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Supplemental online content for:

Frailty in Patients With Newly Diagnosed Diffuse Large B-Cell Lymphoma Receiving Curative-Intent Therapy: A Population-Based Study

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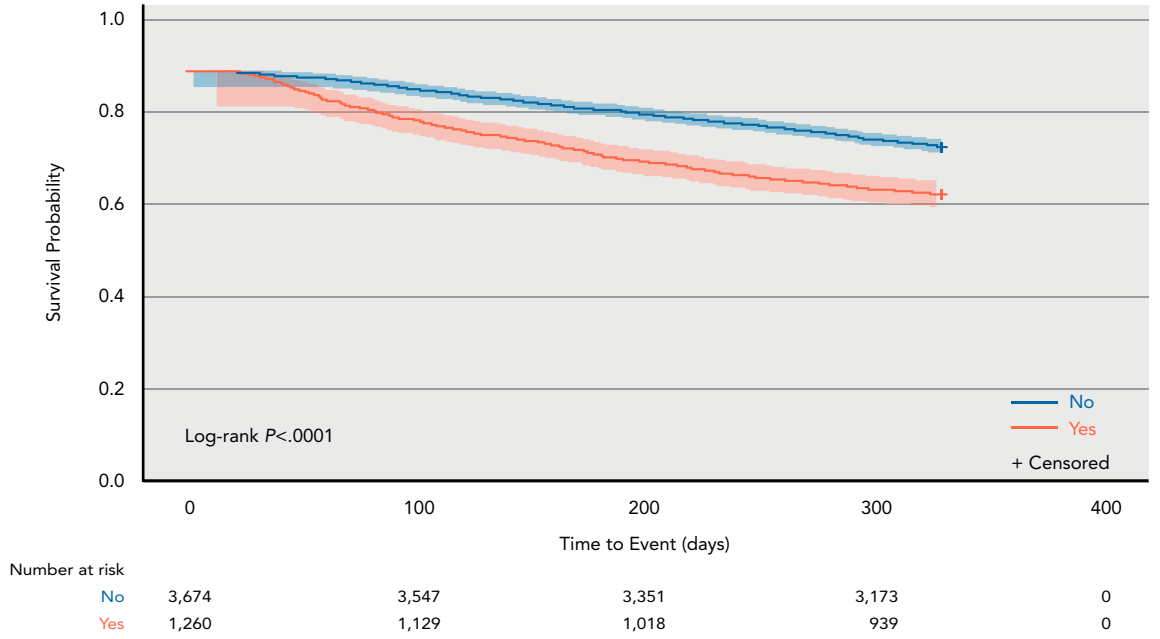
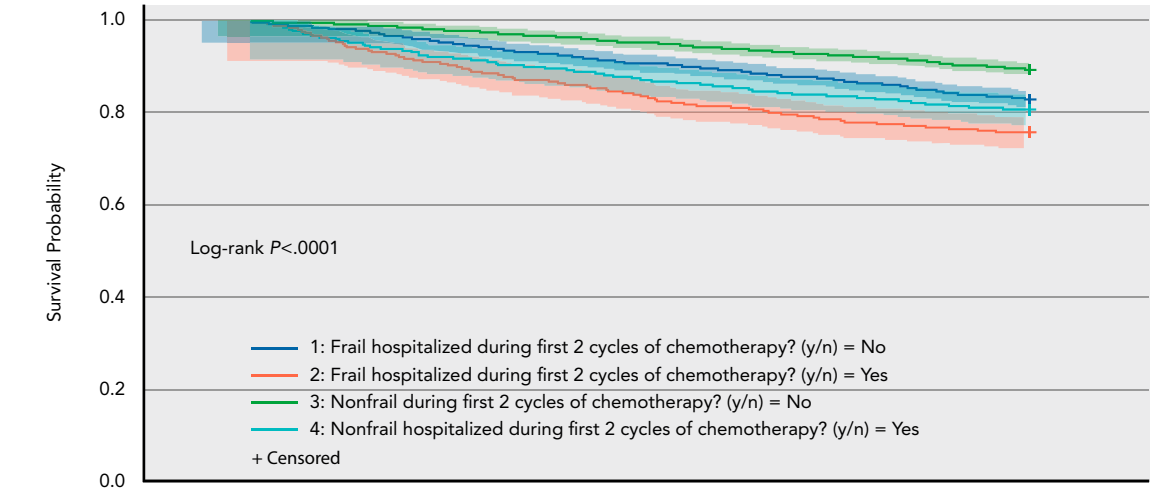


