Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

High mortality rate in cancer patients with symptoms of COVID-19 with or without detectable SARS-COV-2 on RT-PCR

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Abstract ***Background:*** Cancer patients presenting with COVID-19 have a high risk of death. In this work, predictive factors for survival in cancer patients with suspected SARS-COV-2 infection were investigated.

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Cancer patients;
Survival;
RT-PCR;
Risk factors

Methods: PRE-COVID-19 is a retrospective study of all 302 cancer patients presenting to this institute with a suspicion of COVID-19 from March 1st to April 25th 2020. Data were collected using a web-based tool within electronic patient record approved by the Institutional Review Board. Patient characteristics symptoms and survival were collected and compared in SARS-COV-2 real-time or reverse-transcriptase PCR (RT-PCR)−positive and RT-PCR −negative patients.

Results: Fifty-five of the 302 (18.2%) patients with suspected COVID-19 had detectable SARS-COV-2 with RT-PCR in nasopharyngeal samples. RT-PCR−positive patients were older, had more frequently haematological malignancies, respiratory symptoms and suspected COVID-19 pneumonia of computed tomography (CT) scan. However, respectively, 38% and 20% of SARS-COV-2 RT-PCR−negative patients presented similar respiratory symptoms and CT scan images. Thirty of the 302 (9.9%) patients died during the observation period, including 24 (80%) with advanced disease. At the median follow-up of 25 days after the first symptoms, the death rate in RT-PCR−positive and RT-PCR−negative patients were 21% and 10%, respectively. In both groups, independent risk factors for death were male gender, Karnofsky performance status <60, cancer in relapse and respiratory symptoms. Detection of SARS-COV-2 on RT-PCR was not associated with an increased death rate ($p = 0.10$). None of the treatment given in the previous month (including cytotoxics, PD1 Ab, anti-CD20, VEGFR2…) correlated with survival. The survival of RT-PCR−positive and −negative patients with respiratory symptoms and/or COVID-19 type pneumonia on CT scan was similar with a 18.4% and 19.7% death rate at day 25. Most (22/30, 73%) cancer patients dying during this period were RT-PCR negative.

Conclusion: The 30-day death rate of cancer patients with or without documented SARS-COV-2 infection is poor, but the majority of deaths occur in RT-PCR−negative patients.

1. Introduction

The death rate of COVID-19 patients is reported to be close to 2% [1]. Cancer patients are a group at higher risk of serious and lethal complications of COVID-19 [2–5]. The 30-days survival of patients with cancer presenting with documented COVID-19 has been reported to be 60%–70% in recent series [2–5]. These results were reported in particular from large oncology hospital in China and were compared with patients with COVID-19 without cancer. Variability in death rates has been reported across countries and within countries, possibly related to differences in screening strategies but also different population susceptibility [6–10].

The mechanisms by which the associated condition of cancer influences the risk of death to COVID-19 remain unclear. Whether this is related to the age group of cancer patients, coexisting causes (tobacco, comorbidities …), to cancer staging or to cancer treatment recently applied is not clear. Identifying the characteristics of cancer patients with COVID-19 at risk of a severe complication or death would be useful to propose specific preventive measures and to adapt clinical trials.

The number of cancer patients affected with COVID is possibly underestimated. The sensitivity of real-time or reverse-transcriptase PCR (RT-PCR) diagnostic tests for COVID-19 ranges from 37% to 55% according to published evidence for patients with typical clinical presentation of COVID-19 [11–13]. Repeated testing may increase improve detection rate in patients with initial negative SARS-COV-2 RT-PCR [12].

It is therefore important to further analyse the clinical presentation and outcome of cancer patients presenting with suspicion of COVID-19 to identify predictive factors for unfavourable outcome.

In this study (named PRE-ONCOVID-19), the survival of the exhaustive cohort of 302 patients presenting with clinical suspicion of COVID-19 consulting in a comprehensive cancer centre was investigated, and the presence of the virus was tested using a RT-PCR diagnostic test. The RT-PCR−positive and RT-PCR−negative subgroups were compared. Cancer patients with documented COVID-19 were found at high risk of death after diagnosis, but cancer patients without documented SARS-COV-2 infection presenting with similar symptoms were also at high risk of death. The latter subgroup represented the majority of patients succumbing during this period, suggesting an important underdiagnosis of the SARS-COV-2 infection in cancer patients.

