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Research Article

Screening for Frailty in Older Patients With Early-Stage Solid Tumors: A Prospective Longitudinal Evaluation of Three Different Geriatric Tools

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Abstract

Background: Frailty increases the risk of adverse health outcomes and/or dying when exposed to a stressor, and routine frailty assessment is recommended to guide treatment decision. The Balducci frailty criteria (BFC) and Fried frailty criteria (FFC) are commonly used, but these are time consuming. Vulnerable Elders Survey-13 (VES-13) score of ≥7, a simple and resource conserving function-based scoring system, may be used instead. This prospective study evaluates the performance of VES-13 in parallel with BFC and FFC, to identify frailty in elderly patients with early-stage cancer.

Methods: Patients aged ≥70 years with early-stage solid tumors were classified as frail/nonfrail based on BFC (≥1 criteria), FFC (≥3 criteria), and VES-13 (score ≥ 7). All patients were assessed for functional decline and death.

Results: We evaluated 185 patients. FFC had a 17% frailty rate, whereas BFC and VES-13 both had 25%, with poor concordance seen between the three geriatric tools. FFC (hazard ratio = 1.99, $p = .003$) and VES-13 (hazard ratio = 2.81, $p < .001$) strongly discriminated for functional decline, whereas BFC (hazard ratio = 3.29, $p < .001$) had the highest discriminatory rate for deaths. BFC and VES-13 remained prognostic for overall survival in multivariate analysis correcting for age, tumor type, stage, and systemic treatment.

Conclusions: A VES-13 score of ≥7 is a valuable discriminating tool for predicting functional decline or death and can be used as a frailty-screening tool among older cancer patients in centers with limited resources to conduct a comprehensive geriatric assessment.

Keywords: Frailty—Vulnerable Elders Survey-13—Balducci frailty criteria—Fried frailty criteria—Cancers

Aging is associated with a progressive decline in functional reserve of multiple organs and systems. This physiological event occurs at varying degrees in the older population implying different levels of susceptibility. Susceptible patients are at higher risk of a number of negative health outcomes and are more likely to develop treatment complications (1). This is concerning in older cancer patients where age-related changes can affect tolerance to anticancer therapy and can shift the overall risk–benefit ratio of treatment. Early recognition of patients at risk may allow for "risk-adapted" therapy approaches.

Frailty is a clinical state in which there is an increased vulnerability to develop dependency and/or mortality when exposed to a stressor (2). Both cancer and its treatment are significant stressors, making the concept of frailty a relevant issue (3), as frail older cancer patients are at risk of overtreatment. In the geriatric medicine setting, frailty is not considered to be the end point of the continuum of "fit to completely dependent." Rather, it represents a state where an individual may be independent but at high risk of developing disability (4). Frailty is often subtle or asymptomatic (5), is either physical, psychological, or both, and is a dynamic condition that can improve or worsen over time (6). A consensus group consisting of delegates from six major international, European, and U.S. societies has agreed that all persons aged ≥70 years should be screened for frailty for the purpose of optimally managing individuals with physical frailty (6), and a systematic review of observational studies that reported data on the prevalence and/or outcomes of frailty in older cancer patients support routine frailty assessment in older cancer patients to guide treatment decision (7), yet there remains an inconsistent use of this concept in oncology and geriatric medicine (4).

