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Original Article

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Prehabilitation for medically frail patients undergoing surgery for epithelial ovarian cancer: a cost-effectiveness analysis

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ABSTRACT

Objective: To assess the potential cost-effectiveness of prehabilitation in medically frail patients undergoing surgery for epithelial ovarian cancer (EOC).
Methods: We created a cost-effectiveness model evaluating the impact of prehabilitation on a cohort of medically frail women undergoing primary surgical intervention for EOC. Cost was assessed from the healthcare system perspective via (1) inpatient charges from 2018–2019 institutional Diagnostic Related Grouping data for surgeries with and without major complications; (2) nursing facility costs from published market surveys. Major complication and non-home discharge rates were estimated from the literature. Based on published pilot studies, prehabilitation was determined to decrease these rates. Incremental cost-effectiveness ratio for cost per life year saved utilized a willingness-to-pay threshold of $100,000/life year. Modeling was performed with TreeAge software.
Results: In a cohort of 4,415 women, prehabilitation would cost $371.1 Million (M) versus $404.9 M for usual care, a cost saving of $33.8 M/year. Cost of care per patient with prehabilitation was $84,053; usual care was $91,713. When analyzed for cost-effectiveness, usual care was dominated by prehabilitation, indicating prehabilitation was associated with both increased effectiveness and decreased cost compared with usual care. Sensitivity analysis showed prehabilitation was more cost effective up to a cost of intervention of $9,418/patient.
Conclusion: Prehabilitation appears to be a cost-saving method to decrease healthcare system costs via two improved outcomes: lower complication rates and decreased care facility requirements. It represents a novel strategy to optimize healthcare efficiency. Prospective studies should be performed to better characterize these interventions in medically frail patients with EOC.

Keywords: Prehabilitation; Cost effectiveness; Healthcare Systems; Medical Frailty; Gynecologic Cancer; Health Care Costs; Outcomes Research; Ovarian Cancer

Synopsis
Prehabilitation cost-effectiveness analysis was performed for medically frail epithelial ovarian cancer patients undergoing surgery. It was cost-saving for the healthcare system via lower complication rates and discharge care requirements. Prehabilitation was cost effective up to a cost of $9,418/patient.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: D.J., C.D.E., D.S.E.; Data curation: D.J.; Formal analysis: C.D.E., D.S.E.; Methodology: D.J., C.D.E., S.J.M., D.S.E.; Supervision: C.D.E., S.J.M.; Validation: S.J.M.; Writing - original draft: D.J., D.S.E.; Writing - review & editing: D.J., C.D.E., S.J.M., D.S.E.

INTRODUCTION

Medically frail patients experience higher complications, readmissions, and mortality rates from surgical procedures [1-4]. As a definition, frailty incorporates chronic co-morbidities or functional status limitations, often related to but not exclusive to aging, that compromise physiologic resilience and response to stressors (**Table 1**) [2]. These limitations can include difficulties with activities of daily life and medical conditions such as hypertension or diabetes mellitus, but also include consideration of nutritional status, social support, and psychological health. These factors can be qualified via survey or objective examination, and aim to provide a multidimensional assessment of a patient's vulnerability to stress. Indices such as the comprehensive geriatric assessment, Fried scale, and National Surgical Quality Improvement Program modified frailty index (NSQIP mFI) [5,6] incorporate functional status and physical fitness with medical and psychologic co-morbidities and have shown consistent correlations between frailty, morbidity, and mortality. These trends have also been observed in gynecologic oncology patients. Compared to non-frail women, medically frail elderly women experience significantly higher rates of 30-day postoperative complications, higher 90-day mortality, and an increased likelihood of requiring increased levels of care at discharge [6-9]. It is imperative to incorporate the impact of frailty and develop tailored management strategies to optimize care for this higher-risk demographic.

Medical frailty also incurs a substantial cost to the healthcare system. Direct cost estimates for major complications range from hundreds to tens of thousands of dollars per incident [10-12]. It is estimated that a post-operative complication functionally decreases a hospital's operating margin on that encounter from 5.8% to 0.1% [13]. Major complications also increase patient length of stay, limiting healthcare system resources for additional patients. Furthermore, medically frail patients have significantly higher rates of post-surgical non-home discharge and discharge admissions to care facilities [4], a finding supported in the gynecologic oncology literature [8,14]. The cost of these facility stays, as well as the costs involved in discharge planning, compounds the long-term increased healthcare system costs associated with medical frailty [15,16].

