







ORIGINAL ARTICLE



Severity and 1-month outcome of SARS-CoV-2 infection in patients with solid cancers: a Danish nationwide cohort study

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ABSTRACT

Background: Cancer patients are vulnerable to infections, are older and often have comorbidities in comparison to the general population, which increases the risk for severe outcomes related to COVID-19 diagnosis.

Methods: This study is a prospective, nationwide study in patients with solid cancer and SARS-CoV-2 infection included between 10 March to 15 June 2020. Patient's baseline characteristics were collected. The study's primary outcome was overall survival within 30 days of verified SARS-CoV-2 infection. Secondary outcomes were hospital admission, admission to an ICU, and need for supplemental oxygen.

Results: A total of 112 patients with a cancer diagnosis and verified SARS-CoV-2 infection were identified. After one month of follow up, hospitalization was required for 54% ($n=61$) and 21% of the patients had died and 14 of the 23 deceased cancer patients were ≥ 70 years. Most patients were classified with mild COVID-19 symptoms (66%, $n=74$); however, 48% ($n=23$) of the ≥ 70 -year-olds patients were classified with severe or critical COVID-19 symptoms. Among the total study population, 61% ($n=68$) had comorbidities and comorbidity were more frequently observed among the deceased (91%, $n=21$) and older cancer patients (≥ 70 years, 81%, $n=39$).

Conclusions: Acknowledging the low sample size in this study, our work shows that age and comorbidities, but not recent cytotoxic therapy, are associated with adverse outcomes of SARS-CoV-2 infection for patients with solid cancer. Particularly, patients with progressive disease seem to be at greater risk of a fatal outcome from COVID-19.

HIGHLIGHTS

- Age, performance status, and comorbidities are strong predictors of adverse outcome in cancer patients with SARS-CoV-2 infection.
- Patients with progressive cancer disease seem to be at greater risk of a fatal outcome from COVID-19.
- Recent cytotoxic therapy, however, did not seem to be associated with increased risk for adverse outcomes of SARS-CoV-2 infection for patients with solid cancer.

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SARS-CoV-2; COVID-19; cancer; prognosis; survival; comorbidity


Introduction

Cancer patients are in general particularly vulnerable to infections due to the immunosuppression caused by cancer itself [1] as well as certain types of oncologic treatments [2]. Furthermore, cancer patients are older (i.e. aged ≥ 70 years), often have comorbidities and poorer performance status in

comparison to the general population [3], which gives an increased risk for adverse events such as morbidities and mortality related to infections.

Severe acute respiratory syndrome coronavirus (SARS-CoV)-2 and the resulting infectious disease, coronavirus disease (COVID)-19, began in Wuhan, China in December 2019

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 Supplementary data for this article can be accessed [here](#).

[4,5] and has emerged as a global pandemic. The clinical spectrum of symptoms is wide, encompassing asymptomatic infection or mild through moderate symptoms with cough and fever to critical symptoms with respiratory failure and even death [6,7]. Several risk factors for adverse outcomes have been reported in the population of SARS-CoV-2 positive patients, including advanced age, male sex, and smoking [7–10]. Cancer patients appear to be more vulnerable to SARS-CoV-2 infection in comparison to patients without cancer [11]. Specifically, cancer patients with metastatic progressive disease are at increased risk for COVID-19 related adverse events [11–13].

In a study of patients with thoracic cancer types and COVID-19, it was observed that most patients died due to complications of COVID-19 rather than to cancer progression [9]. Similar results have been seen in other observational studies, evaluating COVID-19 patients with different kinds of cancer [12,14].

Most previous studies were restricted to regions in countries where the healthcare systems were overwhelmed by the pandemic. The current study is a nationwide prospective study of verified SARS-CoV-2 positive patients with solid cancers in Denmark, where the COVID-19 burden of the healthcare system has so far been low. In this study we aim to study the course and complications of SARS-CoV-2 infection in adult Danish patients with oncological disorders. The primary outcome of this study was overall survival within 30 days of verified SARS-CoV-2 infection. Secondary outcomes were hospital admission, admission to an ICU, mechanical ventilation, and need for supplemental oxygen.