There is still no consensus on the measurement of frailty in older adults with cancer (3). The Balducci frailty criteria (BFC) and Fried frailty criteria (FFC) are two common measures used to identify frail patients (8–10). BFC define frailty based on fulfilling any of the following criteria from the components of comprehensive geriatric assessment (CGA): dependence in one or more activities of daily living (ADL), three or more comorbidities, and/or one or more geriatric syndromes (8,11). FFC are based on the cardiovascular health study (CHS) tool, an instrument developed to identify frailty based on the presence of three or more of the following: unintentional weight loss (≥10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow observed walking speed, and/or low physical activity based on an algorithm that translates patient-reported activities into kilocalories expended (10). A prospective observational study on frailty status has reported these criteria to be predictive of incidental falls, worsening mobilization or ADL function, incidence of hospitalization, and death (10). The Vulnerable Elders Survey-13 (VES-13) is a self-reported function-based scoring system that considers age, self-rated health, physical performance, and functional status (12). It defines a group of patients with a score of ≥3 as vulnerable, which has 4.2 times the risk of death or functional decline over a 2-year period compared with patients with scores <3 (12). Min and colleagues have shown in prospective studies that higher VES-13 scores are associated with a greater predicted probability of death and decline among older patients, both at short- and long-term follow-ups (13,14). This has been proven as a useful screening tool for detecting risk of health deterioration in already vulnerable older patients, with higher VES-13 scores (7–10) reflecting an even much greater risk than those with lower VES-13 scores (3–6) (13). Rodin and Mohile have suggested that VES-13 score of ≥7 could be used to identify frail cancer patients (15).

Our group previously published the results of a prospective observational study that evaluated the role of CHS and VES-13 in predicting CGA abnormalities in a mixed population of older cancer patients with early or advanced disease (16). Because frail patients are more susceptible to functional decline and death (2,8,17,18), we then prospectively evaluated the performance of three geriatric assessment tools in defining frailty by observing the incidence of these two events over time. We were particularly interested in evaluating the performance of VES-13, a simple and resource conserving test, in parallel with two well-established assessment tools for frailty, such as CGA-based BFC and CHS-based FFC. We present the results of these analyses in this article.

Materials and Methods

Patients

Eligible patients aged ≥70 years with early-stage solid tumors referred to Medical Oncology Clinic for systemic adjuvant therapy and/or surveillance/follow-up after surgical resection of the primary tumor were recruited consecutively and classified as frail/nonfrail based on BFC (domains investigated in CGA, tests, and scores used have been described elsewhere) (16), FFC, and VES-13 scores. Patients were classified as frail if they had ≥1 disability in ADL, and/or ≥3 Grade 3 or ≥1 Grade 4 comorbidities at cumulative illness rating scale modified for geriatric patients (CIRS-G), and/or ≥1 geriatric syndrome at CGA; ≥3 abnormalities at CHS; or a score of ≥7 at VES-13. CIRS-G was used to evaluate comorbidities as it provides a more comprehensive assessment, allows severity rating for all the diseases identified, and is more sensitive to individual variation (19). Patients had a follow-up, planned visit or phone interview at a 6-monthly interval. All patients were assessed for functional decline and death.

The protocol was approved by the institutional review board and ethics committee. All patients provided written informed consent before study entry.

Statistical Analysis

The distributions of demographic, clinical, and biologic characteristics of all studied patients were summarized as frequencies and percentage. Continuous variable was reported as median and range of variation. The concordance between the results of the three geriatric tests was evaluated by kappa concordance ($k > 0.7$ was considered concordant).

The outcomes of interest were time to functional event (TFE), overall survival (OS), and event-free survival (EFS). Functional decline or functional event (FE) was defined as either occurrence of dependence—a change from no ADL or instrumental ADL impairment to any ADL or instrumental ADL impairment—or worsening of previous dependence—a loss of ≥2 in instrumental ADL or ≥1 in ADL score. Date and cause of death (tumor related or tumor independent, the latter defined as an event occurring in patients free from cancer recurrence) were documented. Global event (GE) was defined as the occurrence of a FE or death without previous functional loss, whichever occurred first. TFE was defined as the time interval between the date of informed consent and FE. OS was computed as the interval between the date of informed consent and death. EFS was defined as the time interval between the date of informed consent and GE. Observation time of patients alive and/or without functional decline at the last follow-up was censored. Inability to ascertain outcomes 18 months after last contact was defined as loss to follow-up.

The distributions of TFE, EFS, and OS were estimated using the Kaplan–Meier method and compared with the log-rank test. BFC, FFC, and VES-13 (nonfrail vs frail) were investigated for their impact on TFE, EFS, and OS. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using the Cox proportional hazards model. Likelihood ratio test was used to determine the statistical significance of all coefficients.

