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Determinants of health-related quality of life in elderly ovarian cancer patients: The role of frailty and dependence

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HIGHLIGHTS

- Frailty and dependence are main determinants of deterioration of HRQOL in elderly ovarian cancer patients.
- Age is not a significant determinant of HRQOL in our population.
- Functionality is a better determinant of HRQOL in our patients than age or clinical and sociodemographic factors.

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ABSTRACT

Objective. To investigate the impact of frailty and dependence on health-related quality of life (HRQOL) in elderly women diagnosed with epithelial ovarian cancer (EOC).

Methods. Data was gathered from a prospectively collected data biobank, OncoLifeS (Oncological Life Study) at the University Medical Center of Groningen. Women with a diagnosis of EOC, ≥65 years of age, with baseline assessment available from January 2016 to May 2018 were included. HRQOL was determined using the EORTC QLQ-C30 yielding scores on Global Health Status, five functional scales, three symptom scales, and six single items. The summary score was also calculated. Frailty was measured using the Groningen Frailty Indicator (GFI), and dependence using the Instrumental Activities of Daily Living (IADL). To evaluate the impact of frailty and dependence on HRQOL, linear regression was performed. Analyses were adjusted for age and tumor stage.

Results. 84 patients were included. Median age was 71 years (IQR: 68–75), 78% had advanced stage and 81% serous histology. Overall, the median global health status was 67 (IQR: 50–83). HRQOL scales with lowest scores were: role functioning (median: 66.7; IQR: 33–100), fatigue (median: 33.3; IQR: 22–56) and insomnia (median: 33.3; IQR: 0–67). Being frail was associated with worse functioning on all HRQOL scales and higher symptom scores ($p = .001$). Conversely, being independent was associated with better functioning on all HRQOL scales and lower symptom scores. These associations remained significant after adjusting for age and tumor stage.

Conclusion. In women ≥65 years, diagnosed with EOC, frailty and dependence are associated to reduced HRQOL. These associations remain significant adjusting for age and stage.

1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy and associated with high morbidity [1]. The risk of developing EOC increases with age, with only 10–15% of cases diagnosed before menopause [2]. With increasing age, there is an increased prevalence of comorbid conditions, frailty, dependence and other functional limitations [3]. Given these factors, impairments in health-related quality of life (HRQOL) domains are expected.

HRQOL is particularly important in older patients. In shared decision making, elderly patients are less willing to trade increased survival duration for reductions in HRQOL [4–6]. This fact led the EORTC elderly task force to suggest that HRQOL might be an appropriate outcome for elderly-specific trials [7]. However, to better understand HRQOL results,

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the factors related to this outcome in elderly patients must be addressed. Frailty at baseline is associated with worse health-related and self-perceived quality of life in general cancer population [8]. In this study, differences in HRQOL between older people with and without a cancer diagnosis are explained to a large extent by differences in frailty levels, emphasizing the importance of assessing frailty during the care for oncological patients. In another study with 768 patients with cancer, aged ≥65 years patients reporting decreased ability to participate in daily activities revealed poorer HRQOL [9]. Data on the characteristics of elderly EOC patients especially regarding HRQOL is scarce. The majority of available studies focuses on the effects of age alone [10–13].

The aim of this study was to assess determinants of HRQOL in the elderly EOC population, with special focus on the impact of frailty and IADL dependence on HRQOL.

2. Methods

2.1. Study design

For this analysis, data from OncoLifeS were used. OncoLifeS is a data biobank at the University Medical Center of Groningen (UMCG) in which patients with a diagnosis of cancer are asked for informed consent to use their clinical data and biomaterials for research. After informed consent, patients are requested to complete a baseline assessment. This assessment includes questionnaires regarding marital status, education, living conditions, dependence, frailty and HRQOL. Patients could complete this questionnaire either online or on paper. This baseline assessment was performed following diagnosis but prior to treatment. All collected data from questionnaires is stored in the data biobank together with selected clinical data. Between 2016 and May 2018, 500 women with gynecological cancer provided informed consent for participation in OncoLifeS, of which 207 women were diagnosed with ovarian cancer during this period and these patients were considered for inclusion in this study.