Methods

Study design and participants

In this analytical observational prospective cohort study, with one month follow-up, we report data on Danish patients with solid tumors with verified SARS-CoV-2 infection included from all Danish Departments of Oncology, located at public hospitals providing free access to health care for all Danish residents. The Danish Civil Registration System (CPR), provides easy access to clinical information to the patient's medical history and is a key tool for epidemiological research in Denmark [15], allowing for long-term follow-up with accurate censoring at emigration or death. In the present study, no patients were lost to follow-up. Patients eligible for inclusion were adults (aged ≥ 18 years), diagnosed with a solid malignant tumor at any time, had a verified SARS-CoV-2 infection, were either receiving active cancer treatment or were in follow-up after the end of treatment in any oncological setting (palliative or curative intended) at any of the 11 Danish Departments of Oncology. The first positive SARS-CoV-2 test in Denmark was observed on 26 February 2020. Patients were included from 10 March to 15 June 2020. Outcomes were monitored until 15 July 2020, allowing for a minimum of one month follow-up.

Confirmed SARS-CoV-2 infection was defined as a positive result by real-time polymerase chain reaction (RT-PCR) testing [16] of a nasal- or oropharyngeal swab or a lower

respiratory tract specimen. Patients were included irrespective of the severity of the infection and regardless of whether in-hospital admission was required. Patients with a radiologically or clinically suspected diagnosis of COVID-19, without a positive RT-PCR test, were not included in this study.

Cancer type was defined according to the International Classification of Disease (10th revision) diagnostic codes [17]. Patients with noninvasive cancers including non-melanomatous skin cancer and *in-situ* carcinoma are usually not treated at Oncology Departments in Denmark and are therefore excluded from this study.

Patients who presented with symptoms of infection, such as fever or upper/lower respiratory tract symptoms, as well as patients planned for endoscopy procedures were routinely SARS-CoV-2 tested throughout the study period. From 27 April 2020, all patients who were planned for in-hospital admission, regardless of symptoms, were tested routinely in Denmark.

Baseline data

Baseline data included age, sex, height, weight, Eastern Cooperative Oncology Group (ECOG) performance status (PS), home care, type of malignancy, cancer status (remission, stable or progressive disease), comorbidity, current and previous anticancer therapy, and current medication at the time of SARS-CoV-2 infection. Comorbidities were summarized using the Charlson Comorbidity Index (CCI) [18]. Individual comorbid conditions of particular interest concerning SARS-CoV-2, such as diabetes and obesity (body mass index ≥ 30) were also registered [7,18]. Recent therapy refers to cancer treatment given within four weeks (28 days) of a positive test for SARS-CoV-2. Active antineoplastic therapy included cytotoxic chemotherapy and other anticancer therapies (targeted drugs, endocrine therapy, immunotherapy, radiotherapy).

SARS-CoV-2 infection and COVID-19 severity

The COVID-19 severity category was determined according to previous classifications [18]. In brief, the severity of the SARS-CoV-2 infection was graded as either asymptomatic/mild, severe, or critical. The infection was classified as asymptomatic or mild if patients had no symptoms or only mild non-pneumonia/pneumonia symptoms. Patients with severe infection had fever, respiratory symptoms, dyspnea, respiratory frequency ≥ 30 /min, blood oxygen saturation $\leq 93\%$, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 , and/or lung infiltrates $> 50\%$ of the lungs within 24 to 48 h from the presentation. Patients classified as critically ill met one of three criteria: respiratory failure, septic shock, or multiple organ failure [18].

Follow up and outcomes

The registered data were abstracted from medical files by local investigators and entered into the research electronic data capture (REDCap) application [19]. Baseline data was

entered during the study period and outcome data after ending the study period.

The primary endpoint was overall survival within 30 days of verified SARS-CoV-2 infection. Secondary outcomes were hospital admission, admission to an ICU, mechanical ventilation, and need for supplemental oxygen during the course of COVID-19.

Statistical analysis

Baseline characteristics, SARS-CoV-2 findings, and outcomes were described by medians/proportions across the pre-defined diagnosis groups and classification of SARS-CoV-2 severity. Missing data of all variables are listed in the tables.

Overall survival (OS) was measured from the date of verified SARS-CoV-2 infection until death or censoring (one month after SARS-CoV-2 infection), whichever came first. One month OS was estimated as the proportion alive one month after verified infection. The risk of admission to an ICU was estimated by the proportion of patients admitted to an ICU within one month of verified SARS-CoV-2 infection. Associations between SARS-CoV-2 severity or ICU admission and clinical risk factors were tested using Fishers' exact test. Only subgroups based on characteristics already reported or suggested in guidelines to be associated with increased risk of complications, such as age and comorbidity-specific treatments, were considered. All analyses were conducted in R (version 3.6.1).

