Turning costs into actionable insights for value-based health care

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Part II

Real-World Evaluations

Chapter 5

Allocation and Value of Curative Oncological Treatment in Frail and Fit Older Patients with Esophageal Cancer: *An Observational Cohort Study*

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ABSTRACT

Introduction

The Value-Based Health Care (VBHC) model of care provides insights into patient characteristics, outcomes, and costs of care delivery that help clinicians counsel patients. This study compares the allocation and value of curative oncological treatment in frail and fit older patients with esophageal cancer in a dedicated VBHC pathway.

Methods

Data was collected from patients with primary esophageal cancer without distant metastases, aged 70 years or older, and treated at a Dutch tertiary care hospital between 2015-2019. Geriatric assessment was performed. Outcomes included treatment discontinuation, mortality, quality of life (QoL), and physical functioning over a one-year period. Direct hospital costs were estimated using activity-based costing.

Results

In this study, 89 patients were included with mean age 75 years. Of 56 patients completing GA, 19 classified as frail and 37 classified as fit. For frail patients, the treatment plan was chemoradiotherapy and surgery (CRT&S) in 13/19 (68%) and definitive chemoradiotherapy (dCRT) in 6/19 (32%), for fit patients CRT&S in 31/37 (84%) and dCRT 6/37 (16%). Frail patients discontinued chemotherapy more often than fit patients (5/19, 26% vs 4/37, 11%, p=0.03) and reported lower QoL after 6 months (mean 0.58 (SD0.35) vs 0.88 (0.25), p=0.05). After one year, 11% of frail and 30% of fit patients reported no decline in physical functioning and QoL and survived. Frail and fit patients had comparable mean direct hospital costs (€24K (SD€13K) vs €23K (SD€8K), p=0.82).

Conclusions

The value of curative oncological treatment was lower for frail than for fit patients because of slightly worse outcomes and comparable costs. The utility of the VBHC model of care depends on the availability of sufficient data. Real-world evidence in VBHC can be used to inform treatment decisions and optimization in future patients by sharing results and monitoring performance over time.

INTRODUCTION

Value-Based Health Care (VBHC) is a management strategy that aims to improve the value of care delivery to the patient[1]. Value is defined as patient-relevant outcomes relative to the costs incurred to achieve those outcomes[2]. VBHC supports the organization of care in integrated practice units (i.e. care pathways) around a medical condition and defining and measuring real-world outcomes and costs. Proper insights into patient population characteristics, outcomes, and costs of care delivery can help clinicians counsel patients in treatment decision-making.

For older patients specifically, clinicians and patients have to weigh the benefits and harms of intensive oncological treatment. Frailty in older patients increases the risk of poor health outcomes and discontinuation of oncological treatment[3]. In addition, frailty is associated with higher total hospital costs after surgical treatment[4] and overall healthcare costs in community-dwelling older adults [5]. Decision-making based on geriatric assessment (GA) has proven to reduce chemotoxicitiy and to increase quality of life (QoL) in older patients who receive chemotherapy[6-8]. Furthermore, GA has the potential to be cost-effective[9]. However, to our knowledge, no studies combine real-world data on GA, clinical and patient-relevant outcomes, and costs of older patients with cancer.

The upper gastrointestinal (GI) oncology routine care pathway at the Leiden University Medical Center (LUMC) in the Netherlands implemented GA for older patients in 2015[10] and showed geriatric deficits associated with outcomes in older patients with esophageal cancer[11]. The care pathway follows an integrated VBHC approach by measuring and analyzing real-world outcomes and costs. Results on treatment outcomes and costs can be used to inform treatment decisions and optimization in future patients. The care pathway strives to achieve optimal outcomes in frail and fit patients by tailoring treatment allocation to the individual patient. In this study, we aimed to compare the allocation and value of curative oncological treatment in frail and fit older patients with esophageal cancer.

METHODS

Study design and participants

This observational study was performed in the routine clinical care pathway for geriatric gastrointestinal oncology at Leiden University Medical Center (LUMC), a Dutch tertiary care hospital. The LUMC is a referral center for

esophageal cancer care for surrounding hospitals. Patients with esophageal cancer aged 70 years or older referred to the care pathway between June 2015 and June 2019 and able to understand the Dutch language were eligible for this study. Patients were excluded if they presented with stage IVB (palliative care) and/or recurrent esophageal cancer, were treated with endoscopic resection, or received (part of) treatment in the initial referring hospital. Data collection was in the context of the Triage Older Patients Needing Treatment (TENT) study[10], approved by the Medical Ethics Committee of the LUMC (ID number NL53575.058.15). Patients provided written informed consent or a 'certificate of no objection' for retrospective data collection of patients not participating in GA.

Geriatric assessment

After initial diagnosis, patients in the routine clinical care pathway were seen by a multidisciplinary team of surgeons, medical oncologists, radiation oncologists, and gastroenterologists. A short geriatric screening performed by a trained nurse was implemented for patients aged 70 years or older using the Geriatric 8 (G8) questionnaire[12] and Six-item Cognitive Impairment Test (6CIT)[13]. When screening was abnormal, patients were referred for GA to the geriatric outpatient clinic[10]. Patients with normal geriatric screening results not referred to GA were contacted by telephone to complete GA as part of the TENT study to determine their frailty status. Frailty status is, therefore, available for patients with both normal and abnormal results of geriatric screening.

Oncological treatment

There were two curative treatment options according to the local standard in case of non-metastatic esophageal cancer. Firstly, chemoradiotherapy and surgery (CRT&S), which consisted of a 5-week schedule neoadjuvant CRT of 23 fractions of 1.8 Gray (Gy) external beam radiotherapy and simultaneous chemotherapy consisting of paclitaxel (50 mg/m^2) and carboplatin (area under the curve (AUC) 2). Esophageal resection used a transthoracic or transhiatal approach depending on the location of the tumor. Second, definitive chemoradiotherapy (dCRT) was recommended for patients unfit for surgery, with a T4b stage tumor, or proximal location of the tumor in the esophagus. dCRT consisted of a 6-week schedule of 28 fractions of 1.8 Gy and simultaneous chemotherapy carboplatin (AUC 2) and paclitaxel (50 mg/m^2).

Demographic and clinical data

Electronic medical records were reviewed for demographic and clinical data including age, sex, comorbidity, number of medications, body mass index (BMI), smoking and alcohol status and history, WHO performance score, histopathological cancer type, and clinical stage of disease (TNM classification according to the American Joint Committee on Cancer Staging Form Supplement, eighth edition). In the patients that underwent GA, patients were classified as frail when they scored abnormal on at least two domains out of the four geriatric domains: the somatic, psychological, functional and/or social domains. Malnutrition was excluded from the somatic domain because in esophageal cancer malnutrition often is a consequence of disease instead of geriatric frailty.

