AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS MAIN RESEARCH ARTICLE

Comorbidity is an independent prognostic factor in women with uterine corpus cancer: a nationwide cohort study

METTE C. NOER[1], CECILIE SPERLING[2], Ib J. CHRISTENSEN[3], MARIE L.S. NIELSEN[4], ØJVIND LIDEGAARD[1] & CLAUS HØGDALL[1]

[1]Gynecologic Clinic, Rigshospitalet University Hospital, University of Copenhagen, [2]Quality and Patient Safety, Danish Cancer Society, [3]Finsen Laboratory, Rigshospitalet University Hospital, and Biotech Research and Innovation Centre (BRIC), University of Copenhagen, and [4]Section of Clinical Information & Data and Center of Quality and Health Information East, Copenhagen, Denmark

Key words
Uterine corpus cancer, comorbidity, survival, Charlson Comorbidity Index, prognostic factor, performance status

Correspondence
Mette C. Noer, Gynecologic Clinic, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail: mette.calundann.noer@regionh.dk

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Noer MC, Sperling C, Christensen IJ, Nielsen MLS, Lidegaard Ø, Høgdall C. Comorbidity is an independent prognostic factor in women with uterine corpus cancer: a nationwide cohort study. Acta Obstet Gynecol Scand 2014; 93:325–334.

Received: 29 June 2013
Accepted: 12 January 2014

DOI: 10.1111/aogs.12338

Abstract

Objective. To determine whether comorbidity independently affects overall survival in women with uterine corpus cancer. *Design.* Cohort study. *Setting.* Denmark. *Study population.* A total of 4244 patients registered in the Danish Gynecologic Cancer database with uterine corpus cancer from 1 January 2005 until 13 October 2011. *Methods.* All patients included in the study were assigned a comorbidity score according to the Charlson Comorbidity Index. Multivariate survival analyses were performed to investigate the prognostic impact of comorbidity adjusting for known prognostic factors. As performance status might capture the prognostic impact of comorbidity and because information on the variable grade was missing in some special histological subtypes, we included different models in the multivariate analyses with and without PS and grade, respectively. *Main outcome measures.* Overall survival. *Results.* Univariate survival analysis showed a significant ($p < 0.001$) negative association between increasing level of comorbidity and overall survival. Multivariate analyses adjusting for other prognostic factors showed that comorbidity is a significant independent prognostic factor with hazard ratios ranging from 1.27 to 1.42 in mild, 1.69 to 1.74 in moderate, and 1.72 to 2.48 in severe comorbidity. Performance status was independently associated to overall survival and was found to slightly reduce the prognostic impact of comorbidity. *Conclusion.* Comorbidity is an independent prognostic factor in uterine corpus cancer and increasing levels of comorbidity are associated with shorter survival.

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CCS, Charlson comorbidity score; CI, confidence interval; DGCD, Danish Gynecological Cancer Database; EC, endometrial carcinoma; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OS, overall survival.

Introduction

Uterine corpus cancer is the most common malignancy of the female genital tract, and the 5-year survival is approximately 75% (1). Endometrial carcinoma (EC) accounts for 95% of the malignant tumors in the uterine corpus. The remaining 5% are sarcomas. Tumor stage has

Key Message

Comorbidity classified according to the renowned Charlson Comorbidity Index is an independent prognostic factor in uterine corpus cancer. This significant finding demonstrates the need for individualized treatment strategies when treating cancer patients with comorbidity.

been demonstrated to be the most important prognostic factor in uterine corpus cancer. However, tumor grade, histology, and age are also factors found to influence survival significantly (2,3).

Comorbidity, defined as the presence of other diseases not related to the index disease, is another possible prognostic factor that should be considered. Comorbidity has been shown to be a significant prognostic factor in indolent cancer types such as breast cancer and prostate cancer, but the evidence of comorbidity as a prognostic factor in uterine corpus cancer is limited (4,5).

Existing studies of comorbidity in uterine corpus cancer have been conducted among patients with EC and most of those studies have focused exclusively on medical comorbidities associated with the metabolic syndrome (obesity, diabetes mellitus, cardiovascular disease, hypertension). Results suggest that comorbidity related to the metabolic syndrome might be an important prognostic factor in EC (6–9). There is, however, a need for further investigations to clarify if comorbidity classified according to a validated comorbidity index is prognostic in all subtypes of uterine corpus cancer.

The objective of this study was to determine whether comorbidity has an impact on the survival of women diagnosed with uterine corpus cancer when adjusting for other prognostic factors.