2. Patients material and methods

2.1. Objectives

The objective of the PRE-ONCOVID-19 study was to describe the clinical characteristics and survival of cancer patients presenting with COVID-19 symptoms,

comparing (1) patients with documented SARS-COV-2 by RT-PCR and (2) patients with negative SARS-COV-2 RT-PCR test.

2.2. Study design

PRE-ONCOVID-19 is a retrospective study of cancer patients presenting to the Comprehensive Cancer Center of Lyon (Centre Leon Berard, CLB) with a suspicion of COVID-19 from March 1st to April 15th 2020. Patient cases were collected using a web-based tool, enabling the collection of clinical information integrated to the electronic patient record, after Institutional Review Board approval. Patients not agreeing for the use of their clinical data for an academic study were excluded, according to the national and European laws. The study was approved by the Institutional review board of the Centre Leon Berard on 12 March of 2020.

2.3. Patients

The inclusion criteria were an histological diagnostic of cancer and the prescription of a diagnostic test of SARS-COV-2 with RT-PCR on a nasopharyngeal sample from March 1st 2020 to April 15th. For SARS-COV-2 RT-PCR, the cobas® SARS-CoV-2 Test (Roche, Neuilly, France) was used, exploring *ORF1/a & the Pan SARS* gene E. Cancer patients presenting with clinical symptoms of COVID-19, fever and/or dry cough and/or dyspnoea and/or dysgeusia anosmia and/or diarrhoea and/or suspect images on computed tomography (CT) scan with or without a contact with a COVID-19-suspected or demonstrated contact person, were included in this study. The median follow-up of the present series is 25 days.

2.4. Clinical definition of a group of patients with respiratory symptoms

We identified a group of patients with respiratory symptoms suspect of COVID-19 which was defined as patients presenting with at least two of the three following symptoms: fever, dry cough and dyspnoea. The observation period was from March 1st to April 25th. SARS-COV-2 RT-PCR–positive and RT-PCR–negative patients were compared for demographics, cancer presentation, cancer characteristics, cancer treatment, clinical, radiological or biological symptoms of COVID-19 and survival.

2.5. Data collected in this study

The following data were collected retrospectively: demographic characteristics (age, weight, body mass index, gender, …), cancer characteristics (histotypes, stage, relapse), the clinical presentation at the time of COVID-19 suspicion (Karnofsky performance status [KPS], fever, dyspnoea, cough, diarrhoea, O2 requirement, central nervous system (CNS) symptoms and vascular symptoms), presence of characteristic COVID-19 images on CT scan when performed, a selected set of biological analysis at the time of the infectious event (CRP, lymphocyte counts,..), previous cancer treatments in the last month, patient outcome (survival) and co-morbidities (chronic obstructive pulmonary disease (COPD), hypertension and diabetes) in the electronic patient records. As benchmark, the comorbidities reported in the population of 43,171 cancer patients in the CLB since 01/01/2015 are COPD: 2541 (5.8%), hypertension: N = 11,204 (25.9%) and diabetes: N = 8514 (19.7%). Several additional biological factors not systematically collected were available in less than 15% of the patients (D-Dimers, troponine, creatine phosphokinase (CPK)) and for LDH in 35% of the patients and therefore not analysed in this series. Because neutrophil counts are strongly influenced by recent (<1 month) cytotoxic treatments (administered in N = 137, 45% of the patients in this series), we used absolute lymphocyte counts and not neutrophil/lymphocyte ratio in this work.

2.6. Statistical analysis

The distribution of risk factors or clinical characteristics was analysed using the Chi-square test, Fisher exact test, Mann–Whitney U test. The Bonferroni correction was used for multiple Chi-square testing. Survival was plotted from the date of first symptoms to the date of death or to the date of last news if alive at the time of the analysis (April 25th, 2020). Survival was plotted according to the inverse Kaplan–Meier method, and groups were compared using the log-rank test. Risk of death was evaluated using Cox proportional hazard model in univariate and then multivariate analysis. Backward selection procedure was used to determine the final model by removing non-significant variables ($p > 0.10$) one at a time. All statistical analyses will be performed using SPSS 23.0 software, SPSS (IBM, Paris, France).

3. Results

3.1. Clinical characteristics of 302 cancer patients consulting for a suspicion of COVID-19 (Table 1)

As shown on Table 1, only 55 of 302 (18.2%) patients consulting for suspicion of COVID-19 had detectable SARS-COV-2 with RT-PCR on nasopharyngeal samples. SARS-COV-2 RT-PCR–positive patients were older, had more frequently haematological malignancies, respiratory symptoms, diarrhoea and anosmia/ageusia, as well as suspected COVID-19 pneumonia of CT scan (Table 1). No single solid tumour subtypes were

Table 1
Characteristics of the patients.

