
Bachelor's Degree	2,795 (16.8)	1,584 (18.8)	676 (15.3)	535 (14.0)
Master's Degree	1,172 (7.0)	670 (7.9)	278 (6.3)	224 (5.9)
Doctorate or Professional Degree	537 (3.2)	261 (3.1)	153 (3.5)	123 (3.2)

a All characteristics except race and education were collected for 18,776 patients (9,588 with 1 diagnosis, 4,951 with 2 diagnoses, and 4,237 with 3+ diagnoses). Race was known for 17,029 patients (8,578 with 1 diagnosis, 4,516 with 2 diagnoses, and 3,935 with 3+ diagnoses). Education was known for 16,679 patients (8,444 with 1 diagnosis, 4,417 with 2 diagnoses, and 3,818 with 3+ diagnoses).

model by reintroducing the interaction terms one by one to determine if it had re-gained statistical significance in the updated model. For each of the remaining combinations, I was able to determine the difference in the expected outcome by adding the interaction term to the effect of the individual diseases.

Results

Patient demographics

The sample included 18,776 patients over age 18, who received care in the UW Medicine system, had at least one of the nine chronic conditions, and died during the five-year study period. (See Table 1a.) Nearly half of these patients had two or three or more diseases (26.4% and 22.6%, respectively.) The mean age of the sample was 66, and higher age was associated with more comorbidities. The sample contained more men than women (57.1%). Over eighty percent of the sample is white. White patients were older than every other group except Asian patients (mean age 67.6 vs. 68.0, respectively.) Approximately half of patients had education beyond a high school diploma (55.1%.)

Table 1b: Demographics by diagnosis			
Group	No. of patients	% of total	Mean no. of diagnoses
	(n=18,776)		
Cancer	9,762	52.0%	1.68
COPD	4,855	25.9%	2.66
CAD	4,744	25.3%	2.98
CHF	4,237	22.6%	3.02
Chronic Liver Disease	2,209	11.8%	2.29
Chronic Renal Disease	3,562	19.0%	3.13
Dementia	1,743	9.3%	2.36
Peripheral Vascular Disease	2,353	12.5%	3.26
Diabetes	1,529	8.1%	3.39

Cancer was by far the most common diagnosis, representing more than half the patients in the sample (52.0% of the total) (see Table 1b.) COPD was the next most common diagnosis (25.9%.) Patients with dementia represented the oldest patients, with the average age for that group being 79. Chronic liver disease patients were the youngest, with a mean age of 59 and only

Table 2. Associations between Number of Diagnoses and Outcomes, Adjusted for Confounders[a]

Outcome	n	# of Diagnoses	b	p	95% CI
# Diagnoses Measured with Two Dummy Indicators					
Inpatient Admit in Last Month of Life[b]	18,612	1	0.000	0.0000	
		2	0.156		0.110, 0.203
		3+	0.322		0.263, 0.382
ED Visit in Last Month of Life[c]	18,776	1	0.000	0.0005	
		2	0.116		0.033, 0.198
		3+	0.181		0.075, 0.286
ICU Admit in Last Month of Life[b]	18,612	1	0.000	0.0000	
		2	0.169		0.118, 0.220
		3+	0.381		0.317, 0.445
30-day Readmission in Last 3 Months of Life[d]	18,612	1	0.000	0.0000	
		2	0.104		0.041, 0.166
		3+	0.312		0.235, 0.389
Death in Hospital[b]	18,612	1	0.000	0.0000	
		2	0.084		0.041, 0.127
		3+	0.214		0.157, 0.272

a Each outcome was tested with a probit regression model estimated with mean- and variance-adjusted weighted least squares (WLSMV). The overall association of number of diagnoses with the outcome was tested with a Wald test of parameter constraints.

b Adjusted for age and hospital/clinic system. Sample size reduced to 18,612 (164 decedents did not have more than one outpatient visit to any single hospital/clinic system, so could not be assigned to a system.)

c Adjusted for age and insurance status, with insurance status represented by three dummy indicators (under-insured, unknown insurance type, and no documented insurance)

d Adjusted for age, hospital/clinic system, and insurance status. Sample size reduced to 18,612 (164 decedents did not have more than one outpatient visit to any single hospital/clinic system, so could not be assigned to a system.)

