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Adult Comorbidity Evaluation 27 score as a predictor of survival in endometrial cancer patients

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Abstract

BACKGROUND—The incidence of endometrial cancer increases with age and is associated with medical comorbidities such as obesity and diabetes. While a few cohort studies of less than 500 patients showed an association between comorbidity and survival in endometrial cancer patients, the degree of association needs to be better described. The Adult Comorbidity Evaluation 27 (ACE-27) is a validated comorbidity instrument that provides a score (0–3) based on the number and severity of medical comorbidities.

OBJECTIVE—This study was performed to explore the association between medical comorbidities and survival of endometrial cancer patients.

STUDY DESIGN—Patients diagnosed with endometrial cancer from 2000–2012 were identified from the prospectively maintained Siteman Cancer Center tumor registry. Patients undergoing primary surgical treatment for endometrioid, serous and clear cell endometrial carcinoma were included. Patients primarily treated with radiation, chemotherapy or hormone therapy were excluded. Patients with uterine sarcomas or neuroendocrine tumors were excluded. Patients with missing ACE-27 scores were also excluded from analysis. Information including patient

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demographics, ACE-27 score, tumor characteristics, adjuvant treatment and survival data were extracted from the database. The association of ACE-27 and overall as well as recurrence-free survival was explored in a multivariable Cox regression analysis after controlling for variables found to be significantly associated with survival in univariable analysis.

RESULTS—A total of 2073 patients with a median age of 61 years (range 20–94) at diagnosis were identified. ACE-27 score was 0, 1, 2 and 3 in 22%, 38%, 28% and 12% of patients, respectively. Stage distribution was I (73%), II (5%), III (15%) and IV (7%) and grade distribution was 1 (52%), 2 (23%) and 3 (25%). Most patients had endometrioid histology (87%) followed by serous (11%) and clear cell (3%). The median OS for the entire cohort was 54 months [95% confidence interval (CI) 3, 154 months] and median PFS was 50 months [95% CI 2, 154 months].

On univariable analysis, age, race, marital status, stage, grade, histology and treatment type were significantly associated with overall survival and recurrence-free survival. After adjusting for these covariates, patients with ACE-27 score of 2 had a 52% higher risk of death [95% CI 1.16, 2.00] and patients with ACE-27 score of 3 had a 2.35-fold increased risk of death [95% CI 1.73, 3.21] compared to patients with an ACE-27 score of 0. Similarly, patients with ACE-27 score of 2 had a 38% higher risk of recurrence [95% CI 1.07, 1.78] and patients with ACE-27 score of 3 had a 2.05-fold increased risk of recurrence [95% CI 1.53, 2.75] compared to patients with an ACE-27 score of 0. We found no interaction between ACE-27 score and age, stage or treatment type.

CONCLUSIONS—Our findings demonstrate the importance of comorbidities in estimating the prognosis of endometrial cancer patients, even after adjusting for age and known tumor-specific prognostic factors like stage, grade, histology and adjuvant treatment.

Key words/phrases

Endometrial cancer; comorbidity; survival

INTRODUCTION

The probability of developing endometrial cancer (EC) increases with age and its incidence has increased in all age groups over the last decade.[1] Advancing age is also associated with a higher risk of recurrence and poor survival.[2, 3] As a result, age is used in risk-stratification algorithms of early stage EC trials. [4, 5] Endometrial cancer is also associated with comorbid conditions including obesity and diabetes[6] and more than 50% of patients with early stage EC die from intercurrent illnesses rather than cancer.[4] Therefore, it is important to study the effect of comorbidities on the survival of these patients.

Medical comorbidities can strongly affect cancer patient survival and life-expectancy, independent of cancer stage and disease status.[7, 8] Comorbidity is an independent prognostic factor affecting survival in other gynecologic cancers including cervical and ovarian cancer.[9–11] Nicholas and colleagues showed that a diagnosis of diabetes and/or hypertension in EC patients resulted in a decreased survival even after adjusting for age, stage and grade.[12] Truong and colleagues studied the effect of age, Karnofsky performance status and Charlson comorbidity score on the treatment, recurrence and survival of EC patients.[13] They found that advanced age was associated with a decline in prescribed postoperative radiation therapy. Age and performance status were independent predictors of overall survival (OS)

but not recurrence-free survival (RFS). A Charlson comorbidity scores of 0–1 versus ≥2 was not significantly associated with adjuvant treatment prescribed, OS or RFS. However, there was a trend towards prescribing less radiation therapy in patients with score ≥2 when compared to patients with score 0–1.

