



Comorbidity is an independent prognostic factor for the survival of ovarian cancer: A Danish register-based cohort study from a clinical database[☆]

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HIGHLIGHTS

- Comorbidity is an independent prognostic factor
- PS attenuates the impact of impact of comorbidity

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ABSTRACT

Objective. The aim of the study was to examine whether comorbidity is an independent prognostic factor for 3129 women diagnosed with ovarian cancer from 2005 to 2011. As Performance status (PS) might capture the impact of comorbidity we addressed whether comorbidity can be explained by PS or whether comorbidity has an independent impact on survival.

Methods. The Danish Gynecological Cancer Database (DGCD) is a national clinical database including information on comorbidity and a large number of tumor-related and patient-related factors. The Charlson Comorbidity Index was used to measure the patients' comorbidity based on the registration in DGCD. The overall mortality (OS) from the date of surgery to death or censoring was the outcome measure.

Results. The hazard ratio (HR) for patients with comorbidity was 3.31 (1.14–1.50) compared to patients without comorbidity after adjustment for age, stage, residual tumor, histology and grade. After including PS in the model, comorbidity remained significant for OS. Age, stage, residual tumor, histology and PS prove to be independent prognostic factors as well. No association is found between comorbidity and receiving surgery or not.

Conclusion. Comorbidity is an independent prognostic factor, and has a negative impact on the survival of ovarian cancer patients. However, comorbidity has a smaller impact on survival compared with the other prognostic factors considered.

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Introduction

Every year approximately 450 Danish women are diagnosed with ovarian cancer, which makes ovarian cancer the sixth leading type of cancer among women in Denmark [1–3]. The incidence of the disease is expected to increase due to an aging population and the risk of ovarian cancer increases with age.

Over 60% of the tumors are first diagnosed in advanced stage due to the non-existing or non-specific symptoms [2–4]. The 5 years mortality

is around 40% for Danish ovarian cancer patients though with a remarkable improvement within the last few years. This improvement in survival can be explained by the centralization of treatment and introduction of national guidelines for treatment [1,5,6].

Age, stage, residual tumor and Performance Status (PS) are the most consistently reported independent prognostic factors for the survival of ovarian cancer [2,7–17], and stage, residual tumor and PS often turn out to be the strongest impact on the survival. Grade and histology have in some studies proven to be prognostic factors [7,13,14], but in other studies they lose their independent influence in the multivariate analyses [2,3,12,17].

Comorbidity can be defined as the presence of one or more diseases in addition to the primary disease [18,19]. The evidence supporting comorbidity as a prognostic factor for the survival of ovarian cancer patients is scarce — especially when taking all other clinical prognostic factors into

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Table 1
Translation of the comorbidity into the Charlson Comorbidity Index.

Charlson Comorbidity Index ^a	Score	ICD-10 codes	Comorbidity registered in DGCD
Myocardial infarction	1	I21.x, I22.x, I25.2	Myocardial infarction
Congestive heart failure	1	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
Peripheral vascular disease	1	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	Universal arteriosclerosis Arteriosclerosis in cardiac vessels
Dementia	1	F00.x–F03.x, F05.1, G30.x, G31.1	Dementia
Chronic pulmonary disease	1	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3	Asthma Chronic bronchitis Chronic obstructive lung disease (COLD)
Connective tissue disease	1	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0	Unspecified arthritis
Liver disease ^b (mild and moderate/severe)	1	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	Alcoholic liver disease (unspecified) Acute and sub acute liver insufficiency
Cerebral vascular disease and hemiplegia	1	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 infarct and hemiplegia
Diabetes ^c (with and without end organ damage)	1	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
Moderate or severe renal disease	3	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	Chronic kidney insufficiency
Any tumor including leukemia and lymphoma ^d	2	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x	Data from NPR
Metastatic solid tumor ^d	6	C77.x–C80.x	Data from NPR
AIDS	6	B20.x–B22.x, B24.x	HIV and AIDS

^a The categories “Ulcer disease” are not registered in DGCD, which imply that the categories are not included in the CCI.

