PREDICTING OUTCOMES AT PRIMARY DEBULKING SURGERY FOR ADVANCED EPITHELIAL OVARIAN, FALLOPIAN TUBE, AND PERITONEAL CANCER

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By

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ABSTRACT

INTRODUCTION: Predicting suboptimal primary debulking and perioperative complications will lead to improved outcomes for patients with advanced ovarian, fallopian tube, and peritoneal cancer.

MANUSCRIPT I: A multicenter prospective trial evaluating the ability of preoperative computed tomography (CT) scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer

OBJECTIVE: To assess the ability of preoperative CT scan and CA-125 to predict suboptimal (>1cm residual disease) primary cytoreduction in advanced ovarian, fallopian tube, and peritoneal cancer.

METHODS: This was a prospective multicenter trial of patients who underwent primary cytoreduction for stage III-IV ovarian, fallopian tube, and peritoneal cancer. A CT scan of the abdomen/pelvis and serum CA-125 were obtained within 35 and 14 days before surgery, respectively. Four clinical and 20 radiologic criteria were assessed.

RESULTS: From 7/2001–12/2012, 350 patients met eligibility criteria. The optimal debulking rate was 75%. On multivariate analysis, three clinical and six radiologic criteria were significantly associated with suboptimal debulking: age ≥60 years ($p=0.01$); CA-125 ≥500 U/mL ($p<0.001$); ASA 3-4 ($p<0.001$); suprarenal retroperitoneal lymph nodes >1cm ($p<0.001$); diffuse small bowel adhesions/thickening ($p<0.001$); and lesions >1cm in the small bowel mesentery ($p=0.03$), root of the superior mesenteric artery ($p=0.003$), perisplenic area ($p<0.001$), and lesser sac ($p<0.001$). A ‘predictive value score’

was assigned for each criterion, and the suboptimal debulking rates of patients who had a total score of 0, 1-2, 3-4, 5-6, 7-8, and ≥9 were 5%, 10%, 17%, 34%, 52%, and 74%, respectively. A prognostic model combining these nine factors had a predictive accuracy of 0.758.

CONCLUSIONS: We identified nine criteria associated with suboptimal debulking, and developed a model that was predictive of suboptimal cytoreduction. These results may be helpful in pretreatment patient assessment.

MANUSCRIPT II: Predictive value of the age-adjusted charlson comorbidity index on perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer

OBJECTIVE: To assess the ability of the age-adjusted Charlson comorbidity index (ACCI) to predict perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer (EOC).

METHODS: Data were analyzed for all patients with stage IIIB-IV EOC who underwent primary cytoreduction from 1/2001–1/2010 at our institution. Patients were divided into 3 groups based on an ACCI of 0-1, 2-3, and ≥4. Clinical and survival outcomes were assessed and compared.

RESULTS: We identified 567 patients; 199 (35%) had an ACCI of 0-1, 271 (48%) had an ACCI of 2-3, and 97 (17%) had an ACCI of ≥4. The ACCI was significantly associated with the rate of complete gross resection (0-1=44%, 2-3=32%, and ≥4=32%; p=0.02), but was not associated with the rate of minor

(47% vs 47% vs 43%, p=0.84) or major (18% vs 19% vs 16%, p=0.8) complications. The ACCI was also significantly associated with progression-free (PFS) and overall survival (OS). Median PFS for patients with an ACCI of 0-1, 2-3, and ≥4 was 20.3m, 16m, and 15.4m, respectively (p=0.02). Median OS for patients with an ACCI of 0-1, 2-3, and ≥4 was 65.3m, 49.9m, and 42.3m, respectively (p<0.001). On multivariate analysis, the ACCI remained a significant prognostic factor for both PFS (p=0.02) and OS (p<0.001).

CONCLUSIONS: The ACCI was not associated with perioperative complications in patients undergoing primary cytoreduction for advanced EOC, but was a significant predictor of PFS and OS. Prospective clinical trials in ovarian cancer should consider stratifying for an age-comorbidity covariate.

OVERALL CONCLUSIONS: Nine criteria associated with suboptimal cytoreduction were identified, and a model that was predictive of suboptimal debulking was developed. The ACCI was not associated with perioperative complications, but was a significant prognostic factor for survival outcomes.

BIOGRAPHICAL SKETCH

Rudy S. Suidan earned his Bachelor of Science in Biology and Doctor of Medicine degrees from the American University of Beirut in Beirut, Lebanon, then completed residency in Obstetrics and Gynecology at the University of Medicine and Dentistry in New Jersey. He is currently completing a Pelvic Reconstruction Clinical Research Fellowship at Memorial Sloan Kettering Cancer Center, and will be starting a Gynecologic Oncology fellowship at MD Anderson Cancer Center in July 2015. He is interested in predicting and optimizing outcomes for patients with ovarian cancer and other gynecologic malignancies, and aspires to a career in academics.

Dedicated to my loving parents, Graziella and Joe

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A multicenter prospective trial evaluating the ability of preoperative computed tomography scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

ABSTRACT

OBJECTIVE: To assess the ability of preoperative computed tomography (CT) scan of the abdomen/pelvis and serum CA-125 to predict suboptimal (>1cm residual disease) primary cytoreduction in advanced ovarian, fallopian tube, and peritoneal cancer.

METHODS: This was a prospective, non-randomized, multicenter trial of patients who underwent primary cytoreduction for stage III-IV ovarian, fallopian tube, and peritoneal cancer. A CT scan of the abdomen/pelvis and serum CA-125 were obtained within 35 and 14 days before surgery, respectively. Four clinical and 20 radiologic criteria were assessed.

RESULTS: From 7/2001–12/2012, 669 patients were enrolled; 350 met eligibility criteria. The optimal debulking rate was 75%. On multivariate analysis, three clinical and six radiologic criteria were significantly associated with suboptimal debulking: age ≥60 years ($p=0.01$); CA-125 ≥500 U/mL ($p<0.001$); ASA 3-4 ($p<0.001$); suprarenal retroperitoneal lymph nodes >1cm ($p<0.001$); diffuse small bowel adhesions/thickening ($p<0.001$); and lesions >1cm in the small bowel mesentery ($p=0.03$), root of the superior mesenteric artery ($p=0.003$), perisplenic area ($p<0.001$), and lesser sac ($p<0.001$). A 'predictive value score' was assigned for each criterion, and the suboptimal debulking rates of patients who had a total score of 0, 1-2, 3-4, 5-6, 7-8, and ≥9 were 5%, 10%, 17%, 34%, 52%, and 74%, respectively. A prognostic model combining these nine factors had a predictive accuracy of 0.758.

CONCLUSIONS: We identified nine criteria associated with suboptimal cytoreduction, and developed a predictive model in which the suboptimal rate

was directly proportional to a predictive value score. These results may be helpful in pretreatment patient assessment.

Introduction

Of the estimated 21,980 women diagnosed each year with primary ovarian, fallopian tube, or peritoneal carcinoma in the United States, the majority present with advanced-stage disease [1]. Standard initial therapy for these patients consists of primary cytoreductive surgery, or 'debulking,' followed by platinum and taxane-based chemotherapy [2].

Numerous studies have demonstrated a survival advantage for patients who undergo 'optimal' vs 'suboptimal' debulking [3-6]. Although various cutoff points have been used to define optimal debulking (residual disease ranging from 0 to 3cm), the Gynecologic Oncology Group (GOG) currently uses 1cm as a cutoff [2]. While previously only of prognostic value, this stratification led to significant treatment implications with the publication of GOG–172, a randomized trial in women with optimally debulked (≤1cm residual) ovarian cancer that showed a significant survival advantage for patients who received intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel compared to those who received intravenous paclitaxel and cisplatin chemotherapy [7]. Intraperitoneal chemotherapy is currently not a treatment option for suboptimally debulked women. It is also important to note that for patients who are suboptimally cytoreduced (>1cm residual), survival is equivalent regardless of residual tumor size [8,9]. Reported rates of optimal cytoreduction vary widely in the literature, from 15% to 85% [10]. Therefore it appears that a significant proportion of women with advanced ovarian cancer will undergo a debulking procedure with associated morbidity but without a commensurate improvement in survival.

In order to determine which patients would be less likely to benefit from primary surgery, several attempts have been made to predict cytoreductive outcome, using imaging modalities, tumor markers, and laparoscopic scores [11]. Investigators have evaluated the utility of preoperative computed tomography (CT) scan in an effort to identify radiologic predictors, with inconsistent results [12-16]. The use of preoperative CA-125 has also been evaluated in this setting, with a cutoff value of 500 U/mL used by most researchers. Some studies have found CA-125 to be significantly associated with cytoreductive outcome, while others have not [17-23]. Studies attempting to identify preoperative predictors have been limited by their retrospective design, sample size, broad inclusion criteria, and heterogeneous rates of optimal cytoreduction. The objective of this trial was to prospectively assess the ability of preoperative CT scan of the abdomen/pelvis and serum CA-125 to predict suboptimal primary cytoreduction in patients with advanced epithelial ovarian, fallopian tube, and peritoneal cancer.