Material and methods

This cohort study was based on data from the Danish Gynecologic Cancer Database (DGCD), which is a nationwide clinical database. The DGCD contains data from 97% of Danish patients diagnosed with gynecological cancers since 1 January 2005. For each patient, detailed clinical information on preoperative biopsy diagnosis and patient characteristics including comorbidity are registered. The information on comorbidity is based on a specially developed questionnaire filled out by the patient with the help of the gynecologist upon referral to a specialized gynecological department. This method ensures that registration of comorbidity in the DGCD is based on active secondary diseases affecting the daily life of the patient. Information on the surgical procedure, final pathology, and complications are also registered in the database. Only patients with final registration and validation were included. The study was approved according to rules of the Danish Medical Committee concerning the use of data for register-based studies, and the DGCD is approved by the Data Protection Agency.

We identified 4722 patients registered with uterine neoplasia in the DGCD from 1 January 2005, until the end of the follow-up period on 13 October 2011. Patients with atypia where excluded ($n = 416$), as well as patients with missing date of surgery ($n = 25$) and patients lost to follow-up ($n = 37$). Hence, a total of 4244 cases of uterine corpus cancer were included in the study population. The outcome measure was overall survival (OS) defined as time from date of surgery to death from any cause or to the end of the follow-up period. For varying reasons, 183 patients did not undergo primary surgery, and for these patients, the date of decision about refraining from surgery was used as the starting point.

The Charlson Comorbidity Index (CCI) is one of the most well-known and validated methods for classifying comorbidity (10–12). Table 1 shows the translation of comorbidity registered in the DGCD to a modified version of the CCI and the correlating comorbidity score. An overall Charlson comorbidity score (CCS) for each patient was calculated, and patients were stratified into groups with no (CCS = 0), mild (CCS = 1), moderate (CCS = 2), or severe (CCS $\geq$ 3) comorbidity. A total of 19 conditions registered in DGCD were not found to correlate with any of the conditions included in the CCI. Patient with these diagnoses were therefore considered to have non-prognostic comorbidity and were assigned a CCS of 0. Information on non-prognostic comorbidity is presented in Table 2.

The International Federation of Gynecology and Obstetrics (FIGO) stage classifications were used for both EC and sarcoma. In 2009, FIGO published a revised version of the stage classification for EC. Because most patients with EC included in the present study were registered according to the old FIGO stage classification, we classified all EC patients according to the old FIGO stage classification.

Histology was classified into the following categories: endometrial adenocarcinoma, clear cell adenocarcinoma, carcinoma (including carcinosarcoma), sarcoma and rare types.

Adenocarcinomas were categorized according to grade: the categories were highly differentiated cells (Grade 1), moderately atypical cells (Grade 2) and undifferentiated cells (Grade 3). Other histological subtypes are according to guidelines only graded to a very limited extent. This explains the missing information on grade in almost 11% of the tumors. The nutritional status of the patients was classified with the body mass index (BMI) according to the WHO definition: underweight (BMI $\leq$ 18.5), normal weight (18.5 > BMI $\leq$ 25), and overweight/obesity (25 > BMI). The category residual tumor describes the presence of macroscopic residual tumor tissue after surgery and the categories were no macroscopic residual and macroscopic residual tumor. The Eastern Cooperative Oncology Group's scale for performance status was used (13).

Table 1. Translation of secondary diagnosis in the DGCD to a comorbidity score according to the CCI.

Secondary diagnosis registered in the DGCD	ICD-10 code correlating to condition in the CCI	Condition in the original CCI	Comorbidity score
Myocardial infarct	I21.x, I22.x, I25.2	Myocardial infarction	1
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0,I42.5–I42.9, I43.x, I50.x, P29.0	Congestive heart failure	1
Universal arteriosclerosis Arteriosclerosis in cardiac vessels	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	Peripheral vascular disease	1
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1	Dementia	1
Asthma chronic bronchitis COLD	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3	Chronic pulmonary disease	1
Unspecified arthritis	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0	Connective tissue disease	1
Liver disease:[a] Alcoholic liver disease (unspecified) Acute and sub acute liver insufficiency	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4 I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	Liver disease (mild and moderate/severe)	1
Not registered in the DGCD[b]	K25.x–K28.x	Ulcer disease	1
Cerebral infarct and hemiplegia[c]	G45.x, G46.x, H34.0, I60.x–I69.x G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9	Cerebral vascular disease and hemiplegia	1
Diabetes[d]	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7	Diabetes with and without end organ damage	1
Chronic kidney insufficiency	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2	Moderate or severe renal disease	2
Non-uterine cancer disease including leukemia and lymphoma[e]	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x-C53x, C56–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x The codes for uterine cancer C54x-C55x has been excluded in our study of comorbidity.	Any tumor including leukemia and lymphoma	2
Other metastatic cancer[e]	C77.x–C80.x	Metastatic solid tumor	6
HIV and AIDS	B20.x–B22.x, B24.x	AIDS	6

DGCD, Danish Gynecological Cancer Database; CCI, Charlson Comorbidity Index; COLD, Chronic obstructive lung disease; CCS, Charlson comorbidity score; ICD-10, International Classification of Diseases 10th revision.