Treatment allocation and discontinuation

The treatment plan and actual treatment course were reviewed in electronic medical records by YH and independently validated by MS. Discontinuation of treatment was defined as not completing the intended surgery, radiotherapy fractions and/or chemotherapy courses that were part of the treatment plan at baseline.

Outcomes

Main outcomes included clinical outcomes, survival, physical functioning, and quality of life (QoL). Clinical outcomes were treatment discontinuation, grade 3-5 toxicity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, outpatient treatment, length of hospital stay (LOS), ICU admissions and LOS, and readmissions. LOS was assessed using health care utilization data from the financial administration of the LUMC. Survival was assessed at one-year. Physical functioning was assessed by the Katz Index of Independence in Activities of Daily Living (ADL)[14] (with ADL scores ≤2 rated as abnormal patient dependence and scores >2 rated as patient independence) and the Lawton Instrumental ADL (IADL)[15] for function and independence (with IADL scores ranging between 0 to 5 for men with cut-off value ≤4 for abnormal dependence, and 0 to 8 for women with cut-off value ≤7). QoL was assessed using the Dutch tariff for the three-level EuroQol-5D (EQ-5D)[16] and by the EuroQol Visual Analogue Scale (EQ-VAS) at baseline, 6 and 12 months. QoL decline over time according to the EQ-5D or EQ-VAS was estimated by comparing the difference in 12 month and baseline score to the minimal clinically important difference as defined by Pickard et al. (EQ-5D-3L index score ≥0.06 or EQ-VAS ≥7 points)[17].

Survival and QoL were also combined in a composite utility score at 12 months. This score combined the EQ-5D utility, a value between 0 and 1, at 12 months with mortality at 12 months, in which case patients with an EQ-5D measurement at baseline who died before one-year of follow-up received a utility of 0 (equivalent to death).

Direct hospital costs

Direct hospital costs included all costs related to care delivery, such as personnel and equipment, but not indirect costs like overhead and housing. Patient-level cost data were derived from the financial administration of the LUMC, using activity-based costing at 2020 price level. In activity-based costing, costs consist of the number of care activities performed in the hospital, multiplied by the direct hospital costs per activity[18]. Our analysis included health care utilization and costs from the first visit to the GI oncology routine clinical care pathway until one year after start of treatment. Financial data management was performed using R Studio (2022.02.3).

Statistical analysis

Descriptive analyses were stratified according to frailty status or treatment allocation. Continuous data was presented as means with standard deviations (SD) or medians with interquartile ranges (IQR). Proportions were calculated for categorical variables by the number of available cases. Differences in continuous data across all groups were assessed with independent samples t-test for (un)equal variances. Differences in categorical variables across all groups were assessed using Fisher's exact test. Survival was estimated using Kaplan-Meier analysis. $P<0.05$ was considered statistically significant and all parametric statistical tests were performed using bootstrapping with 1,000 samples. A sensitivity analysis was performed with an extended cohort including patients who received CRT elsewhere for whom data on treatment allocation and outcomes but not costs were available. Statistical analysis was performed using IBM SPSS Statistics (version 29).

RESULTS

Patient characteristics

Between June 2015 and June 2019, 89 older patients with non-metastasized esophageal cancer who visited the GI oncology routine clinical care pathway were included in this study. In total, 56 out of 89 patients completed GA, either in-person or on the phone, 10/89 patients had an incomplete GA,

and 23 patients did not undergo GA (flow chart is provided in **Figure S2**). Of patients who completed GA, 19/56 (34%) patients classified as frail 37/56 (66%) as fit. **Table 1** shows that in the total population, the mean age was 75 years (SD 4.0) and 66/89 (74%) of patients were men. The diagnosis was esophageal squamous cell carcinoma for 29/89 (33%) patients, and esophageal adenocarcinoma for 60/89 (67%). Frail and fit patients had a similar age (75 (SD 3.4) vs 74 (SD 4.3) years). In addition, 14/19 (74%) frail patients were men, compared to 31/37 (84%) fit patients (p=0.48). Tumor histopathology (p=0.77) and clinical stage group (p=0.28) were similar between frail and fit patients. The results of geriatric screening and the geriatric deficits in four frailty domains are provided in the supplementary material (**Table S1**).

Table 1. Baseline characteristics

			Population with complete GA		
	Total population n=89	Population with no or incomplete GA n=33	Frail patients n=37	Fit patients n=19	p Value[a]
Patient characteristics					
Age (years, mean (SD)	74.76 (4.0)	75.24 (4.0)	74.24 (4.3)	74.95 (3.4)	0.52
Male sex, n (%)	66 (74.2)	21 (63.6)	31 (83.8)	14 (73.7)	0.48
Charlson Comorbidity Index, median (IQR)	1.0 (0-2)	0.0 (0-2)	1.0 (0-2)	2.0 (1-3)	0.15
Number of medications, mean (SD)	4.42 (3.5)	3.58 (2.7)	3.95 (3.3)	6.79 (4.0)	0.01
BMI, mean (SD)	25.20 (3.9)	24.8 (4.0)	25.52 (3.8)	25.26 (4.0)	0.81
Smoking, current or history, n (%)	61 (70.1)	16 (52.0)	29 (78.4)	16 (84.2)	0.73
Alcohol, current or history, n (%)	72 (83.7)	24 (80.0)	35 (94.6)	13 (68.4)	0.01
Living situation, n (%)					
At home, alone	22 (25.3)	10 (32.3)	4 (10.8)	8 (42.1)	0.01
At home, with others	65 (74.7)	21 (67.7)	33 (89.2)	11 (57.9)	
WHO Performance Score, n (%)					
WHO 0	31 (43.1)	12 (52.2)	15 (45.5)	4 (25.0)	0.35
WHO 1	38 (52.8)	11 (33.3)	16 (48.5)	11 (68.8)	

Table 1. Continued

	Total population n=89	Population with no or incomplete GA n=33	Population with complete GA		p Value[a]
			Frail patients n=37	Fit patients n=19	
WHO 2	3 (4.2)	0 (0)	2 (6.1)	1 (6.3)	
Disease characteristics					
Histopathological, n (%)					
Squamous cell	29 (32.6)	9 (27.3)	14 (37.8)	6 (31.6)	0.77
Adenocarcinoma	60 (67.4)	24 (72.7)	23 (62.2)	13 (68.4)	
Clinical stage group, n (%)					
Stage I	1 (1.1)	0 (0)	1 (2.7)	0 (0)	0.28
Stage II	18 (20.2)	6 (18.2)	7 (18.9)	5 (26.3)	
Stage III	51 (57.3)	22 (66.7)	22 (59.5)	7 (36.8)	
Stage IVA	19 (21.3)	5 (15.2)	7 (18.9)	7 (36.8)	

[a] P value for comparison between frail and fit patients. Missing data were not accounted for in the frequencies. Missing information for the total population: smoking history (n=2), alcohol history (n=3), living situation (n=2), WHO score (n=17). Abbreviations: GA, geriatric assessment; SD, standard deviation; BMI, body mass index.