Methods

Patient Eligibility

This was a prospective, non-randomized, multicenter clinical trial approved by the institutional review boards of each institution. All patients ≥18 years of age with presumed advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III-IV) epithelial ovarian, fallopian tube, and peritoneal cancer who were assessed by an attending gynecologic oncologist for cytoreductive surgery were eligible. A CT scan of the abdomen/pelvis with intravenous and oral contrast and serum CA-125 were obtained within 35 and 14 days before surgery, respectively. Informed consent was obtained from all

enrolled patients. This occurred at the initial outpatient visit, before the CT scans were evaluated by a protocol radiologist, and before patients' scheduled surgeries. Demographic data were recorded, along with cytoreductive outcome and histologic confirmation of diagnosis postoperatively. Suboptimal cytoreduction was defined as >1cm residual disease, as classified by the GOG. Patients were excluded if they did not have ovarian, fallopian tube, or peritoneal cancer; if they did not have advanced disease; or if they received neoadjuvant chemotherapy (this was at the discretion of the primary surgeon, usually due to findings on a CT scan that was done in-house, or after in-house radiologic review of outside CT imaging, both of which occurred after the initial visit). Additionally, patients were also excluded if there was significant delay in surgery after CT scan (>35 days) or serum CA-125 (>14 days), or if the CT scan was of poor quality, lacking contrast, or not assessed by a protocol radiologist. Patients with carcinosarcoma, mesothelioma, and mucinous histologies were also excluded, as were patients with germ cell, sex-cord stromal cell, low-malignant potential, and benign tumors.

CT scan and Clinical Criteria

CT scans were performed after administration of intravenous and oral contrast; contiguous slices were acquired, with slice thicknesses ranging from 5 to 7.5 mm. CT scans performed at outside institutions were included in the study only if judged to be of acceptable quality by the study radiologists. Five protocol radiologists, all experienced in body CT, analyzed and interpreted the images before surgery. They recorded the presence or absence of 20 radiologic criteria, including: lesions in the porta hepatis, intersegmental fissure of the liver, gallbladder fossa, gastrohepatic ligament, lesser sac, root of the

superior mesenteric artery (SMA), small bowel mesentery, omentum, liver (perihepatic, subcapsular, and intraparenchymal individually), spleen (perisplenic and intraparenchymal individually), pulmonary bases, pleural bases, and retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic). Other criteria included tumor invading the anterior abdominal wall, presacral extraperitoneal disease, the presence of ascites (graded as mild, moderate, or severe), and diffuse small bowel adhesions/thickening. The latter was interpreted radiologically as angulated bowel loops in the presence of small bowel wall thickening. Thickening was subjectively assessed by the radiologists with no specific measurement of bowel wall thickness used, as it was dependent on the caliber of that loop of bowel. Pelvic disease involving the adnexae, uterus, and rectosigmoid colon was not assessed as part of this study, as it is generally resectable and does not usually affect cytoreductive status.

Quantitative bi-dimensional measurements were determined for all visualized lesions. Qualitative analysis (QA) was performed by using the following five-point scale to categorize the degree of radiologic certainty that a lesion identified on CT represented a metastatic neoplasm: 1=definitely normal; 2=probably normal; 3=indeterminate; 4=probably metastatic; and 5=definitely metastatic. There were no specific criteria for assigning a QA score; scores were determined by the radiologists based on their judgment, experience, and the characteristics of the lesions (i.e., solid vs cystic, well defined vs poorly defined). In addition to the CT criteria, four clinical criteria were considered as potential predictors of cytoreductive outcome: serum CA-125, age, stage, and American Society of Anesthesiologists (ASA) class as determined by the anesthesia team.

Statistical Analysis

Sample size was calculated as follows: a previous study from our institution suggested that a cutoff value for the preoperative serum CA-125 that correctly identified 90% of optimally cytoreduced patients correlated with a level that would also correctly identify 40% of suboptimally cytoreduced patients [17]. This protocol was designed to test whether the proportion of suboptimally debulked women correctly classified by the CA-125 cutoff was truly 40% or could be as low as 25%. Similarly, it was designed to test whether CT scan findings could correctly classify a desirable proportion of suboptimally cytoreduced patients. For a type I error of 5% and 80% power, it was estimated that 85 suboptimally debulked patients would be required. At the time of protocol design, we assumed an optimal cytoreduction rate of 45% based on our institutional data [17]. However, coinciding with the start of patient accrual, the rate had increased to greater than 75% following a change in surgical paradigm and the incorporation of upper abdominal surgery into the primary cytoreductive effort [6]. This prolonged the accrual period for the study, as it meant that an estimated 340 women with advanced ovarian cancer would need to be included to have 85 suboptimally debulked patients.

All 20 radiologic and four clinical criteria were assessed for their association with suboptimal debulking. Radiologic criteria were considered present if lesions had a QA of 4 or 5 and measured >1cm (measurable lesions only). Criteria were considered absent if lesions had a QA of 1-3 (any size), or if they had a QA of 4 or 5 and measured ≤1cm. Several cutoffs were assessed for age, and the cutoff most predictive of suboptimal debulking was used to group patients. Due to the small number of patients with an ASA class of 1 and

4, patients with an ASA of 3 or 4 were combined and compared to those who had an ASA of 1 or 2. A receiver operating characteristic (ROC) curve was generated with the data from the current study, and the most predictive cutoff value of CA-125 was determined to be 500 U/mL, which is consistent with previously published reports [17,21-23]. Associations between the criteria and debulking outcome were tested using Fisher's exact test for categorical variables and the Wilcoxon Rank-Sum test for continuous variables. Generalized estimating equations were used to account for differences between the two institution-clusters, assuming independent covariance structure. Based on the results of univariate analysis, backward selection was utilized to build a multivariate model predictive of suboptimal cytoreduction, for which an ROC curve was generated. The radiologic and clinical criteria found to be significant on multivariate analysis were then each assigned a 'predictive value score' according to their odds ratios (OR). Subsequently, the total predictive value score of all patients in the cohort was calculated using their radiologic and clinical findings, and the suboptimal debulking rate corresponding to each total score was determined. All statistical tests were two-sided, and a p value of <0.05 was considered significant. The multivariate model was considered exploratory; therefore, no formal adjustment for multiple comparisons was made. Statistical analysis was performed using SAS statistical software 9.2 (SAS Institute, Cary, NC) and R (R development core team, 2013).

Results

From July 2001 to December 2012, 669 patients were enrolled, and 350 met all eligibility criteria. A CONSORT diagram is shown in Figure 1. Two

hundred sixty-eight (76%) of the eligible patients were enrolled at the primary study institution. The optimal debulking rate was 75% (261 patients). Patient and tumor characteristics are shown in Table 1.