^b Only the presence of liver diseases but not the severity of the disease has been registered in DGCD. Therefore all patients with liver disease are assigned with a score of 1 correlating to the CCI category “mild liver disease”.

^c DGCD does not contain information about complications to the diabetes. The categories “Diabetes” and “Diabetes with end organ damage” have not been possible to separate, why all patients with diabetes are assigned with a score of 1. Complications such as renal disease or peripheral vascular disease will be classified into the other categories in the index.

^d Information about “Any tumor” and “Metastatic solid tumor” are gathered from the NPR. From the NPR information about discharge diagnoses since 1977 concerning “Any tumor” and “Metastatic solid tumor” was extracted. Ovarian cancer diagnoses were excluded from the calculation of the categories as well were diagnoses registered more than 10 years before and up to 90 days before the ovarian cancer diagnosis. This time window was used to avoid misclassifications of diagnoses in the process of diagnosing the cancer disease.

account. The Danish Gynecological Cancer Database (DGCD) is a national clinical database containing validated information about all Danish ovarian cancer patients and a large amount of disease-specific and patients-related factors. The database provides a unique opportunity to examine the impact of comorbidity when adjusting for all other prognostic factors. The aim of this study was to determine whether comorbidity has an impact on the survival of ovarian cancer patients after adjusting for other prognostic factors.

As PS might capture the impact of comorbidity we further examined whether PS can explain the impact of comorbidity or whether comorbidity is an independent prognostic factor.

Materials and methods

Patient and data collection

DGCD is a nationwide clinical database approved by the Danish Data Protection agency and contains data from 97% of Danish patients diagnosed with ovarian, corpus and cervix cancer since 2005 [1]. All data are summarized in a final form where the disease-related and pathway-related factors in relation to hospital stay are validated. In cases of missing data, the departments are contacted for retrospective registration. Only patients with final registration and validation were entered into the study (98.4%) [1].

Patients with ovarian cancer diagnosed between 1st January 2005 and 13th October 2011 were identified in the DGCD, together with information on clinical prognostic factors and comorbidity.

Besides patients registered with ovarian cancer ($n = 2688$), patients with cancer of fallopian tube ($n = 165$) and patients with cancer in the peritoneum ($n = 276$) were included in the study population. Patients

with borderline tumors have a much more favorable outcome with 94.4% surviving after 3 years and the mean age of occurrence being approximately 10 years younger than women with malignant ovarian cancer [1,20]. Hence, patients diagnosed with borderline tumors ($n = 1032$) were excluded from the study population.

In total the study population consisted of 3129 Danish ovarian cancer patients.

Stage was categorized according to the FIGO classification. The categories of grade were well differentiated (“Grade 1”), moderately differentiated (“Grade 2”) or poorly differentiated (“Grade 3”). Histology was classified into the following categories: ‘Mucinous’, ‘Serous’, ‘Endometrioid’ and ‘Clear cell’ or ‘Other’. Residual tumor was divided into either ‘No residual tumor’ when none visible tumor was left at the end of surgery a ‘Residual tumor left’ if visible tumor was left. The Eastern Cooperative Oncology Group’s (ECOG) scale for PS was used [21].

Measuring comorbidity

37 predefined comorbidities can be registered in DGCD. The registration of comorbidity is based on the patient’s reporting as well as the doctor’s assessment. The comorbidities from DGCD was translated into the Charlson Comorbidity Index (CCI), which is the most validated and used index for estimating the impact of comorbidity on the survival [22–24]. The CCI is developed by Mary Charlson at the Cornell Medical Center in New York in 1984. During a one-month period all patients admitted to the Cornell Medical Center were examined and all comorbidities were recorded. A 1-year follow-up was evaluated for these patients and relative risks of the comorbidities were evaluated. The index includes 19 medical conditions that have been selected and weighted based on the strength of their association to mortality [25]. The index is originally

based on information from medical records but has in several studies been adapted to administrative databases [24,26–29]. In this study the translation of comorbidities in DGCD into the index has been based on the work of Quan et al. who have developed and validated a translation of ICD-10 codes into the CCI [29]. Table 1 shows the translation of comorbidities into CCI. As DGCD did not contain information about the categories “Any tumor” and “Metastatic solid tumor” this is based on data from the National Patient Registry (NPR).