The Charlson comorbidity index was developed to predict the probability of mortality in patients with medical comorbidities.[14] A score of ≥3 is associated with an almost 60% 1-year mortality rate. The score is based on age and 16 medical conditions, but the severity of the condition is only accounted for in diabetes, cancer and liver disease. Furthermore, it does not take into account morbidity from obesity, which is a well-established risk factor for EC. In comparison, the Adult Comorbidity Evaluation 27 (ACE-27) is a 26-item comorbidity index accounting for the presence and severity of individual medical illnesses by grading them into 1 of 4 comorbidity classes – none, mild, moderate or severe (Table 1).[15] Comorbid conditions that are controlled with or without medications, do not cause symptoms limiting activities of daily living (ADLs) and have not required hospitalization are considered mild. If patients require active treatment modifications, have residual disability limiting ADLs or required hospitalization or surgery to treat comorbid conditions, they are classified as moderate. Comorbid conditions that have caused major complications, irreversible end-organ damage, uncontrolled symptoms and disability requiring full support in ADLs are considered severe. A body mass index less than 38 received a score of 1 and all others received a score of 2. The overall ACE-27 score can be none (0), mild (1), moderate (2) or severe (3) and is defined according to the highest scored ailment. In cases with two or more grade 1 ailments, a final score of 1 assigned. In cases with two or more grade 2 ailments in different organ systems, a final score of 3 is assigned. ACE-27 has been validated to provide prognostic information about cancer patients in large prospectively maintained tumor registries.[16–18]

Read et al reviewed the prognostic impact of ACE-27 score in different cancer types and found that comorbidity had the most prognostic impact in patients with a high cancer survival rates.[19] In the US, the 5-year survival rate from endometrial cancer is >80%.[1] Therefore, it is important to describe the relationship between comorbidity and survival in these patients. The objective of this study was to assess the association between ACE-27 score and survival outcomes including OS and recurrence-free survival (RFS) in patients with endometrial cancer.

METHODS

Study design and setting

We performed a retrospective cohort study of women diagnosed with endometrial cancer from 2000 to 2012. After Institutional Review Board approval, patients were identified from the prospectively maintained Siteman cancer center tumor registry. The analysis included surgically treated patients with stages I-IV disease. Only patients with endometrioid, serous and clear cell adenocarcinoma were included in the analysis. Thus, we excluded patients with uterine sarcomas. Patients primarily treated with hormones, radiation or chemotherapy were excluded. Patients with missing ACE-27 data were excluded.

Data collection

We extracted demographic data from the database including age of diagnosis, race and marital status. Medical information regarding alcohol use, tobacco use, ACE-27 score, surgical procedure, cancer stage, grade, histology, and adjuvant treatment was also collected. Age was divided into the 3 risk categories described by Keys et al.[4] ACE-27 scores were entered into the database by trained certified tumor registrars after a comprehensive review of patient medical records. Tumor stage was based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) guidelines. Histology was coded as serous or clear cell if more than 10% of the tumor consisted of that histology. The dates of death and recurrence were extracted from the database. Death and recurrence information is updated in the database semiannually by contacting patients, their family, and their physicians. The National and Social Security Death Index is queried for the patients lost to follow-up.

The primary outcome was overall survival (OS) and secondary outcome was recurrence-free survival (RFS). OS was calculated from date of diagnosis to date of death or last follow-up. Patients who were alive at last follow-up were censored for OS analysis. RFS was calculated from date of diagnosis to date of recurrence (after remission) or progression (despite primary treatment) or death. Recurrence and progression was determined by computed tomography imaging or biopsy.

Statistical analysis

Standard descriptive statistics were used to describe the study cohort. Median, range and 95% confidence interval (CI) were used to describe continuous variables like age of diagnosis, follow-up time, OS and RFS. Categorical variables were described as proportions of the entire cohort. Kaplan-Meier survival analysis with log-rank test was used to determine the statistical significance of difference in survival between patients with increasing ACE-27 score. Univariable Cox proportional hazards regression was used to identify factors associated with OS and PFS. Variables identified as significantly associated with OS at alpha level 0.05 were included in the multivariable model. If a covariate did not meet statistical significance on univariate analysis but was deemed clinically important, it was included in the multivariable model. Alcohol use was excluded in the multivariable model as ACE-27 includes this data point. Unadjusted and adjusted hazard ratios (HR_{unadj} and HR_{adj}) for death and recurrence were calculated with 95% CI. The proportional hazards assumptions was tested by log minus log plots.

