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Original Research

Dutch Oncology COVID-19 consortium: Outcome of COVID-19 in patients with cancer in a nationwide cohort study

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KEYWORDS
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Abstract ***Aim of the study:*** Patients with cancer might have an increased risk for severe outcome of coronavirus disease 2019 (COVID-19). To identify risk factors associated with a worse outcome of COVID-19, a nationwide registry was developed for patients with cancer and COVID-19.
Methods: This observational cohort study has been designed as a quality of care registry and is executed by the Dutch Oncology COVID-19 Consortium (DOCC), a nationwide collaboration of oncology physicians in the Netherlands. A questionnaire has been developed to collect pseudonymised patient data on patients' characteristics, cancer diagnosis and treatment. All patients with COVID-19 and a cancer diagnosis or treatment in the past 5 years are eligible.
Results: Between March 27th and May 4th, 442 patients were registered. For this first analysis, 351 patients were included of whom 114 patients died. In multivariable analyses, age $\geq$65 years ($p < 0.001$), male gender ($p = 0.035$), prior or other malignancy ($p = 0.045$) and active diagnosis of haematological malignancy ($p = 0.046$) or lung cancer ($p = 0.003$) were independent risk factors for a fatal outcome of COVID-19. In a subgroup analysis of patients with active malignancy, the risk for a fatal outcome was mainly determined by tumour type (haematological malignancy or lung cancer) and age ($\geq$65 years).
Conclusion: The findings in this registry indicate that patients with a haematological malignancy or lung cancer have an increased risk of a worse outcome of COVID-19. During the ongoing COVID-19 pandemic, these vulnerable patients should avoid exposure to severe acute respiratory syndrome coronavirus 2, whereas treatment adjustments and prioritising vaccination, when available, should also be considered.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, leading to coronavirus disease 2019 (COVID-19) [1,2], has major impact on healthcare [3,4]. In particular, the consequences for oncological care are extensive, as the effects of malignancy or cancer treatments on the outcome of COVID-19 are yet unknown [5–10]. In addition, hospital visits for anticancer therapies may put patients at even more risk of getting infected with SARS-CoV-2 [7,11]. Consequently, oncological treatment was frequently adjusted during the COVID-19 pandemic, even in regions with relatively low COVID-19 incidence [12]. These treatment adjustments were made according to COVID-19 guidelines of (inter) national oncological societies, which were primarily based on expert opinions [13–16].

Awaiting the development of vaccines against SARS-CoV-2, new outbreaks are expected worldwide. A nationwide registry was initiated by the Dutch Oncology COVID-19 Consortium (DOCC). It aims to identify characteristics of patients with cancer and/or their treatments associated with a worse outcome of COVID-19 to facilitate evidence-based decisions in oncological care during this ongoing pandemic. In the Netherlands, all patients have equal access to medical care and open discussions with patients and their families about treatment restrictions, i.e. do-not-intubate or do-not-resuscitate orders, are daily practice.

2. Methods

2.1. Study design

The registry is executed by DOCC, which is a nationwide consortium of oncology physicians (haematologists, medical oncologists, neuro-oncologists and pulmonologists) in the Netherlands. This observational cohort study was designed as a national quality of care registry to support rapid clinical decision-making in oncological practice. A questionnaire was developed to collect pseudonymised patient data on four topics: baseline patient characteristics, diagnosis and treatment of cancer, characteristics of COVID-19 and treatment and outcome of COVID-19 (appendix 2). Some patients with COVID-19 were transferred to another hospital because of capacity issues. Therefore, data of transfer of patients between hospitals were requested to avoid duplicates. This registry was approved by the ethics committee and the Privacy Knowledge Office at Erasmus Medical Centre. According to local hospital guidelines, additional approval was obtained by local committees when needed.

2.2. Inclusion criteria of DOCC registry

All patients with COVID-19 and a cancer diagnosis or cancer treatment in the past 5 years were eligible for inclusion in the DOCC registry. Besides, patients with a

diagnosis or treatment more than 5 years ago could be included if the diagnosis or treatment was expected to have had an impact on COVID-19 outcome (e.g. bone marrow transplantation, chest radiation therapy). The diagnosis of COVID-19 was defined as a positive test for SARS-CoV-2 using reverse transcription polymerase chain reaction (RT-PCR) and/or radiological findings on computed tomography (CT) and/or clinical symptoms of COVID-19. However, as a diagnosis of COVID-19 based solely on clinical symptoms is insecure and subject to bias, it was decided to restrict eligibility to a PCR and/or CT-based COVID-19 diagnosis for this analysis.

2.3. Collection of data

The DOCC registry was initiated on March 27th, 2020, and supported by the Dutch societies of medical oncologists, pulmonologists and neuro-oncologists [17–19]. Dutch oncology physicians in all 69 hospital organisations in the Netherlands were informed about the registry by communications via different cancer societies. Physicians were encouraged to identify cancer patients with COVID-19 and to collect pseudonymised data using the questionnaire. Subsequently, the data provided were centrally entered into an electronic clinical record form (eCRF) using a secured digital database (ALEA Clinical).

