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Risk factors for early death among ovarian cancer patients: a nationwide cohort study

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ABSTRACT

Objective: To characterize ovarian cancer patients who die within 6 months of diagnosis and to identify prognostic factors for these early deaths.

Methods: A nationwide cohort study covering ovarian cancer in Denmark in 2005–2016. Tumor and patient characteristics including comorbidity and socioeconomic factors were obtained from the comprehensive Danish national registers.

Results: A total of 5,570 patients were included in the study. Three months after ovarian cancer diagnosis 456 (8.2%) had died and 664 (11.9%) died within 6 months of diagnosis. Adjusted for age and comorbidity, patients who died early were admitted to hospital significantly more often in a 6-month period before the diagnosis (odds ratio [OR]=1.61 [1.29–2.00], and OR=1.47 [1.21–1.78]), for patients who died within 3 and 6 months respectively). Low educational level (OR=2.11), low income (OR=2.50) and singlehood (OR=1.90) were factors significantly associated with higher risk of early death. The discriminative ability of risk factors in identifying early death was assessed by cross-validated area under the receiver operating characteristic curve (AUC). The AUC was found to be 0.91 (0.88–0.93) and 0.90 (0.87–0.92) for death within 3 and 6 months, respectively.

Conclusions: Despite several admissions to hospital, the ovarian cancer diagnosis is delayed for a subgroup of patients, who end up dying early, probably due to physical deterioration in the ineffective waiting time. Up to 90% of high-risk patients might be identified significantly earlier to improve the prognosis. The admittance of the patients having risk symptoms should include fast track investigation for ovarian cancer.

Keywords: Ovarian Cancer; Mortality; Survival; Comorbidity; Socioeconomic Factors; Prognosis

INTRODUCTION

Ovarian cancer is the leading cause of death from gynecological cancers in the Western countries. Substantial differences in 5-year survival rates are reported in the world, and within Europe, ranging from 26%–51%. Denmark has, along with the UK, for many years ranked at the bottom of the statistics regarding ovarian cancer survival [1-4].

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Also compared to the other Scandinavian countries, Danish ovarian cancer patients have a poor prognosis [5]. Considering ovarian cancer survival curves, Denmark distinguishes itself by having a steep fall in survival during the first 0–6 months, after which the survival curve is parallel to the curves of the other countries [6]. This high short-term mortality may be the primary explanation for the overall poor prognosis of Danish ovarian cancer patients.

The mechanisms behind the inferior Danish short-term survival rates are not fully elucidated. Among suggested causes is an unfavourable stage distribution due to diagnostic delay, as previous benchmarking studies have shown a higher incidence of stage IV patients in Denmark [1]. Severe comorbidity among Danish patients may be a contributing explanatory factor for the survival difference. Several studies have shown that comorbidity has an important negative influence on survival of ovarian cancer [7-9]. Finally, differences in socioeconomic factors such as income, civil status and educational level may influence the surgical outcome and survival [10-14].

To obtain more knowledge about the reasons behind the relatively high short-term mortality among Danish ovarian cancer patients, we aimed to characterize patients who died within 6 months of ovarian cancer diagnosis with regards to clinical and socioeconomical traits. Further, we aimed to identify risk factors for very early (<3 months) and early (<6 months) death.

MATERIALS AND METHODS

1. Setting
The present nationwide cohort study was conducted in Denmark. Denmark has a population of 5.4 million, and all Danish citizens are issued with a personal and unique ID-number in the Danish Civil Registration System (DCRS). The DCRS automatizes survival registration and is also linked to other national registries and databases described below. This provides a unique platform for epidemiological studies.

2. Data sources
The Danish Gynecologic Cancer Database (DGCD) is a nationwide database containing key clinical information on Danish patients diagnosed with gynecological cancers since January 1, 2005 [15]. Reporting to the database is mandatory and the data completeness is 97% according to the most recent annual report from the database [16].

We included women diagnosed with an incident ovarian, fallopian tube, or primary peritoneal cancer in 2005–2015.

The Danish National Patient Register records information on all out-patient and in-hospital contacts on citizens in Denmark including primary and secondary diagnoses for each contact, and whether the patient receives chemotherapy. Data from the the Danish National Patient Register was linked via the unique person-identification number with DGCD. We selected diagnoses from 18 groups of International Classification of Diseases, 10th Revision codes (Listed in **Supplementary Data 1**) for diseases that could match symptoms of ovarian cancer. Admissions due to one or more diagnoses from the eighteen groups, up to 180 days prior to the ovarian cancer diagnosis, were included.

Data on socioeconomic status (income, civil status and educational level) were provided from Statistics Denmark. Statistics Denmark is the central statistical office in Denmark. It collects statistical information from the Danish community for use in governmental administration, research, teaching, etc.

3. Study population

We identified 5,947 patients registered in the DGCD from January 1, 2005 to December 31, 2016 with an incident diagnosis of ovarian cancer (epithelial, mixed epithelial-stromal tumors, and stromal sarcomas), fallopian tube cancer, or peritoneal cancer (borderline tumors were excluded). Excluded were a total of 291 cases because of missing information regarding primary treatment or patients alive with follow up shorter than 6 months, 11 patients because of age <16 years, and 75 patients (1.3%) were excluded because of loss to follow-up, giving a total of 5,570 patients in the study.

4. Variables

Cancer stage was categorised according to the International Federation of Gynecology and Obstetrics 2013 stage classification, and the variable histology was categorised as: 'Serous,' 'Mucinous,' 'Endometrioid,' 'Clear cell,' 'Sarcoma' and 'Rare types.' Nutritional status was assessed with the body mass index (BMI) and the World Health Organization definition of BMI was used to categorise this variable [17]. The variable Smoking was classified as 'Smoker,' 'Ex-smoker' and 'Never smoked' and Alcohol consumption was defined as 'No' (0), 'Low' (1–7 units per week), 'Moderate' (8–21 units per week) and 'Severe' (>21 units per week).