2.2. Eligible patients

The following patients were included for this analysis: Women diagnosed with any stage epithelial ovarian cancer and ≥65 years of age at diagnosis. Patients without available clinical baseline data and baseline questionnaires assessment were excluded (see Fig. 1).

2.3. Quality of life assessment

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC) QLQ-C30 was used to assess HRQOL [14]. The questionnaire includes a global health status scale, five functional scales, three symptom scales, and six single items. In total, 15 scales are evaluated. All scales, except for the global health status scale and the scale related to financial difficulties can be summarized into one score, the summary score [15,16]. Higher scores on the functional scales and global health status indicate better functioning whereas higher scores in symptoms scales indicates higher symptom burden [17].

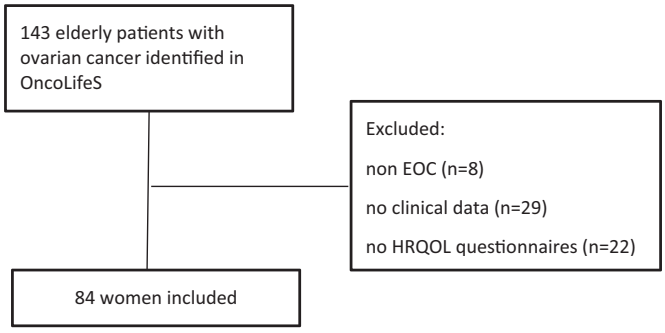

Fig. 1. Flowchart of the in- and exclusion process.

2.4. Dependence and frailty

Dependence was measured using the Lawton and Brody Instrumental Activities of Daily Life (IADL) scale [18]. This questionnaire assesses a person's capacity to perform tasks and activities associated with an independent lifestyle. There are eight domains of function measured by the IADL scale (ability to use the telephone, shopping, food preparation, housekeeping, transportation, ability to handle finances, laundry and responsibility for own medication). For the IADL score, impairment in at least one IADL domain was classified as dependence whether having no impairments was classified as independence [18].

Frailty was measured using the Groningen Frailty Indicator (GFI), a validated tool to determine a person's level of frailty, which includes 15 items on physical, cognitive and psychosocial functional domains [19]. The questions yield information on mobility, physical fitness, vision, hearing, nourishment, morbidity, cognition and psychosocial aspects. Psychometric studies exploring the overall internal consistency of the GFI demonstrate moderate internal consistency (Cronbach's α varied from 0.68 to 0.73), and good construct and discriminant validity [20,21]. As such, it is one of the most frequently used frailty screening methods in geriatric oncology [22]. A GFI score was rated as 'increased vulnerability/frailty' when the total score was equal or >4, a cut-off that has been derived from previous research [20].

2.5. Clinical and sociodemographic data

The following clinical, tumor and sociodemographic data were derived from the data biobank: age, FIGO stage, histology, grade, having a partner, having children, living alone, education level, and treatment received. For the analyses, stage was classified as early (FIGO stage I and II) or advanced (FIGO stage III and IV). Having a partner consisted of those married or cohabiting. Education was categorized into three levels (high = university or higher education; medium = vocational training; low = primary or secondary education or less) [23].