2.4. Data processing

For the first analysis, an update on the course and outcome of COVID-19 was requested for all patients diagnosed with COVID-19 $\geq$ 4 weeks before May 4th, 2020. Also, all clinical data in eCRFs were checked for inconsistencies by experienced oncology physicians (D.D., P.M., A.V.), and the queries generated were sent to the participating hospitals. The returned queries and updated data were processed in eCRFs. Clinical data were both annotated and cleaned, including the processing of transfer data to avoid duplicates.

2.5. Distribution of COVID-19 in the Netherlands

In the Netherlands, the COVID-19 pandemic is monitored by The National Institute for Public Health and the Environment [20]. All patients with a positive RT-PCR test for SARS-CoV-2 are centrally registered. The 12 geographic regions of the Netherlands were classified according to the number of COVID-19 positive patients per 100,000 inhabitants. This allows evaluation of the national coverage of the DOCC registry according to regional incidence of COVID-19.

2.6. Statistical analysis

The characteristics of patients with resolved COVID-19 versus a fatal outcome of COVID-19 were analysed. Descriptive statistics were used for baseline characteristics. To analyse the risk for different age categories, patients were categorised into three age groups; i.e. <65 years, ≥65–75 years and ≥75 years. Pearson's chi-square test was used to identify univariable risk factors for a fatal outcome of COVID-19, and odds ratios were presented with 95% confidence intervals. Variables with $p \leq 0.10$ in univariable analysis were included in multivariable logistic regression analyses. This was done with backward selection with a threshold of $p < 0.05$. All statistical tests were performed two-sided. Data were analysed using IBM SPSS statistics 25.

As patients with metastatic disease and/or active cancer treatment could be more susceptible to a severe course of COVID-19, a separate analysis was performed for this subgroup of patients. Active malignancy was defined as metastatic disease in patients with solid tumours and/or recent cancer treatment (<90 days before diagnosis of COVID-19). In patients with an active malignancy, the impact of cancer treatment on COVID-19 severity was also evaluated. For this group, treatment was defined as any cancer treatment $\leq$ 30 days before COVID-19 diagnosis. Finally, the impact of steroid use was analysed as a possible risk factor for fatal outcome of COVID-19. For this specific analysis, steroid use ($\leq$ 30 days before COVID-19 diagnosis) as supportive medication for cytotoxic treatment (e.g. part of the chemotherapeutic regime or anti-emetic medication) versus steroid use not related to cancer treatment was analysed.

3. Results

3.1. COVID-19 in the Netherlands

At initiation of the registry, March 27th 2020, all Dutch regions experienced an outbreak of COVID-19. At that time, the Southern region of the Netherlands had the highest incidence of COVID-19. Forty-five out of the 69 Dutch hospital organisations participated in the registry. All hospitals that provided care for the majority of patients with COVID-19 participated. The distribution of COVID-19 and the location of participating hospitals show nationwide coverage of this registry (Figure 1).

3.2. Characteristics of COVID-19 patients with cancer

Between March 27th and May 4th, 442 patients were registered. Data from 409 cancer patients were complete for the current analysis. In addition, the following patients were excluded form analyses: one duplicate case, 30 patients because of unconfirmed diagnosis of

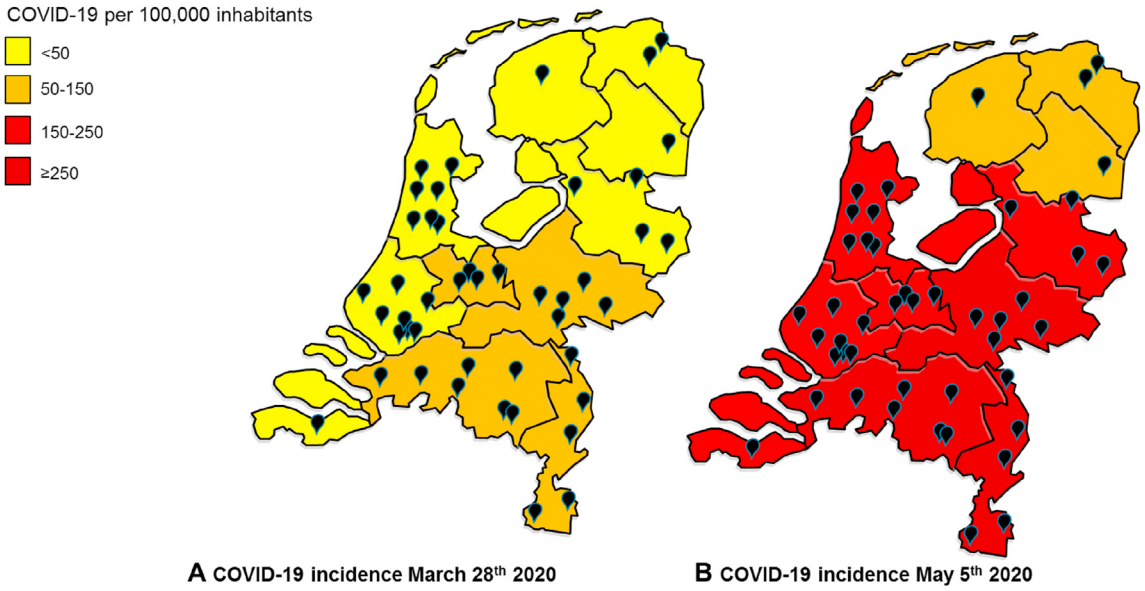

Fig. 1. Prevalence of COVID-19 in the Netherlands. Patients with a positive test for SARS-CoV-2 at start of the DOCC registry March 28th, 2020 (a) and one day after the database lock on (b) May 5th, 2020. The black bullets indicate the hospitals that participated in the registry (n = 45).