An overall Comorbidity Score (CS) for each patient was calculated and the patients has been divided into none (CS = 0), mild (CS = 1), moderate (CS = 2) or severe comorbidity (CS ≥ 3).

Statistical analyses

The outcome measure was overall survival and was defined as the time from date of surgery to death from any cause or to the end of follow-up period (censored). The patients were followed until 13th October 2011.

Kaplan Meier probabilities for the degree of comorbidity were compared by the log rank test. Cox-regressions were performed for multivariate analyses. Estimation of a total effect of an exposure requires inclusion of all potential confounders, but mediators must be excluded [30,31]. If the research question allows it, mediators can be included in the statistical model and the effect of the exposure is the effect that is not going through the mediator. As the PS may to some extent capture the patient’s comorbidity, PS can be interpreted as a mediator. Therefore two multivariate analyses were performed; model 1 emphasizing the total impact of comorbidity on survival adjusted for the prognostic factors with exception of PS, and model 2 where PS was included to examine whether comorbidity is explained by PS or whether comorbidity has an impact on survival that is not captured in PS.

The assumption of proportional hazards has been tested using Schönfeld residuals and showed that the assumption was not rejected. Sensitivity-analyses were performed and showed that the HR did not change significantly over time. Interactions between comorbidity and the covariates were tested as well and showed no significant interactions.

Significance was defined at $p < 0.05$. Data were analyzed using SPSS statistical software version 20.

Results

Of the 3129 patients included in the study population 1454 patients have died at the end of the follow-up period (46.5%).

Table 2
Comorbidities in the study population.

Types of comorbidities	Weight	Prevalence, N	Percent ^a %
Myocardial infarction	1	27	0.86
Congestive heart failure	1	42	1.34
Peripheral vascular disease	1	151	4.83
Dementia	1	25	0.80
Chronic pulmonary disease	1	177	5.66
Cerebrovascular disease	1	29	0.93
Connective tissue	1	49	1.57
Mild liver disease	1	1	0.03
Diabetes (types 1 and 2)	1	153	4.89
Any tumor	2	184	5.88
Moderate or severe renal disease	3	6	0.19
Metastatic solid tumor	6	37	1.18
AIDS	6	0	0.00

^a Percent of the population.

The percentage of patients without comorbidity was 76.9% (CS = 0), 14.1% had mild comorbidity (CS = 1), 6.5% have moderate comorbidity (CS = 2) and 2.6% have severe comorbidity (CS ≥ 3) (Table 2).

In total 881 comorbidities have been registered, where ‘Chronic pulmonary disease’, ‘Peripheral vascular disease’ and ‘Diabetes’ were the most frequent comorbidities together with “Any tumor” (Table 2).

The age ranged from 13 to 96 years, with a median of 64 years. 67.9% of the patients were diagnosed with stage III or IV. The most common histology type was ‘Serous’ (65.6%). Poor differentiated tumors (Grade 3) was found in 44.4% of the patients, and 46.3% have no residual tumor left.

51.2% of the patients were categorized with PS = 0, 31.1% with PS = 1 and 1.4% with PS = 4 (Table 3).

Patients suffering from comorbidity were older, had a higher stage, a higher PS and residual tumor. The histology of patients with comorbidity was more often ‘Endometrioid’ and ‘Serous’ than for patients without comorbidity (Table 3).