Characteristics	All (N,%)	SARS-COV-2 RT-PCR		p
		Negative (n, %)	Positive (n, %)	
All	**302 (100%)**	**247 (81.8%)**	**55 (18.2%)**	
Female	158 (52.3%)	129 (52.2%)	29 (52.7%)	
Male	144 (47.7%)	118 (47.8%)	(47.3%)	0.93
Age (mean, SE)	**58.2 (1.1)**	**56.9 (1.2)**	**63.8 (2.2)**	**0.006**
>60	179 (59.3%)	139 (56.3%)	40 (72.7%)	**0.02**
Cancer type				
Solid tumours[a]	234 (77.5%)	199 (80.6%)	35 (63.6%)	
Haematological	**68 (22.5%)**	**48 (19.4%)**	**20 (36.4%)**	**0.007**
Lung	42 (13.9%)	35 (14.2%	7 (12.7%)	0.78
KPS (mean, SE)	69.8 (1.1)	69.1 (1.2)	72.9 (2.8)	0.15
KPS<60	114 (37.7%)	97 (39.3%)	17 (30.9%)	0.25
BMI (mean, SE)	24.3 (0.3)	24.2 (0.34)	24.7 (0.58)	0.43
BMI>30	120 (39.7%)	100 (40.5%)	20 (36.4%)	0.57
Metastatic disease	161 (53.3%)	132 (53.4%)	29 (52.7%)	0.92
Relapsed disease	177 (58.8%)	146 (59.1%)	31 (56.4%)	0.71
Cancer treatment < 1 month	**194 (64.2%)**	**165 (66.8%)**	**29 (52.7%)**	**0.049**
Symptoms at entry				
Fever	191 (63.7%)	150 (61.2%)	41 (74.5%)	0.06
Cough	**135 (45%)**	**96 (39.2%)**	**39 (70.9%)**	**0.000**
Dyspnoea	94 (31.4%)	75 (30.6%)	19 (35.2%)	0.51
2 or more of the above	**130 (43.5%)**	**94 (38.4%)**	**36 (66.7%)**	**0.000**
Diarrhoea	**42 (14.1%)**	**30 (12.3%)**	**12 (22.6%)**	**0.05**
Anosmia/ageusia	**21 (7%)**	**4 (1.6%)**	**17 (30.6%)**	**0.000**
Neurological	7 (2.3%)	3 (1.2%)	4 (7.3%)	
COVID-19 suspect on CT scan	**59 (29.5%)**	**32 (20.0%)**	**27 (67.5%)**	**0.000**
CRP (mean, SE)	96.2 (6.4)	97.9 (6.9)	86.2 (17.3)	0.55
CRP>50	133 (54.1%)	115 (55.3%)	18 (47.4%)	0.36
CRP>200	40 (16.3%)	35 (16.8%)	5 (13.2%)	0.57
Lymphocyte counts (mean, SE)	1136 (45.4)	1142 (49.8)	1106 (112.1)	0,78
<700/μL	91 (33.5%)	78 (34.1%)	13 (30.2%)	0.57
<400/μL	33 (12.1%)	28 (12.2%)	5 (11.6%)	0.62

Solid tumours: breast adenocarcinoma (N = 42, 13.9%), colorectal adenocarcinoma (N = 18, 5.9%); soft tissue sarcomas (N = 15, 5.0%); renal cell carcinoma (N = 12, 4.0%); pancreas (N = 10, 3.3%); uterine (N = 9, 3.0%); bone (N = 7, 2.3%); peritoneal, oesophagus, adrenal (each N = 4, 1.3%); anal carcinoma, ovarian adeno carcinoma, prostate adenocarcinoma, testis adenocarcinoma, glioma (each N = 3, 1.0%); duodenum, parotid, maxillary sinus, supraglottis, thymoma, bladder carcinoma, CUP (each, N = 2, 0.7%). All other cancer types were N = 1 (0.3%).
KPS, Karnofsky performance status; CT, computed tomography; BMI, body mass index; CUP, carcinoma of unknown primary.
[a] See legend for the different subtypes.