26.3% over the age of 65. Diabetes was most commonly associated with having multiple comorbidities, with diabetes patients having 3.39 total diagnoses on average. Cancer patients had the fewest comorbidities at a mean of 1.68 diagnoses per patient.

Healthcare utilization at the end of life

Table 2 shows the adjusted results of the analysis. Each measure of utilization showed a significant increase with each additional disease. The largest difference was seen in ICU admissions followed by inpatient admission. The difference in visits to the ED was the smallest, although still statistically significant.

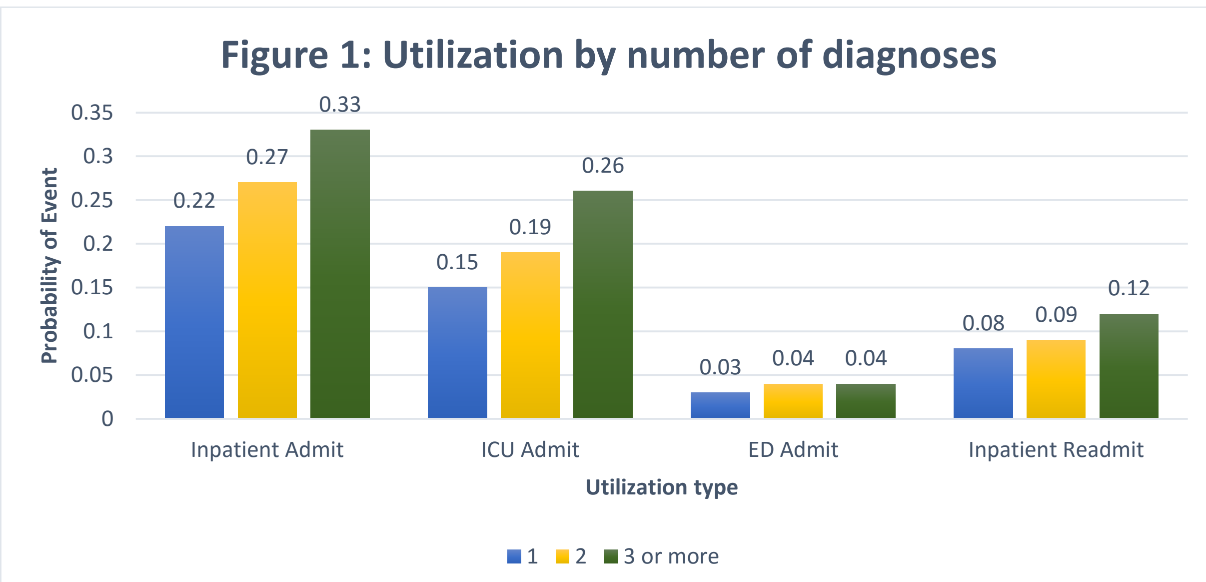
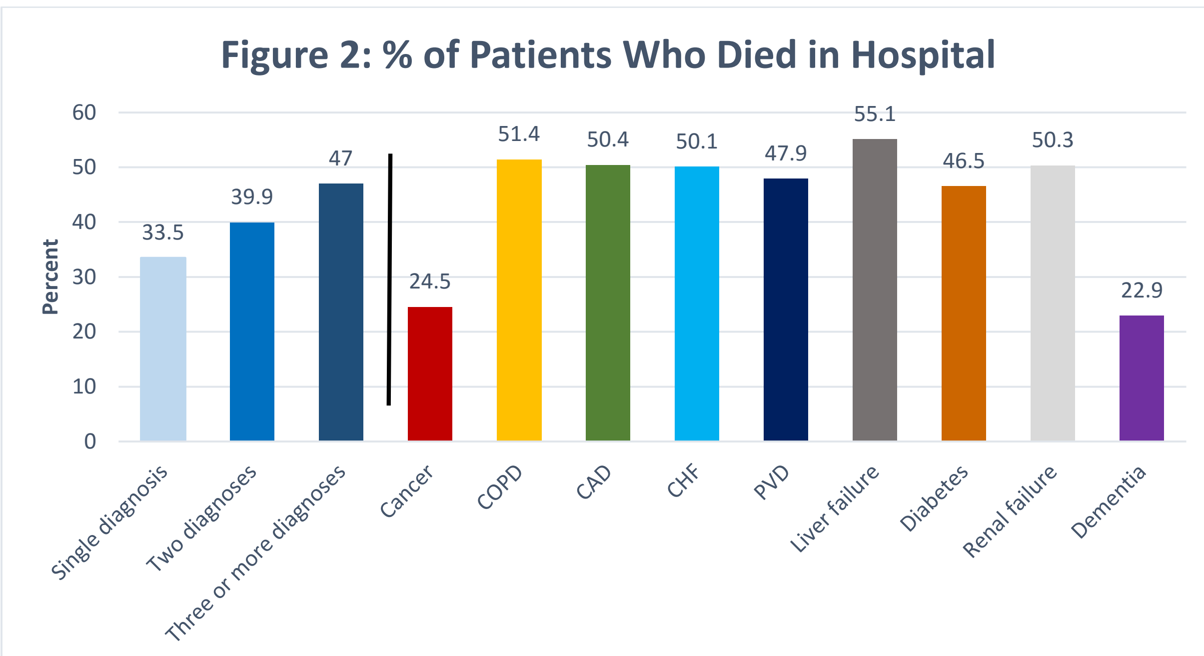