2.6. Statistical analysis

The EORTC QLQ-C30 scales were linearly transformed to continuous scales (0 to 100) according to the scoring EORTC scoring procedures [17]. Missing data were imputed, using linear regression for continuous variables in line with the EORTC instructions [17]. Totals for all scales and the summary score were calculated. Descriptive statistics were used to report population characteristics and the HRQOL outcomes. Categorical variables were presented as numbers and percentages and continuous variables were described using the median and the interquartile range (IRQ). Age, FIGO stage, having a partner, having children, living alone, education level, were considered potential confounders. Linear regression was performed to evaluate the impact of frailty, dependence and the potential confounders on HRQOL. In a next step, the impact of frailty and dependence on HRQOL was evaluated by adjusting the models for age and tumor stage. For all models, tolerance was >0.02, revealing that multicollinearity was not a concern. Since multiple testing was performed, a stricter significance level of $p < .01$ was used. To perform this analysis, SPSS software version 23.0 was used.

3. Results

3.1. Patients included

We identified 143 potentially eligible ovarian patients ≥65 years of age in the OncoLifeS database. After exclusion of patients with non-epithelial ovarian cancer (n = 8), patients without clinical data

recorded in the biobank (n = 29), and patients who did not respond the baseline assessment (n = 22), 84 patients remained for this analysis (Fig. 1).

3.2. Population characteristics

The median age was 71 years (IQR: 68–75) and the majority of patients had advanced stage disease (78%) and serous histology (81%). Seventy-three percent of the women had a partner, 88% had children and a minority lived alone (36%). Most patients had a low educational level (60%). Most patients were classified as independent on the IADL scale (58%). The GFI score revealed that 37% of women were frail. Clinical and sociodemographic characteristics are described in Table 1.

3.3. HRQOL outcome

Overall, the median global health status score was 67 (IQR: 50–83) (Table 2). For the functional scales, role functioning was the component with the lowest score, median 67 (IQR: 33–100), in contrast to cognitive functioning, the scale with highest score (median: 100, IQR: 83–100). On the symptom scales, fatigue and insomnia were the scales with the greatest impairments in HRQOL with median scores of 33 for both (IQR: 22–56 and IQR: 0–67, respectively). The summary score was 82 (IQR: 64–90).

Table 1
Description of the included population (n (%), unless specified otherwise).

Characteristics	Population (n = 84)
Age [median (IQR)]	71 (68–75)
FIGO stage	
I	12 (14.8)
II	5 (6.1)
III	54 (66.7)
IV	8 (11.1)
Unknown	1 (1.2)
Histology	
Serous	68 (81)
Endometrioid	5 (6)
Clear cell	7 (8.3)
Other	4 (4.8)
Grade	
I	3 (3.6)
II	2 (2.4)
III	61 (72.6)
Unknown	18 (21.4)
IADL score	
Dependent (score < 7)	35 (41.7)
Independent (score ≥ 7)	49 (58.3)
GFI score	
No increased frailty (score < 4)	52 (62.7)
Frail (score ≥ 4)	31 (37.3)
Having a partner	
Yes	61 (73.5)
No	22 (26.5)
Having children	
Yes	74 (88.1)
No	10 (11.9)
Live alone	
Yes	26 (35.6)
No	47 (64.4)
Education level	
Low	46 (59.7)
Medium	30 (39)
High	1 (1.3)
Treatment received	
Surgery alone	17 (20.23%)
Chemotherapy alone	10 (11.9%)
Surgery + chemotherapy[a]	57 (67.85%)

[a] Not necessarily in this order.

Table 2
HRQOL outcome.

HRQOL scales	Population	
	N	Median (IQR)
Global health status	84	66.7 (50–83)
Physical functioning	80	86.7 (73–93)
Role functioning	84	66.7 (33−100)
Emotional functioning	84	75 (58–83)
Cognitive functioning	84	100 (83–100)
Social functioning	83	83.3 (67–100)
Fatigue	84	33.3 (22–56)
Nausea and vomiting	84	0 (0–17)
Pain	84	16.7 (0–50)
Dyspnea	84	0 (0−33)
Insomnia	84	33.3 (0–67)
Appetite loss	84	0 (0–33)
Constipation	84	0 (0–33)
Diarrhea	84	0 (0–33)
Financial difficulties	83	0 (0–0)
Summary score	84	82.3 (64–90)

3.4. Determinants of HRQOL

IADL and GFI were significantly associated with global health status scale and summary score, but not associated with the financial difficulties scale. Being independent was associated with higher scores in global health status and summary score, while being frail was associated with lower scores. None of the potential confounders analyzed were associated with the HRQOL scales. The results are summarized in Table 3.