The logrank test demonstrated that there is a significant difference ($p < 0.001$) between comorbidity groups and the probability of surviving. The survival curves of the comorbidities CS = 1 and CS ≥ 3 overlap several times and the survival function for patients with CS = 2 seems to be better than for patients with CS = 1. This is supported by the survival rates, where the rates for patients with CS = 2 are better than for patients with CS = 1 for the 1-year, 3-year and 5-year survival rate (Table 4).

Table 3
Baseline characteristics of the study population.

Covariates	Total		CS = 0**	CS = 1**	CS = 2**	CS ≥ 3**
	N	%				
Event	1454	46.5%	-	-	-	-
Comorbidity						
CS = 0	2405	76.9%	-	-	-	-
CS = 1	440	14.1%				
CS = 2	204	6.5%				
CS ≥ 3	80	2.6%				
Age			$p < 0.001$			
<49	394	12.6%	89.8%	7.1%	2.3%	0.8%
50–59	668	21.3%	84.1%	8.2%	5.5%	2.1%
60–69	949	30.3%	75.9%	15.2%	6.6%	2.3%
70–79	769	24.6%	70.0%	18.1%	8.3%	3.6%
>80	349	11.2%	66.2%	21.2%	8.9%	3.7%
Stage			$p = 0.009$			
I	753	24.4%	80.6%	12.1%	5.7%	1.6%
II	237	7.7%	79.7%	14.3%	5.5%	0.4%
III	1513	48.9%	75.9%	14.9%	6.7%	2.6%
IV	588	19.0%	74.0%	14.5%	7.1%	4.4%
Missing	38					
Histology			$p = 0.28$			
Endometrioid	305	10.9%	77.4%	13.4%	8.2%	1.0%
Mucinous	218	7.8%	78.4%	16.1%	5.5%	0%
Clear cell	148	5.3%	81.1%	10.8%	4.7%	3.4%
Serous	1833	65.6%	77.1%	14.1%	6.3%	2.5%
Other	290	10.4%	80.7%	12.1%	4.8%	2.4%
Missing	335					
Grade			$p = 0.902$			
1	477	20.2%	77.8%	14.5%	5.7%	2.1%
2	832	35.3%	77.5%	13.9%	6.2%	2.3%
3	1047	44.4%	77.7%	12.8%	7.2%	2.3%
Missing	773					
Residual tumor			$p < 0.001$			
No residual tumor	1296	46.3%	75.0%	15.4%	6.6%	3.0%
Residual tumor	1502	53.7%	80.3%	11.9%	6.3%	1.5%
Missing	331					
PS			$p < 0.001$			
PS = 0	1600	51.2%	85.0%	8.2%	5.4%	1.4%
PS = 1	1004	32.1%	74.3%	16.8%	6.5%	2.4%
PS = 2	356	11.4%	62.4%	23.6%	8.4%	5.6%
PS = 3	123	3.9%	43.9%	34.1%	13.8%	8.1%
PS = 4	45	1.4%	48.9%	28.9%	13.3%	8.9%
Missing	1					

*Column percent. ** Row percent.

Table 4
Survival rates.

	Total	CS=0	CS=1	CS=2	CS≥3
1-year survival	79.1 [78.96–79.24]	82.1 [81.94–82.26]	67.6 [63.09–72.11]	73.4 [72.79–74.01]	66.7 [56.31–77.09]
3-year survival	54.0 [52.04–55.96]	57.6 [55.44–59.76]	40.4 [35.30–45.50]	49.1 [41.46–56.74]	36.0 [24.44–47.56]
5-year survival	40.9 [38.74–43.06]	44.4 [41.85–46.95]	26.9 [24.81–35.79]	30.3 [20.89–39.71]	30.4 [18.25–42.55]

However, for all the categories of comorbidities the survival functions are lower than for patients with comorbidity (Fig. 1). An additional analysis of the probability of surviving without including CS=0 showed that there was no significant difference between the groups (log rank, $p=0.09$). Hence, comorbidity was coded as either absent or present for the following analyses.