Treatment allocation

In the total population, the treatment plan was CRT&S for 70/89 (79%) patients and dCRT for 19/89 (21%) patients (**Figure 1**). Among frail patients, the treatment plan was CRT&S for 13/19 (68%) patients in contrast to 31/37 (84%) among fit patients (p=0.30). In the total population, 54/70 (77%) patients with treatment plan CRT&S completed surgery, while 9/54 (13%) patients decided not to undergo surgery because of their own preference, and 7/54 (10%) patients did not undergo surgery because of their declining condition. Furthermore, 6/19 (32%) patients with treatment plan dCRT discontinued treatment. In the subgroup of frail patients with treatment plan dCRT, 3/6 (50%) discontinued dCRT and 1/6 (17%) fit patients. **Figure S2** in the supplementary material provides a flowchart of treatment allocation.

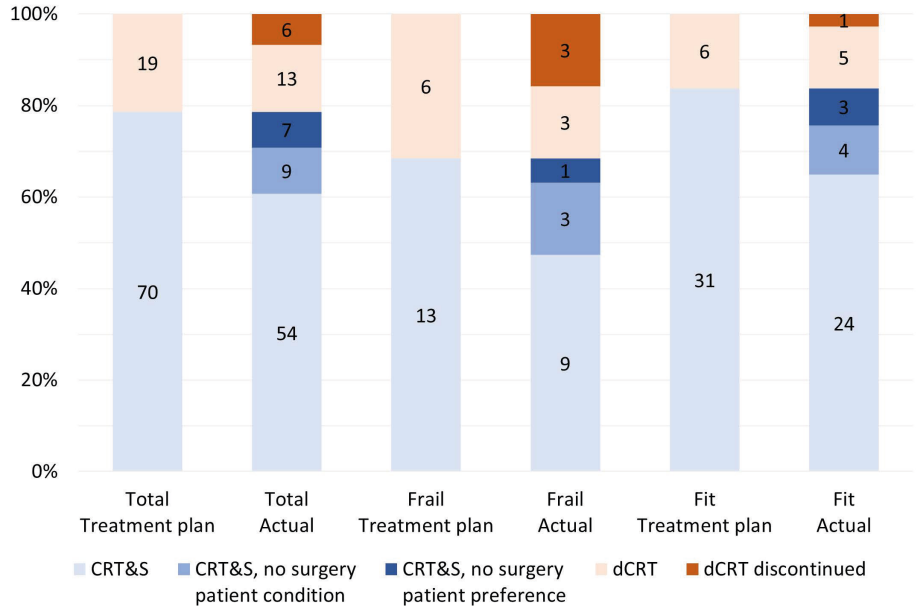

Figure 1. Treatment allocation in the total, frail, and fit population. Abbreviations: CRT&S, chemoradiotherapy and surgery; dCRT, definitive chemoradiotherapy; pT, palliative therapy; BSC, best supportive care.

Outcomes

The outcomes of oncological treatment are presented in **Table 2**. In the total population (n=89), patients received 25 (SD 3.7) fractions of radiotherapy on average and 5 (SD 1.0) chemotherapy cycles. Overall, two patients (2.4%) discontinued radio- and chemotherapy and 13 patients (15.9%) discontinued

chemotherapy. Frail patients discontinued chemotherapy significantly more often than fit patients (n=5 (26.3%) vs n=4 (10.8%), p=0.03). Thirteen frail patients (68.4%) experienced grade ≥3 toxicity and 19 fit patients (51.4%). A similar percentage of frail (n=3 (15.8%)) and fit (n=6 (16.2%)) patients were admitted to ICU, but frail patients had a mean longer LOS at the ICU compared to fit patients although not statistically significant (mean LOS 10.33 (SD 1.5) vs 4.5 (SD 3.3), p=0.06). All-cause mortality after one year was 24% (n=21 out of 89) in the total population, 27% (n=5 out of 19) for frail patients, 30% ((n=11 out of 37) for fit patients, and 15% (n=5 out of 33) for patients with no or incomplete GA (Kaplan Meier Curves in Figure S3).

Physical functioning and QoL measures were available for a subset of patients and prone to loss to follow-up. **Table 2** presents the number of available responses for these measures. At 6 months, 2/10 (20%) frail patients were ADL dependent compared to 0/22 (0%) fit patients, and 7/10 (70%) frail patients were IADL dependent compared to 7/22 (32%) fit patients. QoL measured by the EQ5D-3L at 6 months was significantly lower for frail patients compared to fit patients (mean score 0.58 (SD 0.35) versus 0.88 (SD 0.25), p=0.05). In the sensitivity analysis including the extended cohort (n=100) similar patterns were observed and the composite utility score at 12 months was significantly lower for frail patients (0.37 (SD 0.13) vs 0.73 (0.42), p=0.03) (Supplementary material **S4** and **S5**).