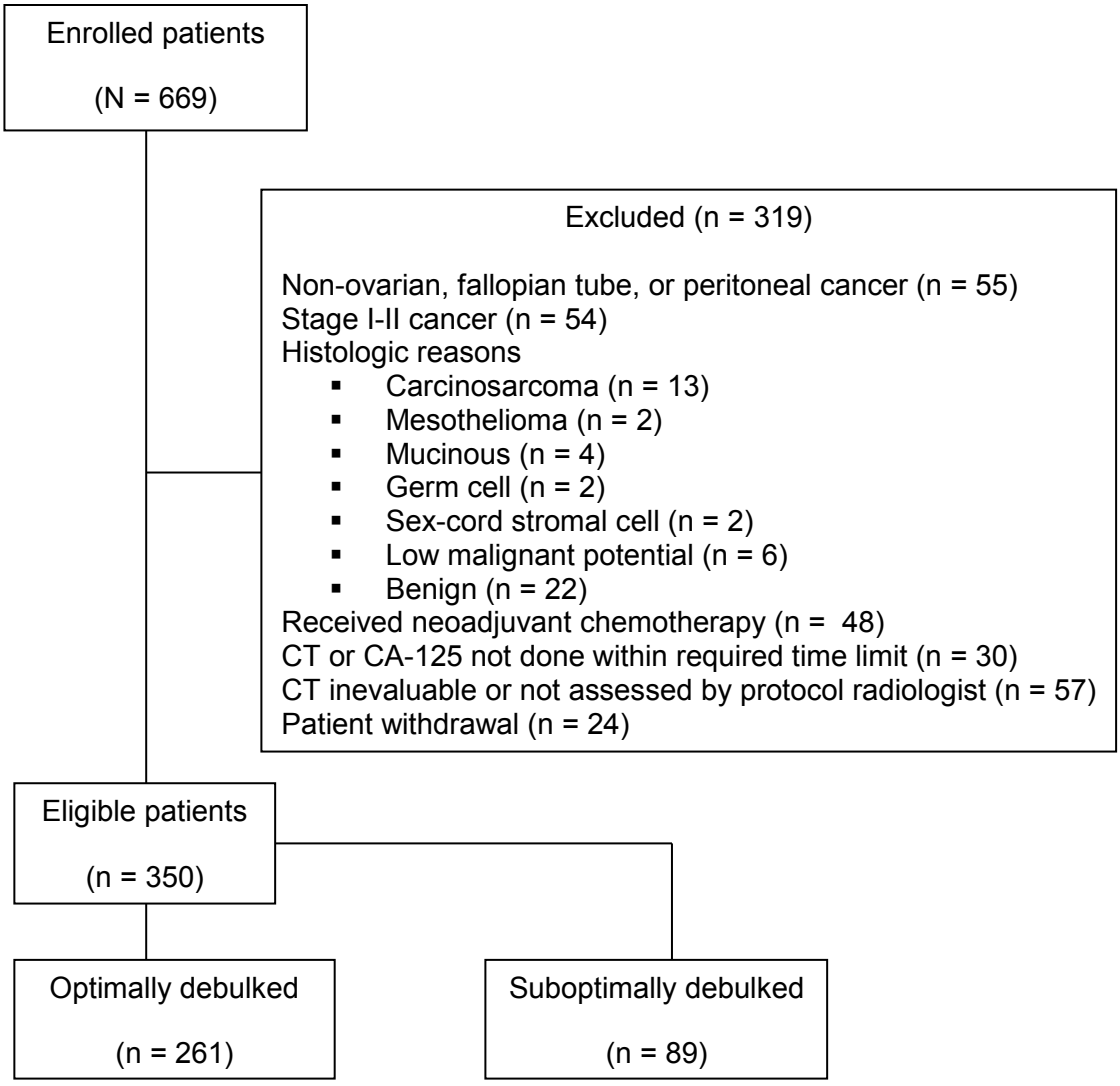

Figure 1: CONSORT diagram of all enrolled patients. CT, computed tomography; IV, intravenous.

Table 1: Patient and Tumor Characteristics (N = 350)

Variable	n (%)
Age (years) Median (range)	61 (34 – 86)
Primary site of disease Ovary Fallopian tube Peritoneal	264 (75%) 42 (12%) 44 (13%)
FIGO Stage III A/B IIIC IV	8 (2%) 248 (71%) 94 (27%)
Grade 1 2 3 N/A	11 (3%) 8 (2%) 328 (94%) 3 (1%)
Histology Serous Endometrioid/Clear cell Mixed/Other	314 (90%) 2 (0.6%) 34 (10%)
Preoperative CA-125 (U/mL) Median (range)	860 (9 – 38,100)
ASA class 1 2 3 4 N/A	10 (3%) 158 (45%) 178 (51%) 3 (1%) 1 (0.3%)

FIGO, International Federation of Gynecology and Obstetrics; ASA, American Society of Anesthesiologists

On univariate analysis, three clinical and 12 radiologic criteria were found to be significantly associated with suboptimal cytoreduction (Tables 2 and 3). Seventy-one percent (63/89) of suboptimally debulked patients had a CA-125 ≥500 U/mL and 41% (106/261) of optimally debulked patients had a CA-125 <500 U/mL. Due to the small number of suboptimally debulked women whose CT scans showed liver intraparenchymal lesions, spleen intraparenchymal lesions, and presacral extraperitoneal disease (<5 patients each), these criteria were excluded from further analysis.

On multivariate analysis, after backward selection, three clinical and six radiologic criteria remained significant: age ≥60 years (OR 1.32, p=0.01); CA-125 ≥500 U/mL (OR 1.47, p<0.001); ASA 3-4 (OR 3.23, p<0.001); retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1cm (OR 1.59, p<0.001); diffuse small bowel adhesions/thickening (OR 1.87, p<0.001); small bowel mesentery lesions >1cm (OR 2.28, p=0.03); root of the SMA lesions >1cm (OR 2.4, p=0.003); perisplenic lesions >1cm (OR 2.27, p<0.001); and lesser sac lesions >1cm (OR 4.61, p<0.001) (Table 4). ROC curves were generated, with a predictive model utilizing the six CT criteria showing an area under the curve (AUC) of 0.688. The six CT criteria and the preoperative CA-125 combined had an AUC of 0.696. The most accurate model combined the six CT criteria, CA-125, age, and ASA, demonstrating an AUC of 0.758 (Figure 2).

Table 2: Clinical Criteria – Univariate Analysis

Criteria	Suboptimal Rate	OR	95% CI	*p*
Age				
≥ 60 years	53/187 (28%)	1.4	1.39 - 1.4	<0.001
< 60 years	36/163 (22%)			
CA-125				
≥ 500 U/mL	63/218 (29%)	1.66	1.31 - 2.1	<0.001
< 500 U/mL	26/132 (20%)			
ASA				
3-4	61/181 (34%)	2.54	1.4 - 4.6	0.002
1-2	28/168 (17%)			
Stage				
IV	26/94 (28%)	1.17	0.75 - 1.84	0.49
III	63/256 (25%)			

ASA, American Society of Anesthesiologists

Table 3: Radiologic Criteria – Univariate Analysis

Criteria	Suboptimal Rate		OR	95% CI	*p*
	Criteria Present	Criteria Absent			
Porta hepatis lesion >1 cm	18/50 (36%)	71/300 (24%)	1.81	1.53 - 2.15	<0.001
Liver intersegmental fissure lesion >1cm	14/48 (29%)	75/302 (25%)	1.25	0.64 - 2.41	0.51
Gallbladder fossa lesion >1 cm	9/25 (36%)	80/325 (25%)	1.72	1.29 - 2.31	<0.001
Gastrohepatic ligament lesion >1 cm	22/38 (58%)	67/312 (21%)	5.03	2.07 - 12.23	<0.001
Lesser sac lesion >1 cm	20/35 (57%)	69/315 (22%)	4.75	4.38 - 5.16	<0.001
Root of the superior mesenteric artery lesion >1 cm	5/8 (63%)	84/342 (25%)	5.12	4.23 - 6.2	<0.001
Small bowel mesentery lesion >1 cm	27/61 (44%)	62/289 (21%)	2.91	1.53 - 5.51	<0.001
Retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1 cm	26/72 (36%)	63/278 (23%)	1.93	1.72 - 2.17	<0.001
Omental lesion >1 cm	52/212 (25%)	37/138 (27%)	0.89	0.61 - 1.29	0.53
Perihepatic lesion >1 cm	24/95 (25%)	65/255 (25%)	0.99	0.58 - 1.68	0.97

Subcapsular liver lesion >1 cm	10/44 (23%)	79/306 (26%)	0.85	0.63 - 1.13	0.26
Liver intraparenchymal lesion >1 cm	4/9 (44%)	85/341 (25%)	2.41	1.87 - 3.11	<0.001
Perisplenic lesion >1 cm	26/59 (44%)	63/291 (22%)	2.85	2.27 - 3.58	<0.001
Spleen intraparenchymal lesion >1 cm	3/7 (43%)	86/343 (25%)	2.24	1.29 - 3.89	0.004
Tumor invading anterior abdominal wall >1 cm	3/11 (27%)	86/339 (25%)	1.1	0.9 - 1.35	0.34
Presacral extraperitoneal disease >1 cm	2/4 (50%)	87/346 (25%)	2.98	2 - 4.44	<0.001
Diffuse small bowel adhesions/ thickening	9/24 (38%)	80/326 (25%)	1.85	1.78 - 1.91	<0.001
Abdominal ascites (moderate-severe)	48/154 (31%)	41/196 (21%)	1.71	1.11 - 2.65	0.02
Pulmonary metastasis (lung bases)	3/13 (23%)	86/337 (26%)	0.88	0.66 - 1.15	0.34
Pleural metastasis (lung bases)	4/17 (24%)	85/333 (26%)	0.9	0.6 - 1.34	0.59

All measurable lesions had a QA of 4 or 5

Table 4: Multivariate Model of Significant Clinical and Radiologic Criteria Predictive of Suboptimal Cytoreduction

Criteria	OR	95% CI	*p*	Predictive Value Score
Age ≥60 years	1.32	1.06 - 1.63	0.01	1
CA-125 ≥500 U/mL	1.47	1.28 - 1.69	<0.001	1
ASA 3-4	3.23	1.76 - 5.91	<0.001	3
Retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1 cm	1.59	1.58 - 1.6	<0.001	1
Diffuse small bowel adhesions/ thickening	1.87	1.86 - 1.87	<0.001	1
Perisplenic lesion >1 cm	2.27	1.7 - 3.03	<0.001	2
Small bowel mesentery lesion >1 cm	2.28	1.08 - 4.8	0.03	2
Root of the superior mesenteric artery lesion >1 cm	2.4	1.34 - 4.32	0.003	2
Lesser sac lesion >1 cm	4.61	4.39 - 4.84	<0.001	4