Number at risk

No	3,674	3,547	3,351	3,173	0
Yes	1,260	1,129	1,018	939	0



Number at risk

1	1,645	1,560	1,447	1,355	0
2	669	594	525	477	0
3	2,029	1,987	1,904	1,818	0
4	591	535	493	462	0

eFigure 1. Time to 1-year mortality among patients with at least 2 cycles of treatment(N=4,394), stratified by **(A)** hospitalization and **(B)** hospitalization and frailty score (binary). Product-limit survival estimates with number of subjects at risk and 95% Hall-Wellner bands.

eTable 1. Modified McIsaac Frailty Index, Developed for Use With Ontario Health Administrative Data

		Points		
Variable	**Source**	**0**	**0.5**	**1**
Anticholinergic risk scale	ODB[a] (1 year lookback)	0	1–2	>2
Arrhythmia	Elixhauser[b]	None		Present
Cancer (non-DLBCL)	OCR	None		Present
Cerebrovascular disease	Charlson	None		Present
COPD	ICES-derived cohort	None		Present
Dementia	ICES-derived cohort	None		Present
Dental	ADG	None		Present
Dermatologic	ADG	None		Present
Diabetes	ICES-derived cohort	None		Present
Dialysis	Elixhauser, procedure/intervention codes from CIHI-DAD, OHIP feecodes, or dialysis record in CIHI-NACRS	None		Present
Drug or alcohol abuse	Elixhauser, CIHI-OMHRS	None	1	Both
Heart failure	ICES-derived cohort	None		Present
Hemiparesis	Charlson	None		Present
History of falls	CIHI-NACRS, CIHI-DAD, CIHI-SDS	None		Present
Home oxygen	ADP	None		Present
ADG score[c]	ADG weighted score without age-sex adjustment	Lowest quartile	2nd–3rd quartile	Highest quartile
Hypertension	ICES-derived cohort	None		Present
Injury	ADG	None	Minor	Major
Liver disease	Elixhauser	None		Present
Multimorbidity	Charlson score	0	1–2	>2
Myocardial infarction	ICES-derived cohort	None		Present
Peripheral vascular disease	Elixhauser	None		Present
Psychosocial	ADG	None	Minor/Stable	Major
Resource use band	ADG	0–1	2–3	4–5
Rheumatic disease	Elixhauser	None		Present
Socioeconomic status	Neighborhood income quintile	Top 2 quintiles (Q4–5)	Middle quintile (Q3)	Bottom 2 quintiles (Q1–2)
Ear, nose, throat	ADG	None	Stable	Unstable
Eye	ADG	None	Stable	Unstable
Supported living environment	CCRS, HCD, OHIP	None		Present
Weight loss	Elixhauser	None		Present

Abbreviations: ADG, aggregated diagnosis groups; ADP, assistive devices program; CCRS, continuing care reporting system; COPD, chronic obstructive pulmonary disease; DAD, discharge abstract database; DLBCL, diffuse large B-cell lymphoma; HCD, home care database; HOMR, Hospital-patient One-year Mortality Risk; ICES-derived cohort, Institute for Clinical Evaluative Sciences validated disease cohort; NACRS, National Ambulatory Care Reporting System; OCR, Ontario Cancer Registry; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Claims; SDS, same day surgery.
[a]Calculated according to methods of Rudolph et al.[1]
[b]Elixhauser calculated per the coding algorithms in Quan et al.[2]
[c]HOMR score in original frailty index replaced by weighted ADG score as there was no index hospitalization used for calculation (D. McIsaac, personal communication, 2018).