Further investigation of the relationship between IADL and GFI with HRQOL was performed, assessing each individual component that comprises the summary score (Fig. 2). IADL and GFI were significantly related to all EORTC functional and symptom scales, except for financial difficulties. Being dependent and frail was associated with lower functioning and higher symptom scores.

Adjusted for age (model 1), stage (model 2), and for both (model 3), being frail continued to be associated with poor HRQOL in both global health status and in the summary score (Table 4). GFI, independent of age or stage, predicted 15% of the variance in global health status and 12% in summary score. Similarly, being dependent, when adjusted for the same covariates, remained associated with lower HRQOL. When adjusted for age and stage, IADL predicted 8% of the variance in global health status and 29% of the variance in summary score (Table 4). Age-adjusted scores with the association of IADL and GFI for all EORTC scales are provided in Supplementary materials (S1). Finally, IADL and GFI were analyzed combined in one model, adjusting for age and stage. For the global health status, the model accounted for 17% of the variance in this scale. IADL and GFI were both significant in the model. For the summary score scale, only IADL had significant impact in the model. This model accounted for 30% of the variance in summary score.

4. Discussion

In our elderly population of patients ≥65 years of age, recently diagnosed with epithelial ovarian cancer, being dependent and frail were strongly associated with reduced HRQOL as measured using the (EORTC) QLQ-C30. This association remained significant after adjusting for age and tumor stage. Other variables considered in these analyses were not associated with HRQOL. To our knowledge, this is the first study to explore the association of frailty and dependence with HRQOL in a population of elderly ovarian cancer patients.

Comparing the HRQOL scores from our EOC population to a general female Dutch population [24], our population reported more impairment in role functioning, emotional functioning and global health status. These differences of >10 points in the mean scores are considered clinically significant. [25]. The symptoms scales fatigue and insomnia

Table 3
Potential determinants of HRQOL.[a]

	Global health status N = 84		Summary score N = 79		Financial difficulties N = 84	
	β (95% CI)	p-Value	β (95% CI)	p-Value	β (95% CI)	p-Value
Independent (IADL ≥ 7)	0.316 (0.108 to 0.525)	0.003	0.556 (0.369 to 0.743)	<0.001	−0.181 (−0.397 to 0.036)	0.101
Frail (GFI ≥ 4)	−0.405 (−0.607 to −0.202)	<0.001	−0.373 (−0.583 to −0.164)	0.001	0.118 (−0.103 to 0.339)	0.292
Age	−0.028 (−0.247 to 0.192)	0.803	0.014 (−0.207 to 0.235)	0.897	−0.041 (−0.261 to 0.178)	0.71
Higher FIGO stage	−0.058 (−0.285 to 0.169)	0.611	−0.2 (−0.43 to −0.03)	0.087	0.001 (−0.226 to 0.227)	0.995
Having a partner	0.025 (−0.197 to 0.247)	0.822	0.091 (−0.135 to 0.317)	0.426	−0.057 (−0.279 to 0.165)	0.612
Having children	0.055 (−0.164 to 0.275)	0.618	−0.022 (−0.252 to 0.208)	0.852	−0.06 (−0.279 to 0.159)	0.587
Living alone	−0.088 (−0.31 to 0.133)	0.43	0.06 to (−0.17 to 0.29)	0.606	0.039 (−0.157 to 0.234)	0.694
Higher education	−0.035 (−0.254 to 0.184)	0.753	0.041 (−0.195 to 0.277)	0.731	0.066 (−0.17 to 0.303)	0.578