ASA, American Society of Anesthesiologists

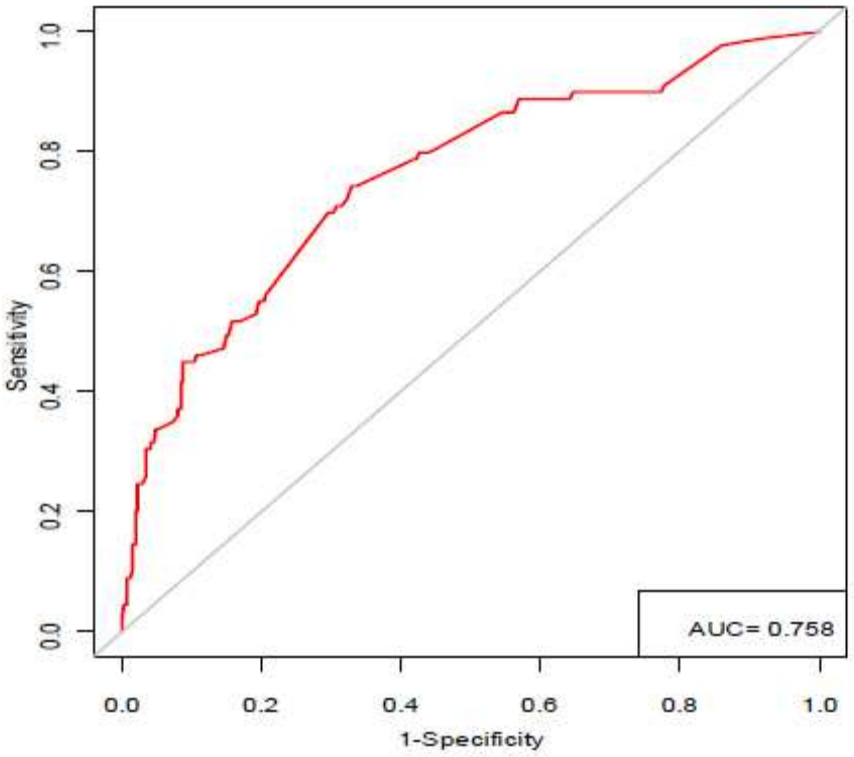

Figure 2: Receiver operating characteristic curve showing correlation between the nine predictive criteria and suboptimal cytoreduction. AUC: area under the curve.

To add clinical utility to our findings, we assigned a 'predictive value score' for the nine criteria significant on multivariate analysis, which was based on their multivariate ORs. Age ≥60 years, CA-125 ≥500 U/mL, retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1cm, and diffuse small bowel adhesions/thickening were each assigned a predictive value score of 1. Perisplenic lesions >1cm, small bowel mesentery lesions >1cm, and root of the SMA lesions >1cm were each assigned a score of 2. ASA 3-4 was assigned a score of 3, and lesser sac lesions >1cm were assigned a score of 4 (Table 4). We then calculated the total predictive value

score of all patients in our cohort using their clinical and CT scan findings, and determined the suboptimal debulking rate corresponding to each total score. The rate was linearly correlated to the predictive value score. Patients who had a score of 0 (none of the criteria present) had a suboptimal rate of 5%. The suboptimal rates of patients who had a score of 1-2, 3-4, 5-6, and 7-8 were 10%, 17%, 34%, and 52%, respectively. The highest suboptimal rate, 74%, was for patients who had a score of 9 or greater (Table 5).

Table 5: Predictive Value Score and Suboptimal Cytoreduction (N = 349)

Total Predictive Value Score	Total Patients n (%)	Optimal (n)	Suboptimal (n)	Suboptimal Rate
0	22/349 (6%)	21	1	5%
1 - 2	79/349 (23%)	71	8	10%
3 - 4	109/349 (31%)	91	18	17%
5 - 6	85/349 (24%)	56	29	34%
7 - 8	31/349 (9%)	15	16	52%
≥ 9	23/349 (7%)	6	17	74%

*1 patient excluded for a missing American Society of Anesthesiologists class

Discussion

In two high-volume ovarian cancer centers, we identified three clinical and six radiologic criteria associated with suboptimal cytoreduction and developed a predictive model in which the suboptimal rate was directly

proportional to a predictive value score. This model had an overall predictive accuracy of 0.758.

Previous investigators assessing the utility of preoperative CT scan in this setting have retrospectively identified different radiologic predictors [12-16]. Axtell et al.'s analysis of 65 patients showed diaphragm disease and large bowel mesentery implants to be significant factors [15]. Dowdy et al.'s review of 89 patients found diffuse peritoneal thickening to be the only variable significantly associated with suboptimal debulking [16]. In our analysis, three out of the six predictive radiologic criteria involved the small bowel, which makes intuitive and physiologic sense. The incorporation of advanced surgical techniques and the ability to resect upper abdominal disease (splenic, perihepatic, etc) has led to higher optimal debulking rates [6,24]. However, there is a limit to how much small bowel and/or mesentery can be resected without compromising essential function. Therefore, extensive disease involving the majority of the small bowel mesentery and serosa is anecdotally cited by expert surgeons as the most common factor precluding optimal debulking.

Chi and colleagues initially reported that a preoperative serum CA-125 >500 U/mL was significantly associated with suboptimal debulking [17]. A follow-up study demonstrated that while the CA-125 was a predictor of upper abdominal disease, it was not necessarily associated with suboptimal cytoreduction if extensive upper abdominal procedures were incorporated into the surgical approach [21]. Other reports have shown conflicting results, and a recent meta-analysis concluded that although a CA-125 >500 U/mL was a strong risk factor for suboptimal debulking, it lacked the accuracy to

independently predict surgical outcome [18-20,22,23]. In our study, a CA-125 value ≥500 U/mL was a statistically significant predictive factor and was the best cutoff based on ROC curve evaluation (not shown). However, it is important to note that it has limited clinical utility on its own, as 29% of patients with a value ≥500 U/mL were suboptimally debulked, compared to 20% of those with a value <500 U/mL. We consequently feel that the preoperative CA-125 level should be used in combination with the other criteria to guide clinical management.

Regarding our model design, which was exploratory, we assigned equal weights to all the criteria in our initial analysis (not shown) and then calculated the suboptimal rate based solely on the number of criteria present. The rate increased proportionally to the number of criteria. However, our data revealed that certain factors were more predictive than others (for example, lesser sac lesions >1cm had an OR of 4.61, while age ≥60 years had an OR of 1.32). The final model was therefore based on weighted criteria with a predictive value score assigned, as this was considered a more accurate way to model the actual effects. In addition, in the model, lesser sac lesions >1cm had a predictive value score of 4, significantly higher than other criteria. The 35 patients who had lesser sac lesions >1cm had a median predictive value score of 8, with a range of 4 to 12. This suggests that in patients with carcinoma that is extensive enough to involve the lesser sac, the disease has likely spread to several other anatomic locations as well.

While previous studies have assessed the utility of preoperative CT scan in predicting outcome, they were limited by their retrospective nature, small sample size, inclusion of early-stage disease, and variable rates of optimal

cytoreduction (49% to 78%) [12-16]. Our study's strength lies in its prospective design; the CT scans were evaluated by a dedicated group of radiologists prior to patients' surgeries, thereby guaranteeing their blinding with regard to surgical outcomes and findings. We also had a large patient cohort, with 350 women included. The study was carried out in two institutions, which increases the external validity of our analysis. The two institutions are tertiary cancer centers with a high rate of optimal debulking (75%), and only patients with advanced-stage cancer were included. In our model, we were able to combine the predictive value of radiologic criteria with that of clinical criteria. This not only takes into account patients' extent of disease but also their overall medical status and ability to undergo general anesthesia and extensive surgery. We feel the inclusion of clinical factors increases the strength of our model, as age and medical status are critical factors in the complex decision-making process for gynecologic oncologists when determining if a patient is a candidate for primary debulking, as opposed to neoadjuvant chemotherapy. Although a patient's disease sites may render her amenable for optimal resection based on a surgeon's technical ability and surgical armamentarium, one with a poor overall medical condition may not be able to tolerate the prolonged complicated procedure often necessary to achieve optimal debulking [25].