Comorbidity was classified with a modified version of the Charlson comorbidity index (CCI) and the categories were: 'No comorbidity' (CCI=0), 'Mild comorbidity' (CCI=1) and 'Moderate/severe comorbidity' (CCI ≥2) [7,18]. We also used the ovarian cancer comorbidity index (OCCI) as a comorbidity measure as this index previously has been found to be a stronger predictor of prognosis in ovarian cancer than the CCI [9]. The OCCI is age-specific, combining the risk ascribed to patient age and comorbidity when calculating the risk score. Patients were classified as 'Low risk,' 'Moderate risk' and 'High risk' according to expected overall survival (OS). Physical Status was classified according to American Society of Anesthesiologists (ASA) Classification System [19]. Performance status (PS) was classified according to the Eastern Cooperative Oncology Group definition [20].

In Denmark "Centre" is tantamount to highly specialised departments. For ovarian cancer, there are 4 Gynecologic oncology centres in Denmark. Non-centre departments are obligated by the Danish Health Authority to refer patients with ovarian cancer to one of these centres, where they are treated by gynecological oncologist.

The socioeconomic variable 'Income' was categorised as the patient's private income, and the disposable income, which is the total income of the household. The variable family type was dichotomized in 'Couple' or 'Living alone.' Educational level was categorised as 'Primary and lower secondary school,' 'High school,' 'Further education,' 'Medium length education' and 'Higher education/scientist.'

Death from any cause (OS) was used as outcome measure. The outcome 'Very early death' was defined as death within 3 months of ovarian cancer diagnosis whereas 'Early death' was survival less than 6 months from diagnosis.

5. Statistical analyses

Univariate logistic regression models provided crude odds ratios (ORs) with 95% confidence intervals (CIs) of very early death and early death respectively, for all assessed risk factors.

Multiple logistic regression models provided adjusted OR with 95% CI for risk factors of special interest.

To estimate the predictive value of the risk factors, the cohort was divided into a training data set, consisting of women having been diagnosed in 2005–2011, and a validation data set including women diagnosed in 2012–2015. A model created by backward selection of a logistic regression model including all assessed risk factors was fitted on the training data set and tested on the validation data set. This was done for both very early death and early death as the outcome. Areas under the receiver operating characteristic curves (AUCs) with 95% CIs are reported. As a sensitivity analysis, we also randomly split the data into a training and validation data set, with the same sizes as for the calendar year-based split.

All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

6. Ethics

According to Danish law, approval from the Committee on Health Research Ethics was not required, as no direct patient intervention was part of the study. The study was conducted in accordance to the declaration of Helsinki concerning human rights.

The study was approved by the Danish Gynecological Cancer Group and the Danish Data Protection Agency (file No. 02856/30-1213).

RESULTS

A total of 5,570 incident ovarian, fallopian tube or primary peritoneal cancer patients were included. In the cohort, 4,906 (88.1%) patients were alive 6 months after the diagnosis, whereas 456 (8.2%) patients died within 3 months, and 664 (11.9%) patients within 6 months.

1. Characteristics

The univariate analysis showed that early death was associated with different pre-diagnostic demographics and different clinical aspects at the time of diagnosis compared to patients who lived beyond 6 months after ovarian cancer diagnosis (**Table 1**).

Patients who died early were admitted to hospital significantly more often in a period of 6 months before diagnosis than patients who survived for more than 6 months: OR=1.78 (1.47–2.19) and OR=1.59 (1.33–2.61) for death within 3 and 6 months, respectively. This difference was even more pronounced when admissions for "benign ovarian tumor" were excluded. Referral for "benign ovarian tumor" was associated to improved survival (OR=0.17 [0.06–0.45] and OR=0.17 [0.08–0.39], respectively). Among the explored diagnoses, admissions for unspecific cancer, anaemia, thromboembolism, respiratory symptoms, urological diseases, ascites and pain were significantly more often observed among patients with early death.

Among socioeconomic factors, low educational level and low income (personal as well as disposable) was more common among patients with early death. More patients in the early