Table 1. Factors contributing to medical frailty

Component	Assessment methods
Functional status	- Independence in daily activities - Survey: fatigue, exhaustion, decreased activity - Timed Up-and-Go test - Grip strength - Balance, gait speed
Medical co-morbidities	- Presence of COPD, heart failure, hypertension, pneumonia, diabetes mellitus, anemia
Cardiopulmonary reserve	- Forced expiratory volume in 1 second - 6-minute walk test - Maximal oxygen consumption (VO_2max)
Nutritional status	- Laboratory testing: Albumin, Creatinine - Weight loss - Appetite - Body mass index - Sarcopenia
Mental health and cognition	- Depression/anxiety screening - Dementia screening
Social support	- Social Vulnerability Index - Financial health screening

Table 2. Potential components of prehabilitation interventions

Component	Interventions
Medical optimization	- Tobacco use: cessation, nicotine replacement - Diabetes: pharmacologic and dietary intervention - Anemia: iron supplementation - Chronic Disease (hypertension, chronic heart disease, COPD, diabetes mellitus): pharmacologic optimization
Nutritional support	- Dietary counseling - Oral protein supplementation - Meal planning and provision
Physical exercise/functional reserve intervention	- Exercise programming (video or Web-based) - Home aerobic and weight-based physical activity (assessed by patient or objectively measured via pedometer/step tracker) - In-person physical therapy and exercise classes - Pulmonary physical therapy (home incentive spirometry or in-person sessions with therapist)
Psychological support	- Stress management education - Counseling
Social support	- Social work consultation - Financial health assistance

Optimizing the highest-risk patients is therefore not only in the patient's best interest, but in the interest of the healthcare system. Prehabilitation programs aim to improve patient functional status during the pre-operative period in order to decrease complications and enhance outcomes [17] by incorporating components of aerobic exercise, resistance training, nutritional supplementation, and mental health counseling (**Table 2**) [18,19]. Common components include protein supplementation, medical optimization of co-morbid conditions, aerobic and resistance exercises, pulmonary therapy, and stress and anxiety management. Program duration can vary from the week prior to surgery to a period of months prior to procedure, via in-person visits or telemedicine [20,21].

Although research in prehabilitation has been largely limited to pilot studies, it has been associated with decreased length of hospital stay, decreased rates of post-operative complications, and faster return to baseline functional status [19,22-24]. The diversity of pilot models described in the literature provides many examples from which to customize an intervention for medically frail patients. One prospective study estimated that prehabilitation resulted in a significant cost savings for the health system on a scale of tens of thousands of dollars per patient [24].

No studies have been conducted in gynecologic oncology patients to estimate the large scale benefits and costs from a prehabilitation program. We performed a cost-effectiveness analysis to evaluate the potential impact of the use of a prehabilitation program in patients undergoing non-emergent primary debulking surgery (PDS) in epithelial ovarian cancer (EOC). We hypothesized that prehabilitation would decrease the rates of major complications and non-home discharge, thereby decreasing healthcare costs.

MATERIALS AND METHODS

We developed a decision tree model to evaluate the cost-effectiveness of a prehabilitation intervention on healthcare system costs for medically frail women undergoing PDS for EOC. The primary outcome was incremental cost-effectiveness ratio (ICER) of prehabilitation compared to no pre-operative intervention. The ICER represents the cost per one life year gained with prehabilitation compared to standard of care; a lower ICER represents a cost-effective strategy. For this model, we utilized a conservative standard willingness-to-pay ratio of $100,000 per life year; this represents the amount that society is willing to pay for one additional year of life [25]. One-way sensitivity analyses were performed to account for uncertainty in our model inputs. First, a simultaneous one-way sensitivity analysis was run in a tornado analysis to demonstrate the variables with the largest impact on the ICER. Threshold values were then calculated to determine the probabilities of these variables at which the preferred strategy would change. The model was constructed using TreeAge software (TreeAge Pro 2019, Williamstown, MA, USA). This study was exempt from Institutional Review Board approval.