The main limitation of our trial is the study period needed to accrue the required number of suboptimally cytoreduced patients, as CT imaging technology and surgical practice may have changed over time. Surgeons were aware of preoperative CT findings, as being blinded to the imaging would have been detrimental to patient care. While this can be seen as a potential bias, it is essential to note that all six CT criteria that were significantly associated with

suboptimal debulking in our study only came to light when the data was analyzed and the multivariate model built, which occurred after the trial was closed to accrual. Therefore, despite knowledge of patients' preoperative imaging, surgeons were not aware which of these findings would ultimately be associated with suboptimal cytoreduction. Selection bias is another potential limitation, as 48 patients who received neoadjuvant chemotherapy were excluded. This was at the discretion of the attending gynecologic oncologist, who upon reviewing CT imaging after the initial visit, deemed certain patients to not be amenable for optimal primary cytoreduction. This was a subjective assessment based on each surgeon's own experience, judgment, and technical abilities, with no specific criteria employed. These patients did not undergo an attempt at primary debulking, and it is possible that some may have been optimally cytoreduced. Nonetheless, had these patients undergone primary surgery, it is possible that additional imaging criteria may have been significantly associated with cytoreductive outcome. With regards to the evaluation of imaging, the QA scale used to assess the lesions, while described before [26], has not been validated, and is admittedly used in an attempt to objectively quantify subjective findings. In addition, each CT scan was read by one protocol radiologist. As such, the reproducibility of the findings and interobserver variability were not assessed. We also have not validated our scoring system in another population at this time.

The GOG definition of optimal debulking uses 1cm as a cutoff [2]. However, several studies have shown a survival advantage for patients with no gross residual compared to those with ≤1cm gross residual [5,9,27]. Based on that data, many gynecologic oncologists currently feel that the goal of primary cytoreduction for ovarian cancer should be complete gross resection

to no gross residual. Nevertheless, our trial was designed to assess preoperative predictors based on a definition of optimal debulking that uses a 1cm cutoff. We therefore did not feel it would be statistically valid to report outcomes based on a changed endpoint. One can hypothesize that if preoperative findings suggest that a gross residual of ≤1cm cannot be achieved, then the same findings would imply that cytoreduction to no residual disease is unlikely. As this assertion cannot be formally supported with the current analysis, we plan on addressing this question with a secondary analysis of our data in the future. It is important to note however that even if the goal of cytoreduction is complete gross resection, that may not necessarily align with the goal of predicting surgical outcome; as there may still be a potential survival benefit for patients with ≤1cm but grossly visible disease after primary debulking, compared to those who are treated with neoadjuvant chemotherapy [9,27,28,29,30,31].

In our predictive model, the suboptimal debulking rate increased progressively from 5% to 74% based on the predictive value score. With further validation, these results may be helpful in pretreatment patient assessment and counseling, and in guiding clinical management. At this time, we do not advocate a certain cutoff rate above which neoadjuvant chemotherapy should be administered to a patient. We feel it is reasonable for each individual surgeon and center to determine what threshold to use; based on their own experience, outcomes, treatment philosophy, and ability to employ extensive surgical techniques in order to achieve optimal cytoreduction.

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APPENDIX

Chapter 1 has been published as a peer-reviewed manuscript in *Gynecologic Oncology*:

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CHAPTER 2:

Predictive value of the age-adjusted charlson comorbidity index on perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer

TITLE PAGE

Predictive value of the age-adjusted charlson comorbidity index on perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

ABSTRACT

OBJECTIVE: To assess the ability of the age-adjusted Charlson comorbidity index to predict perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer (EOC).

METHODS: Data were analyzed for all patients with stage IIIB-IV EOC who underwent primary cytoreduction from 1/2001–1/2010 at our institution. Patients were divided into 3 groups based on an age-adjusted Charlson comorbidity index of 0-1, 2-3, and ≥4. Clinical and survival outcomes were assessed and compared.

RESULTS: We identified 567 patients; 199 (35%) had an age-adjusted Charlson comorbidity index of 0-1, 271 (48%) had an index of 2-3, and 97 (17%) had an index of ≥4. The index was significantly associated with the rate of complete gross resection (0-1=44%, 2-3=32%, and ≥4=32%; p=0.02), but was not associated with the rate of minor (47% vs 47% vs 43%, p=0.84) or major (18% vs 19% vs 16%, p=0.8) complications. The index was also significantly associated with progression-free (PFS) and overall survival (OS). Median PFS for patients with an index score of 0-1, 2-3, and ≥4 was 20.3m, 16m, and 15.4m, respectively (p=0.02). Median OS for patients with an index score of 0-1, 2-3, and ≥4 was 65.3m, 49.9m, and 42.3m, respectively (p<0.001). On multivariate analysis, the index remained a significant prognostic factor for both PFS (p=0.02) and OS (p<0.001).

CONCLUSIONS: The age-adjusted Charlson comorbidity index was not associated with perioperative complications in patients undergoing primary

cytoreduction for advanced EOC, but was a significant predictor of PFS and OS. Prospective clinical trials in ovarian cancer should consider stratifying for an age-comorbidity covariate.

Introduction

Of the estimated 21,290 women diagnosed each year with epithelial ovarian, fallopian tube, or peritoneal carcinoma in the United States, the majority present with advanced-stage (International Federation of Gynecology and Obstetrics [FIGO] III/IV) disease [1]. Standard therapy for these patients consists of primary debulking surgery, followed by adjuvant chemotherapy [2]. Numerous studies have shown a survival advantage for patients who undergo 'optimal' vs 'suboptimal' cytoreduction [3][4].

In order to achieve optimal surgical outcomes, primary debulking surgery is frequently lengthy and complex, requiring bowel resection and/or aggressive upper abdominal surgery [5]. Such extensive procedures are commonly associated with significant perioperative complications [6][7][8][9][10][11]. Given this risk, neoadjuvant chemotherapy followed by interval debulking is offered by certain providers to patients who are poor operative candidates due to age and/or medical comorbidity [12][13][14][15]. However, this is subjective and surgeon dependent, and no consensus exists on which comorbid conditions or age render a patient a poor operative candidate.

The Charlson comorbidity index is a prognostic index that was developed to predict 1-year mortality based on medical comorbidity [16]. It is a score derived by the summation of the weighted scores of 19 medical conditions found to be associated with survival, and has been validated in several populations [17][18][19]. Age was subsequently found to be predictive of death from comorbid disease by the authors. It was incorporated to create a combined score accounting for both comorbidity and age, the age-adjusted Charlson comorbidity index, which has been validated as well [20].

Researchers have attempted to predict morbidity or survival in this patient population using a variety of prognostic factors and models [13][14][21][22][23][24][25][26]. However, limited data exists assessing the prognostic significance of a validated comorbidity index on these outcomes. The objective of our study was to assess the ability of the age-adjusted Charlson comorbidity index to predict perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian, fallopian tube, and peritoneal cancer.

Methods

After obtaining institutional review board approval, we identified all patients with FIGO stage IIIB-IV epithelial ovarian, fallopian tube, and peritoneal cancer who underwent primary cytoreduction at our institution from January 2001 to January 2010. Patients were excluded if they had non-epithelial ovarian cancer, tumors of low-malignant potential, or if they received neoadjuvant chemotherapy. Clinical data, perioperative complications, and survival outcomes were retrospectively reviewed from the medical records. Data abstracted included: age, medical comorbidity, body mass index, primary disease site, FIGO stage, histology, tumor grade, preoperative albumin, preoperative platelet count, preoperative CA-125, presence and amount of ascites at surgery, presence of gross residual disease after cytoreductive surgery, and intraperitoneal chemotherapy administration.

The age-adjusted Charlson comorbidity index was assigned to all patients using their individual medical conditions and age at the time of primary debulking. The scoring system as described by Charlson et al. is shown in Table 6 [20]. The overall score is calculated based on the total of

each patient's comorbid conditions (which are weighted according to severity) and age. As all patients had advanced ovarian cancer, that condition was excluded from the scoring system. Patients were categorized into three groups based on an age-adjusted comorbidity index score of 0-1 (low), 2-3 (intermediate), and ≥4 (high).

Table 6: Age-adjusted charlson comorbidity index (N = 567)

Score	**Comorbidity**	n (%)
1	Diabetes mellitus without end-organ damage	27 (5%)
	Cerebrovascular disease	10 (2%)
	Myocardial infarction	14 (2%)
	Congestive heart failure	0 (0%)
	Peripheral vascular disease	9 (2%)
	Dementia	2 (0.4%)
	Chronic pulmonary disease	55 (10%)
	Connective tissue disease	37 (7%)
	Peptic ulcer disease	16 (3%)
	Mild liver disease	5 (1%)
2	Diabetes mellitus with end-organ damage	2 (0.4%)
	Moderate/severe renal disease	0 (0%)
	Hemiplegia	0 (0%)
	Solid tumor without metastasis (exclude if >5 years from diagnosis)	32 (6%)
	Leukemia	2 (0.4%)
	Lymphoma	9 (2%)
3	Moderate/severe liver disease	0 (0%)
6	Metastatic solid tumor	0 (0%)
	AIDS (not just HIV positive)	0 (0%)

Age adjustment: For each decade after 40 years, add 1 point to total score (i.e. 1 point for age group 50-59 years, 2 points for age group 60-69, etc)
AIDS, Acquired immune deficiency syndrome; HIV, Human immunodeficiency virus

In 2001, our institution established a prospectively maintained adverse events database of all surgical cases. Data on perioperative complications at up to 30 days postoperatively is collected for all patients. Complications are graded for severity on a scale of 1-5 using a standardized institutional grading system: 1 = use of oral medications and/or bedside intervention to treat an event; 2 = use of intravenous medications, parenteral nutrition, enteral nutrition, or blood transfusion to treat an event; 3 = interventional radiology, therapeutic endoscopy, intubation, or operation required to treat an event; 4 = residual and lasting disability requiring major rehabilitation or organ resection; and 5 = event resulting in death of patient [27]. This grading system has been validated, with Grade 1-2 complications considered minor and Grade 3-5 complications considered major [28]. Complications are also classified by system, including but not limited to gastrointestinal, cardiac, pulmonary, and neurologic systems.