[a]The original CCI contains the category "moderate or severe liver disease," which correlates with a CCS of 3. In the DGCD, only the presence of liver disease but not the severity of the disease has been registered. Hence, all patients with liver disease have been assigned a CCS of 1 in our study.

[b]Peptic ulcer disease has not been registered separately in the DGCD, and patients with gastrointestinal diseases in our study have been assigned a CCS of 0.

[c]The condition hemiplegia correlating with a CCS of 2 in the original CCI has not been registered separately in the DGCD. Patients with this complication with cerebral infarction are therefore included in the category "cerebrovascular disease" and assigned a CCS of 1 in our study.

[d]The original CCI distinguishes between "diabetes" correlating with a CCS of 1 and "diabetes with end organ damage" correlating with a CCS of 2. In the DGCD, the presence of diabetes has been reported, but information on complications has not been registered. Conservatively, we have assigned all patients with diabetes a CCS of 1.

[e]The DGCD only contains information on gynecological cancers; information on other cancers (including leukemia and lymphoma) and/or metastases was obtained from the National Patient Registry. When extracting information on discharge diagnoses from the National Patient Registry, we excluded cancers and metastases registered <90 days before the uterine corpus cancer was diagnosed. This 90 days' time window was used to avoid any misclassification of the uterine corpus cancer as an existing comorbidity.

Statistical analyses

Data were analyzed using SPSS statistical software version 20 (IBM Corp., Armonk, NY, USA). Relations between comorbidity and other characteristics of patient, tumor and treatment were analyzed using chi-squared tests for independence. Kaplan–Meier survival statistics was used for calculating CCS-specific OS rates, and survival curve differences were tested using log-rank tests. Multivariate Cox regression analyses were performed to detect associations between survival and comorbidity adjusting for potential confounders.

Table 2. Non-prognostic comorbidity registered in the DGCD.

Comorbidity registered in the DGCD	*n*	%
Hypertension	1528	36.0
Myxoedema	131	3.1
Depression (periodic)	103	2.4
Thyreotoxicosis	63	1.5
Osteoarthritis	52	1.2
Angina pectoris	42	1.0
Epilepsy	22	0.5
Unspecified tachycardia	16	0.4
Alcohol-dependent syndrome	14	0.3
Constipation	9	0.2
Confusion	7	0.2
Ventral hernia (postoperative)	6	0.1
Sideropenic anemia	4	0.0
Irritable bowel disease	4	0.0
Enteritis (unspecified)	4	0.0
Diarrhea/gastroenteritis	4	0.0
Fecal incontinence	3	0.0
Sexual neurosis	1	0.0
Myositis	1	0.0

DGCD, Danish Gynecological Cancer Database.

Grade is a known prognostic factor in endometrial adenocarcinoma, which is the most common histological subtype in uterine corpus cancer. Other histological subtypes are however only graded to a very limited extent. To achieve the best possible estimate of the prognostic impact of comorbidity, we had to adjust for both the variable grade and the variable histological subtype. We therefore conducted two different Cox regression analyses: Cox A (Table 5): all tumors of the uterine corpus and *not* the variable grade and Cox B (Table 6): Only endometrial adenocarcinomas *and* the variable grade.

Performance status might capture some of the prognostic impact of comorbidity because patients with comorbidity are suspected to have higher performance status (poorer daily performance). To further investigate this relation, we included two models in the multivariate analyses (model I and model II) without and with performance status, respectively. The assumption of proportional hazards was assessed using Schönfeld residuals, and the assumption was not rejected. No significant interactions were observed between comorbidity and the other variables. Sensitivity analyses demonstrated no significant changes in hazard ratios (HRs) in the study period. Significance was defined at $p < 0.05$.

Results

General characteristics of the study population are shown in Table 3. The distribution of age showed that 74.5% were older than 60 years and 20.2% had died at follow-up in October 2011. Complete surgical tumor debulking was achieved in 91.2%. This reflects that most patients presented with early-stage disease (81.3% FIGO I–II). EC [including the histological subtypes endometrial adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, and carcinoma (including carcinosarcoma)] accounted for 94.5% of the tumors, whereas sarcomas were diagnosed in 3.9% patients. Overweight/obesity was observed more often in patients with EC compared with sarcoma, 63.0 vs. 48.7%, respectively (data not shown).