Table 1. Clinical and socioeconomic characteristics of the cohort

Variables (n=5,570)	No. (%)		
	Alive after 6 mo (n=4,906 [88.1% of the study group])	Death within 3 mo (n=456 [8.2% of the study group])	Death within 6 mo* (n=664 [11.9% of the study group])
Mean age (yr)	63.2	73.4	71.7
Age groups (yr)			
<44	366 (7.5)	3 (0.7)	9 (1.4)
45–54	776 (15.8)	21 (4.6)	30 (4.5)
55–64	1,327 (27.0)	59 (12.9)	103 (15.5)
65–74	1,485 (30.3)	134 (29.4)	190 (28.6)
>75	952 (19.4)	239 (52.4)	332 (50.0)
Comorbidity			
OCCI			
Low risk	1,269 (25.9)	27 (5.9)	46 (6.9)
Moderate risk	2,610 (53.2)	174 (38.2)	266 (40.1)
High risk	1,027 (20.9)	255 (55.9)	352 (53.0)
CCI			
No comorbidity	3,904 (79.6)	286 (62.7)	422 (63.6)
Mild comorbidity	620 (12.6)	117 (25.7)	166 (25.0)
Moderate/severe comorbidity	382 (7.8)	53 (11.6)	76 (11.4)
Lifestyle characteristics			
Alcohol consumption			
No	2,983 (60.8)	308 (67.5)	442 (66.6)
Low	810 (16.5)	39 (8.6)	61 (9.2)
Moderate	320 (6.5)	16 (3.5)	27 (4.1)
Severe	232 (4.7)	22 (4.8)	28 (4.2)
Unknown	561 (11.4)	71 (15.6)	106 (16.0)
BMI			
<18.5	219 (4.5)	52 (11.4)	77 (11.6)
18.5–24	2,345 (47.8)	214 (46.9)	305 (45.9)
25–29	1,320 (26.9)	80 (17.5)	121 (18.2)
30–34	487 (9.9)	34 (7.5)	55 (8.3)
≥35	233 (4.7)	24 (5.3)	33 (5.0)
Unknown	302 (6.2)	52 (11.4)	73 (11.0)
Smoking			
Never	2,473 (50.4)	191 (41.9)	292 (44.0)
Ex-smoker	1,050 (21.4)	106 (23.2)	153 (23.0)
Current smoker	894 (18.2)	88 (19.3)	116 (17.5)
Unknown	489 (10.0)	71 (15.6)	103 (15.5)
Education			
Municipal primary and lower secondary school	1,790 (36.5)	250 (54.8)	347 (52.3)
High school	142 (2.9)	11 (2.4)	15 (2.3)
Further education	1,746 (35.6)	112 (24.6)	173 (26.1)
Medium length education	856 (17.4)	49 (10.7)	76 (11.4)
Higher education/scientist	200 (4.1)	11 (2.4)	16 (2.4)
Country of origin			
Danish	4,586 (93.5)	440 (96.5)	635 (95.6)
Western	84 (1.7)	7 (1.5)	12 (1.8)
Non-Western	130 (2.6)	6 (1.3)	11 (1.7)
Work			
In employment	1,605 (32.7)	24 (5.3)	52 (7.8)
Unemployed	117 (2.4)	3 (0.7)	6 (0.9)
Retirement pension	2,646 (53.9)	385 (84.4)	546 (82.2)
Employment and support allowance	318 (6.5)	28 (6.1)	40 (6.0)
Unknown (including patients under education; 40, 18 and 4, respectively)	220 (4.5)	16 (3.5)	20 (3.0)
Income (DKK)			
<150,000	1,099 (22.4)	179 (39.3)	255 (38.4)
150,000–191,000	1,187 (24.2)	113 (24.8)	158 (23.8)
191,001–262,000	1,239 (25.3)	80 (17.5)	123 (18.5)
>262,000	1,299 (26.5)	36 (7.9)	67 (10.1)
Unknown	82 (1.7)	48 (10.5)	61 (9.2)

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Table 1. (Continued) Clinical and socioeconomic characteristics of the cohort

Variables (n=5,570)	No. (%)		
	Alive after 6 mo (n=4,906 [88.1% of the study group])	Death within 3 mo (n=456 [8.2% of the study group])	Death within 6 mo* (n=664 [11.9% of the study group])
Disposable income (DKK)			
<177,000	1,080 (22.0)	201 (44.1)	275 (41.4)
177,000–257,000	1,178 (24.0)	103 (22.6)	162 (24.4)
257,001–394,000	1,249 (25.5)	76 (16.7)	117 (17.6)
>394,000	1,317 (26.8)	28 (6.1)	49 (7.4)
Unknown	82 (1.7)	48 (10.5)	61 (9.2)
Family type			
Couple	3,005 (61.3)	164 (36.0)	250 (37.7)
Living alone	1,850 (37.7)	289 (63.4)	411 (61.9)
Unknown	51 (1.0)	3 (0.7)	3 (0.5)
Stage			
Stage I	1,307 (26.6)	9 (2.0)	24 (3.6)
Stage II	375 (7.6)	10 (2.2)	23 (3.5)
Stage III	2,213 (45.1)	222 (48.7)	335 (59.0)
Stage IV	868 (17.7)	162 (35.5)	217 (32.7)
Unknown	143 (2.9)	53 (11.6)	65 (9.9)
Ascites (mL)			
None	2,048 (41.7)	81 (17.8)	127 (19.1)
<500	826 (16.8)	51 (11.2)	81 (12.2)
500–1,999	471 (9.6)	51 (11.2)	80 (12.0)
2,000–3,999	336 (6.8)	54 (11.8)	84 (12.7)
>4,000	352 (7.2)	51 (11.2)	70 (10.5)
Unknown	873 (17.8)	168 (36.8)	222 (33.4)
PS			
0	2,607 (53.1)	56 (12.3)	110 (16.6)
1	1,548 (31.6)	114 (25.0)	188 (28.3)
2	478 (9.7)	132 (28.9)	179 (27.0)
3	120 (2.4)	92 (20.2)	116 (17.5)
4	12 (0.2)	53 (11.6)	58 (8.7)
Unknown	141 (2.9)	9 (2.0)	13 (2.0)
ASA			
1	1,666 (34.0)	29 (6.4)	60 (9.0)
2	2,311 (47.1)	128 (28.1)	217 (32.7)
3	558 (11.4)	164 (36.0)	220 (33.1)
4	33 (0.7)	56 (12.3)	61 (9.2)
5 & 6	49 (1.0)	12 (2.6)	16 (2.4)
Unknown	289 (5.9)	67 (14.7)	90 (13.6)
Diagnostic procedures			
None	4,457 (90.8)	173 (37.9)	544 (81.9)
Ultrasound-guided biopsy	175 (3.6)	20 (4.4)	70 (10.5)
Laparoscopy	138 (2.8)	6 (1.3)	17 (2.6)
Laparotomy	136 (2.8)	9 (2.0)	33 (5.0)
Treatment			
Primary surgery	3,720 (75.8)	219 (48.0)	349 (52.6)
None	147 (3.0)	136 (29.8)	160 (24.1)
Palliative	1 (0.0)	0	0
NACT	1,038 (21.2)	101 (22.1)	155 (23.3)
Residual tumor >R0†			
Not relevant	1,186 (24.2)	237 (52.0)	315 (47.4)
Unknown	88 (1.8)	3 (0.7)	6 (0.9)
Yes	1,173 (23.9)	186 (40.8)	274 (41.3)
No	2,459 (50.1)	30 (6.6)	69 (10.3)
Histology			
Unknown	544 (11.1)	136 (29.8)	180 (27.1)
Serous	3,090 (63.0)	250 (54.8)	353 (53.2)
Endometrioid	461 (9.4)	10 (2.2)	18 (2.7)
Clear cell	232 (4.7)	4 (0.9)	8 (1.2)