The three age-adjusted index groups were assessed for their association with Grade 1-2 (minor) and Grade 3 (major) perioperative complications. As only one patient each had a Grade 4 or 5 complication, those grades were not included in any analysis. Given that the complexity and number of procedures during primary debulking is correlated with the rate and severity of surgical complications [6][22], we stratified our cohort into three subgroups according to a validated surgical complexity score [22][29]. As described by Aletti and colleagues, that score is calculated based on the specific procedures performed in a cytoreductive case, and classifies surgeries as having low, intermediate, and high complexity. We then performed a secondary analysis, assessing the association between the age-adjusted index and complications

within those subgroups. The age-adjusted index was also evaluated for its ability to predict specific systems-based complications.

Progression-free survival (PFS) and overall survival (OS) were additional endpoints in our study. The date of progression was determined by computed tomography (CT) scan and/or CA-125 levels. When determined by CT scan, the progression date was taken as the first appearance of one or more new lesions or increased size of existing lesions. When determined by CA-125 level, the progression date was defined as the first date of the initial CA-125 of greater than or equal to two times the nadir value or upper limit of normal, as applicable [30][31]. When a subsequent CT scan confirmed that the rise in CA-125 indicated progression, the progression date was defined as the date of CA-125 rise. PFS was defined as the time interval from the date of primary debulking to the date of disease progression, death, or last follow-up. OS was defined as the time interval from the date of surgery to the date of death or last follow-up.

Categorical variables were compared using the χ^2 test, and continuous variables were compared using the Kruskal-Wallis test. All statistical tests were two-sided, with a p of <0.05 considered significant. When testing the association between the age-adjusted index and specific systems-based complications, logistic regression analysis was performed adjusting for surgical complexity. The Kaplan–Meier method was used to estimate survival rates. Univariate analysis of all assessed categorical and continuous variables was performed for prognostic significance using the log-rank test and Cox proportional hazards model for significance, respectively. Differences in survival were calculated using the Cox proportional hazards model. Variables

with a p of <0.05 on univariate analysis were then included in a multivariate Cox regression analysis. Statistical analysis was performed using SPSS 22.0 (IBM Corporation, Armonk, NY).

Results

Five hundred and sixty-seven patients were included over the study period. One hundred and ninety-nine patients (35%) had an age-adjusted Charlson comorbidity index score of 0-1, two hundred and seventy-one patients (48%) had an index score of 2-3, and 97 patients (17%) had an index score of ≥4. The most common comorbid conditions were 'chronic pulmonary disease' (n = 55, 10%), 'connective tissue disease' (n = 37, 7%), 'other solid tumors' (n = 32, 6%), and 'diabetes mellitus' (n = 27, 5%) (Table 6). Patient and tumor characteristics are shown in Table 7. The high index group (≥4) had the highest median age, while the low index group (0-1) had the highest proportion of patients with Stage IV disease and the highest median preoperative platelet count. The age-adjusted index was significantly associated with both the rate of optimal debulking (≤1 cm residual disease) (p=0.01) and the rate of complete gross resection (p=0.02).

Table 7: Patient and tumor characteristics (N = 567)

Characteristic	ACCI 0-1 (Low) n = 199 (35%)	ACCI 2-3 (Intermediate) n = 271 (48%)	ACCI ≥4 (High) n = 97 (17%)	p
Median age (range)	51 years (23 – 59)	65 years (43 – 79)	74 years (60 – 96)	<0.001
Median Body mass index (range)	25.2 kg/m^2 (16.3 – 43.7)	25.7 kg/m^2 (17.6 – 54.6)	25 kg/m^2 (18.3 – 50.1)	0.49
FIGO Stage IIIB IIIC IV	 10 (5%) 148 (74%) 41 (21%)	 8 (3%) 226 (83%) 37 (14%)	 5 (5%) 86 (89%) 6 (6%)	0.01
Primary disease site Ovary Fallopian tube Peritoneum	 167 (84%) 16 (8%) 16 (8%)	 204 (75%) 28 (10%) 39 (15%)	 74 (76%) 9 (9%) 14 (15%)	0.19
Histology Serous Endometrioid Clear cell Mixed/Other	 181 (91%) 1 (1%) 2 (1%) 15 (8%)	 249 (92%) 2 (1%) 0 (0%) 20 (7%)	 81 (84%) 2 (2%) 0 (0%) 14 (14%)	0.1
Tumor grade 1 2 3	 8 (4%) 16 (8%) 175 (88%)	 7 (3%) 14 (5%) 250 (92%)	 3 (3%) 5 (5%) 89 (92%)	0.6
Median preoperative albumin (range) *	4.1 g/dL (2.5 – 4.8)	4.1 g/dL (2.1 – 5)	4.1 g/dL (2.4 – 4.8)	0.97
Median preoperative platelet count (range)	367 K/µl (204 – 1067)	366 K/µl (175 – 920)	314 K/µl (113 – 1067)	<0.001
Median preoperative CA-125 (range) †	681 U/mL (3 – 28,503)	496 U/mL (3 – 38,100)	444 U/mL (9 – 24,500)	0.05

Ascites				
None	50 (25%)	74 (27%)	38 (39%)	0.09
1 – 1000	57 (29%)	71 (26%)	24 (25%)	
1001 – 5000	73 (37%)	92 (34%)	31 (32%)	
>5000	19 (9%)	34 (13%)	4 (4%)	
Residual disease				
None	87 (44%)	86 (32%)	31 (33%)	0.02
≤1 cm	77 (39%)	107 (39%)	37 (38%)	
>1 cm	35 (17%)	78 (29%)	29 (30%)	
Intraperitoneal chemotherapy administration (optimally debulked patients 2005 – 2010)	64/101 (63%)	60/124 (48%)	20/36 (56%)	0.08

ACCI: Age-adjusted charlson comorbidity index
Data missing for: * eight, and † twenty four patients.

Among the entire cohort, two hundred and sixty-one patients (46%) had a Grade 1-2 (minor) complication, and 101 patients (18%) had a Grade 3 (major) complication. One patient with an index score of 1 had a Grade 4 complication, and one patient with an index score of 4 had a Grade 5 complication. The age-adjusted index was not associated with the overall rate of Grade 1-2 or Grade 3 complications. For patients with an age-adjusted index of 0-1, 2-3, and ≥4, the overall rate of Grade 1-2 complications was 47% (n = 93/199), 47% (n = 126/271), and 43% (n = 42/97) respectively (p=0.84). Similarly, the overall rate of Grade 3 complications was 18% (n = 36/199), 19% (n = 50/271), and 16% (n = 15/97) respectively (p=0.8).

As the extent of a debulking procedure is related to perioperative complications, we stratified our cohort into three subgroups based on a

surgical complexity score [29]. One hundred and fifty patients (27%) had a surgery of low complexity, two hundred and fifty-five patients (45%) had a surgery of intermediate complexity, and 162 patients (29%) had a surgery of high complexity (Table 8). After this stratification, the age-adjusted index was still not associated with the overall rate of Grade 1-2 or Grade 3 complications.