over-represented in the SARS-COV-2 RT-PCR–positive subgroup (Table 1, legend). Present tobacco use (N = 35, 11.6%), former tobacco use (N = 61, 20.2%), report of COPD (N = 26, 8.6%), diabetes (N = 55, 18.2%) and hypertension (N = 79, 26.2%) in the electronic patient records were not significantly different between the SARS-COV-2 RT-PCR–positive and RT-PCR–negative subgroups. Recent cancer treatments (any, cytotoxics, PD1 Ab, anti-CD20, mTOR inhibitors and antiangiogenic tyrosine kinase inhibitors) were not different between the two groups (Table 2). However, 94 of 247 (38%) RT-PCR–negative patients at the date of symptoms also had COVID-19 respiratory symptoms (defined as at least two of the following: fever, dry cough and dyspnoea), and 32 of the 247 (20%) had characteristic CT scan images of COVID-19 pneumonia. The majority of patients in both subgroups were lymphopenic: 91 (33.5%) had deep lymphopenia<700/μL at the time of the infection. Similarly, both subgroups of patients had major inflammatory syndrome with a median CRP level of 96 mg/L at the date of RT-PCR and over 16% of patients with CRP levels above 200 mg/L.

3.2. Survival of RT-PCR–positive and RT-PCR–negative cancer patients

Fig. 1 shows the survival of SARS-COV-2 RT-PCR–positive and RT-PCR–negative patients in the observation period between March 1st and April 25th. Eight of the 55 RT-PCR–positive patients and 22 of the 147 RT-PCR–negative patients had died at the time of the analysis. With a median follow-up of 25 days, the death rates of RT-PCR–positive and RT-PCR–negative patients 25 days after the first symptoms were 21% and 10%, respectively, and were not significantly different. Both the RT-PCR–negative and RT-PCR–positive groups had therefore a high death rate. None of the 302 patients of this series have received azithromycine, chloroquine, lopinavir/ritonavir or remdesivir. One patient each received GNS561 (a

Table 2
Cancer treatment in the last 30 days and patient outcome.

Treatment	n of deaths/N of patients (%) SARS-CoV2 RT-PCR*		
	All series (N = 302)	Negative (N = 247)	Positive (N = 55)
No. of deaths†	**30 (10%)**	**22 (8.9%)**	**8 (14.5%)**
Treatment			
No cancer treatment	13/108 (12%)	8/82 (9.7%)	5/26 (19.2%)
Any cancer treatment	17/194 (8.8%)	14/165 (8.4%)	3/29 (10.3%)
Cytotoxics	11/137 (8.0%)	11/121 (9.1%)	0/16 (0%)
Anti-CD20	1/14 (7.1%)	0/9 (0%)	1/5 (20%)
Anti-PD1/PDL1	3/26 (11.5%)	3/23 (13.0%)	0/3 (0%)
Antiproteasomes	1/8 (12.5%)	1/7 (14.2%)	0/1 (0%)
Anti-HER2	0/12 (0%)	0/10 (0%)	0/2 (0%)
Everolimus (mTORi)	0/4	0/4 (0%)	0
Antiangiogenic TKI	3/18 (16.6%)	2/12 (16.6%)	1/6 (16.6%)

*Rates of SARS-COV-2 RT-PCR positivity were not significantly different for any of the treatment categories after correction for the number of tests performed (n = 8, significant p value of $p > 0.00625$): all p values were above 0.04 using the Chi-square test.). PD1, programmed death protein 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor.
†Death rates were not significantly different for any of the subgroups of treatments after correction for the number of tests performed (n = 8, significant p value of $p > 0.00625$): all p values were above 0.15 using the Chi-square test.

chloroquin analogue) and tocilizumab as part of an ongoing randomised clinical trial as standard treatment (Immunoncovid-20, NCT04333914).

The majority (24/30, 80%) of cancer patients who died in this observation period had metastatic disease, both in the RT-PCR–positive and RT-PCR–negative patients. Five patients had febrile neutropenia and none died (not shown). Present or past tobacco use, body mass index, histological subtype of the solid tumour, haematological malignancies, smoking history and comorbidities as described above were not correlated to the risk of death in these series (not shown). The administration of any cancer treatment in the month before the date of the first symptoms was not associated to an increased risk of death. Treatment with cytotoxics, anti-CD20, anti-PD1/PDL1,