RESULTS

Description of cohort

We identified 2519 patients with endometrial cancer from the Siteman Cancer Center tumor registry. We excluded 175 patients who did not undergo surgery, 206 patients with ineligible histology and 65 patients with missing ACE-27 scores (Figure 1). The distribution of variables was not different in the 65 patients with missing ACE-27 score. Most patients had a mild comorbidity score followed by moderate, none, then severe. The distribution of variables is presented in Table 2. Most patients were white, married or in a partnership and had never used alcohol or tobacco. Most patients had stage I and grade 1 cancers with

endometrioid histology. The median age of the entire cohort and the patients with recurrence was 61 (range 20–94) and 65 (range 34–92) years, respectively. Of the 2073 evaluable patients, 310 (15%) recurred, 515 (25%) died and 242 (12%) recurred and died. The majority of patients were alive without disease (72%) with a median follow-up time of 63 months [95% CI 5, 158]. The median OS and PFS was 54 [95% CI 3, 155] and 51 months [95% CI 2, 155], respectively.

Kaplan-Meier survival by ACE-27 score

Kaplan-Meier survival plots of OS and PFS for the 4 different ACE-27 scores are shown in Figure 2. The overall log-rank test shows there is a significant difference in OS ($p<0.001$) and PFS (Chi-square 16.9, $p=0.001$) between the different ACE-27 scores. Pairwise comparisons between the difference ACE-27 scores show that the OS and PFS for patients with a severe ACE-27 score is worse than a score of none, mild or moderate. The proportions of death was 100/456 (21.9%), 214/798 (26.8), 124/576 (21.5) and 77/243 (31.7%) for none, mild, moderate and severe score, respectively. The median time to death was 12.7 years for patients with moderate comorbidity and 10.4 years [95% CI 7.2, 13.5] for patients with severe comorbidity. Median survival was not reached for patients with none or mild comorbidity. After stratifying by stage, a higher grade of comorbidity was still associated worse survival for stages 1, 3 and 4 (Figure 3).

Univariable and multivariable Cox regression

The association between patient and tumor characteristics and survival outcomes is shown in Table 2. On univariable analysis, both OS and PFS were worse with increasing age, black race, widowed or single marital status, increasing ACE-27 score, higher tumor stage, higher grade and serous or clear cell histology. PFS was also associated with the same covariates.

After adjusting for age, race, marital status, tobacco use, tumor stage, grade, histology and adjuvant treatment, higher ACE-27 score was still associated with worse survival (Table 3). Patients with moderate comorbidity had a 52% higher risk of death [HR_{adj} 95% CI 1.16, 2.00] and patients with severe comorbidity had a 2.35-fold increased risk of death [HR_{adj} 2.35, 95% CI 1.73, 3.21] compared to patients with a comorbidity category of none. Also, patients with moderate comorbidity had a 38% higher risk of recurrence [HR_{adj} 95% CI 1.07, 1.78] and patients with severe comorbidity had 2.05-fold increased risk of recurrence [HR_{adj} 95% CI 1.53, 2.75] compared to patients with comorbidity score of none. Age, marital status, tobacco use, tumor stage, grade and serous histology remained independent predictors of survival and recurrence.

We also used Cox regression modeling to evaluate for interactions between variables. There was no interaction between ACE-27 score and age, stage or adjuvant treatment type. There was also no interaction between age and stage or adjuvant treatment type. There was an anticipated significant interaction between stage and treatment type. As expected, most stage I patients (83%) did not receive adjuvant therapy. Stage II patients were more likely to receive radiation (46%), most stage III patients (41%) received a combination of chemotherapy and radiation, and most stage IV patients (73%) received chemotherapy alone ($p<0.001$) (Table 4). Adjuvant treatment with chemotherapy was associated with a 35%

reduction in risk of death [HR_{adj} 0.65, 95% CI 0.47, 0.90] and combination chemo-radiation was associated with a 51% reduction in risk of death [HR_{adj} 0.49, 95% CI 0.35, 0.70] compared to patients not receiving adjuvant therapy for all patients when adjusted for all covariates included in multivariable analysis (Table 3).

