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The role of preoperative frailty assessment in patients affected by gynecological cancer: a narrative review

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ABSTRACT

The following article aims to highlight the importance of the assessment of frailty in patients affected by gynecological cancer and to discuss current data available on scores commonly used to predict adverse postoperative outcomes and overall survival in this group of patients.

A narrative review was performed in Medline (PubMed) and Embase database until February 28, 2022. This study includes randomized and observational studies about patients undergoing non-emergent surgery for gynecological malignancies with preoperative frailty assessment.

Fourteen studies, for a total of 85957 women, were included. The Modified Frailty Index (mFI) is the most commonly used tool for definition of frail patient. Results highlighted that frail patients had lower disease-free survival rates and overall survival rates than non-frail patients. Additionally, frail patients were more at risk of developing 30-day postoperative complications, non-home discharge and Intensive Care Unit admission than the other group.

In gynecologic oncology, the assessment of the state of women's frailty is fundamental to predict adverse outcomes and to customize treatment strategies. Modified Frailty Index is the most used tool to assess the frailty state of gynecologic oncologic patients. We advise that this index should be part of the patients' standard evaluation and that it may be used in the daily practice to aid in shared decision making for tailored therapeutic strategies.

In this manuscript we provide an update on the importance of the use of preoperative frailty scores to predict complications among patients treated for gynecological cancer.

INTRODUCTION

There is a rapid rise of the mean age of patients with gynecological cancer due to increased global quality of life and a substantial improvement of the health-care offered. It has been estimated that by 2050, the population over 65 will double that of 2012 [1].

Given the greater frailty and psychological distress and the lesser possibility to undergo surgery of older patients, gynecologists oncologists must customize treatment of this patient category more than the younger counterpart [2-6].

All this underlines the importance of assessing the frailty of elderly patients before any type of oncological treatment.

Frailty has been defined as “a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death” from World Health Organization in 2012 [7].

Frailty is a syndrome characterized by increased vulnerability, reduced health response, increased falls, need for long-term care and mortality [8-11], but it is incorrect to consider all patients over the age of 65 as frail because some of them would not receive the best treatment possible [12]. In fact, frailty, disability and multimorbidity are very different concepts and cannot be used synonymously [13].

Many scores, with the aim of customizing the treatment, are commonly used for the assessment of frailty and there is no unanimous consensus on which is the best to use [14-22].

The aim of this study is to emphasize the importance of frailty by evaluating the currently available literature and to underline the use of frailty assessment tools to predict postoperative adverse outcomes and overall survival in frail patients with gynecological cancer.

MATERIALS AND METHODS

On March the 1st, 2022, the authors conducted research on Medline (PubMed) and Embase database. The keywords used for the research included: “frailty” or “frail” or “fragility” and “ovarian” or “ovary” or “endometrial” or “endometrium” or “uterus” or “cervical cancer” or “cervix” or “vulvar” or “vaginal” or “gynecological” or “gynecologic”.

The inclusion criteria were: 1) prospective or retrospective randomized controlled trials; 2) patients

with gynecological malignant tumors undergoing non-emergent surgery; 3) preoperative assessment of patients' frailty using a defined frailty score (e.g., Clinical Frailty Scale (CFS-7), Frailty Index (FI), modified Frailty Index (mFI).)

Case reports, case studies and conference abstracts were excluded, as well as studies in which the assessment of patients' state of frailty was not evaluated or was evaluated using non-specific scores.

In the end, fourteen studies, for a total of 85957 women, were included.

RESULTS

The characteristics for each included study are summarized in **Table 1**.

In 2012, M. Courtney-Brooks *et al.* published the first prospective monocentric study in gynecological oncology patients over 65 years of age who underwent surgery, assessing complications within 30 days as their primary endpoint. 37 patients were enrolled, and the state of frailty was calculated using the Fried frailty criteria (FFC) score. 16% of women were frail, 27% were intermediately frail and 57% were not frail. Women in the 1st group had a significantly higher BMI than those in the other groups (36.0, 31.5 and 26.1 kg/m², $p = 0.02$) and the rate of complications within 30 days was 24% versus 67% in non-frail patients compared to frailer patients ($p = 0.04$) [23].