Ethics

This study was approved by the Danish Data Protection Agency (record no. 20/13067). Since the study is purely observational and only utilizes information from routine clinical practice, the Danish council for patient safety (record no. 31-1521-230) and ethics committee (record no. 20202000, 53) waived informed consent. Data are reported according to STROBE (Strengthening the reporting of observational studies in epidemiology) guidelines [20].

Role of the funding source

The Danish Cancer Society provided funding for the study (record: R-274-A6402). The funder had no role in study design, patient recruitment, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 112 patients with solid tumors and SARS-CoV-2 infection were identified during the study period and all patients were eligible and included in the study. Age has previously been shown to have an impact on COVID-19 severity, and the population was therefore divided in three age groups (<50 years, 50–69 years, and ≥ 70 years) and the clinical characteristics for these groups are shown in Table 1. The clinical characteristics for the population divided into deceased and alive at the study's endpoint are shown in

Table 2. The specific cancer types in the study population are shown in Supplementary Table 1.

The primary endpoint of this study was overall survival and the one month OS following verified SARS-CoV-2 infections was 79% ($n = 89$) giving a mortality of 21% ($n = 23$). Of the 23 deceased cancer patients 14 patients (61%) were ≥ 70 years. Nine patients below 70 years died of whom seven had a CCI score ≥ 2 .

Comorbidities were common among the total study population (61%, $n = 68$), including pulmonary diseases, especially in the group of ≥ 70 -year-old cancer patients (81%, $n = 39$). The majority of the patients (62%, $n = 70$) had a PS of 0 or 1, and 14% ($n = 16$) had a PS of ≥ 2 . Especially old cancer patients (≥ 70 years) had a poor PS (29%, $n = 14$). Additionally, 29% of the hospitalized patients had a PS of ≥ 2 in contrast to 7% in non-hospitalized patients.

Chemotherapy was the most common type of systemic anti-cancer treatment given at the time of SARS-CoV-2 infection (29%, $n = 20$). Especially the younger patients (<50 years) were treated with curative intent (82%, $n = 9$), whereas the majority of older cancer patients (≥ 70 years) were treated with palliative intent (62%, $n = 30$).

The most common COVID-19 symptoms were fever (66%, $n = 57$) and cough (64%, $n = 56$) but most patients were classified with mild COVID-19 symptoms (66%, $n = 74$), especially within the group of young (<50 years) cancer patients (91%, $n = 10$). Almost half (48%, $n = 23$) of the ≥ 70 -year-olds patients were classified with severe or critical COVID-19 symptoms. Hospitalization was required for 54% ($n = 61$) of the patients with a median hospitalization of 8 days (range 1–30 days). Especially the old cancer patients (≥ 70 years) were hospitalized (79%, $n = 38$) and 40% ($n = 19$) of these were hospitalized more than 8 days.

The median age of the deceased patients was 72 years, seven years older than for the group of survivors (Table 2) and were predominantly male patients (61%, $n = 14$). Of the 23 deceased patients, 91% ($n = 21$) had comorbidities ($p = .004$) and comorbidity were more frequently observed among older cancer patients (≥ 70 years, 81%, $n = 39$) in comparison to younger patients (<70 years, 45%, $n = 29$, $p < .001$). Cancer patients with SARS-CoV-2 infection and comorbidity were also at increased risk of hospitalization (68% vs. 34%, $p < .001$). After one month, 41% of survivors ($n = 28$) reported more fatigue than usual, and fatigue was particularly more frequent among older patients (70%, $n = 19$, $p < .001$).

Among patients who died following SARS-CoV-2 infection, 65% ($n = 15$) experienced severe or critical COVID-19 symptoms and 39% ($n = 9$) needed prolonged hospitalization, whereas survivors primarily experienced mild COVID-19 symptoms (74%, $n = 66$).

Discussion

This study is a nationwide prospective study of 112 verified SARS-CoV-2 positive patients with solid cancers in Denmark. We found that during the first month, hospitalization was required for 54%, 28% required supplementary oxygen, and

Table 1. Patient characteristics, COVID-19 clinical presentation and one month follow-up of all ($n = 112$) patients, patients <50 years old, patients 50–69 years old, or patients ≥ 70 years old with solid tumors infected with SARS-CoV-2.