The prevalence of comorbidities in the study population is shown in Table 4. No prognostic comorbidity was registered in 73.0% of patients in the study population. A total of 17.0% had mild comorbidity, 7.3% had moderate comorbidity, and 2.8% had severe comorbidity. Diabetes and peripheral vascular diseases were the most common Charlson comorbidities. Kaplan–Meier survival curves according to CCS are presented in Figure 1. We observed that an increasing level of comorbidity was significantly associated to shorter OS ($p < 0.001$). Cox regression analyses identified comorbidity, performance status, age, and BMI as patient-related variables independently associated with OS (Tables 5 and 6). In Cox A, HRs for comorbidity were 1.27 [95% confidence interval (CI), 1.04–1.55], 1.69 (95% CI 1.32–2.16) and 1.72 (95% CI 1.21–2.45) in mild, moderate and severe comorbidity, respectively (model II). A more pronounced prognostic impact of comorbidity was observed in the population of patients with endometrial adenocarcinoma (Cox B). In this analysis, comorbidity was associated with an HR of 1.42 (95% CI 1.11–1.82), 1.74 (95% CI 1.27–2.40) and 2.48 (95% CI 1.61–3.86) in mild, moderate, and severe comorbidity, respectively (model II). In both Cox regression analyses, a minor decrease in the HR for comorbidity was observed in model II compared with model I.

Stage and grade were tumor variables found to be strongly predictive of OS (Tables 5 and 6). Also the histological subtypes serous adenocarcinoma, carcinoma (including carcinosarcoma), sarcoma, and rare types were associated with a significantly increased mortality compared with endometrial adenocarcinoma in both univariate (data not shown) and multivariate analyses. In contrast, clear cell adenocarcinoma was only significant in univariate analysis (HR 2.20; 95% CI 1.52–3.20) but was not significant in the multivariate analyses (HR 1.13; 95% CI 0.71–1.8) (model II). The treatment variable macroscopic residual tumor was predictive of poor prognosis with HRs of 2.50 (95% CI 1.98–3.17) and 2.41 (95% CI 1.75–3.32) in Cox A and Cox B, respectively, compared with no macroscopic residual.

A total of 183 patients in the study population did not receive surgical treatment. Reasons for abstaining from

Table 3. General characteristics of the study population, $n = 4244$.

Covariates	Total *n*	Total %[a]	CCS = 0 %[b]	CCS = 1 %[b]	CCS = 2 %[b]	CCS ≥ 3 %[b]	Chi-square, *p*-value
Comorbidity							
CCS = 0	3097	73.0	–	–	–	–	
CCS = 1	720	17.0					
CCS = 2	309	7.3					
CCS ≥ 3	118	2.8					
Events	857	20.2	–	–	–	–	
Age							
<49 years	218	5.1	85.8	10.1	3.7	0.5	<0.001
50–59 years	862	20.3	81.7	11.3	5.0	2.1	
60–69 years	1484	35.0	75.1	16.2	6.9	1.8	
70–79 years	1071	25.2	67.7	20.4	8.1	3.8	
>80 years	609	14.3	60.3	23.3	11.2	5.3	
FIGO stage							
I	2894	68.2	73.5	17.1	7.2	2.2	<0.001
II	558	13.1	72.2	16.8	7.5	3.4	
III	548	12.9	72.4	16.6	8.4	2.6	
IV	170	4.0	73.5	12.4	5.3	8.8	
Missing information	74	1.7	60.8	24.3	6.8	8.1	
Histology							
Endometrial adenocarcinoma	3511	83.2	73.2	17.2	6.9	2.6	0.047
Clear cell adenocarcinoma	93	2.2	73.1	15.5	8.6	3.2	
Serous adenocarcinoma	190	4.5	72.1	13.7	10.5	3.7	
Carcinoma (including carcinosarcoma)	199	4.7	66.3	19.1	10.1	4.5	
Sarcoma	166	3.9	80.7	9.6	7.8	1.8	
Rare types	60	1.4	60.0	26.7	8.3	5.0	
Missing information	25	0.6	76.0	20	0	4.0	
Grade							
Grade 1 (highly differentiated cells)	2204	51.9	73.3	17.5	6.9	2.4	0.212
Grade 2 (moderately atypical cells)	1011	23.8	74.5	16.0	7.0	2.5	
Grade 3 (undifferentiated cells)	567	13.4	70.7	16.8	8.5	4.1	
Missing information	462	10.9	71.0	16.7	8.4	3.9	
Nutritional status							
Normal weight: 18.5 > BMI ≤ 25	1461	34.4	81.4	10.5	6.4	1.7	<0.001
Overweight/obesity: 25 > BMI	2563	60.4	68.9	20.4	7.5	3.2	
Underweight: BMI ≤ 18.5	94	2.2	68.1	17.0	10.6	4.3	
Missing information	126	3.0	62.7	21.4	10.3	5.6	
Residual tumor							
No macroscopic residual	3875	91.3	73.8	16.7	7.1	2.4	0.025
Macroscopic residual tumor	221	5.2	68.8	16.7	9.0	5.4	
Missing information	148	3.5	58.1	23.0	10.1	8.8	
ECOG performance status							
0: Asymptomatic	2682	63.3	82.2	10.4	5.7	1.0	<0.001
1: Few signs of disease	1139	26.9	61.2	27.0	7.6	4.1	
2: Out of bed >50% of the day	272	6.4	41.9	34.6	16.2	7.4	
3: Confined to bed >50% of the day	116	2.7	39.7	25.9	16.4	18.1	
4: Bedbound	30	0.7	46.7	23.3	23.3	6.7	
Missing information	5	0.1	80.0	20.0	0.0	0.0	