COMMENTS

In our cohort of over 2000 endometrial cancer patients, increasing ACE-27 score was associated with decreased overall and recurrence-free survival. Moreover, this association was still seen after adjusting for known prognostic factors like age, race, tobacco use, cancer stage, grade, histology and adjuvant therapy. Specifically, the risk of death in patients with a severe comorbidity score is double the risk in patients without comorbidities. The association was also apparent in both early and late stages of cancer, although the magnitude of association was higher in early-stage disease. This is consistent with previous studies which show that comorbidity is particularly important in patients with indolent cancers and longer mean survival.[16, 19] Therefore, accurate assessment and documentation of comorbidities is of utmost importance in early-stage EC patients.

Nicholas and colleagues showed that diabetes and hypertension were associated with decreased survival, whereas obesity, estrogen exposure and smoking were not associated with survival in EC patients.[12] While obesity may put patients at higher risk of surgical morbidity, Temkin et al and Modesitt et al showed that it was not an independent predictor of progression or overall survival but likely related to other comorbid conditions.[20,21] Given the possibility of multi-collinearity between individual comorbid conditions and survival, the use of a standardized comorbidity index while studying survival in EC patients is more appropriate. Truong and colleagues showed that age and performance status were independent predictors of survival but the Charlson comorbidity index was not.[13] They also showed that advanced age was associated with less aggressive adjuvant therapy and Charlson comorbidity score of ≥2 had a trend towards less aggressive radiation therapy. We studied a much larger cohort with more than 4 times the patients as previous studies. Unlike previous studies, the ACE-27 index evaluated in this study was significantly associated with overall survival and there was no significant interaction between age or ACE-27 score and administration of postoperative adjuvant treatment.

The ACE-27 tool was developed by Drs. Piccirillo and Littenberg after modification from the Kaplan-Feinsten index. Individual comorbid conditions assessed in this instrument include a combination of previously researched comorbidities and other important conditions not included in the Kaplan-Feinstein or Charlson comorbidity index.[15] It is the preferred comorbidity tool for our purposes as it was developed for cancer patients, it takes into account the presence and severity of multiple medical ailments that can affect cancer treatment, it includes obesity as an ailment which is a well-known risk factor for endometrial cancer and it is determined after a thorough medical record chart review rather than billing codes. The prognostic use of this instrument has been validated in a hospital-based cancer registry that included 2535 patients with gynecologic cancers.[16] We showed that ACE-27 score was a predictor of OS and PFS in EC after adjusting for age and well-established cancer-related prognostic factors like stage, grade, histology and adjuvant treatment. Age

has already been incorporated into risk-stratification algorithms for early-stage endometrial cancer. Adding ACE-27 scores to prognostic prediction models may allow more accurate assessments of survival as well as benefit from adjuvant therapy.

The strengths of this study include a large cohort size, a prospectively maintained database, the use of a well-characterized comorbidity tool that has been previous validated in cancer patients and a long median follow-up period. The ACE-27 score also accounts for morbidity due to obesity, which was not a part of previously described comorbidity tools. The ACE-27 score was determined at that time of EC diagnosis after a thorough abstraction of important clinical data from the medical records by registrars who completed a comorbidity education program. We only included patients who underwent staging surgery as this is usually the standard of care in the initial treatment of EC. Therefore, our results are only generalizable to patients able to undergo surgery. Stage information was available on all patients and was based on the current FIGO guidelines released in 2009. We did not include patients with carcinosarcomas or other sarcomas since prognosis is much worse and uterine sarcomas are considered a separate disease than endometrial cancer.

Limitations include the inherent biases of retrospective research and information abstracted from large databases. While we adjust for known confounders in our multivariable analysis, we cannot adjust for unmeasured and unknown confounders. Information on disease-specific survival would be the ideal outcome of interest in patients with prolonged survival after a cancer diagnosis; however, this information was not available in our database. These results do not apply to patients that were too ill to undergo surgery and were managed conservatively with hormone therapy or primary definitive radiation therapy. Finally, our data is based on patients treated at a single center and our findings may not be generalizable to the entire U.S. population of EC patients. Nonetheless, this study is the largest in the literature specifically evaluating the impact of medical comorbidities on survival outcomes of surgically treated EC patients.