In 2015, Uppal *et al.* retrospectively evaluated, with the Modified Frailty Index (mFI), the state of frailty of 6551 women undergoing surgery for gynecological oncological pathologies. Patients were divided as follows: mFI = 0: 45.2%; mFI = 1: 36.7%; mFI = 2: 15%; mFI = 3: 2.5%; mFI \geq 4: 0.6%. The complications at 30 days Clavien-Dindo IV/V were respectively 2%, 2.7%, 4.4%, 7.4% and 24.4% ($p < 0.001$) [24].

In 2017, Ferrero *et al.* conducted a multicentric retrospective study of 78 women over 70 who underwent surgery for Epithelial Ovarian Cancer (EOC). Complications at 30 days were significantly higher in patients considered frail using mFI than the non-frail counterpart (23.5% vs 4.3%, $p = 0.03$), and median overall survival was more favorable in younger patients (98 vs 30 months, $p = 0.016$) and less frail (56 vs 27 months; $p = 0.07$) [25].

In the same year, Driver *et al.* conducted a retrospective monocentric study on 88 patients undergoing surgery for endometrial carcinoma, subsequent chemotherapy and adjuvant radiotherapy.

Table 1. Description of included studies with main results.

Authors	Years	Study type (R-P)	Number of Patients	Age	Score Type (mFI-FI-FFC-ACG-FFC-Driver's)	Setting (EOC-EC-GC)	Results
Courtney-Brooks et al. 2012	2012	P	37	Mean 73 (range, 65-95)	FFC	GC	67% in frail vs 24% in non-frail (p = 0.04). Frail women had a significantly higher BMI compared to pre-frail and non-frail (36.0, 31.5 and 26.1 kg/m ² , respectively; p = 0.02).
Uppal et al.	2015	R	6551	Pts without complications (97%): mean 60.53 ± 12.75 (SD) Pts with complications (3%): mean 64.86 ± 12.41 (SD)	mFI	GC	2%, 2.7%, 4.4%, 7.4% and 24.4% for mFI of 0, 1, 2, 3 and ≥ 4, respectively (p < 0.001).
Ferrero et al.	2017	R	78	Low-frail: median 75.6 (range, 70-89) High-frail: median 75.3 (range, 70-87)	mFI	EOC	23.5% in high-frailty vs 4.3% in low-frailty (p = 0.03). Median OS was in favor of younger (98 vs 30 mo; p = 0.016) and less frail patients (56 vs 27 mo; p = 0.07).
Driver et al.	2017	R	88	Mean 68.5 (range, 60-88)	Driver's tool	EC	48% in frail vs 77% in non-frail (p = 0.02). Frailty predicted shortened OS (HR, 2.34 [95% CI, 1.08-5.03]) and frail pts. had twice the risk of disease recurrence (HR, 2.21 [95% CI, 1.02-4.80]) when adjusted for age, stage, grade and Charlson score.
Kumar et al.	2017	R	535	Mean 64.3 ± 11.3 (SD)	FI (30 items)	EOC	Compared to non-frail, frail pts. were more likely to have an Accordion grade 3+ complication (28.2% vs 18.8%; aOR: 1.62, 95% CI: 1.00-2.62; p = 0.02), to die within 90 days (16.0 vs 5.2%; aOR: 2.60, 95% CI 1.32-5.10; p < 0.001), to be admitted to the ICU (48.9% vs 20.5%; aOR: 3.20, 95% CI: 2.03-5.06; p < 0.001), to undergo CT within 42 days (62.6% vs 77.1%; p = 0.02), to have a non-home discharge (24.2% vs 7.0%; aOR 2.58, 95% CI: 1.35-4.93; p = 0.004). OS (median 26.5 vs 44.9 mo; p < 0.001) and PFS (median 15.8 vs 17.4 mo; p = 0.002) were shorter in frail pts.
Adedayo et al.	2018	R	1216	Mean 62.39 ± 10.8 (SD)	mFI	EC	Pts who were discharged to a non-home facility were older (OR 1.09 [95% CI 1.04-1.14]; p = 0.001), had a higher BMI (OR 1.08 [95% CI 1.04-1.12]; p = 0.001), and were frail (5.4% vs 1.3%; OR 1.95 [95% CI 1.91-5.01]; p = 0.008).
Yao et al.	2019	R	535	Mean 64.3 ± 11.3 (SD)	FI (30 items)	EOC	Compared to non-frail, frail pts. were more likely to have an Accordion grade 3+ complication (28.2% vs 18.8%; aOR: 1.62, 95% CI: 1.00-2.62; p = 0.02), to die within 90 days (16.0 vs 5.2%; aOR: 2.60, 95% CI 1.32-5.10; p < 0.001), to be admitted to the ICU (48.9% vs 20.5%; aOR: 3.20, 95% CI: 2.03-5.06; p < 0.001), to undergo CT within 42 days (62.6% vs 77.1%; p = 0.02), to have a non-home discharge (24.2% vs 7.0%; aOR 2.58, 95% CI: 1.35-4.93; p = 0.004). OS (median 26.5 vs 44.9 mo; p < 0.001) and PFS (median 15.8 vs 17.4 mo; p = 0.002) were shorter in frail pts.
Mullen et al.	2019	R	163	Mean 57.4 (range, 20-83)	mFI	GC	50% frail vs 22.4% in non-frail (RR 2.23 [95% CI, 1.29-3.85]).