[a] This table reports the regression coefficients (β) and its 95% confidence interval and the p-value for the model assessing the association between the HRQOL scales and each independent variable.

had higher scores in our population. The general Dutch population group was, however, younger than our group (mean age 50.8, SD ± 15.5). Nonetheless, in keeping with our findings, fatigue is a well-described symptom in OC patients. It is outlined as the most frequent symptom in those patients, with substantial impact in HRQOL [26,27]. Besides fatigue, insomnia was also commonly reported, with similar rates to a prospective longitudinal study that investigated sleep disturbance in a younger ovarian cancer population (mean age: 60, SD: 12.46) [28].

It can be concluded that dependency and frailty were significant determinants of HRQOL in elderly EOC patients. From the other analyzed variables, stage was not a significant determinant of HRQOL, which is in line with other reports in EOC populations [11,12]. Additionally, having a partner, having children and living alone were not associated with HRQOL. In a prospective cohort trial in elderly patients with cancer aged ≥65 years, features of social support were also not significantly related with HRQOL [27], although in younger patients, social support and network seems to play an important role [29,30]. However, we acknowledge that social support and network was not sufficiently addressed in this study, as we did not include specific tools to adequately measure this feature, which limits our ability to further evaluate this aspect.

Age is not a significant determinant of HRQOL in our population. However, IADL and GFI have substantial impact on HRQOL. These observations reinforce that chronological age does not equal functional status. Moreover, functional status is a better determinant of HRQOL in elderly population than age. When one model including both GFI and IADL, adjusted for age and stage was explored, both clinical scales remained significant in the model for the global health status. However, for the summary score, only IADL was significant in the model. This observation suggests that being dependent is a determinant with higher impact in functional and symptoms domains of HRQOL than being frail. Nevertheless, on the global health status scale, in which patients are asked to rate their overall health and quality of life, frailty and dependence have significant impact. Financial difficulties is the only scale that IADL and GFI were not significantly associated to, which could be related with reports that this scale is less affected in older patients [31].

A pooled analysis of randomized controlled trials investigating the effect of age on QOL in cancer populations, reported that many elderly patients are excluded from certain standard treatments given their age [31]. In addition, they are less likely to receive standard treatment and they receive less aggressive therapy when treated, even in the absence of comorbidity. Regardless, evidence suggests that elderly ovarian cancer patients can derive similar survival benefits to younger patients from aggressive treatments [32]. The strong relationship between frailty and dependence and HRQOL supports the recent discussion that judgment of fitness for treatment would ideally incorporate a patient's HRQOL and a geriatric assessment, rather than age alone since elderly patients are a heterogeneous group.

Recently, a pooled analysis on three phase II studies in elderly EOC patients reported that IADL is an independent prognostic factor for overall survival [33]. In another study, the ability to complete four cycles of chemotherapy was associated to independence in IADL score and higher HRQOL score. Moreover, HRQOL improved over time with cumulative chemotherapy cycles [34]. With our finding that higher IADL is associated with higher HRQOL, it can be inferred that independent

