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A new clinically applicable age-specific comorbidity index for preoperative risk assessment of ovarian cancer patients

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HIGHLIGHTS

- Self-reported comorbidity is useful for risk-assessment in ovarian cancer.
- This new comorbidity index risk-scores patients according to overall survival.
- The index may help to ensure individualized treatment of ovarian cancer patients.

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ABSTRACT

Objective. To develop and validate a new feasible comorbidity index based on self-reported information suited for preoperative risk assessment of ovarian cancer patients.

Methods. The study was based on patient self-reported data from ovarian cancer patients registered in the Danish Gynecological Cancer Database between January 1, 2005 and December 31, 2012. The study population was divided into a development cohort (n = 2020) and a validation cohort (n = 1975). Age-stratified multivariate Cox regression analyses were conducted to identify comorbidities significantly impacting five-year overall survival in the development cohort, and regression coefficients were used to construct a new weighted comorbidity index. The index was applied to the validation cohort, and its predictive ability in regard to overall and cancer-specific five-year-survival was investigated. Finally, the performance of the new index was compared to that of the Charlson Comorbidity Index.

Results. Regression coefficients of age and five comorbidities (atherosclerotic cardiac disease, chronic obstructive pulmonary disease, diabetes, dementia and hypertension) were included in the new comorbidity index. The validation study found the new index to be significantly associated to both overall survival (HR 1.44, $p = 0.013$) and cancer-specific survival (HR 1.51, $p = 0.017$) in multivariate analyses adjusted for other prognostic factors. The index was a significantly better predictor than the Charlson Comorbidity Index.

Conclusion. This new age-specific comorbidity index based on self-reported information is a significant predictor of overall and cancer-specific survival in ovarian cancer. It can be used to quickly identify those ovarian cancer patients requiring special attention in terms of preoperative optimization and postoperative care.

1. Introduction

Ovarian cancer is often diagnosed in women older than 65 years who also have other chronic diseases called comorbidity [1,2]. Cancer patients with comorbidity places higher demands on health care resources, experience decreased quality of life and poorer prognosis [3,4]. Despite extensive research during the last three decades, comorbidity remains a major challenge to the health care system and to researchers. Evidence on how to account for comorbidity in clinical practice, when designing clinical trials or developing clinical practice guidelines is still sparse, which partly is explained by the fact that

Abbreviations: CCI, Charlson Comorbidity Index; ECI, Elixhauser Comorbidity Index; ACE-27, Adult Comorbidity Evaluation-27; NACT, neoadjuvant chemotherapy; DGCD, Danish Gynecological Cancer Database; DNPR, Danish National Patient Register; DRCD, Danish Register of Causes of Death; OS, overall survival; CI, Confidence Interval; HR, Hazard Ratio; RC, regression coefficient; C-index, Classification-index; FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index; PS, performance status; OCCI, Ovarian Cancer Comorbidity Index.

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elderly and/or comorbid patients often have been excluded from clinical trials [5–7].

A fundamental challenge to clinicians and researchers is how to identify and obtain a useful measurement of the "comorbidity burden". Several methods of varying complexity have been proposed [8]. Some researchers have merely counted the number of comorbidities or have focused only on a few of the most prevalent comorbidities. Others have classified comorbidity according to an index and thereby obtaining a comorbidity risk score. Most of these indices were proposed and validated on non-cancer study populations but have later been applied to studies of comorbidity in cancer patients. The most commonly used is the Charlson Comorbidity Index (CCI) [9], but also the Elixhauser Comorbidity Index (ECI) [10], the National Cancer Institute Index [11] and the Adult Comorbidity Evaluation-27 (ACE-27) [12,13] are indices commonly used for research. A dilemma that commonly confronts researchers constructing comorbidity indices is that of obtaining maximum sensitivity (i.e., including many different diagnoses and addressing severity, and acuteness) vs. gaining clinical feasibility. Introducing some simplicity would be beneficial in order to ensure routine assessment of comorbidity in a clinical setting.

Standard treatment for the majority of ovarian cancer patients is extensive surgery followed by adjuvant chemotherapy. Patients not fit for this aggressive treatment due to severe comorbidity and patients with macroscopic unresectable tumors may instead be offered neoadjuvant chemotherapy (NACT) followed by debulking surgery. The aim of the present study is to develop and validate a new comorbidity index suited specifically for preoperative risk assessment in ovarian cancer. The new index should be simple and quick to use and hence applicable in a busy clinical setting. It is our goal that the new index will provide health care takers with a feasible tool for risk assessment once a patient with comorbidity is referred to ovarian cancer treatment.