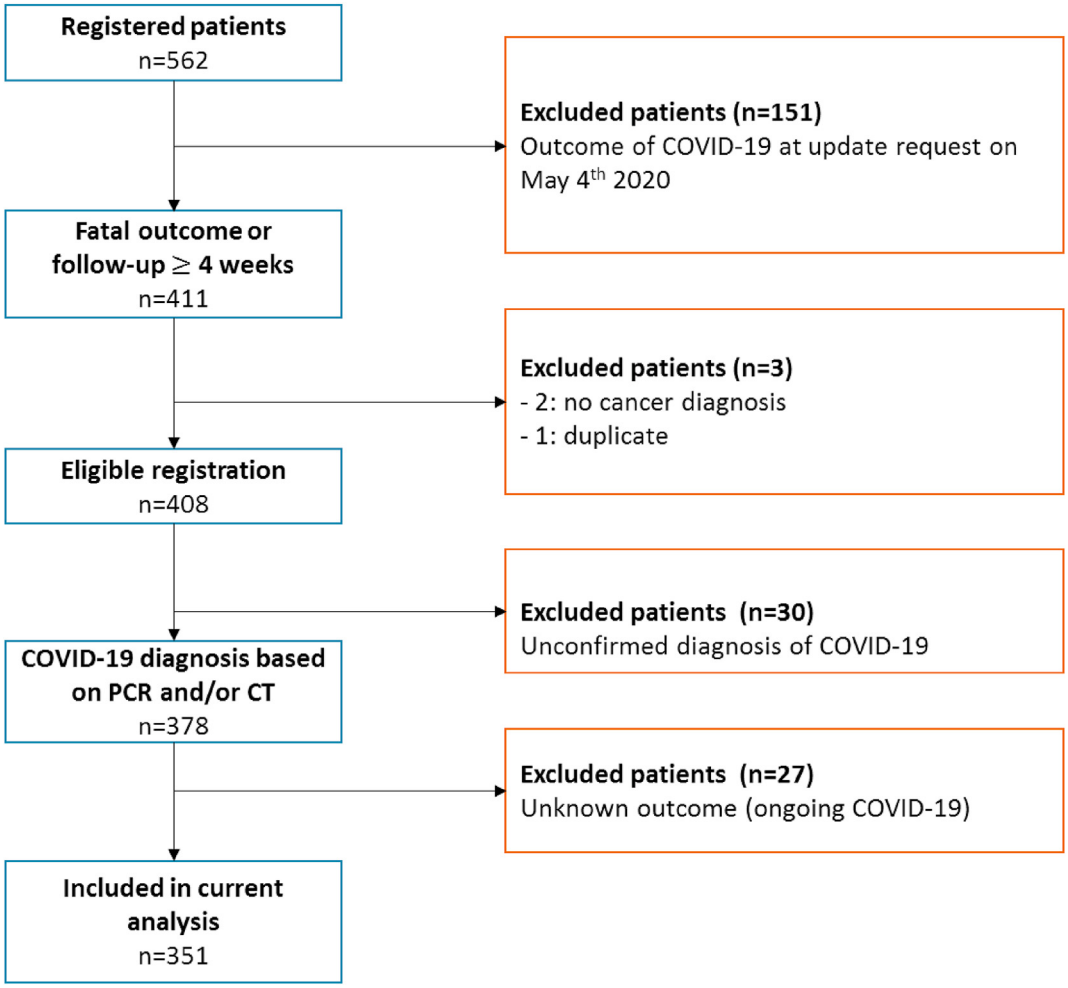

Fig. 2. Patient selection. Flowchart of patient selection for the current analysis.

Table 1
Patients' characteristics.