We applied our model to a hypothetical cohort of 4,415 medically frail women who undergo PDS for EOC in one year. Of the estimated 22,530 women newly diagnosed with ovarian cancer annually [26], 55%–80% of these women will undergo PDS [27]. A recent systematic review identified the prevalence of frailty in gynecologic oncology patients ranges between 6.1%–60%; We approximated that a prevalence of 24.5% based on data from the Mayo Clinic [6,8,28,29]. Probabilities of a major complication, death from major complication, and need for discharge to an increased level of care facility were included in the model (**Fig. 1**).

1. Probabilities

Our model considered the impact of major complications that would fall under Clavien-Dindo Grade IV and V or Accordion Grade 3-4 [30,31]. Kumar et al. [6] found that 28.8% of medically frail patients undergoing PDS for EOC experience such complications. The magnitude of clinical benefit via decreased morbidity and mortality is variable within the prehabilitation literature; not all patients will benefit from intervention. Howard et al. [24] found that multimodal prehabilitation decreased the rate of major complications in patients undergoing major abdominal surgery from 16% to 10%. This is the largest prospective study of prehabilitation on a patient population undergoing similar operative stress to PDS in EOC, and represents a 37.5% relative risk reduction (RRR). We conservatively estimated a RRR of

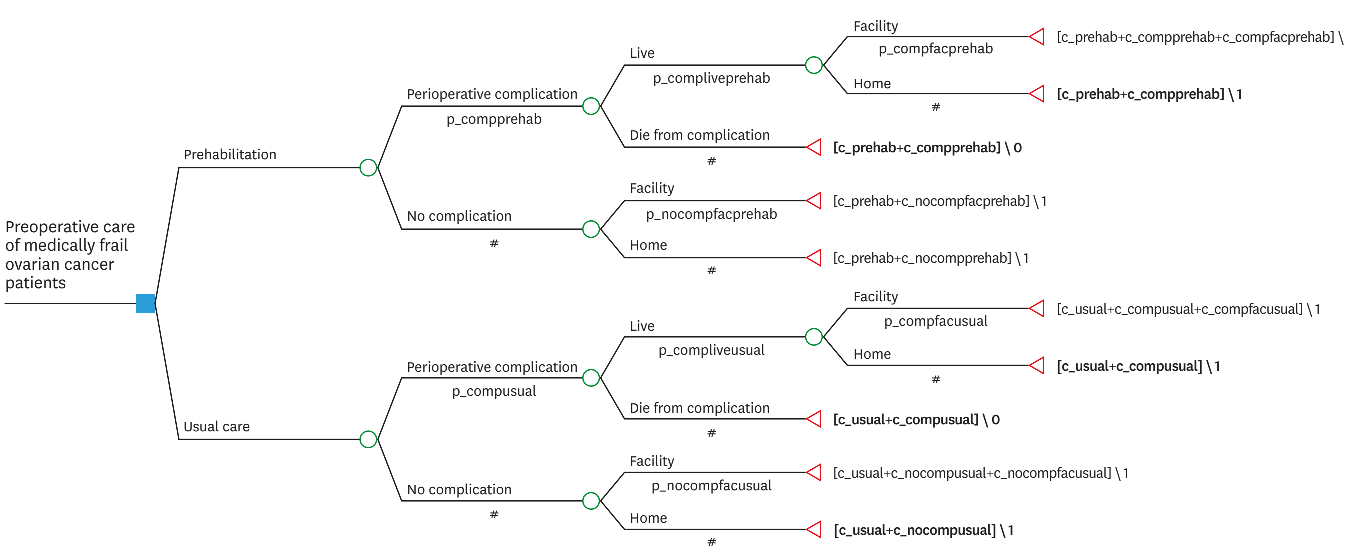

Fig. 1. Graphical depiction of the computational model.

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Table 3. Baseline probabilities

Variables	Probability	Reference
Peri-operative complication		
After prehabilitation	0.26	6,20
No prehabilitation	0.29	6
Living after peri-operative complication (90-day)		
After prehabilitation	0.67	6
No prehabilitation	0.65	6,27
Non-home (facility) discharge without experiencing a peri-operative complication		
After prehabilitation	0.10	13
No prehabilitation	0.11	13
Non-home (facility) discharge after peri-operative complication		
After prehabilitation	0.51	13
No prehabilitation	0.56	13

10%. Kumar et al. [6] and Shinall et al. [32] found a 35.1% rate of 90-day mortality after a serious complication; in non-frail patients, this risk was 18.4%, consistent with larger studies on mortality in the medically frail. Prospective literature is limited in this area. As a result, we estimated a 5% RRR in patients who underwent prehabilitation. We estimated rates of non-home discharge after uncomplicated vs. complicated courses to be 11.2% and 56.25%, respectively [14]. Using a 10% RRR estimate, the impact of prehabilitation decreased these rates to 10.1% and 50.6%, respectively. Probability estimates can be seen in **Table 3**.