BMI, body mass index; CCS, Charlson comorbidity score; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

[a]Column percent.

[b]Row percent.

Table 4. Comorbidity registered among patients in the cohort.

Diagnosis	*n*	%	Comorbidity score
Myocardial infarction	44	1.0	1
Congestive heart failure	73	1.7	1
Peripheral vascular disease	217	5.1	1
Dementia	45	1.1	1
Chronic pulmonary disease	190	4.5	1
Unspecified arthritis	103	2.4	1
Cerebral infarction and hemiplegia	49	1.2	1
Diabetes	438	10.3	1
Chronic kidney insufficiency	7	0.2	2
Non-uterine cancer (including leukemia and lymphoma)	249	5.9	2
Other metastatic cancer	24	0.6	6
HIV and AIDS	1	0.0	6

surgery were patient refusal (n = 24), poor patient condition (n = 85) and primary oncologic treatment (n = 56). For 18 patients, no reason was recorded in the DGCD. As comorbidity might affect all these reasons for abstaining from primary surgery, a multivariate logistic regression analysis was performed. The variables age, stage, grade, histology, macroscopic residual tumor, BMI, and performance status were included in the regression analysis, and the treatment procedure (operation vs. no operation) was the dependent variable. Comorbidity was insignificant in this analysis (p = 0.42).

Discussion

To our knowledge, this is the largest European study of prognostic factors in uterine corpus cancer and it is unique by including all histological subtypes of malignant tumors of the uterine corpus. We identified comorbidity as an independent prognostic factor adjusted for other known prognostic factors. We also found a clear association between increasing levels of comorbidity and OS.

Few other studies have investigated the impact of comorbidity classified according to a validated comorbidity index and results are diverging (14–19). For example, in a study conducted by Boll et al. (14) among 2099 women with stage I EC. In this study there was a significant correlation between 5-year OS and a number of comorbidities classified according to a modified version of the CCI observed. In contrast, Truong et al. (18) did not find any significant independent impact of comorbidity on survival in 401 women diagnosed with EC. The inconsistency in results calls for more investigations paying careful attention to the method of classifying comorbidity to obtain comparable results.

We observed a minor decrease in the HR of comorbidity when adjusting for performance status in the multivariate analyses. This suggests that some of the prognostic impact of comorbidity is explained by higher performance status among patients with comorbidity, but comorbidity retained a significant impact on OS not explained by performance status. Our finding of comorbidity and performance status being independent measures corresponds to conclusions drawn in other studies (20–22).

In accordance with other studies, we also observed that a BMI > 18.5 is a significantly better prognostic variable than BMI < 18.5 (8,9). A plausible explanation for this finding is that obesity is known to be associated with estrogen-dependent type I EC, which is more indolent than type II. It is also plausible that low weight can be due to wasting associated with advanced malignant disease, suggesting an association between advanced stage and low BMI.

We found that serous adenocarcinoma, carcinoma (including carcinosarcoma), sarcoma, and rare types of tumors are histological subtypes significantly associated with higher mortality. This is in agreement with the findings of previously published research. Clear cell histology is also usually associated with a poor prognosis but we noted that clear cell tumors had no significant impact on survival

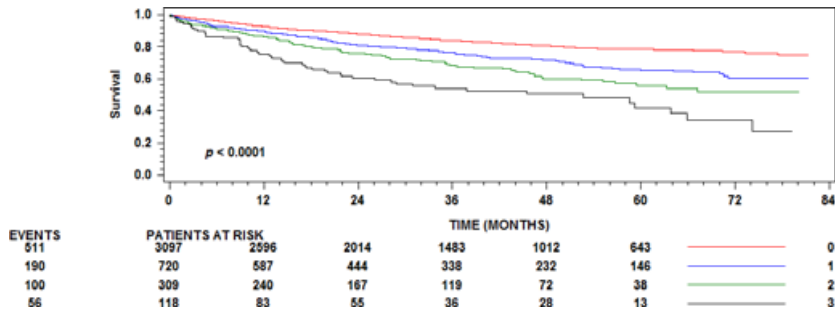

Figure 1. Kaplan–Meier survival curves for comorbidity. The number of patients at risk at 0, 12, 24, 36, 48 and 60 months and are shown below for each Charlson Comorbidity Index group with the number of events to the left.