Variable	Resolved (n = 237)	Fatal (n = 114)	Total group (n = 351)
Sex—n (%)			
Male	112 (47.3)	75 (65.8)	187 (53.3)
Female	125 (52.7)	39 (34.2)	164 (46.7)
Age			
Median age in years (interquartile range)	68 (59–76)	74 (68–80)	70 (61–77)
<65 years—n (%)	99 (41.8)	12 (10.5)	111 (31.6)
≥65 years < 75 years—n (%)	71 (30.0)	46 (40.4)	117 (33.3)
≥75 years—n (%)	67 (28.3)	56 (49.1)	123 (35.0)
Smoking—n (%)			
All smokers	112 (47.3)	67 (58.5)	179 (51.0)
Current smoker	12 (5.1)	12 (10.5)	24 (6.8)
History of smoking	100 (42.2)	55 (48.2)	155 (44.2)
Comorbidities—n (%)			
Cardiovascular disease	119 (50.2)	71 (62.3)	190 (54.1)
BMI ≥ 30	48 (20.3)	16 (14.0)	64 (18.2)
COPD	26 (11.0)	20 (17.5)	46 (13.1)
Diabetes mellitus	34 (14.3)	21 (18.4)	55 (15.7)
Autoimmune disease	13 (5.5)	9 (7.9)	22 (6.3)
Prior/other malignancy	31 (13.1)	32 (28.1)	63 (17.9)
Use of steroids at COVID-19 diagnosis	53 (22.4)	40 (35.1)	93 (26.5)
As part of cancer treatment (<1 week)	32 (13.5)	23 (20.2)	55 (15.7)
Use >1 week (not related to cancer treatment)	21 (8.9)	17 (14.9)	38 (10.8)
Cancer type—n (%)			
Non-small-cell lung cancer	25 (10.5)	22 (19.3)	47 (13.4)
Breast cancer	40 (16.9)	7 (6.1)	47 (13.4)
Chronic lymphocytic leukaemia	22 (9.3)	9 (7.9)	31 (8.8)
Colorectal cancer	26 (11.0)	5 (4.4)	31 (8.8)
Prostate cancer	19 (8.0)	10 (8.8)	29 (8.3)
Multiple myeloma	14 (5.9)	14 (12.3)	28 (8.0)
Non-Hodgkin lymphoma	17 (7.2)	11 (9.6)	28 (8.0)
Urinary cell cancer	8 (3.4)	5 (4.4)	13 (3.7)
Myeloproliferative neoplasms	7 (3.0)	3 (2.6)	10 (2.8)
Myelodysplastic syndrome	4 (1.7)	5 (4.4)	9 (2.6)
Renal cell cancer	6 (2.5)	3 (2.6)	9 (2.6)
Melanoma	7 (3.0)	1 (0.9)	8 (2.3)
Endometrial cancer	6 (2.5)	1 (0.9)	7 (2.0)
Neuro-endocrine tumour	6 (2.5)	1 (0.9)	7 (2.0)
Oesophageal cancer	1 (0.4)	5 (4.4)	6 (1.7)
Chronic myeloid leukaemia	4 (1.7)	1 (0.9)	5 (1.4)
Ovarian cancer	4 (1.7)	0 (0)	4 (1.1)
Pancreatic cancer	4 (1.7)	0 (0)	4 (1.1)
Small-cell lung cancer	1 (0.4)	3 (2.6)	4 (1.1)
Other	14 (5.9)	8 (7.0)	24 (6.8)
Last oncological treatment—n (%)			
Surgery	25 (10.5)	17 (14.9)	42 (12.0)
Radiotherapy	43 (18.1)	24 (21.1)	67 (19.1)
Thoracic radiotherapy	27 (11.4)	16 (14.0)	43 (12.3)
Chemotherapy	104 (43.9)	49 (43.0)	153 (43.6)
Immunotherapy	41 (17.3)	16 (14.0)	57 (16.2)
Targeted therapy	39 (16.5)	17 (14.9)	56 (16.0)
Hormonal therapy	35 (14.8)	13 (11.4)	48 (13.7)
Disease stage solid tumours—n (%)			
Metastatic	81 (34.2)	31 (27.2)	112 (47.1)
Intention most recent cancer treatment given—n (%)			
Curative	105 (44.3)	45 (39.5)	150 (42.7)
Non-curative	122 (51.5)	66 (57.9)	188 (53.6)
Unknown	10 (4.2)	3 (2.6)	13 (3.7)
Treatment restrictions—n (%)			
Do-not-intubate	82 (34.6)	95 (83.3)	177 (50.4)

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table 2
Univariable analysis of features of patients related to a fatal outcome of COVID-19.

Variable	Odds ratio (95% CI)	*p* value
Sex (male)	2.15 (1.35–3.41)	0.001
Age (years)		
<65 years	–	–
≥65 years < 75 years	5.35 (2.64–10.81)	<0.001
≥75 years	6.90 (3.44–13.84)	<0.001
Smoking		
All smokers	–	–
History of smoking	1.72 (1.03–2.88)	0.040
Active smoker	3.13 (1.28–7.64)	0.012
Comorbidities		
Cardiovascular disease	1.64 (1.04–2.58)	0.034
BMI ≥ 30	0.64 (0.35–1.19)	0.158
COPD	1.73 (0.92–3.25)	0.087
Diabetes mellitus	1.35 (0.74–2.45)	0.325
Autoimmune disease	1.48 (0.61–3.56)	0.383
Prior/other malignancy	2.59 (1.49–4.52)	0.001
Use of steroids at COVID-19 diagnosis	–	–
As part of cancer treatment (<1 week)	1.94 (1.06–3.57)	0.033
Use >1 week (not related to cancer treatment)	2.18 (1.08–4.41)	0.029
Cancer type		
Other	–	–
Haematological malignancy	2.15 (1.30–3.57)	0.003
Lung cancer	3.13 (1.64–5.95)	0.001
Last oncological treatment		
Surgery	1.49 (0.77–2.88)	0.238
Radiotherapy	1.20 (0.69–2.10)	0.516
Thoracic radiotherapy	1.27 (0.65–2.47)	0.479
Chemotherapy	0.96 (0.61–1.51)	0.874
Immunotherapy	0.78 (0.42–1.46)	0.437
Targeted therapy	0.89 (0.48–1.65)	0.712
Hormonal therapy	0.74 (0.38–1.47)	0.390
Disease stage		
Metastatic	0.87 (0.54–1.41)	0.575
Intention most recent cancer treatment given		
Non-curative	1.30 (0.83–2.03)	0.259

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CI, confidence interval.