Table 2. Outcomes of oncological treatment

	Total patient population n=89	Population with no or incomplete GA n=33	Population with complete GA		P-value[a]
			Frail patients n=19	Fit patients n=37	
Clinical outcomes					
Radiotherapy fractions, mean (SD)	24.94 (3.7)	25.34 (2.5)	24.11 (6.3)	25.03 (2.5)	0.55
Chemotherapy cycles, mean (SD)	5.02 (1.0)	5.21 (0.6)	4.58 (1.5)	5.11 (0.9)	0.16
Treatment discontinuation					
Radiotherapy, n(%)	2 (2.3)	0 (0)	2 (10.5)	0 (0)	0.11
Chemotherapy, n(%)	13 (15.9)	4 (15.4)	5 (26.3)	4 (10.8)	0.03
Radio- and chemotherapy, n(%)	2 (2.4)	0 (0)	2 (10.5)	0 (0)	
Surgery prematurely halted, n(%)	2 (3.6)	1 (4.5)	1 (10.0)	0 (0)	0.29
Chemotherapy dose reduction, n(%)	7 (8.8)	2 (8.3)	3 (15.8)	2 (5.4)	0.32
Chemotherapy dose delayed, n(%)	11 (13.8)	4 (16.7)	3 (15.8)	4 (10.8)	0.68
Radio grade 3-5 toxicity, n(%)	29 (32.6)	9 (27.3)	7 (36.8)	13 (35.1)	1.00
Chemo grade 3-5 toxicity, n(%)	48 (53.9)	16 (48.5)	13 (68.4)	19 (51.4)	0.26

Table 2. Continued

	Total patient population n=89	Population with no or incomplete GA n=33	Population with complete GA		P-value[a]
			Frail patients n=19	Fit patients n=37	
Hematological, n(%)	27 (56.3)	9 (56.3)	9 (69.2)	9 (47.4)	0.29
Non-hematological, n(%)	35 (72.9)	10 (62.5)	11 (84.6)	14 (73.7)	0.67
Hospital stay					
ICU admissions, n (%)	13 (14.6)	4 (12.1)	3 (15.8)	6 (16.2)	0.54
ICU LOS, mean (SD) in days	8.77 (10.4)	14.00 (18.35)	10.33 (1.5)	4.50 (3.3)	0.06
Outpatient treatment, n (%)	80 (89.9)	27 (81.8)	18 (94.7)	35 (94.6)	0.48
Outpatient treatment, mean (SD) in days	6.93 (3.4)	13.04 (8.4)	6.39 (2.8)	7.06 (3.0)	0.45
Hospital LOS, n (%)	62 (69.7)	26 (78.8)	12 (63.2)	24 (64.9)	0.24
Hospital LOS, mean (SD) in days	12.52 (6.9)	7.11 (4.2)	11.58 (5.8)	12.42 (5.8)	0.69
Readmissions, n (%)					
0-6 months	34 (38.2)	14 (57.6)	9 (47.3)	11 (29.7)	0.08
6-12 months	13 (18.1)	7 (21.2)	4 (10.5)	8 (21.6)	0.68

Table 2. Continued

	Total patient population n=89	Population with no or incomplete GA n=33	Population with complete GA		P-value[a]
			Frail patients n=19	Fit patients n=37	
Mortality					
One year all-cause mortality, n (%)	21 (23.6)	5 (15.2)	5 (26.7)	11 (29.7)	0.88
Mean survival time, days (SD)	334.33 (74.1)	347.55 (58.8)	314.42 (105.5)	332.76 (66.5)	0.50
Physical functioning					
ADL dependent	*n=64*	*n=8*	*n=19*	*n=37*	
Baseline	1 (1.6)	0 (0)	1 (5.3)	0 (0)	0.34
	n=35	*n=3*	*n=10*	*n=22*	
6 months	2 (5.7)	0 (0)	2 (20.0)	0 (0)	0.09
	n=28	*n=3*	*n=7*	*n=18*	
12 months	1 (3.6)	0 (0)	1 (14.3)	0 (0)	0.28
IADL dependent	*n=56*	*n=0*	*n=19*	*n=37*	
Baseline	7 (12.5)	-	7 (36.8)	0 (0)	<0.001
	n=35	*n=3*	*n=10*	*n=22*	

Table 2. Continued

	Total patient population n=89	Population with no or incomplete GA n=33	Population with complete GA: Frail patients n=19	Population with complete GA: Fit patients n=37	P-value[a]
6 months	15 (42.9)	1 (33.3)	7 (70.0)	7 (31.8)	0.06
	n=27	*n=3*	*n=7*	*n=17*	
12 months	10 (37.0)	1 (33.3)	5 (71.4)	4 (23.5)	0.06
Quality of life (EQ5D-3L)	n=38	*n=0*	*n=12*	*n=26*	
Baseline	0.86 (0.2)	-	0.82 (0.24)	0.88 (0.17)	0.49
	n=28	*n=2*	*n=8*	*n=18*	
6 months	0.80 (0.30)	0.83 (0.02)	0.58 (0.35)	0.88 (0.25)	0.05
	n=28	*n=3*	*n=7*	*n=18*	
12 months	0.85 (0.27)	0.91 (0.16)	0.64 (0.40)	0.93 (0.17)	0.11
	n=37	*n=3*	*n=10*	*n=24*	
Composite utility score at 12 months	0.65 (0.44)	0.91 (0.16)	0.44 (0.45)	0.70 (0.44)	0.15

[a] For differences between frail and fit patients, calculated with independent samples t-test for means, Fisher's exact test for proportions upon 1,000 bootstrap samples. Missing data were not accounted for in the frequencies. N presents QoL measurements at different time points. Abbreviations: SD, standard deviation, QoL; quality of life; ADL, activities of daily living; IADL, instrumental ADL.

Direct hospital costs

Health care utilization and costs were available for all 89 patients (**Table 3**). In the total population, the majority of the total mean costs (€23,621 (SD €12,387)) consisted of the cost of radiotherapy (€4,969 (€2,646), hospital admissions (€2,767 (€2,770)), laparotomy and endoscopy (€2,790 (€3,018), resection (€2,662 (€3,238)), consultations (mean €2,045 (SD €823)), and outpatient visits (€1,713 (€843)). The mean direct hospital costs irrespective of treatment modality for frail and fit patients were comparable (frail: €23,822 (SD € 13,216) versus fit: €23,081 (SD €8,286), t-test for unequal variance p=0.82).