	All patients ($n = 112$)	<50 yrs ($n = 11$)	50-69 yrs ($n = 53$)	≥ 70 yrs ($n = 48$)
CCI ≥ 2 , n (%)	39 (38)	1 (9)	18 (36)	20 (47)
Missing values	8 (7)	0 (0)	3 (6)	5 (10)
Comorbidities, n (%)				
None	44 (39)	8 (73)	27 (51)	9 (19)
Obesity	17 (22)	2 (22)	10 (27)	5 (16)
Diabetes	13 (12)	0 (0)	4 (8)	9 (19)
Pulmonary	27 (34)	2 (25)	6 (16)	19 (56)
Any (≥ 1 comorbidity)	68 (61)	3 (27)	26 (49)	39 (81)
Performance status				
0-1	70 (62)	9 (82)	37 (70)	24 (50)
2	11 (10)	0 (0)	1 (2)	10 (21)
3	5 (4)	0 (0)	1 (2)	4 (8)
Unknown	26 (23)	2 (18)	14 (26)	10 (21)
Home care, n (%)	10 (12)	0 (0)	2 (5)	8 (28)
Missing values	32 (29)	1 (1)	12 (23)	19 (40)
Cancer treatment status				
No current treatment	44 (39)	2 (18)	21 (40)	21 (44)
Ongoing (<28 days prior to SARS-CoV-2 test)	68 (61)	9 (82)	32 (60)	27 (56)
Latest cancer treatment				
Palliative	50 (45)	2 (18)	18 (34)	30 (62)
Curative/neoadjuvant	22 (20)	4 (36)	10 (19)	8 (17)
Adjuvant	36 (32)	5 (45)	23 (43)	8 (17)
Not relevant/missing	4 (4)	0 (0)	2 (4)	2 (4)
Cancer status (of palliative patients)				
CR	6 (5)	0 (0)	4 (8)	2 (4)
PR/SD	25 (22)	1 (9)	10 (19)	14 (29)
PD	19 (17)	1 (9)	6 (11)	12 (25)
Unknown	62 (55)	9 (82)	33 (62)	20 (42)
COVID-19 severity, n (%)				
Mild	74 (66)	10 (91)	39 (74)	25 (52)
Severe	23 (21)	1 (9)	8 (15)	14 (29)
Critical	12 (11)	0 (0)	3 (6)	9 (19)
Unknown	3 (3)	0 (0)	3 (6)	0 (0)
COVID-19 symptoms, n (%)				
Any	87 (78)	7 (64)	36 (68)	44 (92)
Fever ^a	57 (66)	4 (57)	25 (69)	28 (64)
Cough	56 (64)	5 (71)	24 (67)	27 (61)
Dyspnea	36 (41)	3 (43)	12 (33)	21 (48)
Hospitalization, n (%)	61 (54)	2 (18)	21 (40)	38 (79)
Prolonged hospitalization (>8 days)	30 (28)	2 (29)	9 (17)	19 (40)
Missing values	5 (4)	4 (36)	1 (2)	0 (0)
Supplementary oxygen, n (%)	28 (28)	1 (14)	7 (14)	20 (45)
CPAP/NIV	4 (4)	0 (0)	1 (2)	3 (7)
ICU	5 (5)	0 (0)	0 (0)	5 (10)
Ventilator	3 (3)	0 (0)	0 (0)	3 (7)
Missing values	12 (11)	4 (36)	4 (8)	4 (8)
Outcome 1 month, n (%)				
Alive	89 (79)	11 (100)	44 (83)	34 (71)
Deceased	23 (21)	0 (0)	9 (17)	14 (29)
Reductions in functional level after 1 month (of survivors)				
More fatigued than usual (%)	28 (41)	0 (0)	9 (26)	19 (70)
Missing values	20 (22)	3 (27)	10 (23)	7 (21)
More dyspnea than usual (%)	14 (21)	1 (11)	3 (9)	10 (40)
Missing values	22 (25)	2 (18)	11 (25)	9 (26)
Functional abilities reduced (%)	18 (26)	0 (0)	3 (9)	15 (56)
Missing values	20 (22)	3 (27)	10 (23)	7 (21)

Data are n (%) where n represents number of patients in each category. Due to rounding not all variables might add up to 100%. CCI: Charlson comorbidity index score; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease. ICU: intensive care unit; CPAP: continuous positive airway pressure; NIV: noninvasive ventilation.