Demographic and clinical variables were dichotomized and investigated for their impact on OS: age at study entry (<80 vs ≥80 years), site of tumor (breast vs nonbreast), stage of tumor (I–II vs III), and systemic adjuvant therapy (yes vs no). A multivariate Cox regression model evaluated the independent effect of each covariate on OS. Using stepwise selection, we created a model that includes all significant covariates, a probability of .05 was used for both entry

and stay criteria. Median follow-up time was estimated according to the Kaplan–Meier inverse method. Data were analyzed using the statistical software SAS 9.3 (SAS Corporation, Cary, NC).

Results

We identified 192 patients with early-stage cancers from Sandro Pitigliani Medical Oncology Department, between November 2008 and June 2011; 7 (3.6%) patients refused geriatric assessments and were excluded from the study. The remaining 185 patients had frailty assessments and were evaluable for analyses; 2 patients were loss to follow-up after 30 and 49 months, respectively. Major patient and disease characteristics are reported in Table 1. The median age was 77 years, median Eastern Cooperative Oncology Group (ECOG) performance status was 0 (range 0–3), majority were women (80%) and had breast cancer (65%); 81% received adjuvant systemic therapy. The frailty rate was 17% in FFC and 25% for both BFC and VES-13. The three geriatric tools had poor concordance in classifying frailty, with only 9% categorized as frail in all three evaluations (Supplementary Table).

There were 162 events (functional and death) reported at a median follow-up of 55.2 months (interquartile range = 47.3–65.5 months). Details are reported in Table 2.

Table 1. Baseline Patient and Disease Characteristics

Baseline Characteristics	Number	%
Median age, y (range)	77 (70–91)	
Gender		
Male	37	20
Female	148	80
Education, y		
0–4	59	32
5–7	102	55
8–12	15	8
13–18	9	5
ECOG performance status		
0	102	55
1	61	33
2	16	9
3	5	3
Missing	1	—
Primary disease		
Breast	121	65
Colorectal	55	30
Gastric	7	4
Other	2	1
Prior surgery	185	100
Tumor stage		
I	61	33
II	70	38
III	45	24
Missing	9	5
Frailty status at BFC		
Frail	47	25
Nonfrail	138	75
Frailty status at FFC		
Frail	31	17
Nonfrail	154	83
Frailty status at VES-13		
Frail	47	25
Nonfrail	138	75

Note: BFC = Balducci frailty criteria; ECOG = Eastern Cooperative Oncology Group; FFC = Fried frailty criteria; VES-13 = Vulnerable Elders Survey-13.

Functional Events

FE were reported in 114 patients. In 55% of the cases, the FE was related to ADL impairment. Table 3 summarized the distribution of FE at different time points based on baseline frailty status according to BFC, FFC, and VES-13. Based on FFC, median TFE in nonfrail and frail patients was 26.4 and 14.4 months, respectively, HR = 1.99 (95% CI = 1.24–3.19), $p = .003$. From VES-13, TFE was 36.5 months in nonfrail and 12.9 months in frail patients, HR = 2.81 (95% CI = 1.88–4.21), $p < .001$. There was no difference in FE between nonfrail and frail patients with BFC. Kaplan–Meier curves for FE are shown in Figure 1.

Death Events

Overall, 48 patients died during the study period, with date of death ranging from 20 days to 64 months after study enrolment. All three tools showed significant prognostic value for OS (Figure 2) and predicted both early and long-term outcomes (Table 3). Of the three tools, BFC had the highest discriminatory power and FFC the lowest. Median survival times were 57.2 and 63.8 months for frail patients from BFC and VES-13, respectively. Median survival was not reached in all three groups of nonfrail patients. HR for survival (nonfrail vs frail) were 3.29 (95% CI = 1.86–5.80), $p < .001$ for BFC, 2.03 (95% CI = 1.07–3.84), $p = .026$ for FFC, and 2.61 (95% CI = 1.48–4.62), $p = .001$ for VES-13. In multivariate analysis correcting for age, tumor type, stage of disease, and systemic treatment, BFC and VES-13 remained prognostic factors for OS (Table 4).