Table 3. Health care utilization and costs

	Total population n=89			Population with complete GA: Frail patients n=19			Population with complete GA: Fit patients n=37			Mean diff. €	p Value[a]
	Use, %	Mean, €	SD, €	Use, %	Mean, €	SD, €	Use, %	Mean, €	SD, €		
GA and multidisciplinary meetings	88	479	455	95	634	571	100	509	392	125	0.40
Consultations	100	2045	823	100	2388	1235	100	2272	555	117	0.70
Diagnostics											
Clinical chemistry and hematology	100	341	260	100	478	432	100	330	195	147	0.17
Imaging	98	876	661	95	950	937	97	884	513	67	0.78
Pathology	80	465	333	90	420	360	73	461	337	-41	0.69
Diagnostics	70	571	833	84	758	958	62	576	829	182	0.49
Microbiology	39	54	114	47	105	195	35	27	50	78	0.10
Lab, other	27	4	9	32	4	8	32	2	4	2	0.34

Table 3. Continued

	Total population n=89			Population with complete GA: Frail patients n=19			Population with complete GA: Fit patients n=37			Mean diff. €	p Value[a]
	Use, %	Mean, €	SD, €	Use, %	Mean, €	SD, €	Use, %	Mean, €	SD, €		
Therapy											
Radiotherapy	85	4969	2646	95	5566	2219	95	5512	2196	54	0.93
Chemotherapy	85	265	133	95	254	111	95	296	92	-42	0.17
Expensive drugs	34	191	414	32	109	269	38	225	434	-116	0.22
Resection	58	2662	3238	47	1861	2019	60	2467	2096	-606	0.30
Laparotomy, endoscopy, other	87	2790	3018	90	2529	3167	84	3040	3077	-510	0.57
Blood products	20	131	329	26	258	465	8	83	331	175	0.15
Stents	2	20	136	0	0	0	0	0	0	0	
Stent placement	6	74	414	0	0	0	3	21	127	-21	0.32
Anesthesia and IV placement	89	23	169	5	9	37	3	8	48	1	0.95

Table 3. Continued

	Total population n=89			Population with complete GA: Frail patients n=19			Population with complete GA: Fit patients n=37				
	Use, %	Mean, €	SD, €	Use, %	Mean, €	SD, €	Use, %	Mean, €	SD, €	Mean diff. €	p Value[a]
Hospital stay											
Outpatient visits	91	1713	843	95	1755	830	97	1902	668	-147	0.51
Hospital admissions	67	2767	2770	68	1947	2116	62	2596	2523	-649	0.32
ICU stay	6	470	2372	11	1516	4629	5	297	1472	1219	0.28
ICU consultation outside of ICU	3	3	15	0	0	0	8	6	23	-7	0.09
Other											
Paramedical care	79	254	288	78	261	294	68	235	241	26	0.74
Other care[b]	100	810	677	100	1004	758	100	758	724	736	0.36
No profile[c]	33	65	65	42	51	63	32	101	336	-50	0.38
Total		23621	12387		23822	13216		23081	8286	741	0.82

Use presents the proportion of patients that incurred a certain hospital cost. Direct hospital costs presented as means and standard deviations. [a] P value for comparison between frail and fit patients. [b] Other care includes tariffs for processing of patient material [c] No profile consists of miscellaneous care activities without a distinguishable category. Abbreviations: SD, standard deviation; GA, geriatric assessment; ICU, intensive care unit.

Value

Figure 2 presents the outcomes after one year relative to the incurred hospital costs stratified by frailty status or treatment allocation. After one year, 11% of frail patients reported no decline in physical functioning or QoL and survived compared to 30% of fit patients (**Figure 2A**). Costs between frail and fit patients were similar in the diagnostic, treatment, and follow-up phase, and the majority of costs were incurred in the treatment phase (**Figure 2B**). Direct hospital costs by treatment allocation, irrespective of frailty, show patients completing CRT&S incurred the highest costs (mean €28,014) (**Figure 2D**) compared to the other groups, including patients completing dCRT (mean €16,792) (**Figure 2F**).

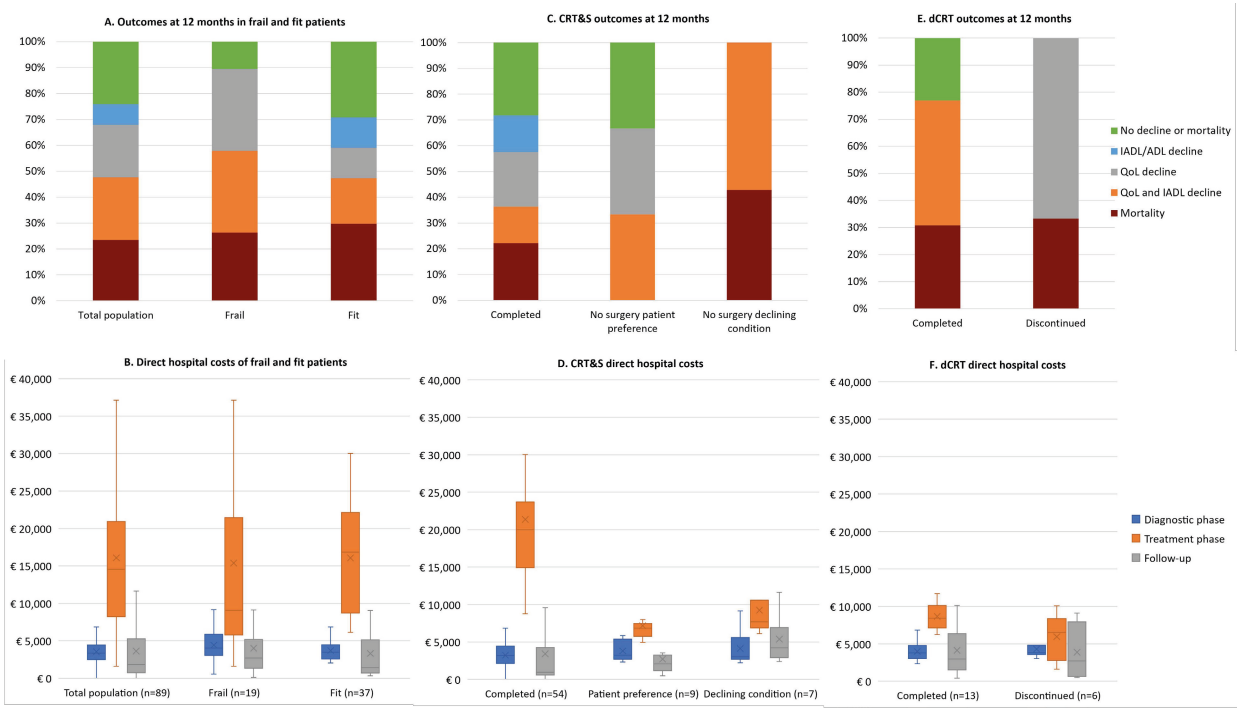

Figure 2. Outcomes and direct hospital costs at 12 months. After one year, patients were classified as not alive or categorized based on their physical functioning (IADL/ADL) and/or QoL relative to baseline. Mortality and costs were available for all patients and missing QoL observations were not included. Direct hospital costs are presented from diagnosis until one year after start treatment categorized by the phase of treatment: diagnostic, treatment, or follow-up. A and B) outcomes and costs for the total population, frail patients, and fit patients; C and D) outcomes and costs for patients with treatment plan CRT&S stratified by acutal treatment received; E and F) Outcomes and costs for patients with treatment plan dCRT stratified according to actual treatment received. Abbreviations CRT&S, chemoradiotherapy and surgery; dCRT, definitive chemoradiotherapy; IADL, instrumental activities of daily living; ADL, activities of daily living; QoL, quality of life.