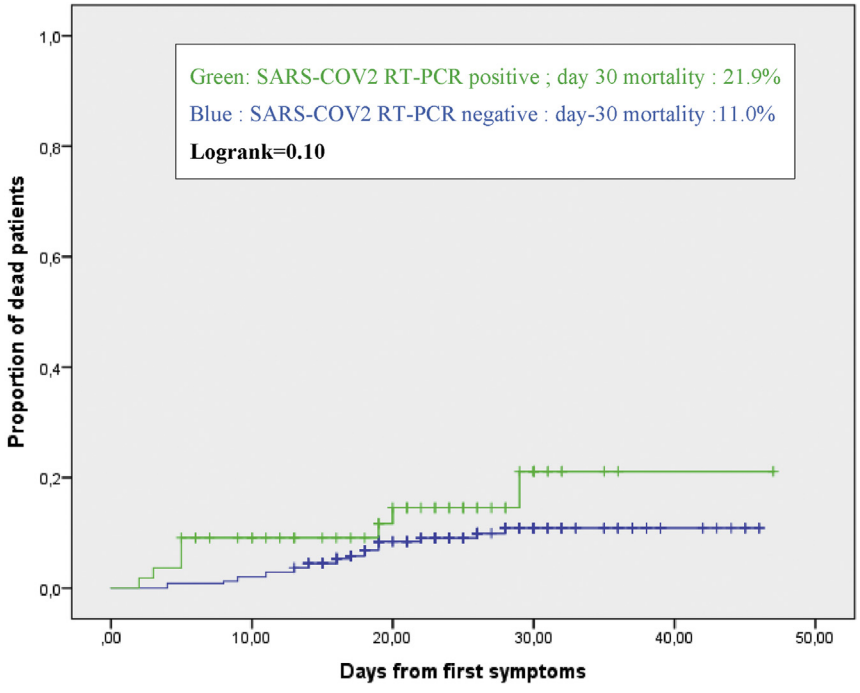

Fig. 1. Survival of SARS-COV-2 RT-PCR–positive and RT-PCR–negative cancer patients with a suspected COVID-19 infection.