References

1. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–1139.
2. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med 2008;168:508–513.

eTable 2. Frailty Scores

	Frail n (%)	Not Frail n (%)	Total n (%)
Total, N	2,699	2,828	5,527
Modified McIsaac frailty score (continuous)			
Min	0.22	0.02	0.02
Mean [SD]	0.27 [0.05]	0.15 [0.04]	0.21 [0.07]
Median (IQR)	0.25 (0.23–0.3)	0.17 (0.13–0.18)	0.2 (0.17–0.25)
90th percentile	0.33	0.20	0.30
Max	0.57	0.21	0.57
Modified McIsaac frailty score (quartiles)			
Q1 (0.02–0.15)	0 (0.0%)	1,376 (48.7%)	1,376 (24.9%)
Q2 (0.17–0.20)	0 (0.0%)	1,452 (51.3%)	1,452 (26.2%)
Q3 (0.21–0.25)	1,415 (52.4%)	0 (0.0%)	1,415 (25.6%)
Q4 (0.26–0.57)	1,284 (47.6%)	0 (0.0%)	1,284 (23.2%)

Abbreviation: IQR, interquartile range.

eTable 3. Univariable Models of Clinical Characteristics Associated With 1-Year Mortality

Variable	Level	Univariable HR (95% CI)	*P* Value
Age		1.05 (1.04–1.06)	<.0001
Frailty (binary)	Frail vs nonfrail	1.81 (1.62–2.01)	<.0001
Frailty (quartiles)	Q2 (0.16–0.20) vs Q1 (0.02–0.15)	1.59 (1.34–1.89)	<.0001
	Q3 (0.21–0.25) vs Q1 (0.02–0.15)	2.04 (1.7–2.4)	<.0001
	Q4 (0.26–0.57) vs Q1 (0.02–0.15)	2.68 (2.28–3.15)	<.0001
Number of ADG comorbidities		1.06 (1.04–1.07)	<.0001
Diagnosis as inpatient	Inpatient vs other	1.53 (1.36–1.72)	<.0001
Number of treatment cycles received (binary, time-varying)	≥3 cycles vs <3 cycles	0.29 (0.25–0.33)	<.0001
Healthcare utilization during treatment (binary, time-varying)		1.38 (1.23–1.54)	<.0001
Sensitivity analyses			
Stage	Stage III/IV (advanced) vs stage I/II (limited)	2.39 (2.00–2.86)	<.0001
	Missing vs stage I/II (limited)	2.24 (1.89–2.64)	<.0001
Year of treatment	2010–2013 (vs 2006–2009)	0.90 (0.81–1.02)	.109
	2014–2017 (vs 2006–2009)	0.74 (0.65–0.84)	.001
Healthcare utilization during treatment, including hospitalizations resulting in death (binary, time-varying)		2.30 (2.04–2.60)	<.0001

Abbreviations: ADG, aggregated diagnosis groups; HR, hazard ratio.

eTable 4. Multivariable Models of Clinical Characteristics Associated With 1-Year Mortality

Variable	Level	Multivariable HR (95% CI)	*P* Value
Model 1: Frailty as a binary variable			
Age		1.04 (1.03–1.05)	<.0001
Frailty (binary)	Frail vs nonfrail	1.50 (1.32–1.70)	<.0001
Number of ADG comorbidities		1.00 (0.98–1.02)	.8356
Diagnosis as inpatient	Inpatient vs other	1.40 (1.25–1.58)	<.0001
Number of treatment cycles received (binary, time-varying)	<3 vs ≥3 cycles	0.34 (0.29–0.39)	<.0001
Health care utilization during treatment (binary, time-varying)		1.23 (1.09–1.37)	.0005
Model 2: Frailty in quartiles			
Age		1.04 (1.03–1.04)	<.0001
Frailty (quartiles)	Q2 (0.16–0.20) vs Q1 (0.02–0.15)	1.49 (1.25–1.78)	<.0001
	Q3 (0.21–0.25) vs Q1 (0.02–0.15)	1.84 (1.53–2.22)	<.0001
	Q4 (0.26–0.57) vs Q1 (0.02–0.15)	2.20 (1.79–2.69)	<.0001
Number of ADG comorbidities		0.99 (0.97–1.01)	.1315
Diagnosis as inpatient	Inpatient vs other	1.36 (1.21–1.53)	<.0001
Number of treatment cycles received (binary, time-varying)	<3 vs ≥3 cycles	0.34 (0.30–0.40)	<.0001
Health care utilization during treatment (binary, time-varying)		1.22 (1.09–1.37)	.0007