Authors	Years	Study type (R-P)	Number of Patients	Age	Score Type (mFI-FI-FFC-ACG-FFC-Driver's)	Setting (EOC-EC-GC)	Results
Sia <i>et al.</i>	2020	R	76441	< 40: 6.9% 40–49: 12.7% 50–59: 25.2% 60–69: 28.4% 70–79: 19.4% ≥80: 7.4%	mFI	EOC	Frail pts: had an increased risk of intensive level of care (45% vs 17%; aRR, 1.76 [95% CI, 1.68–1.85]; p < 0.01), non-routine discharge (22% vs 6%; aRR, 1.39 [95% CI, 1.33–1.45]; p < 0.01), and inpatient mortality (5% vs 1%; aRR, 1.91 [95% CI, 1.63–2.23]; p < 0.01). Frail patients were more likely to be readmitted within 90 days (35.3% vs 23.6%; aRR, 1.11 [95% CI, 1.04–1.18]; p < 0.01), sustain mortality during 90-day re-admission (aRR, 1.31 [95% CI, 1.01–1.69]; p < 0.01), and have longer and costlier index hospital stays.
Orlandini <i>et al.</i>	2020	R	200	Mean 73.5 ± 6.2 (SD)	FI (40 items)	GC	FI is the strongest predictor for 1-year mortality confirmed after all adjustments for confounders (OR 3.40 [95% CI, 1.55–7.45]; p < 0.01) and by ROC curve analyses (0.66 [95% CI, 0.51–0.81]; p = 0.01).
Giannini <i>et al.</i>	2020	R	100	Mean 66.44 ± 10.43 (SD)	mFI	EC	mFI > 3 was an independent predictor of overall (OR 7.19 [95% CI, 1.43–36.25]; p = 0.021) and severe (OR 5.16 [95% CI, 1.07–24.94]; p = 0.047) complications. Elevated mFI > 3 was related to a statistically higher ICU/HDU access rate in frail patients (33.3% vs 6.6%; p = 0.013).
Di Donato <i>et al.</i>	2020	R	263	Mean 55.2 ± 12.5 (SD)	mFI	EOC	BMI ≥ 30 (p = 0.04), increased mFI (p = 0.04) and high SCS (p < 0.001) were independent predictors of severe complications (G3–G5). Patients with mFI ≥ 3 who underwent high-SCS surgery were at higher risk of severe complications ranging from 29.4% to 50%.
Guelhan Inci <i>et al.</i>	2021	P	144	58 (18–87)	FI	EOC	Frailty Index > 0.26 is associated with severe postoperative complications in patients with ovarian cancer. Besides tumor residuals > 1 cm, albumin levels < 35.5 g/dl, and a Frailty Index > 0.15 predict poor survival in patients with ovarian cancer.
Chambers <i>et al.</i>	2021	R	141	Non Frail: 59.3 ± 10.9. Frail: 64.1 ± 9.7	mFI	GC	Frailty, defined by the modified frailty index, is predictive of ≥ grade 2 postoperative complications following CRS with HIPEC in women with gynecologic cancer. Frailty screening before CRS with HIPEC may assist patient selection and improve postoperative outcomes.