There were 14 deaths classified as tumor independent (Table 2). Analysis of tumor-independent deaths showed a strongly significant prognostic value for OS for both BFC and VES-13 ($p < .001$; Supplementary Figure).

Global Events

There were 136 GE registered. All three tools predicted both early and long-term EFS (Table 3). Median EFS was 24.2, 25.3, and 26.6 months in nonfrail patients and 18.8, 12.2, and 12.2 months in frail patients at BFC, FFC, and VES-13, respectively. Corresponding HR were 1.50 (95% CI = 1.04–2.17), $p = .029$ for BFC, 2.29 (95% CI = 1.51–3.48), $p < .001$ for FFC, and 2.94 (95% CI = 2.04–4.25), $p < .001$ for VES-13.

Discussion

Frailty confers a greater risk for adverse events or negative health outcomes, that is, falls, disability, toxicity, hospitalization, and mortality when exposed to stressors. Thus, measuring frailty in older adults with cancer may identify those at higher risk for these outcomes. Because frail patients are more susceptible to functional decline and death, we observed the incidence of these events prospectively, comparing the performance of three geriatric assessment tools to define frail versus nonfrail in older cancer patients with early-stage disease.

A systematic review including 21 studies of frailty in persons aged ≥65 years found a 4%–17% prevalence of physical frailty, and this increased further when psychosocial frailty was included (20). Because cancer is a stressor, it is expected to find an even higher frailty rate in older cancer patients. More recently, Handforth and colleagues performed a systematic review of 20 observational studies in older cancer patients (all stages) and reported a frailty prevalence of 6%–86% (7). Our study identified a 17%–25% frailty status. These highlight the major role of geriatric assessment in identifying

Table 2. Distribution of Events Based on Baseline Frailty Status According to BFC, FFC, and VES-13

	BFC		FFC		VES-13	
	Nonfrail	Frail	Nonfrail	Frail	Nonfrail	Frail
Events	$n = 138$	$n = 47$	$n = 154$	$n = 31$	$n = 138$	$n = 47$
Global event, n	95	41	107	29	90	46
Functional event, n	85	29	92	22	76	38
Deaths, n	25	23	35	13	27	21
Tumor-independent deaths, n	3	11	9	5	4	10

Note: BFC = Balducci frailty criteria; FFC = Fried frailty criteria; VES-13 = Vulnerable Elders Survey-13.

Table 3. Cumulative Probability of Functional Decline or Death, Probability of Functional Decline, and Probability of Death at Different Time Points Based on Baseline Frailty Status According to BFC, FFC, and VES-13

	BFC		FFC		VES-13	
	Nonfrail	Frail	Nonfrail	Frail	Nonfrail	Frail
Time Points	$n = 138$ (%)	$n = 47$ (%)	$n = 154$ (%)	$n = 31$ (%)	$n = 138$ (%)	$n = 47$ (%)
Probability of functional event						
1 y	27	21	24	32	21	41
2 y	46	38	41	65	37	68
3 y	56	68	55	82	50	88
4 y	62	76	61	88	56	96
5 y	66	76	65	88	60	96
Probability of death						
1 y	2	15	3	16	3	13
2 y	8	28	11	23	9	23
3 y	11	40	16	32	13	34
4 y	13	40	18	32	15	34
5 y	20	52	26	46	23	48
Probability of global event						
1 y	29	32	27	45	23	49
2 y	49	51	45	74	41	74
3 y	59	81	60	90	55	94
4 y	66	86	67	94	62	98
5 y	71	89	72	94	68	98

Note: BFC = Balducci frailty criteria; FFC = Fried frailty criteria; VES-13 = Vulnerable Elders Survey-13.

frailty even among patients with excellent ECOG performance status (88% of patients had ECOG 0–1).