COVID-19 and 27 patients because of ongoing COVID-19 with unknown outcome. For this first analysis, 351 patients were included (Figure 2).

Detailed baseline characteristics are presented in Table 1. Overall, the median age was 70 years (interquartile range [IQR] 61–77) and 187 (53.3%) patients were male. The main cancer diagnoses were non-small cell lung cancer (13.4%), breast cancer (13.4%) and chronic lymphocytic leukaemia (8.8%). Metastatic disease was present in 112 (47.1%) out of 238 patients with solid tumours. In more than half of all patients (53.6%), the last cancer treatment was with non-curative intent. Besides cancer diagnosis, most patients had one or more relevant comorbidities, and 51% of the patients had a history of smoking.

Before the COVID-19 diagnosis, cancer treatment had been completed in 108 (30.8%) patients. In 101 (28.8%) patients, cancer treatment was not adjusted during the COVID-19 outbreak. Adjustments before the COVID-19 diagnosis included dose reduction (n = 4, 1.1%), premature withdrawal of treatment (n = 14, 4.0%), administration of higher dose (e.g. immunotherapy or radiotherapy) at longer interval (n = 16, 4.6%), cancellation of recent treatment cycle (n = 35, 10.0%) and/or temporarily interruption of treatment (n = 70, 19.9%).

Table 3
Multivariable analysis of features of patients related to a fatal outcome of COVID-19.

Variable	Odds ratio (95% CI)	*p* value
Sex (male)	1.84 (1.04–3.23)	0.035
Age (median age in years)		
<65 years	–	–
≥65 years < 75 years	4.26 (1.89–9.58)	<0.001
≥75 years	5.75 (2.56–12.92)	<0.001
Comorbidities		
Prior/other malignancy	2.02 (1.02–4.02)	0.045
Cancer type		
Other	–	–
Haematological malignancy	1.89 (1.01–3.53)	0.046
Lung cancer	3.40 (1.51–7.64)	0.003

CI, confidence interval.

Table 4
Univariable analysis for the subgroup of patients with active malignancy and COVID-19.

Variable	Total group (n = 227)		
	Frequency n (%)	Odds ratio (95% CI)	*p* value
Sex (male)	115 (50.7)	1.79 (1.01–3.17)	0.045
Age (median age in years)			
<65 years	84 (37.0)	–	–
≥65 years < 75 years	77 (33.9)	4.72 (2.12–10.55)	<0.001
≥75 years	66 (29.1)	6.55 (2.89–14.86)	<0.001
Smoking			
All smokers	115 (50.7)	–	–
History of smoking	99 (43.6)	1.20 (0.64–2.26)	0.579
Active smoker	16 (7.0)	2.63 (0.89–7.78)	0.082
Comorbidities			
Cardiovascular disease	107 (47.1)	1.86 (1.06–3.29)	0.031
BMI ≥ 30	39 (17.2)	0.61 (0.27–1.36)	0.225
COPD	23 (10.1)	1.47 (0.61–3.58)	0.392
Diabetes mellitus	30 (13.2)	1.12 (0.49–2.52)	0.794
Autoimmune disease	10 (4.4)	1.49 (0.41–5.46)	0.543
Prior/other malignancy	38 (16.7)	1.77 (0.87–3.63)	0.115
Use of steroids at COVID-19 diagnosis	134 (59.0)	–	–
As part of cancer treatment (<1 week)	53 (23.3)	2.26 (1.16–4.40)	0.017
Use >1 week (not related to cancer treatment)	25 (11.0)	1.65 (0.67–4.09)	0.275
Cancer type			
Other	127 (55.9)	–	–
Haematological malignancy	62 (27.3)	3.64 (1.89–7.04)	<0.001
Lung cancer	38 (16.7)	2.53 (1.16–5.53)	0.020
Last oncological treatment			
Surgery	15 (6.6)	1.51 (0.52–4.41)	0.451
Radiotherapy	49 (21.6)	0.85 (0.42–1.70)	0.645
Thoracic radiotherapy	31 (13.7)	0.88 (0.39–2.03)	0.772
Chemotherapy	117 (51.5)	0.88 (0.50–1.54)	0.648
Immunotherapy	46 (20.3)	0.84 (0.41–1.71)	0.621
Targeted therapy	49 (21.6)	1.22 (0.63–2.38)	0.560
Hormonal therapy	39 (17.2)	0.72 (0.33–1.57)	0.404
Disease stage for solid tumours			
Metastatic	118 (52.0)	0.93 (0.53–1.63)	0.795
Intention most recent cancer treatment given			
Non-curative	148 (65.2)	1.89 (1.01–3.53)	0.044
Treatment restrictions			
Do-not-intubate	121 (53.3)	–	–

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CI, confidence interval.

3.3. Outcome of COVID-19 in patients with cancer

In total, 114 (32.3%) of the patients died from COVID-19. Patients with a fatal outcome of COVID-19 had a higher median age as compared with patients with non-fatal outcome (74 [IQR 68–80] versus 68 [IQR 59–76] years). Patients with age ≥65 years had an increased risk of fatal outcome ($p < 0.001$). In univariable analyses (Table 2), male gender, smoking, cardiovascular disease, chronic obstructive pulmonary disease, prior or other malignancy, use of steroids at COVID-19 diagnosis, a current diagnosis of haematologic malignancy and lung cancer were associated with fatal outcome of COVID-19.