DISCUSSION

The present study compares the allocation and value of curative oncological treatment in frail and fit older patients with esophageal cancer following a VBHC model. In the dedicated upper-GI care pathway for older patients, 68% of frail patients and 84% of fit patients received the most intensive treatment, CRT&S, as treatment plan. Frail patients discontinued chemotherapy more often compared to fit patients and had lower QoL at 6 months. 11% of frail and 30% of fit patients reported no decline in physical functioning or QoL and survived after one year. Direct hospital costs from diagnosis until one-year after start of treatment were comparable between frail and fit patients. Total hospital costs in the first year consisted largely of costs in the treatment phase relating to surgery and chemoradiotherapy.

This study combines real-world evidence on frailty, treatment allocation, clinical and patient-relevant outcomes, and hospital costs of older patients with esophageal cancer from a VBHC model. This VBHC model supports the optimization of treatment decisions and value of care for future patients in two ways. First, real-world evidence is a powerful tool to inform clinicians and older oncological patients in treatment decision-making. Accurate selection of patients for oncological treatment is required to obtain beneficial treatment outcomes[19, 20]. Second, real-world evidence on the outcomes and costs of care delivery can be used to study the performance of a care pathway over time and compared to other providers. This allows for the identification of opportunities to improve care delivery. Both these applications require the widespread use of GA and sharing of results.

The results in this study should be approached with caution because of the limited availability of GA data. However, the comparison of frail and fit patients points to interesting results. Frail patients altered or discontinue treatment somewhat more frequently than fit patients despite receiving more conservative treatment plans, also when compared to the total population. Irrespective of treatment modality, frail patients discontinue chemotherapy significantly more often than fit patients (26% vs 11%,). Furthermore, 50% of frail and 17% of fit patients discontinued dCRT. Frailty is generally recognized as risk factor for discontinuation of oncological treatment[3], but no studies report on both GA and treatment discontinuation of esophageal cancer treatment except a previous study in this cohort[11]. General rates for discontinuation of esophageal cancer treatment reported are 3-58%[21-27]. A retrospective review by Rahimy et al concludes 72% of patients aged ≥75

years with esophageal cancer with preoperative intent underwent surgery[21], and a multicenter analysis by Bostel et al. of 161 patients with median age 73 years reports 41% needed chemotherapy de-escalation because of toxicity[28]. These proportions of treatment alteration and discontinuation are comparable to this study.

In VBHC, the outcomes relative to the costs of care delivery determine the value of care. In terms of outcomes, similar percentages of frail and fit patients were admitted to the ICU, but frail patients had a longer mean LOS. In addition, 47% of frail and 30% of fit patients were readmitted in the first 6 months. Whereas mortality was comparable, frail patients were more likely to be ADL/IADL dependent during follow-up and have worse QoL at 6 (significant at $p<0.05$) and 12 months. Furthermore, 11% of frail and 30% of fit patients reported no decline in physical functioning or QoL and survived after one year. This points to somewhat worse outcomes for frail patients.

The results on health care utilization and costs shows that the bulk of hospital costs occurs in the treatment phase and were comparable between frail and fit patients. Costs were driven by treatment allocation and highest for patients receiving surgery, which is similar to previous studies[29-31]. Discontinuation was associated with lower hospital costs because of no surgery or fewer courses of chemotherapy and related costs. Thus, frail patients had comparable costs compared to fit patients despite receiving more conservative treatment and discontinuing treatment more often. The disaggregated cost data shows frail patients have lower costs for surgery and chemoradiotherapy but higher costs for ICU stay and other care. Overall, the slightly worse outcomes and comparable costs results in a slightly lower value of care for frail patients.

Our study has both strengths and limitations. A major strength of our study is that we combine real-world data on geriatric assessment, outcomes, and health care utilization to contextualize the treatment of older adults with cancer. Still, several limitations should be kept in mind. First, the data may be confounded by indication. As confirmed by our analyses, geriatric deficits are associated with treatment intent and consequently the outcomes and costs. Therefore, treatment outcomes cannot be compared one-on-one and results should be interpreted with caution. Second, the sample size of this study is limited, due to the limited number of patients presenting with esophageal cancer in our hospital. In addition, GA was not performed in all patients,

further limiting the sample size. Last, while we provide a detailed overview of disaggregated hospital costs from diagnosis until the first year after start of treatment, no data was available on health care utilization outside of the hospital. These data are important to understand the needs of this population and optimize an integrated approach to care after hospital admission.

In this observational study, the value of curative oncological treatment is slightly lower for frail than for fit patients because of slightly worse outcomes and comparable costs. Frail patients receive more conservative treatment but discontinue chemotherapy more often and have lower QoL at 6 months. Direct hospital costs in the first year constitute largely of treatment-related costs. All in all, the utility of the VBHC model of care depends on the availability of sufficient data. Real-world evidence in VBHC can be used to inform treatment decisions and optimization in future patients by sharing results and monitoring performance over time.

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SUPPLEMENTARY MATERIAL

Table S1. Geriatric deficits

Geriatric characteristics	Patients with geriatric assessment n=66	Patients classified as frail n=19	Patients classified as fit n=37	p Value[a]
Geriatric screening				
Abnormal G-8, n (%)	45 (68.2)	15 (78.9)	26 (70.3)	0.54
Abnormal 6CIT, n (%)	4 (6.1)	4 (21.1)	0 (0)	0.01
Abnormal G-8 or 6CIT, n (%)	45 (68.2)	15 (78.9)	26 (70.3)	0.54
Geriatric assessment				
Social status				
Living situation, n(%)				
At home, alone	16 (24.6)	8 (42.1)	4 (10.8)	0.01
At home, with others	49 (75.4)	11 (57.9)	33 (89.2)	
Somatic status				
CCI≥1, n (%)	43 (65.2)	15 (78.9)	22 (59.5)	0.23
Polypharmacy, n (%)	34 (51.5)	15 (78.9)	12 (32.4)	<0.01
Malnutrition, n (%)	39 (60.0)	13 (68.4)	24 (64.9)	1.00
Psychological status				
History of delirium, n (%)	2 (3.2)	2 (10.5)	0 (0)	0.11
History of dementia, n (%)	0 (0)	0 (0)	0 (0)	-
Functional status				
Fall in past 6 months, n (%)	9 (14.1)	6 (31.6)	2 (5.4)	0.01
ADL dependent, n (%)	1 (1.7)	1 (5.3)	0 (0)	0.34
IADL dependent, n (%)	7 (12.5)	7 (36.8)	0 (0)	<0.001

[a] P value for comparison between frail and fit patients. Abbreviations: SD, standard deviation; ADL, activities of daily living; IADL, instrumental activities of daily living. Missing data were not accounted for in proportions. Missing information for patients with geriatric assessment: living situation (n=1), malnutrition (n=1), history delirium (n=3), history of dementia (n=1), fall in past 6 months (n=2), ADL (n=6), IADL (n=10). For n=10 patients, frailty status could not be determined due to missing data.