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Table 1. (Continued) Clinical and socioeconomic characteristics of the cohort

Variables (n=5,570)	No. (%)		
	Alive after 6 mo (n=4,906 [88.1% of the study group])	Death within 3 mo (n=456 [8.2% of the study group])	Death within 6 mo* (n=664 [11.9% of the study group])
Mucinous	328 (6.7)	19 (4.2)	39 (5.9)
Sarcoma	148 (3.0)	21 (4.6)	43 (6.5)
Rare types	103 (2.1)	16 (3.5)	23 (3.5)
Reason for no treatment			
Not relevant (treatment)	4,759 (97.0)	320 (70.2)	504 (75.9)
Condition	49 (1.0)	81 (17.8)	90 (13.6)
Wish	11 (0.2)	32 (7.0)	39 (5.9)
Death	0	4 (0.9)	4 (0.6)
Unknown	87 (1.8)	19 (4.2)	27 (4.1)
Center treatment			
Yes	3,610	286	425
No	1,286 (26.2)	170 (37.3)	239 (36.6)

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; DKK, Danish Krone; PS, performance status; OCCI, ovarian cancer comorbidity index.
*Included are patients death within 3 months; †Subanalysis with patients having primary surgery, only.

death group were disability pensioners and old age pensioners, whereas unemployment was equally distributed among short- and long-term survivors. Race did not influence risk of early death.

Patients who died early were older and had more comorbidity. Significantly more were underweight (BMI <18.5) and had a history of smoking.

Short-term mortality was significantly associated with referral to neoadjuvant chemotherapy (3 months: OR=1.65 [1.29–2.11] and 6 months: OR=1.59 [1.30–1.95]; p<0.001) or had no treatment (3 months: OR=15.72 [12.00–20.59] and 6 months: OR=11.60 [9.04–14.89]). The reasons for no treatment were poor condition or patients own wish.

2. Multivariate analyses

Adjusted for age and comorbidity, patients with early death were admitted to hospital significantly more often in a period 6 month before the diagnose compared to patients who lived more the 6 months after diagnosing: OR=1.61 (1.29–2.00), and OR=1.47 (1.21–1.78) for death within 3 and 6 months, respectively. Still, this was even more distinct, when admission for "benign ovarian tumor" (OR=0.23 [0.09–0.63] and OR=0.24 [0.10–0.54]) was excluded. Admission for unspecified cancer, respiratory symptoms, ascites and pain remained significantly frequent (**Tables 2** and **3**).

In the multivariate analysis socioeconomic factors (low educational level, low income and single life) remained significantly associated with early death (**Table 4**).

Multivariate analyses showed that early death was significantly associated to more self-reported comorbidity as their CCI and OCCI scores were higher (**Table 4**). More patients, who died early, were smokers and significantly more did not drink alcohol. Significantly more patients were underweight (BMI <18.5), (3 month: OR=2.12 [1.47–3.05] and 6 months: OR=2.27 [1.66–3.11]) whereas overweight (BMI 25–29) seemed to protect against early death (3 month: OR=0.63 [0.48–0.83] and 6 months: OR=0.67 [0.53–0.85]). After adjustment for age, stage, PS, ASA and Centre, diagnostic procedures did not differ between the groups.

Table 2. Admission to hospital 6 months prior to diagnosis (numbers and adjusted OR of very early death among ovarian cancer patients)

Variables	Survival more than 6 mo (n=4,906)	Very early death (n=456)	Death within 3 mo vs. alive after 6 mo	
	No. (%)	No. (%)	Adjusted OR (95% CI)*	p-value
Any admission[†]	980 (20.0)	140 (30.7)	1.607 (1.290–2.001)	<0.001
Any admission excluding those for benign ovarian tumor[‡]	733 (14.9)	136 (29.8)	1.982 (1.585–2.479)	<0.001
Benign ovarian tumor[‡]	247 (5.0)	4 (0.9)	0.232 (0.085–0.633)	0.004
Cancer diagnosis[‡]	200 (4.1)	29 (6.4)	1.156 (1.001–2.298)	0.050
Anaemia[‡]	33 (0.7)	5 (1.1)	1.093 (0.414–2.883)	0.858
Thromboembolism[‡]	87 (1.8)	13 (2.9)	1.409 (0.763–2.603)	0.273
Pleural exudate[‡]	73 (1.5)	10 (2.2)	1.328 (0.665–2.650)	0.422
Respiratory symptoms[‡]	50 (1.0)	11 (2.4)	2.164 (1.083–4.321)	0.029
Gastrointestinal disease[‡]	501 (10.2)	51 (11.2)	1.189 (0.867–1.631)	0.282
Ileus[‡]	27 (0.6)	6 (1.3)	1.934 (0.769–4.931)	0.167
Urological diseases[‡]	55 (1.1)	14 (3.1)	2.219 (1.183–4.162)	0.013
Vaginal bleeding[‡]	96 (2.0)	5 (1.1)	0.515 (0.205–1.291)	0.157
Ascites[‡]	276 (5.6)	59 (12.9)	2.313 (1.692–3.161)	<0.001
Pain[‡]	23 (0.5)	11 (2.4)	6.634 (3.009–14.626)	<0.001
Dementia/psychological disorders[‡]	10 (0.2)	3 (0.7)	4.339 (1.060–17.758)	0.041

CI, confidence interval; OR, odds ratio.
*No admissions within 6 months prior to ovarian cancer diagnosis is used as reference (ref=1); [†]Adjusted for age and comorbidity; [‡]Adjusted for age.