Abbreviations: ADG, aggregated diagnosis groups; HR, hazard ratio.

eTable 5. Baseline Demographic and Treatment-Related Characteristics Among Frail Patients Who Survived ≤1 vs >1 Year From First Dose of Rituximab

Characteristic	Survived ≤1 Year n (%)	Survived >1 Year n (%)	Total n (%)	*P* Value[a]
Total, N	868	1,831	2,699	
Demographic characteristics				
Age				
Mean [SD]	77.28 [6.37]	75.72 [6.09]	76.22 [6.22]	**<.001**
Median (IQR)	77 (73–82)	75 (71–80)	76 (71–81)	**<.001**
Sex				**.003**
Female	389 (44.8%)	933 (51.0%)	1,322 (49.0%)	
Male	479 (55.2%)	898 (49.0%)	1,377 (51.0%)	
Neighborhood income quintile				.171
Missing	≤5 (0.3%)	≤5 (0.1%)	≤5 (0.1%)	
Q1 (lowest)	180 (20.7%)	372 (20.3%)	552 (20.5%)	
Q2	221 (25.5%)	455 (24.8%)	676 (25.0%)	
Q3	192 (22.1%)	389 (21.2%)	581 (21.5%)	
Q4	145 (16.7%)	287 (15.7%)	432 (16.0%)	
Q5 (highest)	127 (14.6%)	327 (17.9%)	454 (16.8%)	
Rural dwelling				.352
Urban	743 (85.6%)	1,542 (84.2%)	2,285 (84.7%)	
Rural	125 (14.4%)	289 (15.8%)	414 (15.3%)	
Comorbidities (Note: ADGs exclude cancer)				
Mean ADGs [SD]	13.55 [2.90]	13.35 [2.87]	13.41 [2.88]	.103
Median ADGs (IQR)	14 (12–16)	13 (11–15)	13 (12–15)	
ADG categorical: high (≥10)	797–802 (92.3%)	1,653–1,658 (90.3%)	2,455–2,460 (91.0%)	.241
ADG categorical: moderate (6–9)	66 (7.6%)	173 (9.4%)	239 (8.9%)	
ADG categorical: low (0–5)	≤5 (0.1%)	≤5 (0.2%)	≤5 (0.2%)	
Cancer type				.295
DLBCL	817 (94.1%)	1,741 (95.1%)	2,558 (94.8%)	
Transformed FL	51 (5.9%)	90 (4.9%)	141 (5.2%)	
Status at time of diagnosis (±1 day)				**.003**
Outpatient	593 (68.3%)	1,350 (73.7%)	1,943 (72.0%)	
Inpatient	275 (31.7%)	481 (26.3%)	756 (28.0%)	
Modified McIsaac frailty score (continuous)				
Mean [SD]	0.27 [0.05]	0.26 [0.05]	0.27 [0.05]	**<.001**
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	**<.001**
Modified McIsaac frailty score (quartiles)				**<.001**
Q1 (0.02–0.15)	–	–	–	
Q2 (0.16–0.20)	–	–	–	
Q3 (0.21–0.25)	407 (46.9%)	1,008 (55.1%)	1,415 (52.4%)	
Q4 (0.26–0.57)	461 (53.1%)	823 (44.9%)	1,284 (47.6%)	

(*continued on next page*)

eTable 5. Baseline Demographic and Treatment-Related Characteristics Among Frail Patients Who Survived ≤1 vs >1 Year From First Dose of Rituximab (cont.)