In multivariable analyses, age ≥65 years ($p < 0.001$), male gender ($p = 0.035$), prior or other malignancy ($p = 0.045$) and an active diagnosis of haematological malignancy ($p = 0.046$) or lung cancer ($p = 0.003$) remained independent risk factors for a fatal outcome of COVID-19 (Table 3).

Treatment restrictions with a do-not-intubate order were reported in 117/351 (50.4%) patients and in 95/114 (83.3%) patients with fatal COVID-19 outcome.

Table 5
Multivariable analysis for the subgroup of patients with active malignancy and COVID-19.

Variable	Odds ratio (95% CI)	*p* value
Age (median age in years)		
<65 years	–	–
≥65 years < 75 years	4.09 (1.70–9.89)	0.002
≥75 years	5.56 (2.21–14.02)	<0.001
Cancer type		
Other	–	–
Haematological malignancy	3.60 (1.72–7.53)	0.001
Lung cancer	3.01 (1.20–7.59)	0.019

CI, confidence interval.

Table 6
Overview of previously published registries.

Author	Variable	Dai [5]	Liang [6][c]	Zhang [7]	Lee [9]
Country		China	China	China	UK
Registry (hospital and/or general practitioner)		Hospital only	Hospital only	Hospital only	Hospital only
Number of patients with cancer		105	18 out of 1590 COVID-19 patients had cancer	26	800
Number of hospitals		14	575	3	55
COVID-19 diagnosis		WHO interim guidance	PCR	PCR	PCR
Study design		Multicentre prospective cohort study	Prospective cohort study	Retrospective cohort study	Prospective cohort study
	Informed consent patients	No	Not reported	No	Not reported
	Monitoring of the data	Reviewed by > 2 oncologists	Not reported	Reviewed by two physicians	Not reported
Population	Cancer diagnosis from	Ever, distributed in several cohorts[b]	Ever	Ever	Last 12 months
	Lung cancer	22 (21%)	5/18 (28%)	7 (25%)	90 (11%)
	Haematologic cancer	9 (9%)	1/18 (6%) (lymphoma)	0	169 (21%)
	Other solid tumours	Not reported	12/18 (67%)	21 (75%)	494 (62%)
Treatment status	Definition of 'recent'	Within 40 days	Within 1 month	Within 14 days	Within 4 weeks
	Recent chemotherapy	17	4 (chemotherapy or surgery)	3	281
	Recent surgery	8	4 (chemotherapy or surgery)	0	29
	Recent radiotherapy	13	0	1	76
	Recent immunotherapy	6	0	1	44
	Recent hormonal therapy	0	0	0	0
	In follow-up	Not reported	12	12	Not reported
Treatment restrictions		Not reported	Not reported	Not reported	Not reported

3.4. Active malignancy

A subgroup analysis was performed in 227 patients with active malignancy. The characteristics and results of the univariable analysis are shown in Table 4. Patients with a haematological malignancy or lung cancer had an increased risk of a fatal outcome of COVID-19 compared with patients with other cancer types. In addition, male patients, age ≥65 years, smoking, cardiovascular disease and use of steroids as part of anticancer treatment remained risk factors for fatal outcome in univariable analysis. In this subgroup analysis, treatment in non-curative setting was also associated with fatal outcome.

The above-mentioned characteristics were all included in the multivariable analysis. The risk for a fatal outcome was mainly determined by tumour type and age, as older patients (≥65 years) and patients with a haematological malignancy or lung cancer had a worse outcome of COVID-19 (Table 5).

In total, 165 patients were on active treatment (i.e. ≤30 days between the last treatment and date of COVID-19 diagnosis). In this group, there were no differences in the risk of a fatal outcome of COVID-19

Data registered	Baseline characteristics[a]	Yes	Yes	Yes	Yes (including covid-19 severity)
	Laboratory examination	Not reported	Not reported	Yes	Not reported
	Abnormalities at baseline on X-ray or CT	Not reported	Yes	Yes	Not reported
	Use of antibiotics	Yes	Not reported	Yes	Not reported
	Use of antiviral s	Yes	Not reported	Yes	Not reported
	Use of hydroxychloroquine	Not reported	Not reported	Not reported	Not reported
	Use of glucocorticoids	Yes	Not reported	Yes	Not reported
	Use of anti-IL6	Not reported	Not reported	Not reported	Not reported
	Use of anticoagulants	Not reported	Not reported	Not reported	Not reported
	Admission to ICU	Yes	Yes	Yes	Yes
	Invasive ventilation	Yes	Yes	Yes	Not reported
	Death	Yes	Yes	Yes	Yes
	Other				

DOCC, Dutch Oncology COVID-19 Consortium; ICU, intensive care unit; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; CT, computed tomography.

[a] Age, smoking, comorbidity, cancer type, cancer treatment, COVID-19 symptoms.

[b] <3 months, 1–3 months, 3–6 months, 6–12 months, 1–3 years, >3 year.

[c] On behalf of the National Clinical Research Center for Respiratory Disease.

[d] Or longer if the cancer treatment is expected to have an impact on COVID-19 outcome, for example after bone marrow transplantation or thoracic radiotherapy.