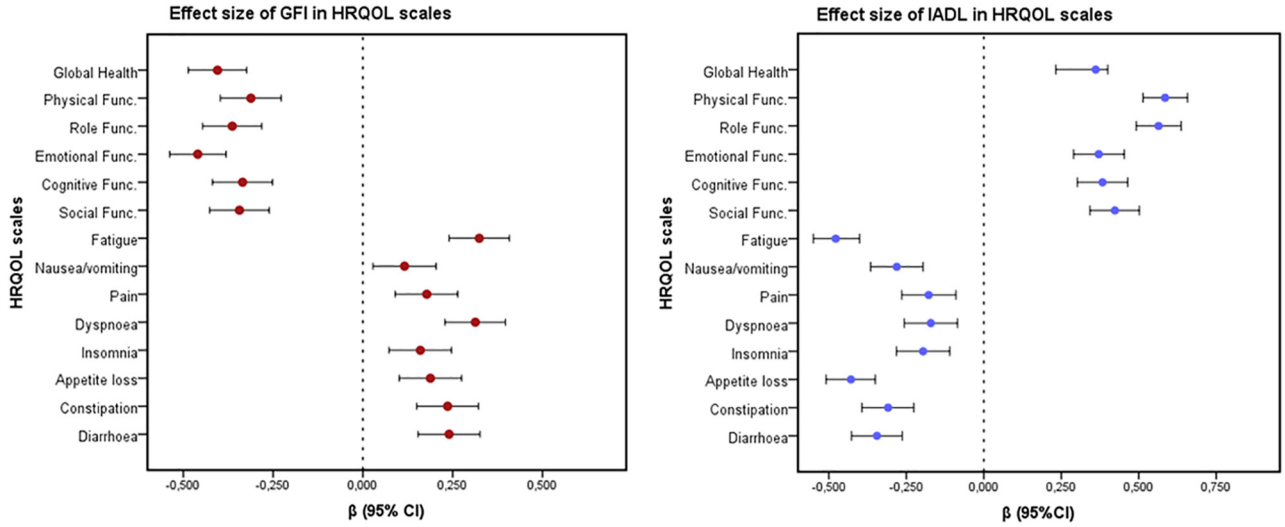

Fig. 2. Impact of being frail and independent in each HRQOL scale. The effect size is demonstrated by the regression coefficient (β) and its confidence interval.

Table 4
Multivariate Analysis for impact of GFI and IADL in global health status and summary score.[a]

	Global health status			Summary score		
	β (95% CI)	p-Value	Adjusted R^2	β (95% CI)	p-Value	Adjusted R^2
IADL						
Univariate						
IADL	0.316 (0.108 to 0.525)	0.003	0.089	0.556 (0.369 to 0.743)	<0.001	0.304
Model 1						
IADL	0.317 (0.234 to 0.401)	<0.001	0.097	0.564 (0.375 to 0.752)	<0.001	0.3
Age	0.009 (−0.075 to 0.093)			0.071 (−0.113 to 0.256)		
Model 2						
IADL	0.294 (0.206 to 0.383)	<0.001	0.082	0.532 (0.332 to 0.731)	<0.001	0.29
Stage	0.001 (−0.088 to 0.089)			−0.101 (−0.302 to 0.099)		
Model 3						
IADL	0.296 (0.208 to 0.385)	<0.001	0.080	0.538 (0.338 to 0.739)	<0.001	0.289
Age	0.024 (−0.063 to 0.111)			0.092 (−0.101 to 0.285)		
Stage	−0.01 (−0.09 to 0.088)			−0.108 (−0.309 to 0.093)		
GFI						
Univariate						
GFI	−0.405 (−0.607 to −0.202)	<0.001	0.153	−0.373 (−0.583 to −0.164)	0.001	0.131
Model 1						
GFI	−0.405 (−0.486 to −0.324)	<0.001	0.16	−0.375 (−0.586 to −0.164)	0.003	0.121
Age	−0.001 (−0.082 to 0.08)			0.042 (−0.166 to 0.251)		
Model 2						
GFI	−0.399 (−0.484 to −0.314)	<0.001	0.15	−0.338 (−0.56 to −0.115)	0.003	0.124
Stage	0.027 (−0.059 to 0.112)			−0.128 (−0.352 to 0.095)		
Model 3						
GFI	−0.399 (−0.484 to −0.314)	<0.001	0.148	−0.339 (−0.562 to −0.115)	0.008	0.116
Age	0.004 (−0.079 to 0.087)			0.06 (−0.115 to 0.275)		
Stage	0.026 (−0.059 to 0.112)			−0.133 (−0.359 to 0.092)		
IADL + GFI						
Age	0.017 (−0.066 to 0.09)			1.63 (−1.83 to 5.1)		
Stage	0.044 (−0.042 to 0.129)	<0.001	0.167	−1.58 (−5.23 to 2.07)	<0.001	0.298
IADL	0.161 (0.069 to 0.254)			8.66 (4.73 to 12.58)		
GFI	−0.334 (−0.426 to −0.241)			−2.67 (−6.59 to 1.25)		