Figure 1 shows the probability of each measure of utilization with an additional chronic disease diagnosis. Patients with three or more diagnoses were 75% more likely to have an ICU admission than were those with a single diagnosis (0.26 vs. 0.15, p<0.001) and 50% more likely to have an inpatient admission in the last 30 days or a 30-day readmission in the last 90 days

(0.33 vs 0.22, p<0.001 and 0.12 vs 0.08, p<0.01, respectively.) ED admissions in the last 30 days also showed a significant, although smaller, increase (0.04 vs 0.03, p<0.001.)

Figure 2 shows information on hospital deaths categorized by number of diagnoses as well as by primary diagnosis. As with the other outcomes, the percent of patients who died in the hospital increased with the number of diagnoses. Patients with a unique diagnosis of either cancer or dementia were significantly less likely to die in the hospital than were patients with other conditions (24.5% and 22.9%, respectively, vs. the overall mean of 33.5%.)



The effect of multiple diseases

Diseases examined in various combinations revealed large variation in their effects on utilization (See Table 3 for selected results; full results can be found in Appendix A.) Cancer had a significant interaction with each of the other diseases for at least one outcome. Patients with cancer and either CHF, diabetes or renal disease experienced higher utilization than would be expected if the conditions were simply additive. Patients with cancer and either COPD, CAD or liver failure experienced lower utilization than would be expected if the conditions were additive, though their utilization was still higher than any of the diseases alone. While cancer and dementia were associated with reduced hospital utilization when combined with most other conditions, this was not true for every condition; for example, the interaction between cancer and CHF caused higher inpatient admissions than expected, leading to a higher rate overall.

COPD had significant interactions with five of the other diseases, including cancer. Only COPD and dementia and COPD and cancer resulted in lower utilization than would be expected if the effect was additive. For CHF, liver failure, and renal failure, COPD plus these conditions resulted in lower utilization than would be expected if the effect was additive, but higher utilization than a single condition.

The other findings of note involve PVD and ED visits and diabetes. PVD only showed a significant interaction with cancer for 30-day readmission in the last 90 days; this disease did not otherwise significantly interact with any of the other conditions. Disease interaction had little impact on ED visits. The only significant interactions affecting ED visits were between COPD and renal failure or between diabetes and dementia. These interactions were both significantly negative, with patients having these two conditions experiencing overall lower ED use than expected. In addition, diabetes had an unexpected negative effect on inpatient and ICU admissions, resulting in reduced utilization.