Garassino (TERAVOLT) [21]	Kuderer (CCC1S) [24]	Scarfo [25]	Pinato (OnCovid) [26]	Lara [27]	Robilotti [28]	Joode (DOCC)
8 countries	USA, Canada and Spain	Europe (mainly Italy and Spain)	Europe (UK, Spain, Italy, Germany)	New York	Memorial Sloan Kettering Cancer Center New York	The Netherlands
Hospital only	Hospital only	Hospital only	Hospital only	Hospital only	Hospital only	Hospital only
200	928	190	890	121	423	442
87	Not reported	118	19	6	1	45
WHO interim guidance	PCR	PCR	PCR	Laboratory confirmation (PCR and/or serology) and/or radiological (X-ray or CT) and/or high clinical suspicion	Laboratory confirmation (PCR and/or serology) and/or symptomatic	PCR and/or CT
Multicentre observational study	Retrospective cohort study	Multicentre retrospective study	Multicentre retrospective observational study	Multicentre retrospective observational study	Retrospective cohort study	Observational cohort study
According to local need	Not reported	Yes	Not reported	Not reported	Not reported	No
Yes (by REDCap)	Not reported	Not reported	Not reported	Not reported	Not reporter	Data cleaned by experienced oncology physicians

Not reported	Not reported	Ever	Ever	Ever	Not reported	Last 5 year[d]
Only thoracic malignancies	91 (10%); thoracic cancer	0	119 (13%)	0	35 (8%)	51 (15%)
0	204 (22%)	All haematologic cancer	137 (15%)	0	102 (24%)	111 (32%)
Only thoracic malignancies	667 (72%)	0	634 (71%)	Only gynaecological cancer	286 (68%)	165 (47%)
Not reported	Within 4 weeks	Within 12 months	Within 4 weeks	Not reported	Within 30 days	Within 30 days
68	160	Not reported	206	35	191	117
0	2	Not reported	0	11	31	15
0	12	Not reported	33	9	Not reported	49
54	38	Not reported	56	8	31	46
0	0	Not reported	92	9	Not reported	39
52 (26%)	Not reported	73	403	52	Not reported	108
Yes	Not reported	Not reported	Not reported	Not reported	Not reported	With a do-not-intubate order
Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yes	Not reported	Not reported	Yes	Yes	Yes	Yes
Yes	Not reported	Not reported	Not reported	Not reported	Yes	Yes
Yes	Not reported	Not reported	Yes	Yes	Yes	Yes
Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yes	Not reported	Not reported	Yes	Yes	Yes	Yes
Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Yes	Not reported	Yes	Not reported	Yes	Not reported	Not reported
Yes	Yes	Not reported	Yes	Yes	Yes	Not reported
Not reported	Yes	Not reported	Yes	Yes	Yes	Not reported
Yes	Yes	Yes	Yes	Yes	Yes	Yes
Length of hospital stay		COVID-19 management at home, COVID-19 resolution	Occurrence of complicated SARS-Cov-2 infection			Adjustment of oncological treatment, treatment restrictions regarding mechanical ventilation and admission to ICU

between the different cancer therapies. The disease setting (non-metastatic versus metastatic) and treatment setting (curative versus non-curative) were not associated with an increased risk of fatal outcome of COVID-19.

4. Discussion

The DOCC registry was initiated to identify clinical characteristics of patients with cancer related to an increased risk of fatal outcome of COVID-19. An active diagnosis of haematological malignancy or lung cancer, age (≥65 years), male gender and diagnosis of a prior or

other malignancy were independent risk factors for a fatal outcome of COVID-19. In the subgroup of patients with active malignancy, age (≥65 years) and a diagnosis of a haematological malignancy or lung cancer remained independent risk factors for increased mortality of COVID-19.

Although chemotherapy has previously been identified as a risk factor for mortality of COVID-19 in cancer patients [21], this could not be confirmed in our registry. This is supported by data from a UK registry [9]. However, steroid use at the time of COVID-19 diagnosis was associated with an increased risk of fatal outcome of COVID-19 in univariable analysis. This result is of particular interest, as a recent randomised clinical trial showed that dexamethasone decreases mortality of COVID-19 in patients requiring respiratory support [22]. Steroids may contribute to an increased viral load of SARS-CoV-2 by an increase in viral replication and a delay of viral clearance [23]. Steroid co-medication is usually prescribed as supportive medication for haematological treatment and/or highly emetogenic chemotherapy regimens. Therefore, systemic treatment or disease itself cannot be excluded as confounding factor.

Apart from the current DOCC registry, other international registries have been published to identify the clinical characteristics of cancer patients with severe COVID-19 [5–7,9,21,24–28]. As the design and data collection of these registries are significantly different, a comparison between results is challenging. Therefore, for appropriate interpretation of data published by these registries, attention should be paid to the different designs and patient selections (Table 6).

At the beginning of the COVID-19 outbreak in the Netherlands, both international and national oncological guidelines were published [13–16]. In summary, the national guidelines were rather reluctant to start or continue oncological therapies. In addition, treating physicians were encouraged to discuss treatment restrictions regarding intubation and ICU admission with their patients. Owing to these conservative guidelines, adjustments in oncological treatment were rather common [12] and probably even more frequent in vulnerable patients. Therefore, the lack of effect of oncological treatments on fatal outcomes of COVID-19 should be interpreted cautiously in the current study, and the impact of anticancer therapies on the course of COVID-19 cannot be excluded.