Table 5. Cox proportional HR, all histological subtypes included, Cox A.

	Model I[b]			Model II[c]		
Covariate	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Comorbidity						
CCS = 0[a]	1			1		
CCS = 1	1.43	1.18–1.73	<0.001	1.27	1.04–1.55	0.02
CCS = 2	1.95	1.53–2.48	<0.001	1.69	1.32–2.16	<0.001
CCS ≥ 3	2.21	1.57–3.10	<0.001	1.72	1.21–2.45	0.002
FIGO stage						
I[a]	1			1		
II	1.87	1.49–2.34	<0.001	1.81	1.44–2.27	<0.001
III	3.54	2.90–4.31	<0.001	3.47	2.84–2.24	<0.001
IV	5.32	3.95–7.17	<0.001	5.10	3.77–6.87	<0.001
Age						
<49 years[a]	1			1		
50–59 years	2.75	1.36–6.56	0.005	2.73	1.35–5.51	0.005
60–69 years	4.71	2.38–9.31	<0.001	4.54	2.29–8.97	<0.001
70–79 years	7.66	3.88–15.15	<0.001	7.21	3.65–14.26	<0.001
>80 years	13.50	6.78–26.90	<0.001	10.85	5.42–21.71	<0.001
Histology						
Endometrial adenocarcinoma[a]	1			1		
Clear cell adenocarcinoma	1.16	0.73–1.85	0.531	1.13	0.71–1.81	0.600
Serous adenocarcinoma	1.78	1.34–2.37	<0.001	1.82	1.37–2.42	<0.001
Carcinoma (including carcinosarcoma)	2.76	2.17–3.52	<0.001	2.92	2.29–3.72	<0.001
Sarcoma	3.57	2.62–4.86	<0.001	3.60	2.64–4.90	<0.001
Rare types	4.22	2.79–6.39	<0.001	4.07	2.67–6.19	<0.001
Residual tumor						
No macroscopic residual[a]	1			1		
Macroscopic residual tumor	2.78	2.23–3.52	<0.001	2.50	1.98–3.17	<0.001
Nutritional status						
Normal weight: 18.5 > BMI ≤ 25[a]	1			1		
Overweight/obesity: 25 > BMI	1.04	0.88–1.22	0.660	1.02	0.86–1.20	0.818
Underweight: BMI ≤ 18.5	2.35	1.65–3.35	<0.001	2.24	1.57–3.21	<0.001
ECOG performance status:						
0: Normal daily activity[a]				1		
1: Few signs of disease				1.14	0.94–1.37	0.181
2: Out of bed >50% of the day				1.88	1.45–2.44	<0.001
3: Out of bed < 50% of the day				2.50	1.75–3.57	<0.001
4: Bedbound				3.74	1.78–7.87	0.001

BMI, body mass index; CCS, Charlson comorbidity score; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratios.

[a]Reference group.

[b]Adjusted for comorbidity, age, stage, grade, residual tumor and BMI.

[c]Adjusted for comorbidity, age, stage, grade, residual tumor, BMI and performance status.

in multivariate analyses. This may be explained by clear cell histology to a great extent, being associated with advanced tumor stage (data not shown), which is an important variable adjusted for in the multivariate analyses.

We did not observe any significant correlation between comorbidity and choice of treatment (operation vs. no operation). Our study was, however, not designed for investigation of this correlation and we are not able to draw any specific conclusions about the impact of comorbidity on choice of treatment. Few studies have investigated the influence of comorbidity on the surgical procedure and especially on the use of primary oncologic treatment (radiotherapy and/or chemotherapy) in uterine corpus cancer (18,19,23–26) and results are diverging. However, the influence of comorbidity of choice of treatment should be subject to further investigation in future studies to understand the causal relation that results in comorbidity being a prognostic factor.

A major strength of this study is its large size and patient completeness. However, the process of translating

Table 6. Cox proportional HR, only endometrial adenocarcinoma included, Cox B.