Conclusions

The Adult Comorbidity Evaluation 27 score is significantly associated with mortality and recurrence in patients with endometrial cancer. The inclusion of comorbidity information during the physician-patient discussion of prognosis is essential and can help patients make informed decisions about adjuvant cancer treatment and management of their comorbid conditions.

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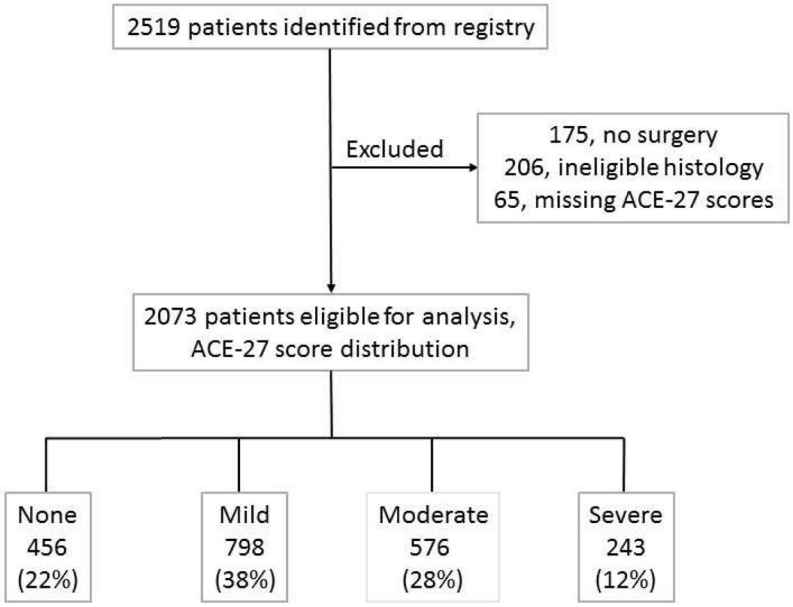

Figure 1.

Flow diagram showing total patients, exclusions and distribution by Adult Comorbidity Evaluation 27 score.

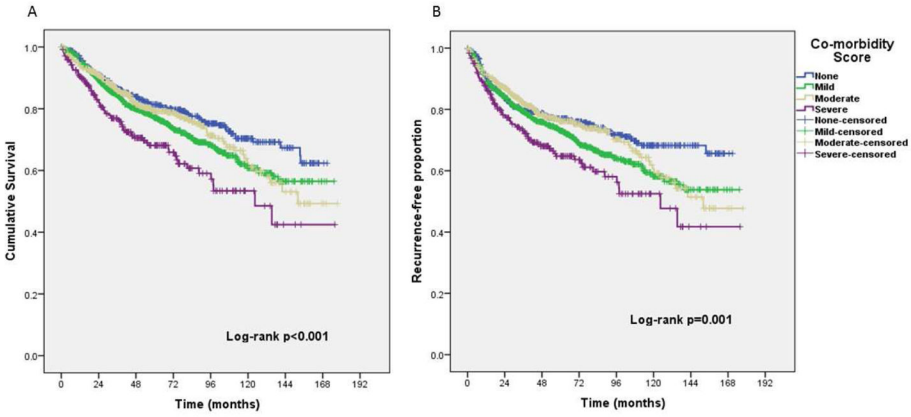

Figure 2.

Kaplan-Meier survival plots for Adult Comorbidity 27 score and A) Overall survival and B) Recurrence-free survival.

