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# 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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## HIGHLIGHTS

- The Age-Adjusted Charlson Comorbidity index was a significant predictor of survival in patients undergoing primary cytoreduction for ovarian cancer.
- The index was not associated with minor or major perioperative complications at primary debulking.

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## ABSTRACT

*Objective.* To assess the ability of the Age-Adjusted Charlson Comorbidity Index (ACCI) to predict perioperative complications and survival in patients undergoing primary debulking 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 20.3, 16, and 15.4 months, respectively ($p = 0.02$). Median OS for patients with an ACCI of 0–1, 2–3, and ≥4 was 65.3, 49.9, and 42.3 months, 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.



## 1. 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' versus 'suboptimal' cytoreduction [3,4].

In order to achieve optimal surgical outcomes, primary debulking surgery is often lengthy and complex, requiring bowel resection and/or aggressive upper abdominal surgery [5]. Such extensive procedures are commonly associated with significant perioperative complications

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[6–11]. 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 [12–15]. This is subjective and surgeon dependent, however, and there is no consensus 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 [17–19]. 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 (ACCI), which has also been validated [20].

Researchers have attempted to predict morbidity and/or survival in patients undergoing primary cytoreduction using a variety of prognostic factors and models [13,14,21–26]. However, there are limited data assessing the prognostic significance of a validated comorbidity index on these outcomes. The objective of our study was to assess the ability of the ACCI to predict perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian, fallopian tube, or peritoneal cancer.

## 2. Patients and 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 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, time to adjuvant chemotherapy, and intraperitoneal chemotherapy administration.

The ACCI 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 1 [20]. The overall score is calculated based on the total of each patient's comorbid conditions (weighted according to severity) and age. As all patients had advanced epithelial ovarian cancer, that specific condition was excluded from the scoring system. Patients were categorized into three groups based on an ACCI of 0–1 (low), 2–3 (intermediate), and ≥4 (high).

**Table 1**
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 up to 30 days postoperatively are collected for all patients. The database is maintained by a research project manager who reviews the medical record of all surgical patients weekly in that time period, then confirms complications with the patients' surgeons. Additionally, attending physicians fill out an adverse events sheet at the time of the postoperative visit, and notify the research manager if patients present to the emergency room and are diagnosed with adverse events. 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 the death of the 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 ACCI 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 [29], that score is calculated based on the specific procedures performed in a cytoreductive case and classifies surgeries into low-, intermediate-, and high-complexity cases. We then performed a secondary analysis, assessing the association between the ACCI and complications within those subgroups. The ACCI was also evaluated for its ability to predict specific system-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. OS included death due to comorbid conditions, and was not disease-specific. Patients who were lost to follow-up were censored from the analysis.

Categorical variables were compared using the $\chi^2$ test, and continuous variables were compared using the Kruskal–Wallis test. All statistical tests were two-sided, with a p value of $<0.05$ considered significant. When testing the association between the ACCI and specific system-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