Table 3. Admission to hospital 6 months prior to diagnosis (numbers and adjusted OR of early death among ovarian cancer patients)

Variables	Survival more than 6 mo (n=4,906)	Early death (n=664)	Death within 6 mo vs. alive after 6 mo	
	No. (%)	No. (%)	Adjusted OR (95% CI)*	p-value
Any admission[†]	980 (20.0)	189 (28.5)	1.466 (1.212–1.775)	<0.001
Any admission excluding those for benign ovarian tumor[‡]	733 (14.9)	183 (27.6)	1.814 (1.492–2.204)	<0.001
Benign ovarian tumor[‡]	247 (5.0)	6 (0.9)	0.235 (0.103–0.536)	0.001
Cancer diagnosis[‡]	200 (4.1)	40 (6.0)	1.476 (1.027–2.121)	0.035
Anaemia[‡]	33 (0.7)	12 (1.8)	1.941 (0.968–3.891)	0.062
Thromboembolism[‡]	87 (1.8)	20 (3.0)	1.517 (0.906–2.539)	0.113
Pleural exudate[‡]	73 (1.5)	14 (2.1)	1.252 (0.688–2.280)	0.462
Respiratory symptoms[‡]	50 (1.0)	16 (2.4)	2.196 (1.208–3.993)	0.01
Gastrointestinal disease[‡]	501 (10.2)	77 (11.6)	1.247 (0.957–1.625)	0.102
Ileus[‡]	27 (0.6)	8 (1.2)	1.787 (0.776–4.117)	0.173
Urological diseases[‡]	55 (1.1)	16 (2.4)	1.752 (0.968–3.170)	0.064
Vaginal bleeding[‡]	96 (2.0)	8 (1.2)	0.565 (0.269–1.186)	0.131
Ascites[‡]	276 (5.6)	75 (11.3)	2.020 (1.525–2.676)	<0.001
Pain[†]	23 (0.5)	23 (3.5)	4.799 (2.254–10.215)	<0.001
Dementia/psychological disorders[‡]	10 (0.2)	6 (0.9)	2.888 (0.717–11.638)	0.136

CI, confidence interval; OR, odds ratio.
*No admissions within 6 months prior to ovarian cancer diagnosis is used as reference (ref=1); [†]Adjusted for age and comorbidity; [‡]Adjusted for age.

At the time of diagnose (**Table 5**) the multivariate analysis showed, that early-death patients still had significantly higher ASA-score and poorer PS. Compared to serous adenocarcinoma, there were significantly fewer early deaths among patients with non-serous carcinomas, whereas early death was significantly associated with sarcomas and rare types of histology. Among patients with early death significantly more patients never had surgery, and if they had, significantly more had residual tumor (3 months: OR=4.28 [2.68–6.83] and 6 months: OR=3.62 [2.57–5.11]).

3. Prediction

Fig. 1 show the receiver operating curves for the prediction tests performed on the calendar year-based division of the cohort for the outcome death within 3 and death within 6 months.

Table 4. Adjusted OR of very early and early death among ovarian cancer patients: clinical risk factors (prediagnosis)

Variables	Death within 3 mon vs. alive after 6 mon		Death within 6 mon vs. alive after 6 mon	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Lifestyle characteristics				
Alcohol consumption*				
No	1.000		1.000	
Low	0.517 (0.362–0.737)	0.0003	0.563 (0.421–0.753)	<0.001
Moderate	0.488 (0.285–0.834)	0.0088	0.592 (0.387–0.907)	0.016
Severe	0.786 (0.485–1.272)	0.3263	0.691 (0.449–1.064)	0.093
BMI†				
<18.5	2.154 (1.504–3.084)	<0.0001	2.356 (1.732–3.205)	<0.001
18.5–24	1.000		1.000	
25–29	0.630 (0.478–0.830)	0.0010	0.672 (0.534–0.846)	0.001
30–34	0.777 (0.525–1.150)	0.2077	0.887 (0.064–1.220)	0.460
≥35	1.418 (0.889–2.261)	0.1426	1.328 (0.886–1.989)	0.169
Smoking‡				
Never	1.000		1.000	
Ex-smoker	1.248 (0.956–1.624)	0.0999	1.182 (0.966–1.476)	0.141
Current smoker	1.526 (1.144–2.035)	0.0041	1.277 (0.995–1.640)	0.054
Education§				
Municipal primary and lower secondary school	1.000		1.000	
High school	1.175 (0.600–1.302)	0.6377	1.081 (0.602–1.940)	0.795
Further education	0.636 (0.500–0.809)	0.0002	0.686 (0.561–0.839)	0.000
Medium length education	0.622 (0.448–0.863)	0.0045	0.670 (0.511–0.879)	0.004
Higher education/scientist	0.758 (0.399–1.440)	0.3980	0.758 (0.441–1.301)	0.315
Country of origin‖				
Denmark	1.000		1.000	
Western	0.608 (0.257–1.435)	0.2560	0.516 (0.224–1.186)	0.119
Non-Western	0.843 (0.434–1.632)	0.6115	0.611 (0.328–1.137)	0.120
Work¶				
In employment	1.000		1.000	
Unemployed	0.627 (0.084–4.693)	0.6500	1.094 (0.387–3.089)	0.866
Retirement pension	9.731 (6.413–14.760)	<0.0001	6.369 (4.760–8.521)	<0.001
Employment and support allowance	5.888 (3.369–10.292)	<0.0001	3.882 (2.527–5.964)	<0.001
Income (USD)**				
<22.536	1.000		1.000	
22,536–28,700	0.679 (0.524–0.880)	0.0035	0.654 (0.523–0.818)	0.000
28,701–39,360	0.686 (0.508–0.925)	0.0135	0.696 (0.542–0.895)	0.005
>39,360	0.400 (0.263–0.608)	<0.0001	0.467 (0.336–0.649)	<0.001
Disposable income (USD)††				
<26,590	1.000		1.000	
26,591–38,610	0.712 (0.530–0.956)	0.0239	0.826 (0.645–1.057)	0.129
38,611–59,200	0.740 (0.511–1.070)	0.1099	0.825 (0.606–1.123)	0.222
>59,200	0.470 (0.278–0.795)	0.0049	0.546 (0.357–0.835)	0.005
Family type†				
Couple	1.000		1.000	
Living alone	1.938 (1.564–2.400)	<0.0001	1.866 (1.559–2.233)	<0.001