	Model I[b]			Model II[c]		
Covariate	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Comorbidity						
CCS = 0[a]	1			1		
CCS = 1	1.59	1.29–2.21	<0.001	1.42	1.11–1.82	0.005
CCS = 2	1.98	2.18–3.66	<0.001	1.74	1.27–2.40	0.001
CCS ≥ 3	3.38	3.29–7.86	<0.001	2.48	1.61–3.84	<0.001
FIGO stage						
I[a]	1			1		
II	1.69	1.26–2.09	<0.001	1.66	1.27–2.18	<0.001
III	2.82	2.56–4.02	<0.001	2.82	2.18–3.66	<0.001
IV	5.08	3.29–6.69	<0.001	4.98	3.19–7.76	<0.001
Age						
<49 years[a]	1			1		
50–59 years	3.43	0.83–14.24	0.089	3.49	0.84–14.49	0.085
60–69 years	6.96	1.72–28.17	0.007	6.88	1.70–27.85	0.007
70–79 years	11.07	2.74–44.75	0.001	10.51	2.60–42.52	0.001
>80 years	21.08	5.20–85.47	<0.001	17.40	4.28–70.76	<0.001
Grade						
Grade 1 (highly differentiated cells)[a]	1			1		
Grade 2 (moderately atypical cells)	1.77	1.41–2.21	<0.001	1.77	1.42–2.22	<0.001
Grade 3 (undifferentiated cells)	3.13	2.41–4.05	<0.001	3.20	2.47–4.14	<0.001
Residual tumor						
No macroscopic residual[a]	1			1		
Macroscopic residual tumor	2.76	2.02–3.78	<0.001	2.41	1.75–3.32	<0.001
Nutritional status						
Normal weight: 18.5 > BMI ≤ 25[a]	1			1		
Overweight/obesity: 25 > BMI	0.99	0.81–1.23	0.994	0.94	0.76–1.16	0.551
Underweight: BMI ≤ 18.5	2.36	1.55–3.61	<0.001	2.42	1.58–3.72	<0.001
ECOG performance status						
0: Normal daily activity[a]				1		
1: Few signs of disease				1.16	0.92–1.47	0.212
2: Out of bed >50% of the day				2.03	1.47–2.79	<0.001
3: Out of bed < 50% of the day				2.92	1.89–4.52	<0.001
4: Bedbound				1.23	0.28–5.33	0.783

BMI, body mass index; CCS, Charlson comorbidity score; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratios.

[a]Reference group.

[b]Adjusted for comorbidity, age, stage, grade, residual tumor and BMI.

[c]Adjusted for comorbidity, age, stage, grade, residual tumor, BMI and performance status.

the secondary diagnoses registered in the DGCD to conditions in the CCI has been subject to some methodological inaccuracy, as described in the notes of Table 1. In general, we have chosen to be conservative when assigning the patients a CCS to avoid inclusion of non-prognostic comorbidity in our statistical analyses. To test whether the comorbidity classified as non-prognostic had any prognostic impact, a multivariate Cox-regression analysis including non-prognostic comorbidity as a variable, was performed. An insignificant HR of 1.01 (95% CI 0.84–1.21, $p = 0.95$) was found (data not shown). This confirms that the comorbidities excluded from our analyses are non-prognostic.

The comorbidity registered in the DGCD is mainly based on active diseases reported by the patients or gynecologists with the purpose of excluding historic non-active and non-significant diseases. Our finding of prognostic comorbidity among 27% of patients diagnosed with uterine corpus cancer is similar to prevalence observed in other studies, whereas other studies have reported a higher prevalence. Several explanations for this exist. First, many studies include all comorbidity instead of including only those medical conditions known to affect survival significantly (15,17,19). Secondly, several different comorbidity indices have been used and evidence of which index is most appropriate for studies of comorbidity in uterine

Table 7. Registered cause of death in the study population.

	n	% of registered deaths	% of study population
Cancer-specific mortality	554	64.6	13.1
Other-cause mortality	303	35.4	7.1
Overall mortality	857	100	20.2

corpus cancer is still sparse. Thirdly, it is possible that our conservative approach when assigning patients a CCS has lead to underestimation of the prevalence of comorbidity among the study population.

The CCI was proposed and published in 1984 and was validated on a group of medical patients. Treatments of most medical conditions have changed dramatically since 1984, and it is therefore likely that the relative risks ascribed to the CCI conditions in 1984 are not in agreement with the prognostic impact today. Furthermore, the CCI does not take into account that the comorbidity weights might not be constant between clinical settings or the diseases being studied. Still, we chose to use the CCI for this study because it is widely accepted and is the most validated comorbidity index. Ideally, a new comorbidity index based on modern treatment suited specifically to surgical patients should be developed for studies of comorbidity in gynecologic cancers. That is, however, beyond the scope of this study.

Uterine corpus cancer is to be considered a rather indolent type of cancer. For that reason, distinguishing between all-cause and cancer-specific mortality would be relevant. However, our data on cause of death (presented in Table 7) are suspected to encompass some inaccuracy, which is why we chose to investigate conservatively all-cause mortality in our study. We conducted, tentatively, some additional Cox analyses and they showed that comorbidity has a smaller impact on cancer-specific mortality (data not shown). The relation between comorbidity and cancer-specific mortality should be addressed in future studies and optimal treatment of comorbidity should always be ensured during the cancer-treatment course, since the comorbidity might be just as life-threating as the uterine corpus cancer itself.