[a] The regression coefficient (β) and its 95% confidence interval is presented for each predictor entered in the model. The p-value and Adjusted R^2 are presented for the model. The impact of having a higher IADL (scored as independent), higher GFI (scored as frail), higher age and higher stage is assessed.

patients have better HRQOL, not only by being more functional but also by being able to go further on treatment. In addition, frailty was associated with decreased overall survival and higher post-operative morbidity and mortality in a retrospective cohort study with 535 advanced EOC patients [35]. These studies emphasize the importance of a geriatric assessment to determine a patient's functional abilities and guide specific efforts to HRQOL and survival improvement [36]. For EOC elderly patients, functional assessment retains an importance mainly in advanced stage disease, since it is still controversial which patients should undergo primary surgery or neoadjuvant chemotherapy. Incorporating the geriatric assessment could add in the decision making, given its impact on their clinical outcome. Unlike age, frailty and dependence may be altered by interventions, which can improve both functionality and the cancer outcome [35]. A randomized trial showed that interventions in the care of elderly cancer patients based on geriatric assessment results lead to an improved functional status as well as survival benefit [37]. However, a phase III trial revealed that a geriatric assessment-based allocation of chemotherapy did not improve the survival outcomes of elderly patients with advanced non-small cell lung cancer [38], indicating that further research is needed to evaluate the impact of geriatric assessment in survival.

The EORTC elderly task force position paper advises the need of a comprehensive geriatric assessment for all older cancer patients. However, aware of the fact that the full assessment might not be feasible (due to time and availability of professionals), a two-step approach is suggested, commencing with a shorter screening tool. One of the screening tools suggested in this paper is the GFI [7]. Besides the EORTC, the International Society of Geriatric Oncology has also suggested the use of the GFI as a reliable screening method in oncological setting [39]. This tool was already tested in an elderly population with solid malignant tumors and was able to predict most of the EORTC QLQ-C30 scales [40]. We now demonstrate that this tool can also significantly predict HRQOL outcome in elderly ovarian cancer patients.

In this analysis, we included patients who underwent surgery, chemotherapy and a combined therapy. Unfortunately, HRQOL data was only available at baseline, therefore it was not possible to measure the influence of different treatment modalities on HRQoL. Analyzing if there is a group of patients who are pre-frail or at high risk of frailty and their HRQOL could also be an important information, but since we do not have retrospective data, this analysis could not be derived. Additionally, comorbidities were not included in our potential confounders. Further research should include an investigation of all components of a geriatric assessment and its impact on HRQOL. The role of interventions based on the geriatric assessment and whether those interventions can change clinical and HRQOL outcomes should also be explored.

5. Conclusion

In summary, IADL score and GFI score are significant determinants of HRQOL in elderly EOC patients. Importantly, we conclude that functional status is a better determinant of HRQOL than age. Besides, functional status has impact on clinical outcomes and can be an important aspect for decision making.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.249.

Conflict of interests statement

The authors were asked to disclose potential conflict of interest information and declare that there are no conflicts of interest.

Authors contributions

Study Concepts and design: GH de Bock, F Nunes de Arruda.
Data Acquisition: MHM Oonk, MJE Mourits.
Data Analysis and Interpretation: F Nunes de Arruda, MHM Oonk, M Jalving, GH de Bock.
Statistical Analysis: F Nunes de Arruda, GH de Bock.
Manuscript Preparation: F Nunes de Arruda.
Manuscript Review: MHM Oonk, MJE Mourits, P de Graeff, M Jalving, GH de Bock.

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