^aPercentages of COVID-19 symptoms are calculated of n given in 'Any' symptoms.

mortality was 21%. One month OS was associated with age and comorbidity. For patients alive after one month, a considerable proportion reported a reduced level of function particularly among the older cancer patients. The Danish health authorities estimated that up to 10% of the population would become infected with SARS-CoV-2. Fortunately this was not the case, and in contrast to several other countries, the healthcare system in Denmark was not

overwhelmed by the pandemic in the spring 2020, and all Danish cancer patients have continued cancer treatment and been consulted by oncologists as before the pandemic.

Similar to other studies, poor outcome of SARS-CoV-2 infected cancer patients was associated with higher age and multiple comorbidities [9,10,12,14]. After one month of follow-up, 21% of the patients, included in the present study, had died. Acknowledging the cohort size in our study

Table 2. Patient characteristics, COVID-19 clinical presentation of all ($n = 112$) patients with solid cancers infected with SARS-CoV-2 and deceased or alive within one month of follow-up.

	All patients ($n = 112$)	Alive ($n = 89$)	Deceased ($n = 23$)
Age, median (range)	66 (40–94)	65 (40–94)	72 (57–89)
Age groups, n (%)			
<50 years	11 (10)	11 (12)	0 (0)
50–69 years	53 (47)	44 (49)	9 (39)
≥ 70 years	48 (43)	34 (38)	14 (61)
Males, n (%)	47 (42)	33 (37)	14 (61)
CCI ≥ 2 , n (%)	39 (38)	25 (30)	14 (64)
Comorbidities			
Any	68 (61)	47 (53)	21 (91)
None	44 (39)	42 (47)	2 (9)
Performance status			
0–1	70 (62)	60 (67)	10 (43)
2	11 (10)	2 (2)	9 (39)
3	5 (4)	3 (3)	2 (9)
Unknown	26 (23)	24 (27)	2 (9)
Cancer type			
Thoracic	15 (13)	10 (11)	5 (22)
Gastrointestinal	17 (15)	13 (15)	4 (17)
Breast	43 (38)	37 (42)	6 (26)
Other ^a	37 (33)	29 (33)	8 (35)
Cancer treatment status			
No current treatment	44 (39)	30 (34)	14 (61)
Ongoing (<28 days prior to SARS-CoV-2 test)	68 (61)	59 (66)	9 (39)
Chemotherapy	20 (18)	17 (19)	3 (13)
Immunotherapy	3 (3)	3 (3)	0 (0)
Radiotherapy	5 (4)	5 (6)	0 (0)
Targeted therapies	5 (4)	5 (6)	0 (0)
Other (incl. Endocrine therapy)	30 (27)	25 (28)	5 (22)
Missing values	5 (7)	4 (7)	1 (11)
Latest treatment goal			
Palliative	50 (45)	38 (43)	12 (52)
Curative/neoadjuvant	22 (20)	17 (19)	5 (22)
Adjuvant	36 (32)	32 (36)	4 (17)
Not relevant/missing	4 (4)	2 (2)	2 (9)
Cancer status			
CR	6 (5)	6 (7)	0 (0)
PR/SD	25 (22)	20 (22)	5 (22)
PD	19 (17)	11 (12)	8 (35)
Unknown	62 (55)	52 (58)	10 (43)
COVID-19 severity, n (%)			
Mild	74 (66)	66 (74)	8 (35)
Severe	23 (21)	17 (19)	6 (26)
Critical	12 (11)	3 (3)	9 (39)
Unknown	3 (3)	3 (3)	0 (0)
Prolonged hospitalization (>8 days)	30 (28)	21 (25)	9 (39)

Data are n (%). Due to rounding, not all variables might add up to 100%. CCI: Charlson comorbidity index score.

^aOther cancer types are specified in Supplementary Table 1.

($n = 112$), other prospective observational studies with larger cohorts have reported a mortality of 13% ($n = 928$) [12] and 28% ($n = 800$) [14] following SARS-CoV-2 infection and a systematic review of 52 pooled studies including a total of 18,650 cancer patients reported a risk of mortality of 26% [21]. Variations in poor outcomes of patients between the different studies could reflect, that the studies differ in median follow-up time, in the method of SARS-CoV-2 testing, or the selection of cancer patients. In this study, we report on 30 days mortality, after having detected SARS-CoV-2 infection and both symptomatic and asymptomatic cancer patients were included.