BMI, body mass index; CCI, Charlson comorbidity index; OCCI, ovarian cancer comorbidity index; OR, odds ratio.

*Adjusted for age, smoking, BMI, OCCI, CCI and education; †Adjusted for age, smoking, alcohol consumption, OCCI, CCI and education; ‡Adjusted for age, BMI, alcohol consumption, OCCI, CCI, and education; §Adjusted for age and country of origin; ‖Adjusted for age; ¶Adjusted for age, education and country of origin; **Adjusted for age, education, country of origin and work; ††Adjusted for age, education, country of origin, work and family type.

For the outcome death within 3 months, the figure shows the prediction performance of a multiple logistic regression model including the variables family type, employment, income, OCCI, CCI, BMI, admission to hospital due to pain or thromboembolism, stage, PS, treatment, histology and residual tumor. The AUC was found to be 0.91 (0.88–0.93).

For the outcome death within 6 months, the figure shows the prediction performance of a multiple logistic regression model including the variables family type, employment, income,

Table 5. Adjusted OR of very early and early death among ovarian cancer patients: clinical risk factors (at time of diagnosis)

Variables	Death within 3 mon vs. alive after 6 mon		Death within 6 mon vs. alive after 6 mon	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Ascites*				
0	1.000		1.000	
<500	1.357 (0.937–1.964)	0.1060	1.376 (1.019–1.858)	0.037
500–1,999	1.877 (1.288–2.735)	0.0010	1.941 (1.425–2.645)	<0.001
2,000–3,999	2.721 (1.868–3.962)	<0.0001	2.768 (2.026–3.783)	<0.001
>4,000	2.361 (1.613–3.457)	<0.0001	2.174 (1.568–3.010)	<0.001
PS†				
0	1.000		1.000	
1	2.127 (1.522–2.972)	<0.0001	1.875 (1.457–2.413)	<0.001
2	6.618 (4.708–9.303)	<0.0001	4.805 (3.669–6.292)	<0.001
3	17.946 (12.005–26.826)	<0.0001	12.171 (8.678–17.070)	<0.001
4	108.893 (50.421–235.172)	<0.0001	66.001 (32.332–134.732)	<0.001
ASA†				
1	1.000		1.000	
2	1.742 (1.146–2.649)	0.0094	1.540 (1.135–2.088)	0.006
3	7.228 (4.734–11.037)	<0.0001	5.151 (3.747–7.083)	<0.001
4	43.222 (23.337–80.049)	<0.0001	24.080 (14.084–41.171)	<0.001
5 & 6	5.969 (2.777–12.833)	<0.0001	4.109 (2.141–7.884)	<0.001
Diagnostic procedures‡				
None	1.000		1.000	
Ultrasound-guided biopsy	1.284 (0.852–1.934)	0.2325	1.343 (0.945–1.909)	0.100
Laparoscopy	0.853 (0.422–1.723)	0.6571	0.837 (0.469–1.493)	0.546
Laparotomy	1.602 (0.953–2.692)	0.0751	1.514 (0.972–2.359)	0.067
Treatment§				
Primary surgery	1.000		1.000	
None	2.514 (1.684–3.756)	<0.0001	2.248 (1.569–3.200)	<0.001
NACT	0.764 (0.570–1.025)	0.0721	0.783 (0.615–0.997)	0.048
Residual tumor‖: subanalysis with only patients having primary surgery				
No	1.000		1.000	
Yes¶	12.997 (8.794–19.232)	<0.0001	8.325 (6.336–10.938)	<0.001
Yes‖	4.282 (2.684–6.830)	<0.0001	3.624 (2.569–5.112)	<0.001
Histology¶				
Serous	1.000		1.000	
Endometrioid	0.268 (0.141–0.508)	<0.0001	0.342 (0.211–0.554)	<0.001
Clear cell	0.213 (0.078–0.577)	0.0024	0.302 (0.148–0.616)	0.001
Mucinous	0.716 (0.443–1.157)	0.1726	1.041 (0.734–1.477)	0.823
Sarcoma	1.754 (1.091–2.820)	0.0204	2.543 (1.780–3.634)	<0.001
Rare types	1.920 (1.116–3.302)	0.0184	1.955 (1.228–3.113)	0.005
Reason for no treatment**				
Not relevant (treatment)	1.000		1.000	
Condition	2.859 (1.771–4.615)	<0.0001	2.470 (1.579–3.864)	<0.001
Wish	11.010 (4.716–25.705)	<0.0001	7.801 (3.592–16.944)	<0.001
Center treatment‖				
No	1.000		1.000	
Yes	0.660 (0.515–0.845)	0.0010	0.659 (0.535–0.806)	<0.001

ASA, American Society of Anesthesiologists; CI, confidence interval; CCI, Charlson comorbidity index; NACT, neoadjuvant chemotherapy; OCCI, ovarian cancer comorbidity index; OR, odds ratio; PS, performance status.
*Adjusted for stage and histology; †Adjusted for age and stage; ‡Adjusted for age, stage, PS, ASA and center; §Adjusted for age, stage, PS, ASA, OCCI, CCI and center; ‖Adjusted for age, stage, PS, ASA, histology and center; ¶Un-adjusted; **Adjusted for age, stage, center, ASA and PS.