For both model 1 and model 2 comorbidity, age, stage, histology, residual tumor and PS were found to be independent prognostic factors in the multivariate analyses. Grade was not significant in both models (Table 5).

In Model 1 the HR for patients with presence of comorbidity was 1.31 (1.14–1.50). Higher age was associated with an increased risk of mortality, with patients aged '50–59' having a HR of 1.37 (1.05–1.79), and patients aged '>80' a HR of 4.25 (3.21–5.64).

Higher stages were also associated with higher HR, patients with stage 'II' have a ratio of 2.42 (1.74–3.36) and patients with stage 'IV' a ratio of 5.65 (4.20–7.58). Patients with residual tumor left have an HR of 2.68 (2.28–3.15). The histology of the tumor affects the mortality, where patients with 'Clear cell histology' have the highest HR of 1.87 (1.31–2.68).

In Model 2 the HR for comorbidity decreases from 1.31 to 1.17 when including PS in the model, but comorbidity remained significant. The HRs for PS were 1.33 (1.15–1.53) for PS=1, 2.04 (1.68–2.47) for PS=2, 3.46 (2.52–4.75) for PS=3 and 12.93 (7.08–23.61) for PS=4.

As comorbidity indirectly might impact survival by affecting the choice of treatment, a multivariate logistic regression was performed to investigate whether comorbidity affects the choice of surgical treatment. The choice of treatment was defined as either receiving surgery or not and does not include the choice of oncologic treatment. The results showed that comorbidity did not impact whether patients received surgery or not ($p=0.098$, OR = 1.29 [0.95–1.74]).

Discussion

Comorbidity as a prognostic factor

This study showed that comorbidity was an independent prognostic factor when adjusting for other known prognostic factors. In seven published studies comorbidity was found to influence the survival of ovarian cancer patients [12,18,32–36]. For example in the study of O'Malley et al. they found increased HR of 1.4 (1.1–1.7) for patients with comorbidity compared with patients without comorbidity in a population of 1.051 ovarian cancer patients who received primary surgery [18].

However, there are also studies reporting no impact of comorbidity on the survival of ovarian cancer [3,37–39]. Tingulstad et al. found that comorbidity did not have any impact on survival among 571 women after adjusting for example age, stage grade, histology and residual tumor [3].

In this study we estimated the impact of comorbidity with and without adjusting for PS. Even after adjustment for PS comorbidity is an independent prognostic factor, however the impact of comorbidity attenuated the HR from 1.31 to 1.17. To our knowledge no other studies provide information on the impact of comorbidity with and without PS. This suggests that PS mediates some of the prognostic impact of comorbidity but that comorbidity has an independent value. The finding of comorbidity and PS being two different independent prognostic factors corresponds to conclusions drawn in other studies [12,32,40].

We identified that comorbidity had a smaller impact on the survival compared with the other prognostic factors considered. Stage and the possibility to perform a radical operation are crucial for the prognosis for ovarian cancer. In the clinical setting the choice of treatment is often based on stage and PS. This might explain why stage, residual tumor and PS are stronger prognostic factor than comorbidity.