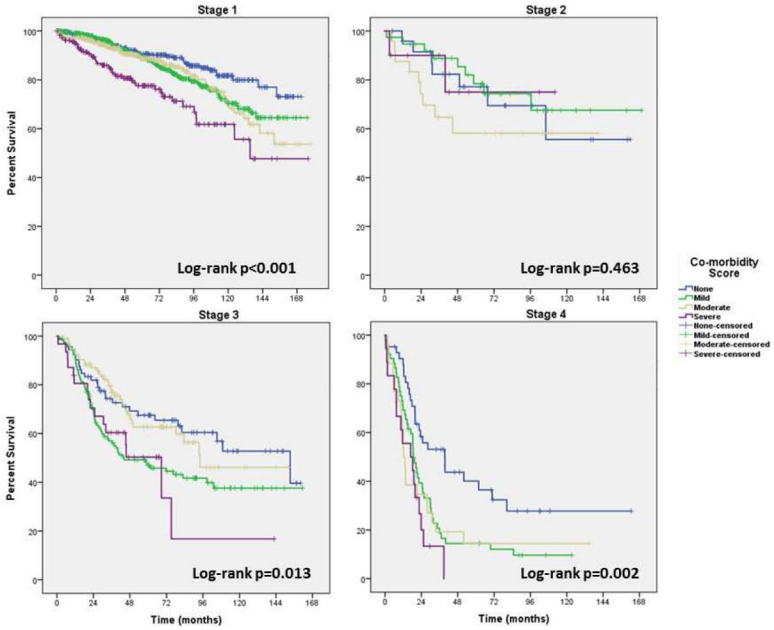

Figure 3.
Kaplan-Meier overall survival plots for Adult Comorbidity 27 score stratified by cancer stage.

Table 1

Organ systems and specific diseases included in ACE-27.

Cardiovascular system
Myocardial infarct
Angina/Coronary artery disease
Congestive heart failure
Arrhythmias
Hypertension
Venous Disease
Peripheral arterial disease
Respiratory system
Gastrointestinal system
Hepatic disease
Stomach or intestinal disease
Pancreatic disease
Renal system
End-stage renal disease
Endocrine system
Diabetes mellitus
Neurologic system
Stroke
Dementia
Paralysis
Neuromuscular
Psychiatric system
Rheumatologic system
Immunologic system
AIDS
Malignancy
Solid tumors
Leukemia and myeloma
Lymphoma
Substance Abuse
Alcohol
Illicit drugs
Obesity

ACE-27: Adult Comorbidity Evaluation-27

Table 2

Baseline characteristics of 2073 patients diagnosed with endometrial cancer, 310 patients with recurrent disease and relationship to overall survival and recurrence-free survival.

Characteristic	N (%) of patients Total=2073	Unadjusted HR for death	95% CI	Unadjusted HR for recurrence	95% CI
Age					
< 50	258 (12)	Ref		Ref	
50–69	1328 (64)	1.41	0.98–2.03	1.54	1.10–2.17
≥ 70	487 (24)	4.36	3.03–6.28	4.15	2.94–5.86
Race					
White	1807 (87)	Ref		Ref	
Black	243 (12)	1.42	1.12–1.80	1.42	1.14–1.78
Other	23 (1)	0.51	0.16–1.59	0.44	0.14–1.37
Marital Status					
Married/Partner	1081 (52)	Ref		Ref	
Divorced/Separated	255 (12)	1.31	0.97–1.75	1.23	0.94–1.62
Widowed	388 (19)	2.70	2.20–3.31	2.55	2.10–3.09
Single	338 (16)	1.37	1.05–1.78	1.35	1.06–1.72
Unknown	11 (1)	2.30	0.95–5.58	1.99	0.82–4.81
Alcohol use					
Never	1314 (63)	Ref		Ref	
Current	427 (21)	0.77	0.60–0.99	0.84	0.67–1.05
Former	34 (2)	1.45	0.80–2.65	1.63	0.96–2.78
Unknown	298 (14)	1.06	0.85–1.32	0.98	0.79–1.22
Tobacco Use					
Never	1267 (61)	Ref		Ref	
Current	207 (10)	1.18	0.88–1.57	1.08	0.82–1.41
Former	329 (16)	1.21	0.95–1.55	1.16	0.93–1.46
Unknown	270 (13)	1.09	0.86–1.38	0.98	0.78–1.24
ACE-27					