CCI, BMI, admission to hospital due to pain or thromboembolism, stage, PS, treatment, histology, residual tumor and age. For this group the AUC was found to be 0.90 (0.87–0.92). The AUCs did not change significantly in separate sensitivity analyses where division of the cohort into validation and training data sets was done randomly.
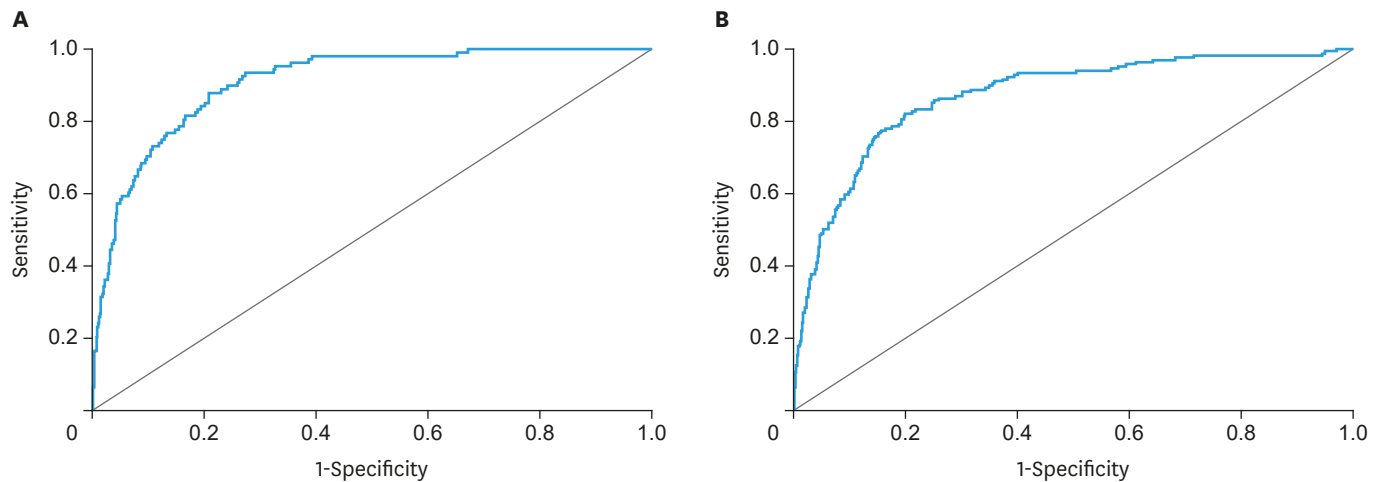
Fig. 1. Receiver operating curves for the prediction performance of a multiple logistic regression model. Which was performed on the calendar year-based division of the cohort for the outcome death within (A) 3 years (including the variables family type, employment, income, OCCI, CCI, BMI, admission to hospital due to pain or thromboembolism, stage, PS, treatment, histology and residual tumor) and (B) 6 months (including the variables family type, employment, income, CCI, BMI, admission to hospital due to pain or thromboembolism, stage, PS, treatment, histology, residual tumor, and age). The AUC were 0.91 (0.88–0.93) and 0.90 (0.87–0.92), respectively.

AUC, area under the receiver operating characteristic curve; CCI, Charlson comorbidity index; BMI, body mass index; OCCI, ovarian cancer comorbidity index; PS, performance status.

DISCUSSION

This is the first study to analyse very early death of ovarian cancer. The novel in this study is the impact of pre-diagnostic baseline factors and hospitalizations in a period of 6 months before the diagnose. We found that patients with early death often had been admitted to hospital with symptoms related to ovarian cancer. Further, several other pre-diagnostic baseline factors at the time of diagnosis influenced the risk of early death. They had advanced stage and poor PS. Therefore, they were more often referred for neoadjuvant chemotherapy rather than primary debulking surgery. A substantial fraction received no treatment at all.

Multivariate analyses exploring risk factors for mortality within 3 and 6 months from ovarian cancer diagnoses also identified civil status, employment, income and admission to hospital due to pain or thromboembolism as independent risk factors together with stage, treatment, residual tumor, histology, comorbidity, BMI, PS. Knowledge about these variables enable us to identify 90% of patients in high risk of early death.

A major strength of this study is the large number of patients included, with a negligible fraction lost to follow-up, ensuring high validity in the analyses. The fact that the study is based on data from nationwide registers with almost complete (>97%) coverage is another strength as selection bias is avoided. A third strength is detailed information on several different socioeconomic variables from Statistics Denmark which has enabled us to explore social risk factors in relation to ovarian cancer survival.

A limitation of the study is the lack of information about pre-ovarian cancer symptoms reported to the general practitioner (GP). We have information regarding circumstances connected to the hospital admission prior to the ovarian cancer diagnosis, but some patients may have consulted their GP with symptoms of the cancer previously. It is therefore, based on our study, not possible to draw any conclusions regarding patient and/or practitioner delays.

Another potential limitation might be that treatment of advanced ovarian cancer was changed during 2010–2011 when the neoadjuvant chemotherapy was introduced. This may compromise the strength of our predictive model as the development and validation cohorts were divided by calendar years. However, the sensitivity analyses based on random spilt of the total study population confirmed our findings. Therefore, we find it unlikely that this change in primary treatment modality over time has introduced substantial bias in our results.