2. Cost estimates

Costs were estimated from the healthcare system perspective. The major drivers were inpatient admission charges and costs associated with non-home discharge. Inpatient costs were estimated using Diagnostic Related Grouping cost estimates for Code 738: ‘Hospital charge: Uterine and adnexa procedure for ovarian or adnexal malignancy without complication,’ and Code 736: ‘Hospital charge: Uterine and adnexa procedure for ovarian or adnexal malignancy with major complication.’ These were consistent with findings that major complications increase hospital costs approximately five-fold [33]. Due to no data on national average costs, we utilized Ohio area estimates of $275 per diem costs for a semi-private nursing home room [15,16,34]. Patients with complications were expected to require more days in a facility than those without complications. These costs were similar to the outcomes of recently published studies using Medicare claims data [20]. Prehabilitation was modeled to shorten length of stay, consistent with findings of shorter lengths of post-operative inpatient admission [19,35]. Cost of prehabilitation itself was set at a minimum of $100 with a range up to $5,000. The prehabilitation program by Howard et al. [24] limited their costs to $100 per patient by utilizing video-based counseling and exercise programming, providing a copy of recordings to each patient for at-home use, along with a pedometer and incentive spirometer. This is a potentially translatable method for other programs: a systemic review demonstrated that technology-supported nutritional and exercise programs in cancer patients have shown high retention and promising short-term results [36]. Other programs have included in-person appointments, nutritional supplementation, and more expensive medical equipment in their protocols; as a result, an upper bound of $5,000 was established to incorporate these costs. For routine pre-operative costs, we assumed that patients received laboratory testing (complete blood count, Chem-10) and/or basic diagnostics (chest x-ray, electrocardiogram) costing on average $200 per patient. Cost estimates can be seen in **Table 4**.

Table 4. Cost estimates

Variables	Cost ($)	Reference
Hospital charge: Uterine and adnexa procedure for ovarian or adnexal malignancy without complication (DRG 738)	66,021	32
Hospital charge: Uterine and adnexa procedure for ovarian or adnexal malignancy with major complication (DRG 736)	152,596	32
Non-home discharge facility charge (after peri-operative complication)		
After prehabilitation	1,925	29,30
No prehabilitation	3,850	29,30
Non-home discharge facility charge (no peri-operative complication)		
After prehabilitation	1,100	29,30
No prehabilitation	1,925	29,30
Prehabilitation program, including usual pre-operative care	300	20
Usual preoperative care without prehabilitation	200	

DRG, Diagnostic Related Grouping.

RESULTS

In a cohort of 4,415 women undergoing PDS for EOC, prehabilitation would cost $371.1 million (M) versus $404.9 M for usual care, a cost saving of $33.8 M/year. Per patient, the cost of care with prehabilitation was $84,053; usual care was $91,713. In the model cohort, prehabilitation prevented serious complications in 132 patients; as a result, 88 fewer patients required non-home discharges. In addition, prehabilitation prevented mortality in 44 patients (**Table 5**). Cost-effectiveness analysis demonstrated that usual care was dominated by prehabilitation, indicating both decreased cost and increased effectiveness of prehabilitation compared to usual care. An ICER was not calculated due to this finding.

Tornado analysis (**Fig. 2**) showed that the mortality rate after a complication in patients who received usual care had the largest influence on the ICER, with a threshold value of 0.97. This was followed by mortality after a complication in a patient who received prehabilitation (threshold 0.31) and the probability of having a surgical complication after either prehabilitation (0.33) or usual care (0.21). As the cost of a prehabilitation program is highly variable in existing data, sensitivity analysis of the baseline cost of prehabilitation versus usual care was performed. This demonstrated cost-savings with prehabilitation up to a predetermined maximum cost of $5,000. Further analysis showed that prehabilitation would be cost-effective relative to usual care up to a threshold value of $9,418/patient.