Discussion

The study showed consistent associations between multimorbidity and increased healthcare utilization at the end of life: patients with an increasing number of conditions were more likely to be admitted to the hospital, have an ICU admission in the last 30 days of life, have a 30-day hospital readmission in the last 90 days of life, and die in the hospital. ED use, although not as striking, similarly showed a significant increase in use that was associated with the patient's number of diseases. However, I also found that utilization was associated not only with the number of conditions experienced by the patient, but also with the kinds of conditions and their interactions with each other. These effects were not merely additive in nature but had higher or lower values than expected based on the influence of each diagnoses taken singly.

A diagnosis of cancer lowered utilization compared to the other chronic conditions. This may be related to providers' improved ability to prognosticate and prepare patients for disease progression. Cancer exhibits a more predictable and progressive course than other chronic diseases and may make it easier for providers to bring up issues like advance care planning and hospice.[x] This finding is consistent with studies showing much higher hospice use among patients with cancer than patients with other life-limiting illnesses.[xi]

In contrast, diseases that involve chronic organ failure, such as COPD, CHF, or end-stage renal disease, follow a less predictable course[xii] and therefore may be associated with increased hospital utilization. For example, patients with COPD may be successfully managed for many years but then experience sudden, unexpected declines for which they are unprepared and which may require unanticipated hospitalizations.[xiii] In addition, one study found patients with

Table 3. Independent Associations of Specific Diseases and Disease-Interactions with Outcomes [a]

Disease or Disease Interaction	Death in hospital		Inpatient admit		ICU admit		ED visit		Readmit	
	b	Total interaction	b	Total interaction	b	Total interaction	b	Total interaction	b	Total interaction
Cancer	-0.557**		-0.005		-0.301**		0.326**		0.772**	
COPD	0.158**		0.273**		0.289**		0.218**		0.353**	
CAD	0.039		0.163**		0.203**		0.034		0.133*	
CHF	0.109**		0.429**		0.549**		0.104*		0.504**	
PVD	0.036		0.162**		0.13**		0.075		0.248**	
Liver failure	0.224**		0.561**		0.522**		0.28**		0.633**	
Diabetes	0.026		-0.242**		-0.151**		0.099		0.097*	
Renal failure	0.137**		0.214**		0.272**		0.285**		0.44**	
Dementia	-0.579**		-0.091*		-0.302**		0.225**		0.182**	
Cancer & COPD									-0.128*	0.997
Cancer & CAD									-0.144*	0.761
Cancer & CHF	0.307**	-0.141	0.192**	0.616	0.246**	0.494				
Cancer & PVD									-0.195*	0.825
Cancer & liver failure			-0.283**	0.273	-0.168*	0.053			-0.606**	0.799
Cancer & diabetes			0.205*	-0.042						
Cancer & renal failure			0.18**	0.389						
Cancer & dementia	0.482**	-0.654	0.339**	0.092	0.36**	-0.243				
COPD & CHF	-0.107*	0.160	-0.225**	0.477	-0.238**	0.600			-0.216**	0.641
COPD & liver failure			-0.165*	0.669						
COPD & renal failure	-0.109*	0.186					-0.22*	0.283		
COPD & dementia	0.189*	-0.232								

*p≤0.05
**p≤0.01
For each outcome, a series of probit regression models, using a weighted least squares (WLSMV) estimator, was run. Beginning with a model that included the nine diagnoses and all possible two-way disease interactions, I sequentially removed the interaction term with the highest *p*-value until only the interactions with $p<0.05$ remained. As a final check of this provisional model, I reintroduced the remaining interaction terms one at a time to see whether that term had regained statistical significance when the only other predictors were those in the provisional model.