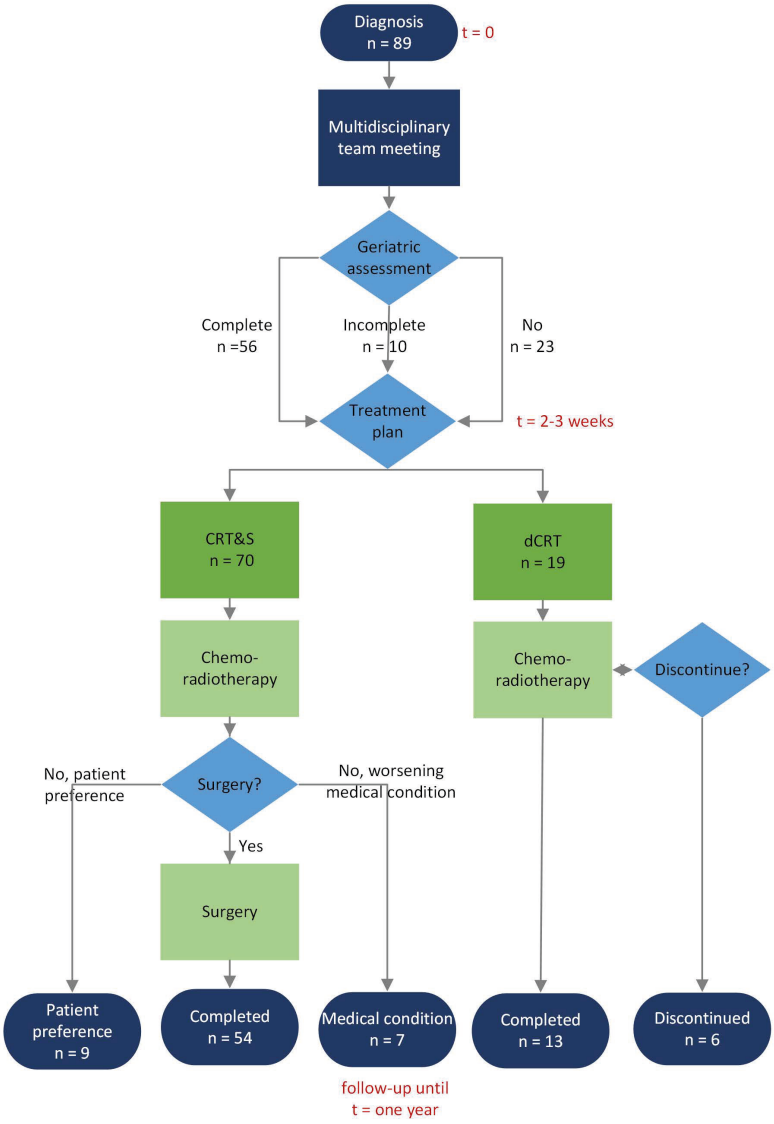

Figure S2. Flow chart of oncological treatment allocation. In the cohort of older patients with esophageal cancer, patients either completed GA, had an incomplete GA, or did not participate in GA. Next, patients received CRT&S or dCRT as curative treatment plan. In case of CRT&S as treatment plan, patients completed treatment as planned or did not undergo surgery because of their own preference of because of their worsening medical condition. In case of dCRT as treatment plan, patients either completed or discontinued treatment. Abbreviations: CRT&S, chemoradiotherapy and surgery; dCRT, definitive chemoradiotherapy.