Table 8: Age-adjusted charlson comorbidity index and perioperative complications based on surgical complexity

Surgical Complexity Score*	**ACCI**	**Patients** n (%)	**Grade 1-2 (Minor) Complications** n (%)	**p**	**Grade 3 (Major) Complications** n (%)	**p**
≤3	0 – 1	40 (27%)	21/40 (52%)	0.64	6/40 (15%)	0.29
	2 – 3	70 (46%)	35/70 (50%)		6/70 (9%)	
	≥4	40 (27%)	17/40 (43%)		2/40 (5%)	
4 – 7	0 – 1	104 (41%)	48/104 (46%)	0.61	11/104 (11%)	0.49
	2 – 3	112 (44%)	56/112 (50%)		14/112 (13%)	
	≥4	39 (15%)	16/39 (41%)		7/39 (18%)	
≥8	0 – 1	55 (34%)	24/55 (44%)	0.67	19/55 (35%)	0.99
	2 – 3	89 (55%)	35/89 (39%)		30/89 (34%)	
	≥4	18 (11%)	9/18 (50%)		6/18 (33%)	

ACCI: Age-adjusted charlson comorbidity index
* Higher score denotes higher surgical complexity

The most common complications were gastrointestinal (n = 146, 26%), followed by wound (n = 131, 23%), infectious (n = 116, 21%), and pulmonary complications (n = 90, 16%) (Table 9). Among the 12 different system-based complications, the age-adjusted index was only significantly associated with cardiovascular complications on univariate analysis: the rate was 3% (n = 6/199), 5% (n = 13/271), and 10% (n = 10/97) for patients with an age-adjusted index of 0-1, 2-3, and ≥4 respectively (p=0.03). However, after adjusting for surgical complexity on logistic regression analysis, that difference was no longer significant (p=0.06).

Table 9: Age-adjusted charlson comorbidity index and complication type (N = 567)

Complication Type	**Total Patients** n (%)	**ACCI 0-1** n = 199 (35%)	**ACCI 2-3** n = 271 (48%)	**ACCI ≥4** n = 97 (17%)	**p**	**Adjusted p***
Infectious	116 (21%)	43 (22%)	55 (20%)	18 (19%)	0.83	0.88
Venous thromboembolism	76 (13%)	18 (9%)	44 (16%)	14 (14%)	0.07	0.1
Hematologic	72 (13%)	21 (11%)	41 (15%)	10 (10%)	0.25	0.47
Gastrointestinal	146 (26%)	52 (26%)	77 (28%)	17 (18%)	0.11	0.14
Genitourinary	46 (8%)	16 (8%)	23 (9%)	7 (7%)	0.93	0.99
Cardiovascular	29 (5%)	6 (3%)	13 (5%)	10 (10%)	0.03	0.06
Pulmonary	90 (16%)	35 (18%)	42 (16%)	13 (13%)	0.63	0.59
Wound	131 (23%)	39 (20%)	67 (25%)	25 (26%)	0.34	0.28

General	14 (3%)	5 (3%)	6 (2%)	3 (3%)	0.89	0.85
Endocrine	2 (0.5%)	0 (0%)	2 (1%)	0 (0%)	0.33	0.99
Musculoskeletal	1 (0.2%)	0 (0%)	0 (0%)	1 (1%)	0.09	0.99
Neurologic	14 (3%)	5 (3%)	4 (2%)	5 (5%)	0.13	0.1

ACCI: Age-adjusted charlson comorbidity index
* P-value adjusting for surgical complexity score

The median PFS and OS for the entire study population were 17.1 months (95% CI, 15.7 – 18.5) and 52.1 months (95% CI, 47.6 – 56.6) respectively, with a median follow-up of 68.1 months (range, 1 – 147.3) for the 181 survivors. The age-adjusted index was significantly associated with PFS and OS (Table 10). Median PFS for patients who had an index score of 0-1, 2-3, and ≥4 was 20.3 months,16 months, and 15.4 months, respectively (p=0.02) (Figure 3). Median OS for patients who had an index score of 0-1, 2-3, and ≥4 was 65.3 months, 49.9 months, and 42.3 months, respectively (p<0.001) (Figure 4). On multivariate analysis, after adjusting for stage, histology, preoperative albumin, ascites volume, residual disease, and intraperitoneal chemotherapy administration, both PFS (p=0.02) and OS (p<0.001) remained significant.

Table 10: Age-adjusted charlson comorbidity index and survival

ACCI	PFS	95% CI	p	Adjusted p*	OS	95% CI	p	Adjusted p*
0 – 1	20.3 m	16.6 – 24	0.02	0.02	65.3 m	54.7 - 75.8	<0.001	<0.001
2 – 3	16 m	14.5 - 17.6			49.9 m	42.9 - 57		
≥4	15.4 m	13 - 17.8			42.3 m	29.9 - 54.8		

ACCI: Age-adjusted charlson comorbidity index; PFS: Progression-free survival; OS: Overall survival; m: months
* P-value adjusting for stage, histology, preoperative albumin, ascites volume, residual disease, and intraperitoneal chemotherapy administration