The table shows two sections: the top shows a prediction of how each individual disease affects the outcome. The bottom shows the coefficient predicting how the interaction between the stated diseases increases or decreases the value of the outcome compared to the expected value if the effects were simply additive. The “Total Interaction” column shows this value added to the effect of the individual diseases to get the total combined effect of the two diseases.

COPD and CHF have less frequent contact with primary care providers and, as a result, may miss opportunities for advance care planning in that setting. [xiv] Patients with COPD are also less likely to see palliative care specialists than patients with cancer.[xv]

Patients with a single chronic condition may be more likely to see a single specialist working in conjunction with a primary care provider or their specialist may assume primary care responsibilities. In contrast, patients with multimorbidity may have multiple specialists, making care coordination and advance care planning more complex.[xvi] Although many healthcare systems attempt to assign a specific provider as the point person to coordinate a patient's care, this may not always be in place. This approach could be used to clearly identify the provider responsible for discussing goals of treatment and care preferences as a patient's health status worsens, and he/she could be the point person responsible for communicating this information to other providers. A primary care provider, a palliative care specialist, a case manager, or the specialist in charge of the most prominent disease might fill this role, Hospital systems should develop a protocol for assigning patients with multimorbidity to the appropriate provider. Trends toward more integrated systems such as accountable care organizations and patient-centered medical homes are expected to improve care coordination and establish the primary care provider as the cornerstone of the patient's care.[xvii][xviii] Finally, accessible, up-to-date EHR with care cautions and warnings may help diverse providers collaborate to manage patients living with multimorbidity.

The clinical implications of the specific disease interactions are complex and difficult to know how to address. However, it may be useful for disease specialists to be aware of the impacts of specific disease combinations. For example, those in oncology may want to be aware that the addition of other significant co-morbidities will increase the likelihood of healthcare utilization at the end of life; it may be particularly important to consider advance care planning with these patients, especially those with COPD, CAD, and liver disease. Similarly, those caring for patients with COPD should be aware that co-morbidities increase the likelihood of healthcare utilization at the end of life, particularly for co-morbidities such as CHF, liver disease and renal disease. Knowledge of the change to a patient's risk for unnecessary hospital utilization can help providers take action to improve the patient's end of life care.

This study has several important limitations. First, I did not consider interactions beyond two-way interactions to see if specific combinations of three or more diseases caused variations in hospital utilization. Three-way combinations affect a smaller number of patients (less than 25%) and increases the complexity of the modeling and interpretation of the results. However, future studies should consider ways to address this complexity. Second, I do not have data to allow assessment of the severity of each chronic condition, such as disease-specific measures of severity. In addition, I cannot assess the role of interactions among therapies for the different diseases. Third, this is a population selected from one hospital system in the Pacific Northwest and may not be representative of patients from other systems or other regions. Also, I focused on only a limited set of diseases, and the findings may therefore not generalize to patients with other types of multimorbidity. Fourth, I did not consider patients' preferences for end-of-life care as those data were not available to us. It is therefore possible that the findings describing associations between multimorbidity and hospital utilization were due, in part, to patient choice and other factors not directly affected by the healthcare system. Finally, the results are based on observational data and are only suggestive of causal relationships.

In conclusion, I found that multimorbidity was associated with increased intensity of care at the end of life, including hospitalization, ICU use, and ED use in the last 30 days of life as well as 30-day readmission in the last 90 days and death in the hospital. The growing number of Americans with multimorbidity should make the management of multimorbidity a research priority. The variability of how diseases interact with one another means it is not enough to look at how many diseases patients have when considering care at the end of life. Rather, providers must consider the patient's overall disease portfolio and specific combinations of disease when determining a patient's treatment plan. Patients depend on the health care system to know how diseases working together affect the expected course of their health and care options. Future research needs to consider patients with specific combinations of diseases rather than simply counting the number of diseases. They also need to consider how treatments and medications for different diseases work together, either to the patient's benefit or detriment. Because patients with multimorbidity are often excluded from participation in clinical trials, the evidence base is quite limited for important clinical questions in this population.[xix] Cancer is the most commonly studied disease with regard to multimorbidity;[xx] these studies need to be expanded to include other comorbidities.