DISCUSSION

Our model found that prehabilitation for medically frail patients undergoing PDS for EOC is a cost-saving intervention for the healthcare system via decreased patient complications and decreased need for non-home discharge. Sensitivity analyses revealed that prehabilitation would be cost-effective up to $9,418 per patient; most prehabilitation programs are estimated to cost well less than this amount. Furthermore, prehabilitation remains the dominant or cost-effective strategy within a wide range of reasonable complication and mortality estimates. For example, as long as the surgical complication rate in a patient who underwent

Table 5. Overview of outcomes

Treatment	Total cost	Cost per patient	Serious complications	Non-home discharges	Mortality
Prehabilitation	$371.1 M	$84,053	1,148	795	397
No prehabilitation	$404.9 M	$91,713	1,280	706	441

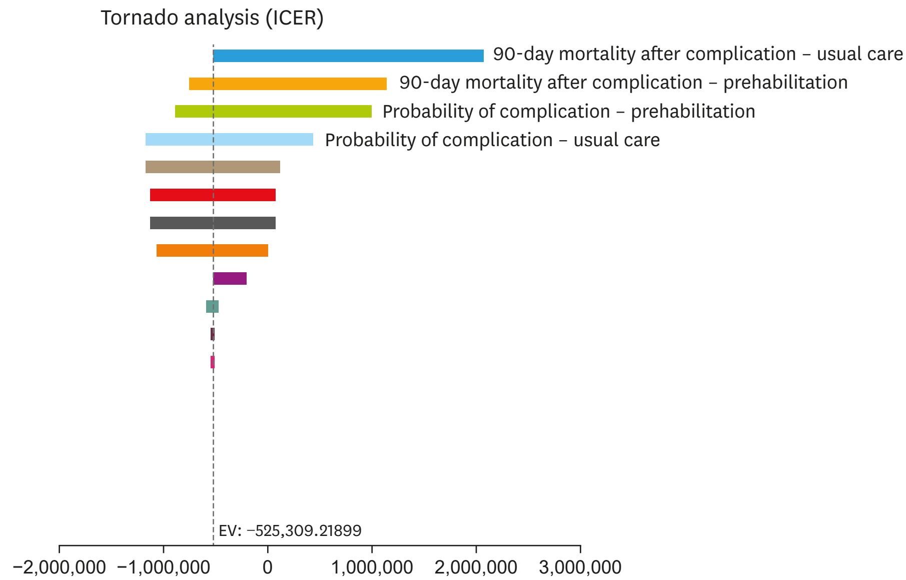

Fig. 2. Tornado analysis. Tornado analysis shows that the mortality rate after a complication in patients who received usual care had the largest influence on the ICER (threshold value 0.97). This was followed by mortality after a complication in a patient who received prehabilitation (threshold 0.31) and the probability of having a surgical complication after either prehabilitation (0.33) or usual care (0.21).
ICER, Incremental cost-effectiveness ratio.

prehabilitation is less than 33%, prehabilitation is the cost-effective strategy compared to usual care.

Our results are concordant with previously published research that suggests prehabilitation as a feasible and cost-effective intervention. A recent multicenter study in Michigan demonstrated that prehabilitation decreased hospital length of stay and total episode payments [20], and also supported the feasibility of prehabilitation programs in varied practice settings. A similar intervention for patients undergoing major abdominal surgery at a single institution found a decreased rate of major complications, with resultant cost savings of $21,946 per patient undergoing colectomy [24]. A meta-analysis in colorectal surgery patients also found that nutritional prehabilitation was associated with decreased length of stay, and multimodal therapy hastened return to baseline functional status [19,35] Our study, in assessing the cost-savings associated with a prehabilitation intervention, aims to provide a framework to support this research.

The association of frailty with adverse outcomes for gynecologic oncology patients has been well-established. A recently published study found that frail patients undergoing laparotomy for ovarian cancer specifically are indeed more likely to experience increased morbidity and mortality [37] and their admissions cost twice that of other patients. Kumar et al. [6] and Yao et al. [14] observed increased rates of morbidity, mortality, and non-home discharge in medically frail patients with advanced ovarian cancer who underwent PDS, and Uppal et al. found that poor nutritional status as defined as hypoalbuminemia <3 g/dL was associated with increased morbidity and 30-day mortality in patients who underwent open surgery for gynecologic malignancy [9]. Although their frailty scoring mechanism found a lower incidence of frailty than in other cohorts, Sia et al. also supported overall findings by showing increased length of stay, higher 90-day readmission rates and higher 90-day mortality rates for frail patients [37].