ACG: Johns Hopkins adjusted clinical groups; BMI: body mass index; CI: confidence interval; CRS: cytoreductive surgery; CT: chemotherapy; EC: endometrial cancer; EOC: epithelial ovarian cancer; FFC: Fried frailty criteria; FI: frailty index; GC: gynecological cancer; HDU: high dependency unit; HIPEC: hyperthermic intraperitoneal chemotherapy; HR: hazard ratio; ICU: intensive care unit; mFI: modified frailty index; OR: odds ratio; OS: overall survival; P: prospective; PFS: progression free survival; pts.: patients; R: retrospective; RR: relative risk; SD: standard deviation; SCS: surgical complexity score.

The frailty assessment was evaluated using the Driver's tool. Of the sample of patients analyzed, 40% were considered non-frail while 60% were considered frail. Three-year disease-free survival was 48% in frail patients and 77% in patients in the other group ($p = 0.02$). Frail patients also had a lower overall survival rate (HR 2.34 [95% CI 1.08–5.03]) and twice the recurrence risk of the counterpart (HR 2.21 [95% CI 1.02–4.80]) [26].

Two monocentric retrospective studies were conducted, respectively by Kumar *et al.* in 2017 [27] and subsequently by Yao *et al.* in 2019 [28], on the same group of 535 patients with advanced EOC and undergoing surgery. Frailty was calculated using the Frailty Index (FI, 30 items). 75.5% of patients were found not to be frail while 24.5% were frail. Evidence showed that frail patients were exposed to a higher risk of severe complications (Accordion grade 3+) (28.2% vs 18.8%; aOR: 1.62, 95% CI: 1.00–2.62; $p = 0.02$), exitus within 90 days (16.0 vs 5.2%; aOR: 2.60, 95% CI: 1.32–5.10; $p < 0.001$), access in intensive care unit (ICU) (48.9% vs 20.5%; aOR: 3.20, 95% CI: 2.03–5.06; $p < 0.001$), to require chemotherapy (CT) within 42 days (62.6% vs 77.1%; $p = 0.002$) and non-home discharge (24.2% vs 7.0%; aOR 2.58, 95% CI: 1.35–4.93; $p = 0.004$). Overall Survival and Disease-Free Survival were also significantly lower in the frail group than their counterpart (median 26.5 vs 44.9 month; $p < 0.001$ and median 15.8 vs 17.4 month; $p = 0.002$, respectively). In 2018, Adedayo *et al.* retrospectively examined 1216 patients undergoing Endometrial Cancer (EC) surgery and considered frail or not using the modified Frailty Index (mFI) score. 21.3% of patients were frail. Patients who were discharged to a non-home facility were older (OR 1.09 [95% CI: 1.04–1.14]; $p = 0.001$), had a higher BMI (OR 1.08 [95% CI: 1.04–1.12]; $p = 0.001$), and were frail (5.4% vs 1.3%; OR 1.95 [95% CI: 1.91–5.01]; $p = 0.008$) [29]. A subsequent retrospective study of Mullen *et al.* of 2019 conducted on 163 patients undergoing gynecological oncological surgery, with BMI ≥ 30 kg/mq showed that complications of surgical wounds were more frequent in frail patients according to the mFI than in the non-frail (50% vs 22.4%, RR 2.23 [95% CI: 1.29–3.85]) [30].

Four retrospective studies were conducted in 2020. Sia *et al.* classified 76441 patients who underwent surgery for EOC into frail and non-frail using the AGC (John Hopkins adjusted clinical groups) score. 93.9% were in the first group and 6.1% in the second group. This study showed that frail pa-

tients had an increased risk of requiring intensive care (45% vs 17%; aRR, 1.76 [95% CI: 1.68–1.85]; $p < 0.01$), non-routine discharge (22% vs 6%; aRR, 1.39 [95% CI: 1.33–1.45]; $p < 0.01$), death during hospitalization (5% vs 1%; aRR, 1.91 [95% CI: 1.63–2.23]; $p < 0.01$), needing readmission within 90 days of discharge (35.3% vs 23.6%; aRR, 1.11 [95% CI: 1.04–1.18]; $p < 0.01$), increased mortality during 90-day readmission (aRR, 1.31 [95% CI: 1.01–1.69]; $p < 0.01$), to require longer hospitalizations times and, therefore, higher costs for society [31].