APPENDIX A

Independent Associations of Specific Diseases and Disease-Interactions with Outcomes[a]

	Death in Hospital		Inpatient Admit		ICU Admit		ED Visit		Readmit	
Disease or Disease Interaction	b	*p*	b	*p*	b	*p*	b	*p*	b	*p*
Cancer	-0.557	0.000	-0.005	0.881	-0.301	0.000	0.326	0.000	0.772	0.000
COPD	0.158	0.000	0.273	0.000	0.289	0.000	0.218	0.000	0.353	0.000
CAD	0.039	0.110	0.163	0.000	0.203	0.000	0.034	0.492	0.133	0.026
CHF	0.109	0.001	0.429	0.000	0.549	0.000	0.104	0.042	0.504	0.000
PVD	0.036	0.222	0.162	0.000	0.130	0.000	0.075	0.200	0.248	0.000
Liver failure	0.224	0.000	0.561	0.000	0.522	0.000	0.280	0.000	0.633	0.000
Diabetes	0.026	0.463	-0.242	0.000	-0.151	0.000	0.099	0.155	0.097	0.047
Renal failure	0.137	0.000	0.214	0.000	0.272	0.000	0.285	0.000	0.440	0.000
Dementia	-0.579	0.000	-0.091	0.028	-0.302	0.000	0.225	0.001	0.182	0.000
Cancer & COPD									-0.128	0.050
Cancer & CAD									-0.144	0.043
Cancer & CHF	0.307	0.000	0.192	0.001	0.246	0.000				
Cancer & PVD									-0.195	0.030
Cancer & liver failure			-0.283	0.000	-0.168	0.016			-0.606	0.000
Cancer & diabetes			0.205	0.019						
Cancer & renal failure			0.180	0.002						
Cancer & dementia	0.482	0.000	0.339	0.001	0.360	0.001				
COPD & CHF	-0.107	0.030	-0.225	0.000	-0.238	0.000			-0.216	0.002
COPD & liver failure			-0.165	0.021						
COPD & renal failure	-0.109	0.044					-0.220	0.020		
COPD & dementia	0.189	0.018								
CAD & CHF			-0.151	0.003	-0.218	0.000			-0.144	0.043
CAD & liver failure					-0.197	0.020				
CAD & diabetes			0.192	0.013						
CHF & renal failure					-0.174	0.002				
Liver failure & dementia	0.578	0.001								
Diabetes & dementia							-0.590	0.034		

a. For each outcome, a series of probit regression models, using a weighted least squares (WLSMV) estimator, was run. Beginning with a model that included the nine diagnoses and all possible two-way disease interactions, we sequentially removed the interaction term with the highest *p*-value until only the interactions with $p<0.05$ remained. As a final check of this provisional model, we reintroduced the remaining interaction terms one at a time to see whether that term had regained statistical significance when the only other predictors were those in the provisional model.

REFERENCES

[i] U.S. Department of Health and Human Services. Multiple Chronic Conditions—A Strategic Framework: Optimum Health and Quality of Life for Individuals with Multiple Chronic Conditions. Washington, DC. December 2010. http://www.hhs.gov/ash/initiatives/mcc/mcc_framework.pdf

[ii] Ward BW, Schiller JS. Prevalence of Multiple Chronic Conditions Among US Adults: Estimates From the National Health Interview Survey, 2010. Prev Chronic Dis 2013;10:120203. DOI: http://dx.doi.org/10.5888/pcd10.120203

[iii] *Chronic conditions: making the case for ongoing care*. Johns Hopkins University, 2004. http://www.fightchronicdisease.org/sites/fightchronicdisease.org/files/docs/ChronicCareChartbook_FINAL_0.pdf

[iv] Wolff, J. L., Starfield, B., & Anderson, G. (2002). Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Archives of internal medicine, 162(20), 2269-2276.