All three geriatric evaluations predicted the probability of GE even if BFC had lower discriminatory power than FFC and VES-13, as suggested by worse HR. This was related to the failure of BFC to predict a different incidence of FE between frail and non-frail patients. Conversely, FFC and VES-13 strongly discriminated for functional decline between the two subgroups. This might be due to FFC and VES-13 being both mainly focused on detecting functional disabilities, whereas BFC assesses other geriatric domains besides function highlighting that different tools might predict different outcome measures. Although functional impairments can be effectively identified with CGA and CGA has been shown to be predictive of treatment tolerance and mortality (21), there have been no clinical studies directly correlating BFC with functional decline.

Several studies have evaluated the role of frailty-screening methods to predict the outcome in elderly patients with cancer. Although the outcome was intended to predict CGA impairments rather than long-term outcomes in the majority of these studies (3), some studies found these screening methods to be predictive of OS (22,23). In our

study, the three frailty measures significantly predicted OS, with BFC having the highest discriminating power, though the CI of the three tests overlaps.

To our best knowledge, this study represents the first longitudinal evaluation of frailty using VES-13 as a predictive tool for decline or death in older cancer patients. The parallel evaluation with BFC and FFC, two common measures used to identify frail patients, allows calibrating the role of VES-13 in this context. A VES-13 score of ≥7 was used to define frail patients as this has been previously shown to predict a greater risk for death and decline than the ≥3 score in vulnerable patients. At a median follow-up of 4.5 years, a VES-13 score of ≥7 was able to distinguish the frail group of elderly cancer patients who nearly had three times the risk of developing functional decline and 2.6 times the risk of dying from the nonfrail group. These data favorably compare with those obtained with FFC for GE, FE, and OS and with BFS for GE and FE. The study also had a good participating (96%) and retention rates (99%), making follow-up bias less likely.

However, the study has limitations that need to be taken into account. First, the study was based on a single-center cohort of elderly patients with early-stage cancers, limiting generalization.
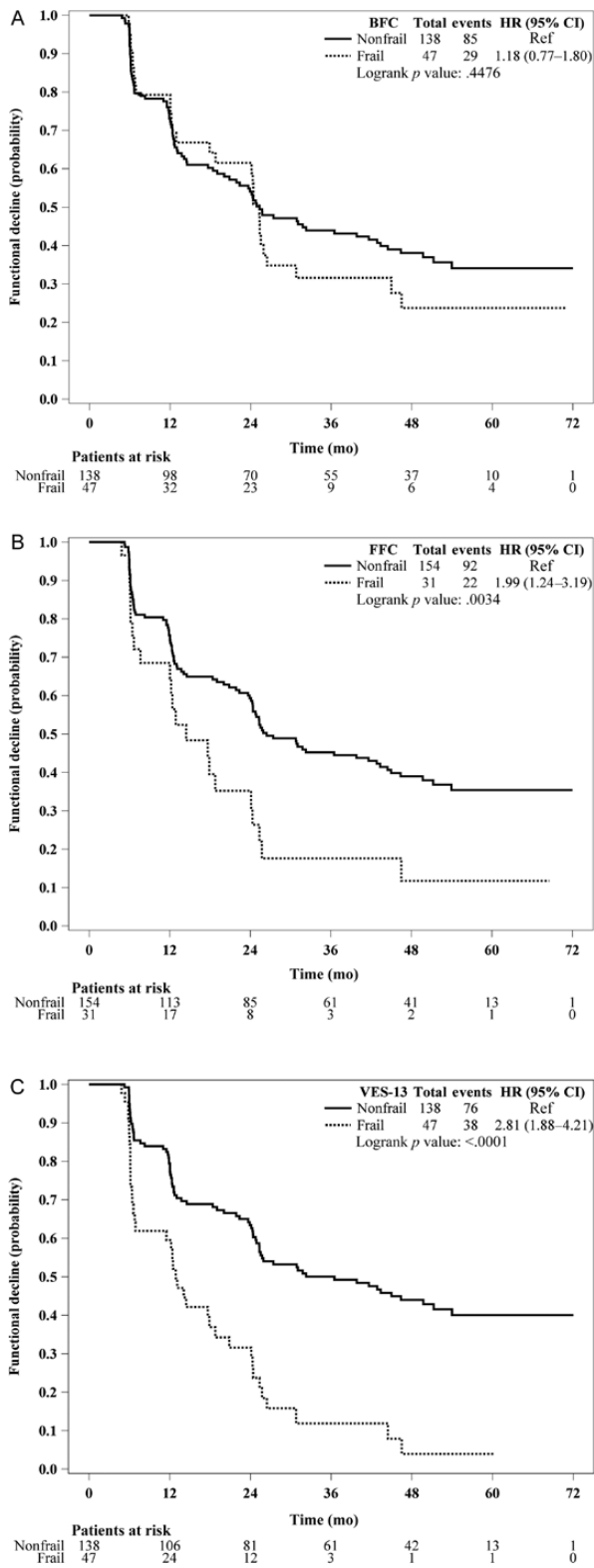
Figure 1. (**A**) Time to functional event (TFE) according to frailty status by Balducci frailty criteria (BFC), (**B**) TFE according to frailty status by Fried frailty criteria (FFC), and (**C**) TFE according to frailty status by Vulnerable Elders Survey-13 (VES-13).