A third limitation is the lack of information on cause of death which forced us to use all-cause mortality as our outcome measure in the survival analyses. It would have been interesting to know if patients had died from their cancer or from other causes (comorbidity, accidents, etc.). However, considering the aggressive nature of ovarian cancer and the treatment offered, we find it likely that death within 6 months from diagnosis may be ascribed to the disease under study, i.e., cancer-specific mortality is probably almost identical to all-cause mortality. Therefore, we found OS a reasonable outcome measure in this study.

In this study, short-term mortality was observed more often among patients who had been admitted to hospital within 6 months prior to the diagnose of ovarian cancer due to ovarian cancer-related, but not pathognomonic, symptoms. These symptoms were more frequent in both early and advanced stage-patients who died early from their disease. The complexity of symptoms may have prolonged the diagnostic process. The above described tendency was even more pronounced when admission for benign ovarian tumors was excluded. Significantly fewer patients who died early had a "benign" ovarian tumor 6 month before the diagnosis, compared to patients who lived longer than 6 months. This indicates that "normal findings" at gynecological examinations and ultrasounds sometimes leads to delay of relevant hospital referral for diagnosing of gynecological malignancy. Patients with primary peritoneal cancer without an ovarian tumor, might not be referred to gynecological department, causing delay in diagnosing. This emphasises how crucial a thorough first gynecologic examination at PG or the private gynecologist may be to detect a pelvic mass in time or even better, special clinics initiating parallel investigating programs, including imaging and a panel of biomarkers to accelerate diagnosing cancer. A previous Danish study showed that patients who received a negative result after investigation in an organ-specific implemented cancer patient pathway (CPP) were re-referred within 6 months to a new organ-specific CPP; many of these were in the same anatomical area as the first CPP. The positive predictive value of 4.4% to be diagnosed with cancer indicates that some cancers may be missed in the diagnostic investigation through the first CPP [21]. The results of this paper stress that ovarian cancer still is hard to diagnose with fatal consequences for a group of patients.

The burden of advanced disease affects the patient's general well-being and may compromise their ability to tolerate extensive surgery. Although half of the patients with advanced stage in the early death group had treatment, they were significantly less often referred to an Oncological Centre for treatment (OR=0.60 [0.49–0.73]). Among patients treated in non-centre hospitals, complete cytoreduction was only achieved in 23.9% compared to 76.1% in Centre-hospitals. Several other authors have demonstrated a clear association between survival and disparities in access to high-volume providers [22-25].

Fragility delineated by certain socioeconomic factors (low income, no association to labour market and living alone), unhealthy living (smoking) and poor general health (poor PS and high levels of comorbidity) have been found to be strongly associated with early death. Even

among high stage patients the heterogeneity is substantial and pre-diagnose risk factors have a significant impact on survival.

The present study found that socioeconomic factors such as low income, no association to labour market and living alone are factors independently associated to short ovarian cancer survival. This is in accordance with other studies, where neighborhood socioeconomic status [11,12] as well as low income [13] has been found to be a predictor of survival in women with ovarian cancer. This study has no information of patient-delay or delay ascribed to the GP which might also have an impact on stage at diagnosis. However, living alone and having no connection to the labour market (i.e., pensioners) were factors significantly associated to early death in our study. This may be explained by more isolation which in turn causes these patients to seek their doctor late.

Race is another factor that in previous studies have been found associated to survival in ovarian cancer [26,27]. However, in our study ethnicity (Danish, Western, non-Western) was not an independent risk for early death, but the figures were small for non-Danish ethnicity (84 Western and 130 non-Western women) why no firm conclusion regarding the impact of race on survival can be drawn.

In our study we found comorbidity to be an independent prognostic factor for early death. There are several possible mechanisms behind this association between comorbidity and prognosis. Some studies have found that cancer patients with comorbidity are not offered as extensive and aggressive treatment as cancer patients without comorbidity [28-30]. Another possible explanation between comorbidity and prognosis is that of delay. Some investigators state that comorbidity is associated to longer patient and/or practitioner delays as symptoms of the cancer may be masked by or confused with symptoms of the comorbidity [31,32]. Furthermore, once referred for cancer treatment, more diagnostic work-up may be needed in patients with comorbidity, which may also increase total delay [33]. However, as we did not find any significant association between comorbidity and stage in this study, we find it unlikely that comorbidity is the primary explanation behind advanced stages leading to high short-term mortality in this study. Thirdly, several studies have demonstrated that comorbidity may be the main cause for not offering cancer treatment according to national guidelines and for deviating from decisions regarding treatment made at the multidisciplinary team conference [34-36]. Whether this applies for Danish ovarian cancer patients is however not quite clear as the evidence is diverging [37,38], and potential effect modification of comorbidity is not evaluated in this paper.

In conclusion, this paper substantiates that ovarian cancer still is difficult to diagnose. Despite several admissions to hospital, the diagnose is delayed for a subgroup of patients, who end up dyeing early, probably due to physical deterioration in the ineffective waiting time.

Further, we identified several independent socioeconomic factors predictive of early mortality and among these where living alone, low income and being unemployed. Based on our backward selection model, 90%–91% of early death of ovarian cancer could be predicted upon admission to the gynecological department by including knowledge about the patient and tumor related risk factors. Thereby, high-risk patients who comprise a complex challenge to the health-care system can be identified significantly earlier to improve the prognosis. The admittance of the patients having risk symptoms should include fast track investigation for abdominal cancer. This could optionally be across conventional specialties, in special clinics

initiating parallel investigating programs, including imaging and a panel of biomarkers to accelerate diagnosing cancer.

SUPPLEMENTARY MATERIAL

Supplementary Data 1

Diagnoses from 18 groups of International Classification of Diseases, 10th Revision (ICD-10) codes for diseases that could match symptoms of ovarian cancer.

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