[v] Ritchie, C. S., & Zulman, D. M. (2013). Research Priorities in Geriatric Palliative Care: Multimorbidity. Journal of Palliative Medicine, 16(8), 843–847. http://doi.org/10.1089/jpm.2013.9491

[vi] Johns Hopkins University. (2004.) *Chronic conditions: making the case for ongoing care*. http://www.fightchronicdisease.org/sites/fightchronicdisease.org/files/docs/ChronicCareChartbook_FINAL_0.pdf

[vii] Steiner CA (AHRQ), Barrett ML (M.L. Barrett, Inc.), Weiss AJ (Truven Health Analytics), Andrews RM (AHRQ). Trends and Projections in Hospital Stays for Adults With Multiple Chronic Conditions (MCC), 2003–2014. HCUP Statistical Brief #183. November 2014. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb183-Hospitalizations-Multiple-ChronicConditions-Projections-2014.pdf.

[viii] End-of-Life Care. (2015). In *The Dartmouth Atlas of Health Care*. Retrieved August 10, 2015, from http://www.dartmouthatlas.org/keyissues/issue.aspx?con=2944

[ix] End-of-Life Care. (2015). In *The Dartmouth Atlas of Health Care*. Retrieved August 10, 2015, from http://www.dartmouthatlas.org/keyissues/issue.aspx?con=2944

[x] Ritchie, C. S., & Zulman, D. M. (2013). Research priorities in geriatric palliative care: multimorbidity. Journal of palliative medicine, 16(8), 843-847.

[xi] Facts, N. H. P. C. O. (2012). Figures: Hospice Care in America. Alexandria, VA: National Hospice and Palliative Care Organization, 10-11.

[xii] Murray SA, Kendall M, Boyd K et al. Illness trajectories and palliative care. BMJ 2005; 330: 1007–11.

[xiii] Spathis, A., & Booth, S. (2008). End of life care in chronic obstructive pulmonary disease: in search of a good death. International journal of chronic obstructive pulmonary disease, 3(1), 11.

[xiv] Janssen, D. J., Spruit, M. A., Uszko-Lencer, N. H., Schols, J. M., & Wouters, E. F. (2011). Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. Journal of palliative medicine, 14(6), 735-743.

[xv] Brown, C. E., Jecker, N. S., & Curtis, J. R. (2016). Inadequate Palliative Care in Chronic Lung Disease: An Issue of Healthcare Inequality. *Annals of the American Thoracic Society*, (ja).

[xvi] Mason, B., Nanton, V., Epiphaniou, E., Murray, S. A., Donaldson, A., Shipman, C., ... & Barclay, S. (2014). 'My body's falling apart.'Understanding the experiences of patients with advanced multimorbidity to improve care: serial interviews with patients and carers. BMJ supportive & palliative care, bmjspcare-2013.

[xvii] Nyweide, D. J., Lee, W., Cuerdon, T. T., Pham, H. H., Cox, M., Rajkumar, R., & Conway, P. H. (2015). Association of Pioneer accountable care organizations vs traditional Medicare fee for service with spending, utilization, and patient experience. *JAMA*, *313*(21), 2152-2161.

[xviii] Rosenthal, M. B., Alidina, S., Friedberg, M. W., Singer, S. J., Eastman, D., Li, Z., & Schneider, E. C. (2015). A difference-in-difference analysis of changes in quality, utilization and cost following the Colorado multi-payer patient-centered medical home pilot. *Journal of general internal medicine*, 1-8.

[xix] Boyd, C. M., McNabney, M. K., Brandt, N., Correa-de-Araujuo, R., Daniel, M., Epplin, J., ... & Shega, J. W. (2012). Guiding principles for the care of older adults with multimorbidity: an approach for clinicians: American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. J Am Geriatr Soc, 60(10), E1-E25.

[xx] Gijsen, R., Hoeymans, N., Schellevis, F. G., Ruwaard, D., Satariano, W. A., & van den Bos, G. A. (2001). Causes and consequences of comorbidity: a review. Journal of clinical epidemiology, 54(7), 661-674.