Characteristic	N (%) of patients Total=2073	Unadjusted HR for death	95% CI	Unadjusted HR for recurrence	95% CI
None	456 (22)	Ref		Ref	
Mild	798 (38)	1.33	1.05–1.69	1.30	1.04–1.62
Moderate	576 (28)	1.20	0.92–1.56	1.11	0.87–1.43
Severe	243 (12)	2.01	1.49–2.72	1.74	1.31–2.31
Stage					
1	1524 (73)	Ref		Ref	
2	97 (5)	1.93	1.29–2.87	1.71	1.16–2.517
3	314 (15)	3.54	2.88–4.37	3.53	2.91–4.293
4	138 (7)	11.45	9.09–14.43	12.40	9.94–15.46
Grade					
1	1080 (52)	Ref		Ref	
2	480 (23)	1.63	1.28–2.07	1.82	1.45–2.27
3	513 (25)	4.52	3.70–5.53	4.67	3.86–5.65
Histology					
Endometrioid	1797 (87)	Ref		Ref	
Serous	223 (11)	3.79	3.09–4.64	3.78	3.12–4.59
Clear cell	53 (2)	3.70	2.52–5.44	3.96	2.76–5.68
Adjuvant therapy					
None	1349 (65)	Ref		Ref	
Radiation	232 (11)	1.87	1.44–2.44	1.80	1.40–2.32
Chemotherapy	268 (13)	4.64	3.76–5.73	5.00	4.10–6.09
Chemo-radiation	224 (11)	1.94	1.48–2.55	2.24	1.75–2.87

HR: hazard ratio; CI: confidence intervals; ACE-27: Adult Comorbidity Evaluation-27; OS: Overall survival; RFS: Recurrence-free survival.

Baseline characteristics of 936 patients with stage II and III colorectal cancer.

Table 3

Multivariable analysis showing adjusted hazard ratio for survival and recurrence.

Characteristic	Adjusted HR for death	95% CI	Adjusted HR for recurrence	95% CI
Age				
< 50	Ref		Ref	
50–69	1.63	1.12–2.37	1.72	1.21–2.45
≥ 70	3.59	2.41–5.35	3.19	2.19–4.65
Race				
White	Ref			
Black	1.06	0.83–1.36	NS	
Other	1.22	0.39–3.82		
Marital Status				
Married/Partner	Ref		Ref	
Divorced/Separated	1.14	0.84–1.54	1.15	0.87–1.53
Widowed	1.48	1.19–1.85	1.56	1.26–1.92
Single	1.41	1.08–1.84	1.38	1.07–1.77
Unknown	3.68	1.50–9.03	3.11	1.27–7.59
Tobacco Use				
Never	Ref		Ref	
Current	1.61	1.20–2.17	1.32	1.00–1.75
Former	1.39	1.08–1.78	1.35	1.07–1.71
Unknown	1.23	0.96–1.57	1.05	0.83–1.34
Histology				
Endometrioid	Ref		Ref	
Serous	1.51	1.15–1.97	1.37	1.06–1.77
Clear cell	1.12	0.74–1.71	1.23	0.83–1.83
Grade				
1	Ref		Ref	
2	1.32	1.02–1.70	1.48	1.17–1.87
3	2.35	1.81–3.06	2.43	1.89–3.11
Stage				
1	Ref		Ref	
2	2.00	1.29–3.01	1.65	1.09–2.49
3	4.26	3.22–5.62	3.79	2.91–4.93
4	12.56	8.93–17.66	11.72	8.46–16.23
ACE-27 score				
None	Ref		Ref	
Mild	1.15	0.90–1.48	1.19	0.94–1.50

Characteristic	Adjusted HR for death	95% CI	Adjusted HR for recurrence	95% CI
Moderate	1.52	1.16–2.00	1.38	1.07–1.78
Severe	2.35	1.73–3.21	2.05	1.53–2.75
Adjuvant therapy				
None	Ref		Ref	
Radiation	0.88	0.65–1.19	0.85	0.64–1.13
Chemotherapy	0.60	0.43–0.83	0.69	0.50–0.95
Chemo-radiation	0.44	0.33–0.68	0.60	0.44–0.83

HR: hazard ratio; CI: confidence intervals; ACE-27: Adult Comorbidity Evaluation-27.

Table 4

Distribution of adjuvant treatment among the four stages of endometrial cancer.

		Adjuvant therapy type			
		None	**Radiation**	**Chemo**	**ChemoRT**
Stage 1	No. of patients	1303	141	62	64
	% within Stage 1	83%	9%	4%	4%
Stage 2	No. of patients	30	46	9	16
	% within Stage 2	30%	45%	9%	16%
Stage 3	No. of patients	43	44	105	133
	% within Stage 3	13%	14%	32%	41%
Stage 4	No. of patients	17	6	103	16
	% within Stage 4	12%	4%	73%	11%

Chemo: Chemotherapy, ChemoRT: Combination radiation and chemotherapy.

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