There is a consensus that cancer patients represent a particularly vulnerable population in the context of the SARS-CoV-2 pandemic [22] and cancer is in general more prevalent among older adults [3]. In a large Danish nationwide population-based cohort study including 11,122 SARS-CoV-2 positive cases [23], 20% were hospitalized and 5.2% died within one month of follow-up with age and comorbidities being

strong predictors of fatal outcome. Among the deceased, the majority (87%) were older than 70 years of age [23]. In our study, 61% of the deceased were older than 70 years. The deceased cancer patients, <70 years, presented a high comorbidity index score, which could explain the high risk of mortality among this subgroup of patients in the present study. Collectively, these results suggest that age, in general, is a predictor of poor outcome of SARS-CoV-2 infection but also that cancer patients seem to be at greater risk for a fatal outcome, also at an age younger than 70 years, especially if they have comorbidities.

The distortion of included SARS-CoV-2 infected cancer patients in PS 0–1 versus PS ≥ 2 , could reflect that patients with poor PS protect themselves from SARS-CoV-2 infection by sheltering at home or reflect that they rarely receive chemotherapy and thereby have few hospital visits, decreasing the risk from SARS-CoV2 infection. Previous results have shown that PS ≥ 2 in cancer patients is associated with an increased risk of adverse outcomes from COVID-19 [12]. In

this study, we found that 29% of the hospitalized patients had a PS of ≥ 2 in contrast to 7% in non-hospitalized patients.

As a result of the pandemic, hospitals in countries worldwide have taken precautions to minimize the risk of infection by reducing patient visits [7,24]. In some cases, but not in Denmark, this has resulted in a major shift in cancer care delivery seen by e.g. an abrupt drop in preventive cancer screenings [25]. In the short term, such restrictions can be necessary to protect older adults from infections and reduce the burden on the healthcare system [12]. Well-argued, as a study of SARS-CoV-2 positive thoracic cancer patients, showed that very few patients died due to the progression of cancer during the early stages of the pandemic whereas most died due to complications of COVID-19. Moreover, patients included in this study even represented a subgroup with a high stage disease undergoing oncological treatment [9].

However, epidemiological data suggest that the pandemic will continue for months if not years and prolonged treatment delays could lead to an increase in cancer-related mortality. Studies including SARS-CoV-2 positive patients with different cancer diagnoses have shown that there is no association between COVID-19 severity and recent surgery or systemic anti-cancer therapy including non-cytotoxic therapy or cytotoxic systemic therapy [9,12–14], suggesting that cancer patients should be given cancer care as before the SARS-CoV-2 outbreak. Our study supports previous findings that chemotherapy administered within 28 days prior to the positive SARS-CoV-2 test does not seem to increase the risk of a fatal outcome from SARS-CoV-2 infection.

Several studies on cancer patients and COVID-19 severity have recently been published and the findings might have important policy implications. An international consortium was recently established to guide oncologists and politicians in cancer management during the COVID-19 pandemic [26]. Following cancer patients in Denmark, where the pandemic has influenced the daily living for all citizens but fortunately has not affected the treatment of cancer patients, has provided insights into risk factors for patients with solid cancers under these circumstances. Our work supports other studies on SARS-CoV-2 infected patients in the general population [23] and in cancer patients [12,14] and provides further evidence that age and comorbidities are associated with risk for adverse outcomes. Whether cancer itself is a risk factor regarding the severity of SARS-CoV-2 infection is unclear. However, patients with progressive disease at the time of SARS-CoV-2 infection seem to be at greater risk of fatal outcome. Thus, protecting especially cancer patients aged 70 years or older, patients with comorbidities, as well as patients in palliative treatment is still recommended. However, the benefit of social distancing in patients with short life expectancy due to active cancer disease should be balanced against preserving the quality of life.

Denmark has a health care system with universal coverage and free access and all patients with cancer are treated at public hospitals. In this study, we have included all consecutive cancer patients infected with SARS-CoV-2. The Danish

Civil Registration System provides easy access to clinical information to the patient's medical history and follow up. Despite that this multicentre cohort study involved all Departments of Oncology in Denmark, our study has limitations. The number of included patients is low, affecting the statistical possibility to perform multivariable analysis of the results. The low number of included patients probably reflect the overall risk for Danish cancer patients to be infected with SARS-CoV-2 in the first months of the pandemic 2020. At time of inclusion, SARS-CoV-2 testing was not as widely applied and most patients who were tested were patients presenting with symptoms as well as patients in need of hospital treatment. Potentially, this could introduce a disproportionate selection of patients with severe infection and contribute to a high mortality.