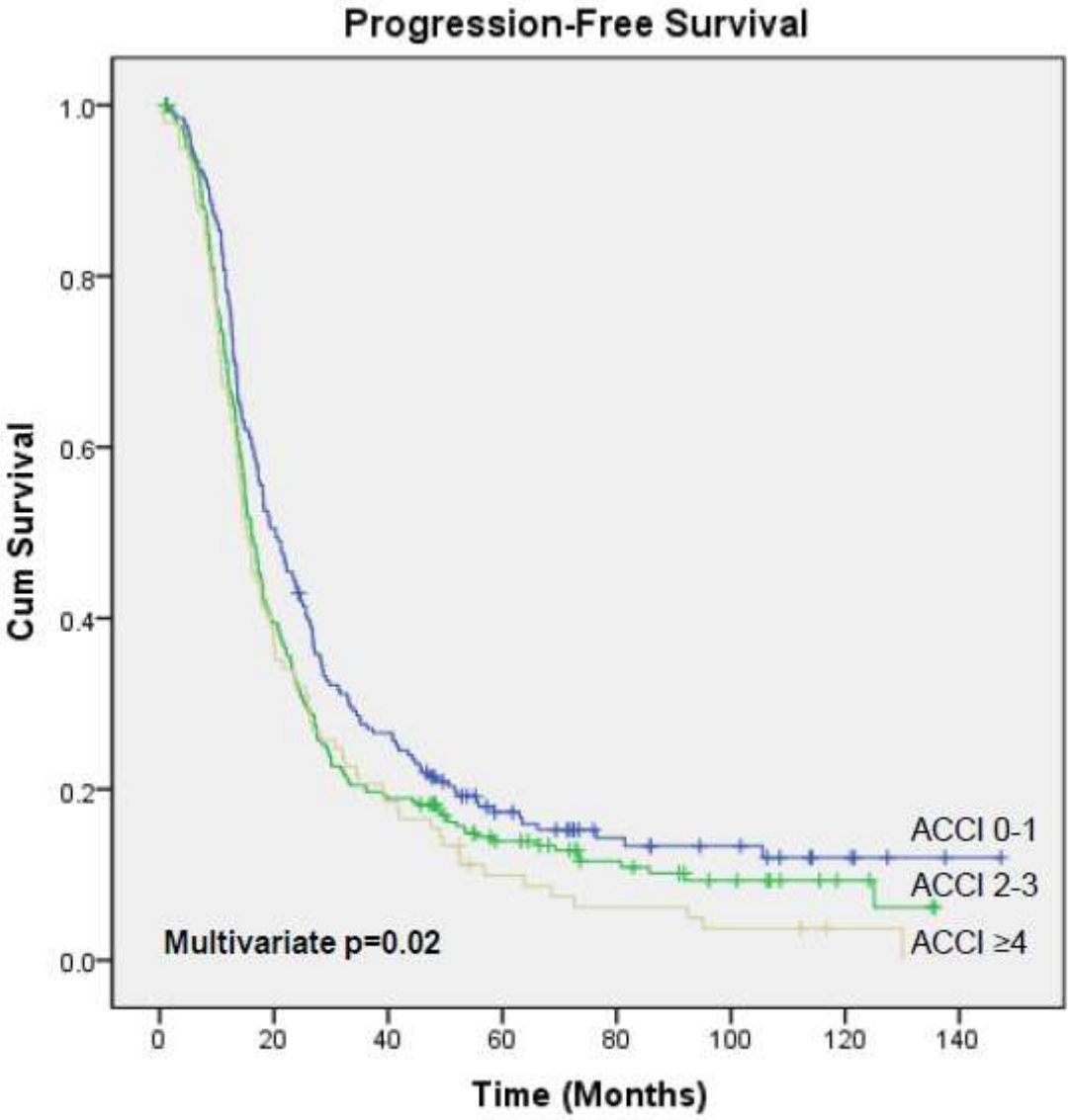

Figure 3: Progression-Free Survival: ACCI 0-1 vs 2-3 vs ≥4

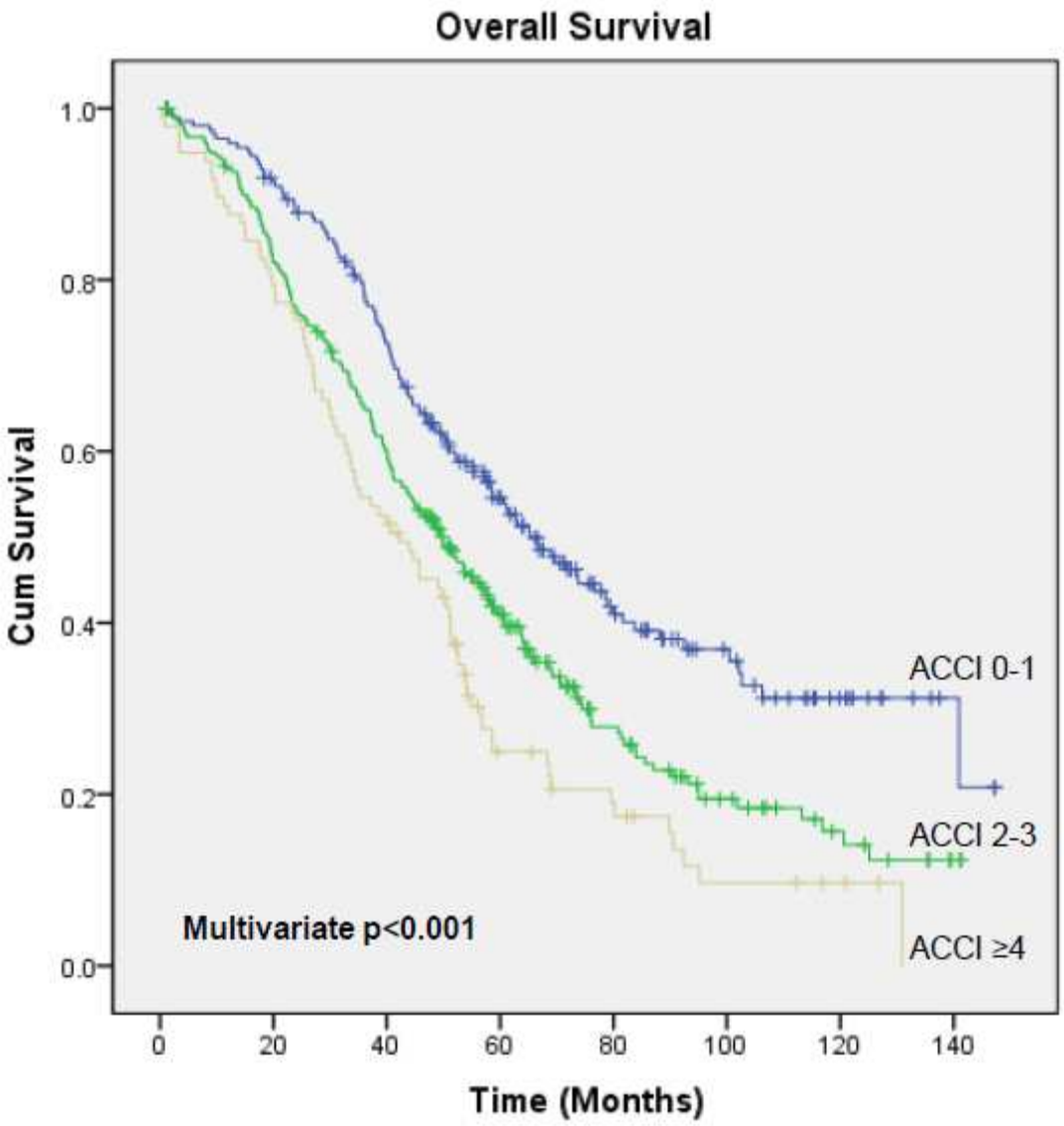

Figure 4: Overall Survival: ACCI 0-1 vs 2-3 vs ≥4

Discussion

In this large institutional cohort of patients undergoing primary cytoreduction for advanced epithelial ovarian, fallopian tube, and peritoneal cancer, the age-adjusted Charlson comorbidity index was a significant predictor of both PFS and OS. It was not associated with minor or major perioperative complications.

Previous investigators have attempted to predict survival outcomes in patients undergoing debulking for ovarian cancer using different prognostic criteria and models [13][14] [22][23][25][26]. Few have used a validated comorbidity score, and we could not identify any studies that used the age-adjusted Charlson comorbidity index. Using a Danish cancer registry, Tetsche et al. evaluated the original Charlson comorbidity index in patients with Stage I-IV disease, and found it to be significantly associated with one and five-year survival [25]. Sperling and colleagues also used a Danish national clinical database to assess patients with all-stage disease, and reported a significant association between the Charlson comorbidity index and OS [26]. Both authors acknowledged the limitations of using administrative databases, including the potential underreporting of comorbidity and misclassification due to reliance on ICD-10 codes. Our study is consistent with those results, but differs in several ways. We used a validated index that not only assessed comorbidity but also took age into account. This is important as age has been found to be an independent prognostic factor for survival [14][32][33]. In addition, we only assessed women with advanced-stage disease, a group that has significantly worse survival outcomes compared to those with early-stage

cancer. We also extracted data directly from medical records, and evaluated both PFS and OS.

It is interesting to note that more patients in the low index group (0-1) had both an optimal debulking outcome and complete gross resection. This suggests that physicians may be more likely to subject patients to an extensive procedure to achieve those outcomes if those patients are younger and/or have less comorbidity. Indeed, patients in the high index group (≥4) comprised 27% of those with a low surgical complexity, compared to 11% of those with a high surgical complexity (Table 8). This is despite the low index group (0-1) having more patients with Stage IV disease. That fact also suggests that patients with an index of ≥4 who were suspected of having Stage IV disease may have been more likely to get neoadjuvant chemotherapy, an outcome not assessed in our study. In addition, the age-adjusted index was not associated with the rate of intraperitoneal chemotherapy administration when only assessing optimally debulked patients. Importantly, the discrepancies mentioned did not affect PFS and OS, as the differences in survival persisted in a multivariate model adjusting for them.

Researchers have also attempted to predict perioperative morbidity in patients undergoing primary debulking [14][21][22][24]. As with survival, there are few reports of a validated comorbidity score being employed in this setting. Using claims data from the Nationwide Inpatient Sample database, Wright et al. showed that the Charlson Comorbidity Index was associated with surgical-site, medical, and infectious complications [21]. The authors recognized that not being able to account for the 'degree' of cytoreduction was an important limitation to their study. On the other hand, our data showed no association

between the age-adjusted index and either minor or major perioperative complications. Our stratification by surgical complexity is a major strength, as the extent of a cytoreductive procedure is correlated with surgical complications, especially when upper abdominal procedures are employed [6][22]. After this stratification, the age-adjusted index was still not associated with either minor or major complications. We also found no association between the index and separate systems-based complications. The use of our adverse events database for our analysis is another strength, in which complications are prospectively reported, classified by system, and graded for severity.

As with our survival analysis, we consider that using a comorbidity index that accounts for age to also be an advantage when assessing perioperative complications. Many providers prefer to administer neoadjuvant chemotherapy for elderly patients, due to a concern for complications and those patients' ability to tolerate them [12][14]. One can hypothesize however, that a healthy 75 year old woman with no comorbidity may be more likely to tolerate an extensive debulking procedure than a 60 year old with significant medical conditions. The rates of both minor and major complications were similar in all age-adjusted index groups in our data, suggesting that patients who are older but have less comorbidity have similar outcomes to those who are younger with more medical problems. This might reinforce the case that healthy elderly women should not be denied the possible benefits of optimal primary debulking and subsequent intraperitoneal therapy based on age alone [14].

The main limitation of our study is the retrospective nature of our analysis. The age-adjusted index was calculated based on comorbidity

reported by patients at the initial visit with the gynecologic oncologist. It is possible that some comorbid conditions may have been underreported by patients at that visit, or undiagnosed at that time. We addressed this by reviewing records from medical clearance notes, outside referring provider documentation, and interdisciplinary consultations, with minimal discrepancy found. We also did not take into account subsequent medical conditions that patients developed during their follow up course, which may have ultimately impacted their survival. We chose not to as the main aim of our study was to predict perioperative complications and survival based on the age-adjusted index at the time of debulking. Despite its validation in numerous populations, the use of the age-adjusted comorbidity index has its own limitations. Owing to advances in medical treatment of different conditions, the survival impact of the comorbid conditions included in its summation may be different today than when the index was developed [16][20].

In addition to being a prognostic factor for survival, our results suggest that the age-adjusted index may have important implications in ovarian cancer research as well. As demonstrated in our data, median PFS decreased from 20.3 months to 15.4 months for patients who had an ACCI of 0-1 and ≥4, respectively. Median OS also decreased from 65.3 months to 42.3 months, respectively. Not accounting for these differences in survival, or considering age or comorbidity alone when designing a trial may lead to an imbalance of patients in different arms, and significant confounding of treatment effects.

In conclusion, the age-adjusted Charlson comorbidity index was significantly associated with survival outcomes in patients undergoing primary debulking for advanced epithelial ovarian, fallopian tube, and peritoneal

cancer. It was not predictive of minor or major perioperative complications. Further investigation is needed to identify women who are at high risk for operative morbidity. Prospective clinical trials in ovarian cancer should consider stratifying for an age-comorbidity covariate.

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