The optimal duration and regimen of a prehabilitation intervention is under investigation. Recognizing that patients who undergo primary cytoreduction for EOC have a short interval between evaluation and surgery, any potential program would need to produce benefit quickly. A systematic review of prehabilitation for patients undergoing surgery for colorectal cancer included studies with promising results after nutritional supplementation for as little as 7–10 days [19]. A review of prehabilitation in thoracic surgery included unimodal interventions as short as 5–7 days, with trends towards significant clinical benefits. However, this analysis also found a lack of benefit in longer programs [38]. This concern about program duration was addressed by Miralpeix et al. [39], who established that interventions for EOC patients intended for primary cytoreduction begin at suspected diagnosis, during outpatient preoperative evaluation.

The existing prehabilitation literature largely consists of pilot studies or small programs tailored towards narrow patient populations. The programs themselves are heterogenous, ranging from single-mode programs focusing on nutrition or pulmonary function to multi-modal regimens including these components in combination with mental health, social support, and aerobic exercise training. This limits the comparability of these studies. Indeed, systemic reviews such as those by Gillis et al. [19] and Moran et al. [22], found that many programs did not result in improved clinical outcomes. It is likely that differences in study design, patient selection, and small sample sizes may contribute to these differences; these factors also represent the challenge with extrapolating and establishing an optimal prehabilitation regimen more broadly. Miralpeix et al. [39] utilized published prehabilitation regimens to propose a multimodal protocol for gynecologic oncology patients ranging from 2–4 weeks in duration, incorporating medical optimization with exercise and nutrition interventions. This publication provides a starting place for well-designed, prospective trials in gynecologic oncology, which are necessary to answer these questions. At this time, there is one NIH-registered prospective clinical trial for prehabilitation + ERAS (enhanced recovery after surgery) in patients with suspected malignancy undergoing gynecologic surgery, compared to normal ERAS protocols (NCT04505111). This trial is sponsored in Brazil and uses a multimodal approach of nutrition, exercise, and psychologic counseling to assess the impact on the primary outcome of post-operative recovery time.

Of note, although a significant proportion of patients undergo PDS, neoadjuvant chemotherapy is increasingly utilized in the treatment of advanced ovarian cancer [40]. Neoadjuvant chemotherapy is associated with improved perioperative morbidity, particularly in patients at high risk for complications [41]. A model which includes more extended courses of prehabilitation for patients with EOC who undergo neoadjuvant chemotherapy may shed additional light on the benefits of prehabilitation for that growing population. Pilot studies in prehabilitation for rectal and esophageal cancer patients undergoing neoadjuvant chemotherapy suggest that it is a feasible intervention with trends towards improved patient outcomes [42,43].

We recognize that our research is a theoretical model limited by the precision of model inputs. While sensitivity analyses account for model uncertainty, assessing the real-world benefits of prehabilitation will require large prospective studies in representative patient populations in order to better elucidate the benefits of prehabilitation. Such research will better characterize the impact of prehabilitation on length of inpatient stay and duration of admission to non-home discharge facilities, as well as the associated costs of these components of care. For example, the true number of patients with gynecologic malignancies who would experience clinical benefit remains to be seen, and can currently only be extrapolated from prehabilitation pilot studies in similar patient populations. Recognizing this, we utilized more conservative risk reduction estimates to prevent over-estimation. Characterization of the impact of intervention for gynecologic oncology patients requires prospective research in our patient population. We therefore postulate that our model may underestimate potential cost savings. Our study focused on patients with ovarian cancer undergoing PDS; however, many patient populations in gynecologic oncology may meet medical frailty criteria and derive benefit from prehabilitation. Examples include patients undergoing neoadjuvant chemotherapy or patients with obesity and endometrial cancer.

Medically frail patients with gynecologic malignancies are at significantly higher risk of adverse outcomes, and interventions to address these risks are necessary to optimize their care. Overall, pilot studies and meta-analyses of prehabilitation programs have shown promising results in decreasing complication rates, shortening length of stay, and improving return to baseline status. Our cost-effectiveness model provides a financial lens on the potential impact of prehabilitation on healthcare costs. Based on our use of conservative estimates, the magnitude of cost savings may even exceed our projections in this analysis. Further investigation into prehabilitation holds promise not only to provide better care for at-risk patients, but to decrease healthcare system costs and improve system efficiency.

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