Characteristic	Survived ≤1 Year n (%)	Survived >1 Year n (%)	Total n (%)	*P* Value[a]
Treatment-related characteristics				
Status at time of treatment (index) (±1 day)				**.001**
Outpatient	817 (94.1%)	1,787 (97.6%)	2,604 (96.5%)	
Inpatient	51 (5.9%)	44 (2.4%)	95 (3.5%)	
Number of NDFP cycles in first-line treatment				
Mean [SD]	3.24 [2.20]	5.18 [1.84]	4.56 [2.16]	**<.001**
Median (IQR)	3 (1–5)	6 (4–6)	5 (3–6)	**<.001**
Completed 1 cycle, n (%)	298 (34.3%)	87 (4.8%)	385 (14.3%)	**<.001**
Completed 6 cycles, n (%)	136 (15.7%)	835 (45.6%)	971 (36.0%)	**<.001**
Healthcare utilization during chemotherapy				
Number of ED visits during first 2 cycles of chemotherapy				
Mean [SD]	0.28 [0.69]	0.41 [0.90]	0.36 [0.84]	**<.001**
Median (IQR)	0 (0–0)	0 (0–1)	0 (0–0)	**<.001**
Number of hospitalizations during first 2 cycles of chemotherapy				
Mean [SD]	0.53 [0.75]	0.35 [0.64]	0.41 [0.68]	**<.001**
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	**<.001**
Number of ED visits from start to end of 1st-line rituximab treatment				
Mean [SD]	0.52 [1.05]	0.85 [1.62]	0.75 [1.47]	**<.001**
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	**<.001**
Number of hospitalizations from start of 1st-line rituximab treatment				
Mean [SD]	0.92 [1.06]	0.78 [1.07]	0.82 [1.07]	**.001**
Median (IQR)	1 (0–1)	0 (0–1)	1 (0–1)	**<.001**

Per ICES reporting requirements to preserve patient privacy, cells with N≤5 are suppressed.
Abbreviations: ADG, aggregated diagnosis group; ED, emergency department; IQR, interquartile range; NDFP, New Drug Funding Program.
[a]Bold indicated statistically significant *P* value.

eTable 6. Sensitivity Analyses

Variable	Level	Multivariable HR (95% CI)	*P* Value
Model 1: Sensitivity analysis including stage variable			
Age		1.04 (1.03–10.05)	<.0001
Frailty (binary)	Frail vs nonfrail	1.46 (1.29–1.66)	<.0001
Number of ADG comorbidities		1.00 (0.98–1.02)	.9035
Diagnosis as inpatient	Inpatient vs other	1.38 (1.23–1.55)	<.0001
Number of treatment cycles received (binary, time-varying)	<3 vs ≥3 cycles	0.34 (0.30–0.39)	<.0001
Healthcare utilization during treatment (binary, time-varying)		1.20 (1.07–1.34)	.0021
Stage	Stage III/IV (advanced) vs stage I/II (limited)	2.35 (1.96–2.81)	<.0001
	Missing vs stage I/II (limited)	2.15 (1.82–2.54)	<.0001
Model 2: Sensitivity analysis including year of treatment variable			
Age		1.04 (1.03–1.05)	<.0001
Frailty (binary)	Frail vs nonfrail	1.52 (1.34–1.73)	<.0001
Number of ADG comorbidities		1.00 (0.98–1.02)	0.8396
Diagnosis as inpatient	Inpatient vs other	1.34 (1.19–1.51)	<.0001
Number of treatment cycles received (binary, time-varying)	<3 vs ≥3 cycles	0.34 (0.30–0.39)	<.0001
Healthcare utilization during treatment (binary, time-varying)		1.22 (1.09–1.37)	.0005
Year of treatment	2006–2009	Ref	–
	2010–2013	0.91 (0.80–1.04)	.1720
	2014–2017	0.78 (0.68–0.89)	.0002
Model 3: Sensitivity analysis including hospitalizations resulting in death in the healthcare utilization variable			
Age		1.04 (1.03–1.04)	<.0001
Frailty (binary)	Frail vs nonfrail	1.47 (1.30–1.67)	<.0001
Number of ADG comorbidities		1.00 (0.98–1.01)	.6919
Diagnosis as inpatient	Inpatient vs other	1.40 (1.24–1.57)	<.0001
Number of treatment cycles received (binary, time-varying)	<3 vs ≥3 cycles	0.35 (0.31–0.40)	<.0001
Healthcare utilization during treatment, including hospitalizations resulting in death (binary, time-varying)		2.08 (1.84–2.34)	<.0001

Abbreviations: ADG, aggregated diagnosis groups; HR, hazard ratio.

eAppendix 1. Supplementary Methods

Cohort Creation

The cohort was created by identifying patients who had received first-line rituximab-based therapy through the New Drug Funding Program (NDFP) in Ontario. The NDFP reimbursement policy in Ontario requires that patients accessing rituximab for diffuse large B-cell lymphoma (DLBCL) must receive curative-intent therapy. The dataset was narrowed to include only patients with confirmed histology showing aggressive B-cell lymphoma, in both the NDFP and the Ontario Cancer Registry, which contains information on approximately 95% of provincial cancer diagnoses.[1] Stage information was collected where available.