In conclusion, we identified comorbidity as an independent prognostic factor in uterine corpus cancer and we observed a clear correlation between increasing levels of comorbidity and survival. The influence of comorbidity on the diagnostic process, oncologic treatment, and disease-specific survival should be addressed in future studies to clarify the causal relations that result in comorbidity being a prognostic factor in uterine corpus cancer. A better understanding of the impact of comorbidity is crucial in order to individualize cancer treatment and improve cancer survival rates in populations with an increasing prevalence of age-related comorbidity.

Acknowledgments

We acknowledge the DGCD for providing us with data free of charge.

Funding

No special funding.

References

1. Klint A, Tryggvadottir L, Bray F, Gislum M, Hakulinen T, Storm HH, et al. Trends in the survival of patients diagnosed with cancer in female genital organs in the Nordic countries 1964–2003 followed up to the end of 2006. Acta Oncol. 2010;49:632–43.
2. Sorosky JI. Endometrial cancer. Obstet Gynecol. 2008;111:436–47.
3. Linkov F, Taioli E. Factors influencing endometrial cancer mortality: the Western Pennsylvania Registry. Future Oncol. 2008;4:857–65.
4. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA. 2004;291:2441–7.
5. Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel EL, et al. Differential prognostic impact of comorbidity. J Clin Oncol. 2004;22:3099–103.
6. Bjorge T, Stocks T, Lukanova A, Tretli S, Selmer R, Manjer J, et al. Metabolic syndrome and endometrial carcinoma. Am J Epidemiol. 2010;171:892–902.
7. Fleming ND, Lentz SE, Cass I, Li AJ, Karlan BY, Walsh CS. Is older age a poor prognostic factor in stage I and II endometrioid endometrial adenocarcinoma? Gynecol Oncol. 2011;120:189–92.
8. Olson SH, Atoria CL, Cote ML, Cook LS, Rastogi R, Soslow RA, et al. The impact of race and comorbidity on survival in endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2012;21:753–60.
9. Ward KK, Shah NR, Saenz CC, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. Gynecol Oncol. 2012;126:176–9.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
11. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. A critical review of available methods. J Clin Epidemiol. 2003;56:221–9.

12. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care. 2005;20:12–9.
13. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
14. Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995–2008. Eur J Cancer. 2011;47:1504–10.
15. Kodama J, Seki N, Ojima Y, Nakamura K, Hongo A, Hiramatsu Y. Correlation of presenting symptoms and patient characteristics with endometrial cancer prognosis in Japanese women. Int J Gynaecol Obstet. 2005;91: 151–6.
16. Kwon JS, Carey MS, Cook EF, Qiu F, Paszat L. Patterns of practice and outcomes in intermediate- and high-risk stage I and II endometrial cancer: a population-based study. Int J Gynecol Cancer. 2007;17:433–40.
17. Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S, Khunnarong J, Tanvanich S, Katanyu K, et al. Endometrial cancer in Thai women: clinico-pathological presentation and survival. Asian Pac J Cancer Prev. 2010;11:1267–72.
18. Truong PT, Kader HA, Lacy B, Lesperance M, MacNeil MV, Berthelet E, et al. The effects of age and comorbidity on treatment and outcomes in women with endometrial cancer. Am J Clin Oncol. 2005;28:157–64.
19. Wang JL, Wang ZQ, Wei LH. Primary clinical analysis of medical disorders in Chinese women with endometrial carcinoma. Int J Gynecol Cancer. 2004;14:502–7.
20. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol. 1998;16:1582–7.
21. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59:255–63.
22. Wedding U, Rohrig B, Klippstein A, Pientka L, Hoffken K. Age, severe comorbidity and functional impairment independently contribute to poor survival in cancer patients. J Cancer Res Clin Oncol. 2007;133:945–50.
23. Bouchardy C, Rapiti E, Blagojevic S, Vlastos AT, Vlastos G. Older female cancer patients: importance, causes, and consequences of undertreatment. J Clin Oncol. 2007;25:1858–69.
24. Byrd LM, Swindell R, Webber-Rookes D, Hannon R, Hunter RD, Livsey J, et al. Endometrial adenocarcinoma: an analysis of treatment and outcome. Oncol Rep. 2008;20:1221–8.
25. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol. 2005;55:231–40.
26. Lee L, Cheung WY, Atkinson E, Krzyzanowska MK. Impact of comorbidity on chemotherapy use and outcomes in solid tumors: a systematic review. J Clin Oncol. 2011;29:106–17.