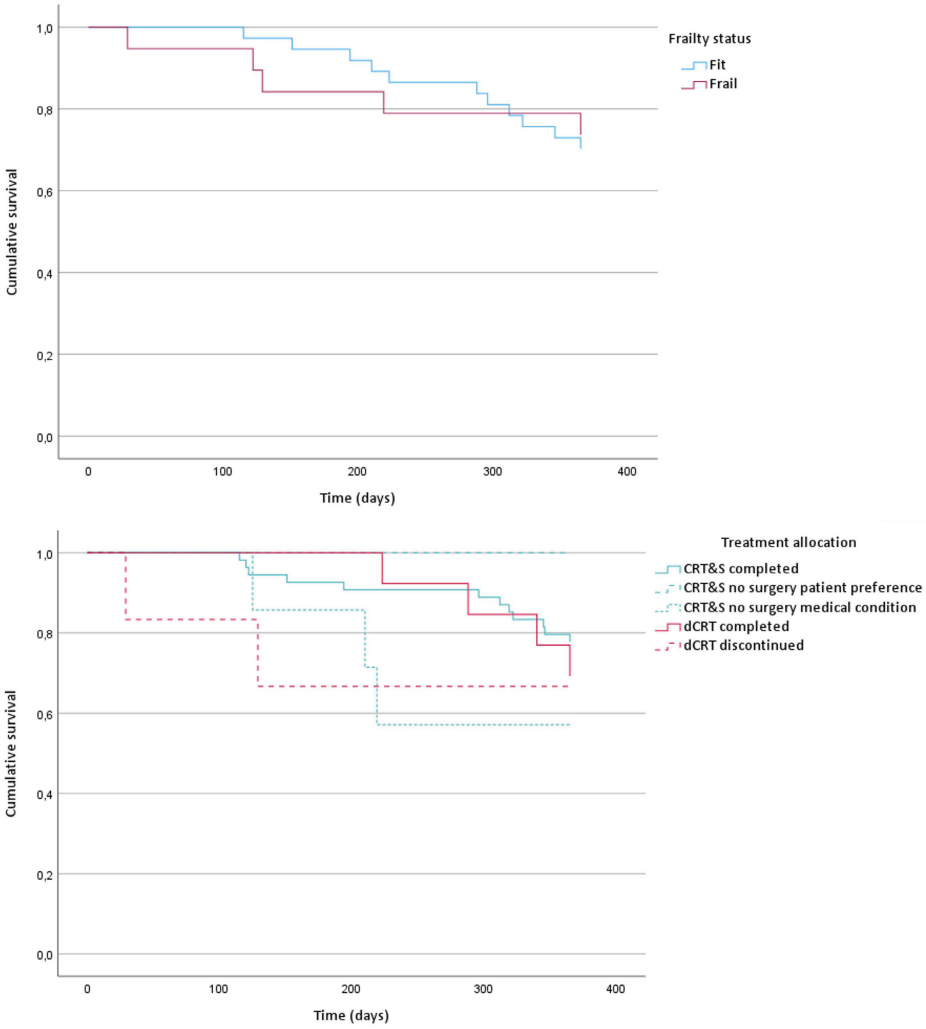

Figure S3. Kaplan Meier curves stratified by a) frailty status, and b) treatment allocation
Abbreviations: CRT&S, chemoradiotherapy and surgery; dCRT, definitive chemoradiotherapy.

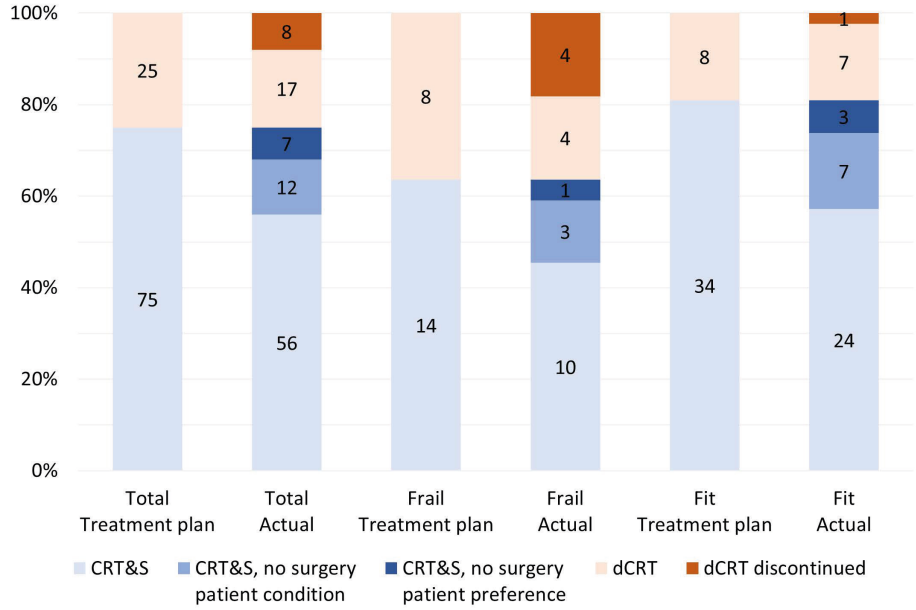

Figure S4. Sensivity analysis of treatment allocation.

Abbreviations: CRT&S, chemoradiotherapy and surgery; dCRT, definitive chemoradiotherapy.

Table S5. Sensitivity analysis of treatment outcomes in an extended sample of patients for who cost data were not available (n=100)

		Population with complete GA		
	Total population n=100	Frail patients n=22	Fit patients n=42	P value[a]
Clinical outcomes				
Radiotherapy fractions, mean (SD)	25.21 (3.6)	24.64 (6.0)	25.33 (2.5)	0.61
Chemotherapy cycles, mean (SD)	5.05 (1.0)	4.64 (1.4)	5.17 (0.9)	0.12
Treatment discontinuation, n (%)				
Radiotherapy	2 (2.1)	2 (9.1)	0 (0)	0.12
Chemotherapy	18 (20.0)	7 (31.8)	6 (14.6)	0.03
Radio- and chemotherapy	2 (2.2)	2 (9.1)	0 (0)	
Surgery prematurely halted	2 (3.6)	1 (10.0)	0 (0)	0.29
Chemotherapy dose reduction	8 (9.1)	3 (13.6)	3 (7.3)	0.41
Chemotherapy dose delayed	12 (13.6)	3 (13.6)	5 (12.2)	1.00
Radio grade 3-5 toxicity	35 (35.0)	10 (45.5)	16 (38.1)	0.60
Chemo grade 3-5 toxicity	55 (55.0)	16 (72.7)	23 (54.8)	0.19
Hematological	32 (58.2)	12 (75.0)	11 (47.8)	0.11
Non-hematological	41 (74.5)	14 (87.5)	17 (73.9)	0.43
Hospital stay				
Readmissions, n (volume %)				
0-6 months	38 (38.0)	12 (55.5)	12 (28.6)	0.12
6-12 months	20 (20.0)	2 (9.)	11 (26.2)	0.27

Table S5. Continued

	Total population n=100	Population with complete GA		P value[a]
		Frail patients n=22	Fit patients n=42	
Mortality				
One year all-cause mortality, n (%)	26 (26.0)	8 (36.4)	11 (26.2)	0.30
Mean survival time, days (SD)	329.60 (77.5)	295.36 (110.0)	336.59 (63.2)	0.13
ADL dependent				
Baseline	1 (1.4)	1 (4.5)	0 (0)	0.34
6 months	3 (7.7)	3 (27.3)	0 (0)	0.02
12 months	1 (3.2)	1 (14.3)	0 (0)	0.25
IADL dependent				
Baseline	8 (12.5)	8 (36.4)	0 (0)	<0.001
6 months	16 (41.0)	8 (72.7)	7 (28.0)	0.02
12 months	10 (33.3)	5 (71.4)	4 (20.0)	0.02

Table S5. Continued

	Total population n=100	Population with complete GA		P value[a]
		Frail patients n=22	Fit patients n=42	
Quality of life	n=45	*n=14*	*n=31*	
Baseline	0.87 (0.18)	0.84 (0.23)	0.88 (0.16)	0.63
	n=32	*n=9*	*n=21*	
6 months	0.78 (0.31)	0.53 (0.12)	0.88 (0.24)	0.02
	n=31	*n=7*	*n=21*	
12 months	0.87 (0.26)	0.64 (0.40)	0.94 (0.16)	0.12
	n=42	*n=12*	*n=27*	
Composite utility score at 12 months	0.64 (0.45)	0.37 (0.13)	0.73 (0.42)	0.03

[a] P value for comparison between frail and fit patients. n reports the number of responses for QoL. Abbreviations: SD, standard deviation; ADL, activities of daily living; IADL, instrumental activities of daily living.