The index date was defined as the date of the first dose of rituximab. Each cycle of therapy was defined as the 3-week period following each rituximab dose. The end date of treatment was defined as 3 weeks after the last dose of rituximab preceding a minimum 6-week gap. This allowed for variation in the total cycles of rituximab administered, as some physicians may have administered up to 8 cycles of rituximab-based therapy during the time period observed. Dose delays were defined as delays between treatment dates of >24 days, which allowed for variation in the traditional 21-day schedule used in the setting of statutory holidays.

Other accessed databases for covariate definition include the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (CIHI-DAD), which contains data on all inpatient hospitalizations, the National Ambulatory Care Reporting System (CIHI-NACRS, which contains information on hospital and community-based ambulatory care), the Ontario Mental Health Reporting System (CIHI-OMHRS, which contains data on patients in adult inpatient mental health beds), the Ontario Health Insurance Plan (which contains claims billed by health-care providers, covered under the universal health program), the Assistive Devices Program (which provides support, funding, and access to personalized assistive devices to Ontario residents with long-term physical disabilities), the Ontario Drug Benefits Database (a database of prescription drug claims, capturing primarily those aged ≥65 years), the Ontario Continuing Care Reporting System (which captures data on residents receiving facility-based continuing care services), and the Home Care Database (which captures all home care services provided or coordinated by local health integration networks).

Comorbidity was measured using the age-adjusted Johns Hopkins ACG System Version 10. Patients were assigned to up to 32 Aggregated Diagnosis Groups (ADGs), based on hospitalizations and emergency department and outpatient visits during the 3 years prior to index, to characterize patients' comorbidity burden, wherein a higher number of total ADGs represents higher burden. Cancer-related ADGs were excluded, given our cohort is made up of patients with cancer.[2] The Elixhauser comorbidity index and Charlson comorbidity index,[3,4] based on inpatient hospitalizations, were also computed based on a 3-year lookback period from index date, in order to calculate the frailty score.

Data Sharing

The dataset from this study is held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers (eg, healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

References

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eAppendix 2. Results: Exploratory Analyses

Association of Early Hospitalization With Death

Among patients who survived at least 2 cycles of treatment (landmark analysis), hospitalization during the first 2 cycles of treatment was significantly associated with 1-year mortality (hazard ratio [HR], 1.81; 95% CI, 1.59–2.06; supplemental eAppendix 1 and eFigure 1). Patients who were frail and hospitalized had the poorest outcomes (1-year survival probability ± standard error: 69% ± 1.8%). Patients who were frail and not hospitalized had a survival probability of 78% ± 1.0% and patients who were not frail and hospitalized had a 1-year survival probability of 75% ± 1.8%; patients who were not frail and not hospitalized had the best outcomes with a 1-year survival probability of 87% ± 0.76%.

Characteristics of Frail Patients Who Survived ≤1 vs >1 Year

Frail patients who survived ≤1 year tended to be older and more likely to be male than frail patients surviving longer than 1 year, but there were no other significant differences in their demographic characteristics (supplemental eAppendix 1 and eTable 2). They also had higher frailty scores. These patients received fewer treatment cycles, had more hospitalizations during treatment, and were more likely to initiate treatment as an inpatient (supplemental eTable 2). When reviewing the frailty score composition differences between these groups, frail patients surviving ≤1 year were significantly more likely to use home oxygen (4.8% vs 2.4%), be on dialysis (4.0% vs 1.6%), have an arrhythmia (24.5% vs 16.5%), and be classified as having multimorbidity (56.1% vs 43.0%) (P<.001; frailty scoring data not shown).