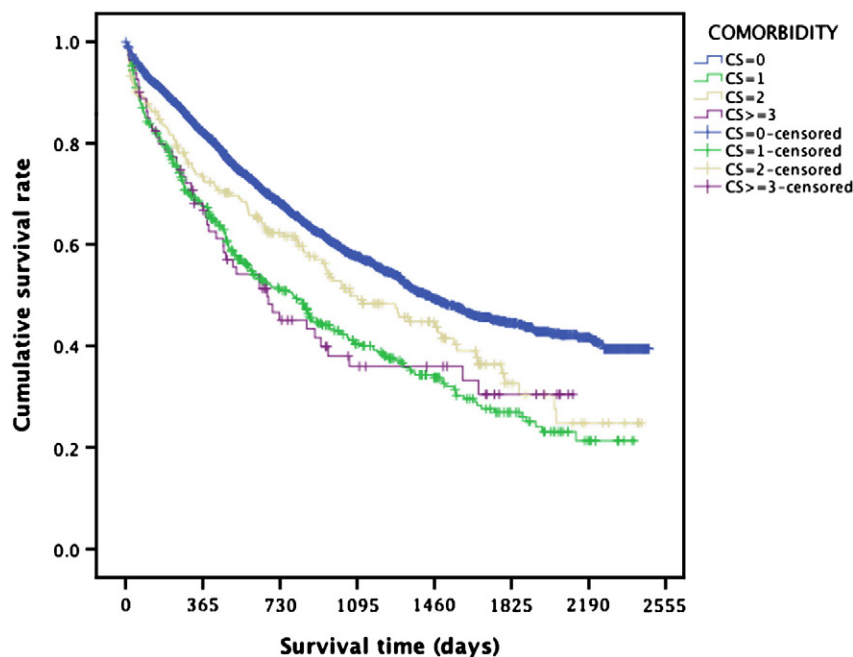


Fig. 1. Kaplan Meier curves for comorbidity.

Table 5
Multivariate survival analyses for Model 1 and Model 2.

Covariate	Model 1 ^a		Model 2 ^b	
	p-Value	HR [95% CI]	p-Value	HR [95% CI]
Comorbidity	<i>p</i> <0.001		<i>p</i> =0.032	
CS = 0 ^c		1		1
CS ≥ 1		1.31 [1.14–1.50]		1.17 [1.01–1.34]
Age	<i>p</i> <0.001		<i>p</i> <0.001	
≤49 ^c		1		1
50–59		1.37 [1.05–1.79]		1.38 [1.049–1.81]
60–69		1.63 [1.27–2.11]		1.62 [1.25–2.10]
70–79		2.15 [1.66–2.78]		2.03 [1.56–2.64]
≥80		4.25 [3.21–5.64]		3.34 [2.50–4.48]
Stage	<i>p</i> <0.001		<i>p</i> <0.001	
I*		1		1
II		2.42 [1.74–3.36]		2.258 [1.63–3.14]
III		4.35 [3.32–5.69]		4.152 [3.18–5.43]
IV		5.65 [4.20–7.58]		5.016 [3.74–6.73]
Histology	<i>p</i> <0.001		<i>p</i> <0.001	
Endometrioid ^c		1		1
Mucinous		1.55 [1.08–2.21]		1.35 [0.34–1.93]
Clear cell		1.87 [1.31–2.68]		1.79 [1.25–2.56]
Serous		0.94 [0.74–1.18]		0.94 [0.74–1.18]
Other		1.55 [1.16–2.08]		1.62 [1.21–2.16]
Residual tumor	<i>p</i> <0.001		<i>p</i> <0.001	
No residual tumor ^c		1		1
Residual tumor		2.68 [2.28–3.15]		2.46 [2.09–2.90]
PS			<i>p</i> <0.001	
PS = 0 ^c		–		1
PS = 1				1.33 [1.15–1.53]
PS = 2				2.04 [1.68–2.47]
PS = 3				3.46 [2.52–4.75]
PS = 4				12.93 [7.08–23.61]

^a Adjusted for age, stage, histology, and residual tumor.

^b Adjusted for age, stage, histology, residual tumour and PS.

^c Reference group.

Grade was eliminated in multivariate models. Several studies have showed that the impact of grade disappears in the multivariate analyses, which has been explained by the fact that grade correlates with stage and that the effect of stage overrides the effect of grade [18].

The underlying mechanisms

It has been suggested that comorbidity can have an indirect impact the survival by affecting the choice of treatment or that the tolerance of treatment is weakened for comorbid patients. However, the evidence on the link between comorbidity and the survival is limited.