Moreover, discussing treatment restrictions with patients in the outpatient clinic was already common practice in the Netherlands prior to COVID-19, especially for patients with cancer in the non-curative setting. In the DOCC registry, more than 50% of patients had a do-not-intubate order prior to infection with SARS-CoV-2. Among patients with fatal outcome of COVID-19, more than 80% had a do-not-intubate order. In addition, in the Netherlands, patients with COVID-19 are almost solely admitted to the ICU when mechanical ventilation is required, whereas most other supportive treatments are given outside the ICU. As a result, <20% of patients with fatal outcome of COVID-19 was admitted to the ICU in the current study, despite the lack of capacity issues of ICUs in the Netherlands. Although discussing treatment restrictions is common practice in the Netherlands and probably more common as compared to other countries, the percentage of patients with a fatal outcome is comparable to other countries [6,7,9,21,24]. Therefore, early discussion of treatment restrictions with vulnerable patients is preferred during this ongoing pandemic.

As the DOCC registry is only executed by oncology physicians in hospitals, a limitation of this study is the potential selection bias. As a result, particular groups of patients may have been underreported. For instance, patients who already had completed oncological treatment, patients who were not admitted to the hospital or patients who died in an out-hospital setting, may not have been registered. Next, the Dutch testing policy for SARS-CoV-2 was restrictive in the beginning of the pandemic, which initially resulted in an underestimation of the total number of patients with COVID-19. Although a potential selection bias may have occurred, this does not directly affect the results of this analysis, as the potentially underreported patient groups mainly included patients without active malignancy and/or recent cancer treatment. In addition, the Dutch healthcare system provides equal access to medical care and cancer treatment decisions are based on the same national guidelines. Therefore, the results of the current study seem to be representative of a national cancer patient population.

As the COVID-19 pandemic overwhelmed healthcare systems worldwide, non-evidence–based decisions had to be made about the treatment of patients with non-COVID-19 diseases such as cancer. Therefore, it is essential to combine data from several international registries and to ensure the collection of new and more comprehensive data during this ongoing pandemic. In particular, more data concerning cancer treatment and supportive medication (e.g. steroids) should be collected.

In conclusion, the findings of the DOCC registry in cancer patients confirm previous findings that older, male patients with comorbidities have an increased risk of a fatal outcome of COVID-19 [29]. Besides, the results of this registry indicate that patients with a haematological malignancy or lung cancer have an increased risk of a poorer outcome. During the ongoing COVID-19 pandemic, these vulnerable patients should

avoid exposure to SARS-CoV-2, whereas treatment adjustments and prioritising vaccination, when available, should be considered as well.

Conflict of interest statement

D.D. reports personal fees from speakers fee MSD, personal fees from speakers fee Roche, personal fees from speakers fee AstraZeneca, personal fees from speakers fee BMS, personal fees from speakers fee Novartis, personal fees from speakers fee Pfizer, outside the submitted work; H.W. reports honoraria from Astellas and Roche and travel expenses from Ipsen, outside the submitted work; K.S. reports personal fees and advisory role for Novartis, personal fees from Roche, personal fees and advisory role for MSD, advisory role BMS, advisory role Pierre Fabre, advisory role Abbvie, outside the submitted work; L.H. reports other from Boehringer Ingelheim, other from BMS, other from Roche Genentech, other from BMS, grants from Roche Genentech, grants from Boehringer Ingelheim, other from AstraZeneca, personal fees from Quadia, grants from Astra Zeneca, other from Eli Lilly, other from Roche Genentech, other from Pfizer, other from MSD, other from Takeda, non-financial support from AstraZeneca, non-financial support from Novartis, non-financial support from BMS, non-financial support from MSD/Merck, non-financial support from GSK, non-financial support from Takeda, non-financial support from Blueprint Medicines, non-financial support from Roche Genentech, other from Amgen, outside the submitted work; A.D. reports personal fees from Roche, personal fees from Eli Lily, personal fees from Boehringer Ingelheim, personal fees from Pfizer, personal fees from BMS, personal fees from Novartis, personal fees from Takeda, personal fees from Pharmamar, non-financial support from Abbvie, grants from BMS, grants from Amgen, outside the submitted work; A.V. reports advisory board of BMS, MSD, Merck, Pfizer, Ipsen, Eisai, Pierre Fabre, Roche, Novartis, Sanofi, outside the submitted work.

All remaining authors declare no competing interests.

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Appendix 1

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.09.027.

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Author contributions

K.J., D.D., J.T., H.W., L.B., F.B., P.M., N.D., O.V., E.O., H.B., H.L., L.H., J.H., E.V., A.D. and A.V. have contributed to the design of the study. All authors except for E.O. contributed to data collection. K.J., D.D., A.D., A.V. have contributed to literature search, data analysis, data interpretation and writing of the manuscript. D.D., P.M. and A.V. have checked all clinical data for inconsistencies. K.J. and E.O. have contributed to statistical analysis of the data. K.J., D.D., J.T., H.W., L.B., F.B., P.M., N.D., O.V., E.O., H.B., H.L., L.H., J.H., E.V., A.D. and A.V. participated in drafting the article and revising it critically for important intellectual content. All authors reviewed the

manuscript and have given final approval of the submitted version.

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