2. Materials and methods

2.1. Study design

The study is a methodologic population-based cohort study using data from ovarian cancer patients registered in the Danish Gynecological Cancer Database (DGCD) from January 1, 2005 till December 31, 2012. The study population was separated into two cohorts: a development cohort used for comorbidity index development and a validation cohort used for comorbidity index validation. Follow-up for all included patients ended on January 17, 2015.

2.2. Study population

For the development cohort we identified all patients registered in the DGCD from January 1, 2005 to December 31, 2008 with a diagnosis of ovarian, peritoneal or fallopian tube cancer (n = 2571). Borderline tumors were excluded (n = 546) and three patients were excluded because of age ≤ 15 years. Two patients were lost to follow-up and a total of 2020 patients were included in the cohort.

The validation cohort consisted of 2586 patients with a diagnosis of ovarian, peritoneal or fallopian tube cancer in the period January 1, 2009 to December 31, 2012. Borderline tumors were excluded (n = 604), five patients were excluded due to age ≤ 15 years and two patients were lost to follow-up. A total of 1975 patients were included in the cohort.

2.3. Outcome measures

The primary outcome measure, used to select comorbidities for the index, was overall survival (OS) up to five years defined as time (months) from date of primary surgery to death from any cause or to the end of the follow-up period (censored). For patients not having primary surgery, the date of the decision to refrain from primary operation was used as the starting date. Our secondary outcome measure, used in the validation study, was cancer-specific survival defined as time (months) from date of primary surgery to death from ovarian cancer or to the end of the follow-up period.

2.4. Data sources

DGCD is a nationwide database containing key clinical information on Danish patients diagnosed with gynecological cancers since January 1, 2005 [14]. Reporting to the database is mandatory and data completeness is of 97% according to the most recent annual report from the database. For each patient, detailed information on tumor and patient characteristics including comorbidity are registered. Information on comorbidity is based on a specially developed questionnaire filled out by the patient upon referral to a specialized gynecological department. The doctor goes through the questionnaire together with the patient during first consultation and may validate information by cross-checking with the patient file. In order to investigate important differences between self-reported comorbidity from the DGCD and administrative data, we also collected information on comorbidity from the Danish National Patient Register (DNPR) [15]. Data from the DNPR was linked via the unique person-identification number, which is assigned to all residents upon birth or immigration [16]. DNPR contains information on all out-patient and in-hospital contacts on citizens in Denmark including primary and secondary diagnoses for each contact. By combining diagnoses from three comorbidity indices all validated in cancer populations (CCI, ACE-27 and ECI), we constructed a comprehensive list of ICD-10 codes separated into 44 comorbidity-groups (Supplementary S1) [13,17] and searched for those in the DNPR. To avoid out-dated information on comorbidity we only included secondary diagnoses registered within 10 years of the ovarian cancer diagnosis. A time-window of 90 days before the cancer diagnosis was also applied when extracting data in order to avoid classification of the ovarian cancer as comorbidity.

Data on cause of death was obtained from the Danish Register of Causes of Death (DRCD) [18] and linkage was performed with the person-identification number.

The study was approved by the Danish Data Protection agency (file. no. 30-1213). According to Danish law, approval from the Committee on Health Research Ethics was not required, as no direct patient intervention was part of the study.

2.5. Statistical analyses – index development

Comorbidities registered in the DGCD and the DNPR with a prevalence of >20 observations equal to 1% were identified in the development cohort. Each comorbidity was analyzed in a univariate Cox model and finally in a multivariate Cox model. The final model was reduced in a backwards fashion based on the Akaike criterion. Model assumptions were assessed using cumulative sum of martingale residuals. A linear predictor of 5-year OS using the pre-specified comorbidities was estimated using the Cox proportional hazards model stratified by age grouped as <45 years, 45–54 years, 55–64 years, 65–74 years, and ≥75 years.

The Classification-index (C-index) was calculated as a measure of discrimination [19]. Tenfold cross validations and 100 bootstraps were performed to assess the problem of over-fitting.

2.6. Obtaining an index score

To obtain a simple and clinically feasible measurement of risk associated to comorbidity the resulting predictor was categorized as low, medium and high risk. A patient was considered in high-risk if the estimated survival probability was <75% at 6 months, medium risk if estimated 75% survival probability was between 6 and 24 months and low risk if the estimated survival probability was at least 75% at 2 years. The thresholds for the risk groups were calculated based on