Conclusions

In this prospective cohort study, increasing age and number of comorbidities were closely related to hospitalization and death in SARS-CoV-2 positive cancer patients. Particularly, patients with progressive disease seem to be at greater risk of a fatal outcome from COVID-19, whereas recent cytotoxic therapy did not seem to affect the outcome. These results may help in identification and protection of high-risk groups of cancer patients.

Author contributions

H. Frederiksen, A.R. Kodahl conceptualized the idea for the study. A.R. Kodahl, H. Frederiksen, A. Glenthøj, L.H. Jakobsen, J. Ryg participated in the design of the study. S. Ehmsen performed the literature search. All authors contributed to collection of data. L.H. Jakobsen performed the data management, data analyses, statistical analysis and computed the tables. All authors participated in interpretation of data. S. Ehmsen, M.E. Lendorf wrote the first draft of the paper. All authors participated in writing subsequent drafts. All authors approved the final version of the manuscript.

Disclosure statement

The authors declare that they have no competing interests.

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References

- [1] Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*. 2004;21(2):137–148.
- [2] Verma R, Foster RE, Horgan K, et al. Lymphocyte depletion and repopulation after chemotherapy for primary breast cancer. *Breast Cancer Res*. 2016;18(1):10.
- [3] Ewertz M, Christensen K, Engholm G, Academy of Geriatric Cancer Research (AgeCare), et al. Trends in cancer in the elderly population in Denmark, 1980–2012. *Acta Oncol*. 2016;55(Suppl 1):1–6.
- [4] WHO. Novel Coronavirus - China, in disease outbreak news. Geneva, Switzerland: World Health Organization; 2020. Available from: <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>
- [5] Zhu N, Zhang D, Wang W, China Novel Coronavirus Investigating and Research Team, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727–733.
- [6] Song F, Shi N, Shan F, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology*. 2020;295(1):210–217.
- [7] Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069.
- [8] Richardson S, Hirsch JS, Narasimhan M, the Northwell COVID-19 Research Consortium, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020;323(20):2052–2059.
- [9] Garassino MC, Whisenant JG, Huang LC, TERA-VOLT investigators, et al. COVID-19 in patients with thoracic malignancies (TERA-VOLT): first results of an international, registry-based, cohort study. *Lancet Oncol*. 2020;21(7):914–922.
- [10] Mcpadden J, Warner F, Young HP, et al. Clinical Characteristics and Outcomes for 7,995 Patients with SARS-CoV-2 infection. Version 4. medRxiv. Preprint 2020. DOI:10.1101/2020.07.19.20157305
- [11] Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov*. 2020;10(6):783–791.
- [12] Kuderer NM, Choueiri TK, Shah DP, COVID-19 and Cancer Consortium, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907–1918.
- [13] Pinato DJ, Zambelli A, Aguilar-Company J, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. *Cancer Discov*. 2020;10(10):1465–1474.
- [14] Lee LY, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020;395(10241):1919–1926.
- [15] Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549.
- [16] Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill*. 2020;25(3):2000045.
- [17] Organization WH. *International Classification of Diseases (ICD) Information Sheet*. 2018. [cited 2018; 11th revision:[Available from: <https://www.who.int/classifications/icd/factsheet/en/>].
- [18] Wu Z, Mcgoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242.
- [19] Harris PA, Taylor R, Minor BL, REDCap Consortium, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
- [20] Von Elm E, Altman DG, Egger M, STROBE Initiative, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806–808.
- [21] Saini KS, Tagliamento M, Lambertini M, et al. Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies. *Eur J Cancer*. 2020;139:43–50.
- [22] Ballout F, Daouk R, Azar J, et al. Cancerona: challenges of cancer management in times of COVID-19 pandemic. *SN Compr Clin Med*. 2020.DOI:10.1007/s42399-020-00549-w
- [23] Reilev M, Kristensen KB, Pottegard A, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. *Int J Epidemiol*. 2020;49(5):1468–1481.
- [24] Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. 2020;31(7):894–901.
- [25] Network EHR. Delayed Cancer Screenings. 2020. Available from: <https://ehrn.org/delays-in-preventive-cancer-screenings-during-covid-19-pandemic>.
- [26] Curigliano G, Banerjee S, Cervantes A, Panel members, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Ann Oncol*. 2020;31(10):1320–1335.