This study showed that comorbidity was not significantly associated with choice of surgical treatment. There are very few studies examining the association between comorbidity and choice of treatment for cancer patients. In the study of Mass et al. they find that patients without comorbidity were more likely to receive standard treatment (primary surgery in combination with chemotherapy) than patients with comorbidity [41]. In another study by the same authors, they investigate the influence of comorbidity on treatment and survival of colorectal, lung and breast cancer and conclude that for cancer diseases where surgery is a cornerstone for length of survival, comorbidity does not affect the surgery rate significantly, whereas chemotherapy is more frequently modified according to the comorbidity of the patient [42]. This might apply to ovarian cancer as well, but have to our knowledge not been studied. No valid information about the oncologic treatment was available in DGCD or NPR why this was not possible to include in this study.

Methodological challenges

This study has a high validity as DGCD contains 97% of the patients diagnosed with gynaecological cancers in Denmark [1]. Further residual confounding emerging from imperfect classification of covariates are minimal as all the data in the clinical database are validated. However,

the registration and measurement of comorbidity implied some methodological challenges.

First of all, using administrative databases instead of medical records has been criticized for lacking the accuracy required for research, as comorbidity is often underreported [12,24,32,40,43,44]. This underestimation might bias the results; the misclassification of comorbidity is however assumed to be homogenous across groups of outcome, which makes the misclassification non-differential [45].

An advantage of using DGCD compared with other administrative databases available is that the comorbidity is registered at the time of diagnosis, which involves that it is only the comorbidity that the patient is currently suffering from that are registered. This is different from using administrative databases, such as NPR, where all discharge diagnoses are included in the index.

Secondly, using the CCI might imply some limitations. Both the treatment and the disease control have changed dramatically since 1984; for example ulcer disease and HIV have a superior outcome today based on newer medical treatments. It is therefore likely that the relative risks ascribed to conditions in 1984 are not in agreement with the prognostic impact today. Further the CCI is also used as a generic index without taking into account that the comorbidity weights are not necessarily constant for the setting, the disease or the outcome being studied [44]. The evidence indicates this as comorbidity less frequently has an impact on aggressive cancers; the patients may simply die of the cancer before their comorbidity has any significant impact on survival [46,47]. The results from this study showed that there was no difference between the degree of comorbidities and the survival, which indicates that the more severe comorbidities did not influence the survival more as the patients usually die from their cancer disease. Using a generic index might imply that patients are not assigned with a weight score that is in agreement with their increased risks. However, the CCI is the most validated and used index and therefore we chose to use this index. A new comorbidity index based on modern treatment should be developed for studies of comorbidity in gynecologic cancers but this has been beyond the scope of this study.

Thirdly, the translation from data into the CCI implied some limitations. In this study we found that 25.7% of the patients were registered with comorbidity according to the CCI. This is comparable to other studies measuring comorbidity based on this index [18,33,34,39]. Data about ulcer disease was not prevalent in DGCD, which is why this category was not included in the index. Ulcer disease is one of the diseases where modern treatment has improved the prognosis radically. The missing registration of the disease might bias the results towards a reduced impact of comorbidity but the bias is expected to be low. The severity of diabetes and liver disease is not registered in DGCD, which also might bias the results as the patients are not registered with the correct weight score. Though, complications of diabetes might be registered in some of the other categories (Table 1). Patients registered with a moderate or severe liver disease was according to Danish study of ovarian cancer found to be 0.2% of the population and the bias is therefore assessed to be limited.

However, 21 conditions registered in the DGCD were not found to correlate with any of the ICD-10 codes used in CCI (Table 1). These comorbidities were considered to be non-prognostic comorbidity. However, we performed a Cox regression analysis including the patients with a non-prognostic comorbidity, adjusted for CCI as well as stage, grade, histology, residual tumor and age. The results showed that the present of a non-prognostic comorbidity does not affect the patients survival (*p* = 0.199).

Conclusion

Comorbidity can be considered to be an independent prognostic factor. PS attenuates the impact of comorbidity but comorbidity does still significantly affects the survival after adjustment for PS. Age, stage, residual tumor, histology and PS are also shown to be

independent prognostic factors and comorbidity has a smaller impact on survival compared to the other prognostic factors.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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