Orlandini *et al.* enrolled 200 patients over 65 years of age who underwent surgery for malignant gynecological tumors and evaluated their state of frailty using Frailty Index (FI, 40 items), achieving a range of 0.08–0.51 (average 0.23). Using this score, they highlighted that FI is the strongest predictor for 1-year mortality confirmed after all adjustments for confounders (OR 3.40 [95% CI: 1.55–7.45]; $p < 0.01$) and by ROC curve analyses (0.66 [95% CI: 0.51–0.81]; $p = 0.01$) [32].

Giannini *et al.*, using mFI, divided into frail and non-frail 100 patients undergoing surgery for EC finding that an mFI > 3 is an independent predictor of severe (OR 5.16 [95% CI: 1.07–24.94]; $p = 0.047$) and total (OR 7.19 [95% CI: 1.43–36.25]; $p = 0.021$) complications, as well as being significantly associated with a higher rate of intensive care needs ($p = 0.013$) [33]. Finally, from Di Donato *et al.*'s study, in which 263 patients with EOC and undergoing surgery were enrolled and their frailty status assessed using mFI, it emerged that BMI ≥ 30 ($p = 0.04$), an increased mFI value ($p = 0.04$) and a high Surgery Complexity Score (SCS) ($p < 0.001$), are all independent predictors for severe complications (G3–G5). In addition, patients classified as frail (mFI > 3) with high SCS (score > 8) were more susceptible to severe complications (from 29.4% to 50%) [34].

In 2021, only two studies were published on the preoperative frailty assessment of patients suffering from gynecological malignant tumors.

Guelhan Inci *et al.* conducted a prospective study of 144 patients with EOC, assessing their state of frailty with FI, concluding that a value of this score above 0.26 is associated with an increased risk of severe postoperative complications (\geq grade IIIb by Clavien-Dindo criteria) and that Frailty Index values > 0.15 , tumor residue > 1 cm and low albumin levels (< 35.5 g/dl) are predictors of poor OS [35].

Lastly, Chambers *et al.* have retrospectively divided, using the mFI, 141 patients affected by gynecological malignant tumors, into frail and non-frail.

All enrolled patients had undergone cytoreductive surgery (CRS) with hyperthermic intra-peritoneal chemotherapy (HIPEC). In a multivariate analysis, patients classified as frail (18.4%, $n = 26$), hence with $mFI \geq 2$, had an increased risk of complications as a result of such procedures ($p < 0.001$) compared to patients not considered frail (81.6%, $n = 115$), as well as increased risk of re-operation ($p = 0.044$), anastomotic leak ($p < 0.001$), respiratory failure ($p < 0.001$), ICU admission ($p = 0.018$), AKI ($p = 0.001$), and non-home discharge ($p = 0.001$) [36].

CONCLUSIONS

Based on the 14 analyzed studies, carried out from 2012 to 2021, the frailty assessment of gynecological oncological patients is fundamental for the efficient prediction of the risk of post-operative complications, and of the outcome in terms of OS and DFS [37]. This assessment correlates statistically with increased inpatient times, increased need for intensive care, increased risk of kidney failure, respiratory failure and death, and increased need for re-admission and re-intervention.

Currently none of the scores used in the articles analyzed in this manuscript are standardized.

In any case, we suggest to evaluate the frailty assessment of all patients suffering from gynecological malignant tumors and to offer them a personalized therapeutic strategy improving the oncological outcome.

Further multicentric studies should be conducted to better investigate the role of patients' frailty in order to reduce post-operative morbidity and mortality.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

A.G., O.D., T.G.D.: Conceptualization. E.B., C.V., E.M.: Supervision. T.G.D., R.V.: Writing – review & editing. E.M., R.M., V.B., B.C.: Supervision, validation, visualization. All authors have read and agreed to the published version of the manuscript.

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The authors declare that they have no conflict of interests.

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