Figure 2. (**A**) Overall survival (OS) according to frailty status by Balducci frailty criteria (BFC), (**B**) OS according to frailty status by Fried frailty criteria (FFC), and (**C**) OS according to frailty status by Vulnerable Elders Survey-13 (VES-13).

Second, the treating oncologists were not blinded to frailty outcome, as they can access the assessment results freely that might lead to interventions to minimize dea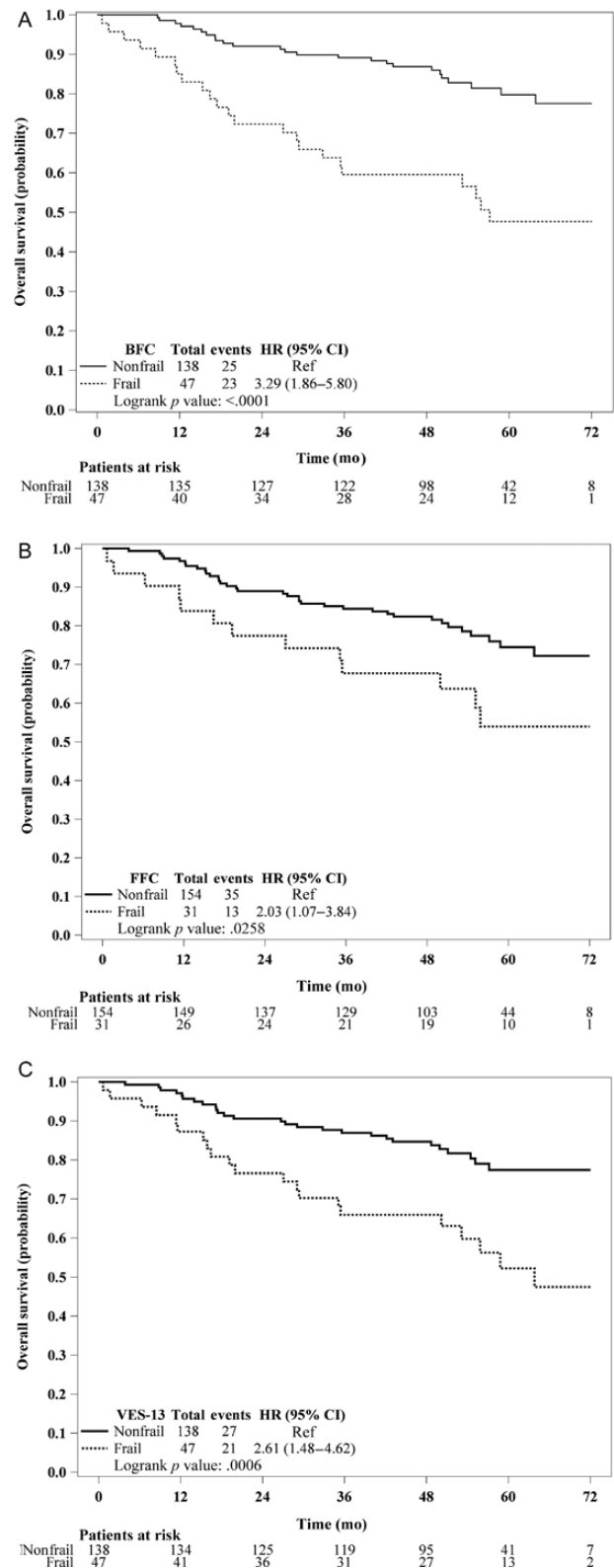th or decline in more vulnerable populations or might expose to the possibility of treatment bias. Third, the performance of the screening tests might be different in various tumor subtypes. However, the study sample size precluded

Table 4. Predictive Models for OS According to Age, Tumor Type, Tumor Stage, Adjuvant Systemic Therapy, and Geriatric Tools

	Unadjusted Model		Adjusted Model	
Characteristics	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (y)				
70–79	1 (ref.)	.003	[a]	
≥80	2.37 (1.34–4.19)			
Tumor type				
Breast	1 (ref.)	.001	1 (ref.)	<.001
Others	2.55 (1.44–4.50)		3.30 (1.84–5.91)	
Tumor stage				
I–II	1 (ref.)	.024	[a]	
III	1.96 (1.09–3.52)			
Adjuvant systemic therapy				
Yes	1 (ref.)	.001	[a]	
No	2.68 (1.52–4.73)			
BFC				
Nonfrail	1 (ref.)	<.001	1 (ref.)	.001
Frail	3.29 (1.86–5.80)		2.92 (1.56–5.46)	
FFC				
Nonfrail	1 (ref.)	.036	[a]	
Frail	2.03 (1.08–3.85)			
VES-13				
Nonfrail	1 (ref.)	.001	1 (ref.)	.018
Frail	2.61 (1.48–4.62)		2.15 (1.14–4.05)	

Note: BFC = Balducci frailty criteria; CI = confidence interval; FFC = Fried frailty criteria; HR = hazard ratio; OS = overall survival; ref. = reference; VES-13 = Vulnerable Elders Survey-13.

[a]Not included in the model (*p* > .05).

us from conducting subgroup analysis. At last, the multivariate analysis for OS included both VES-13 and age. Because VES-13 includes age as a rating factor, this could potentially understate the association between the outcome and VES-13 score.

Despite these limitations, a VES-13 score of ≥7 is a valuable discriminating tool for predicting functional decline. Due to its good prognostic value for OS, it can be used as a screening tool for frailty among older cancer patients, especially in centers, where resources for conducting a comprehensive assessment are limited and a two-step screening approach might be considered, that is, screening with VES-13 and followed by CGA, if abnormal. In centers, where comprehensive evaluation of the health status of cancer patients is routinely done, BFC should be used to detect frailty instead. More importantly, a positive screening test for frailty must not be used to exclude frail patients from a potentially curative treatment. Even with the limitation of the small number of events reported, survival analysis for tumor-independent events (an analysis that is free from the impact of tumor on the risk of dying) showed that 70% of frail patients were alive at 5 years from study entry.

In this study, we did not investigate whether a VES-13 score of ≥7 predicts for higher treatment-related toxicity. However, Luciani and colleagues have previously shown that a standard VES-13 score of ≥3 can identify vulnerable patients at risk for Grades 3–4 hematological and nonhematological toxicities ([24]).

Frailty exposes older patients to adverse outcomes. Identifying frailty in elderly cancer patients may allow for a risk-adapted approach that includes personalized treatments, close monitoring, and proactive management of toxicities. VES-13 might be considered a valuable instrument for this purpose.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology: Series A* online.

Conflict of Interest

The authors have declared no conflicts of interest.

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