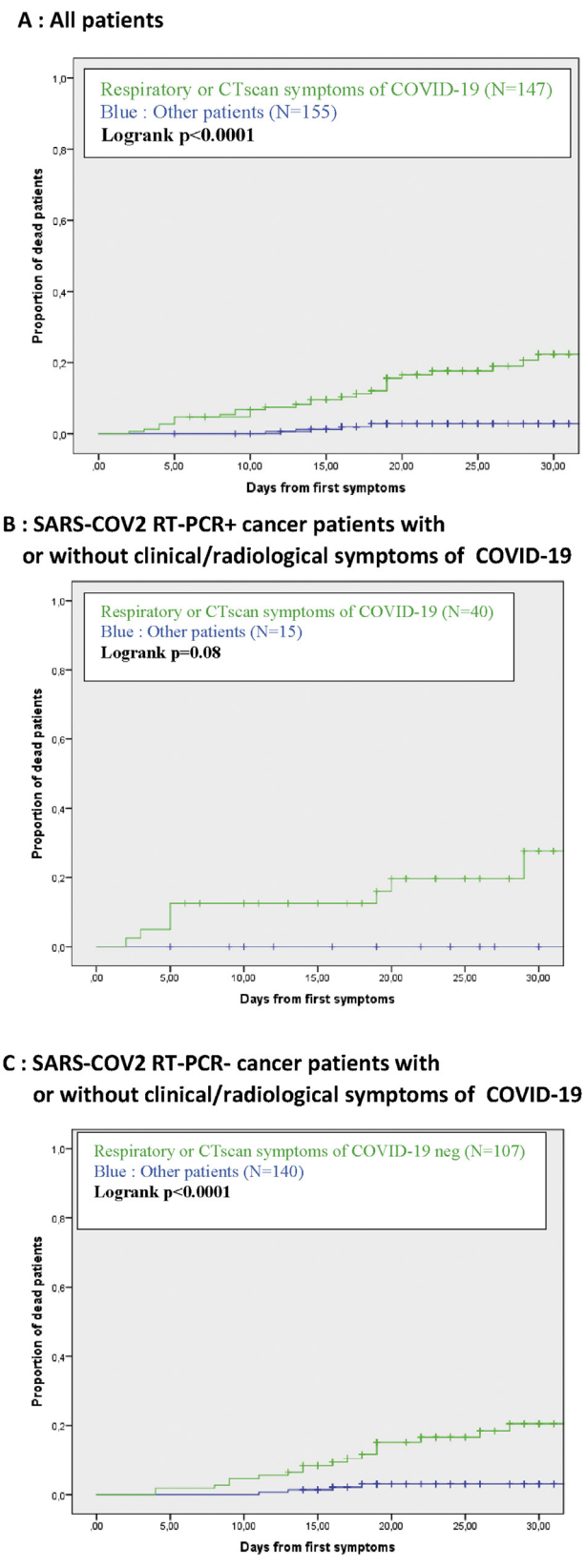

Fig. 2. **Survival of cancer patients consulting for suspected COVID-19 with or without respiratory symptoms.** Patients with respiratory symptoms were defined as patients with at least two of the three following clinical symptoms (fever, dyspnoea and dry cough) and/or typical images of COVID-19 pneumonia on CT scan. A: all patients, B: RT-PCRpositive patients, C: RT-PCR−negative patients. CT, computed tomography.

mTOR inhibitors or antiangiogenic tyrosine kinase inhibitors were not associated with an increased risk of death, neither in the SARS-COV-2 RT-PCR−positive nor in the RT-PCR−negative subgroups (Table 2).

Table 3 shows parameters associated with an increased risk of death in the whole series and in the two SARS-COV-2 RT-PCR−positive and RT-PCR−negative subgroups. Both in the RT-PCR−positive and RT-PCR−negative groups (Table 3), significant risk factors for death in univariate and multivariate analysis were male gender, KPS<60, treatment at relapse and respiratory symptoms (defined as at least two of the three: fever, dry cough, dyspnoea, see patients and methods).

The multivariate analysis of risk factors for death identified these clinical parameters as well as lymphopenia <700/μL as independent risk factors for death, both in the overall population and in the SARS-COV-2 RT-PCR−negative population (Table 3). A multivariate analysis was not performed in the SARS-COV-2 RT-PCR−positive population given the limited sample.

Importantly, the presence of a SARS-COV-2 RT-PCR−positive test was not significantly correlated to the risk of death in the overall population in univariate or multivariate analysis.

In view of these observations, we compared the survival of patients with positive and negative SARS-COV-2 RT-PCR presenting with respiratory symptoms (defined above in patients in methods, i.e. at least two of the following symptoms fever, dry cough, dyspnoea) and/or CT scan images of COVID-19 pneumonia to that of the remaining patients. As shown of Fig. 2, the survival of RT-PCR−positive and −negative patients with respiratory symptoms and/or COVID-19 pneumonia at entry was worse than of other patients. They were also similar in the SARS-COV-2 RT-PCR−negative and −positive subgroups with 18.4% and 19.7% death rate at day 25 after the initial symptoms (Fig. 2). Most of the patients who succumbed during the observation period (22/30, 73%) were negative for SARS-COV-2 on RT-PCR.

4. Discussion

Since January 2020, COVID-19 epidemic has resulted in a very large number of deaths worldwide, in particular in frail patient populations [1−10]. The population of cancer patients has been reported to be particularly at risk of early death during COVID-19, with 30-days death rates up to 39% in the initial report versus 2.3% in the general population [2−5]. Since then, additional series confirmed a high risk of death in cancer patients, which represents one of the highest risk population

Table 3
Prognostic factors for survival.

Characteristics	N	Deaths	Univariate analysis		Multivariate analysis	
		N (%)	HR (95%CI)	p	HR (95%CI)	p
All patients	**302 (100%)**	**30 (10%)**				
Age>60	179	22 (12,2%)	2,01 (1,21–2,81)	0,083		
Male gender	**144**	**21 (14,5%)**	**2,66 (1,90–3,42)**	**0,01**	**2,75 (1,91–3,59)**	**0,019**
KPS < 60	**114**	**20 (17,5%)**	**9,01 (8,07–9,95)**	**< 0,001**	**4,87 (3,87–5,87)**	**0,002**
Relapsing cancer	**177**	**27 (15,2%)**	**6,81 (5,63–7,99)**	**< 0,001**	**3,05 [1,83-4,27]**	**0,073**
Fever & respiratory symptoms	**130**	**25 (19,2%)**	**6,90 (5,94–7,86)**	**< 0,001**	**5,09 (4,11–6,07)**	**0,001**
Lung cancer	42	8 (19,0%)	2,38 [1,58-3,18]	0,03		
Covid-19 suspect CT Scan	59	9 (15,2%)	2,55 (1,63–3,47)	0,051		
SARS-COV2 RT-PCR+	55	8 (14,5%)	1,92 (1,12–2,72)	0,1		
CRP>50	133	22 (16,5%)	3,13 (2,23–4,03)	0,009		
Ly < 700/µL	**91**	**18 (19,7%)**	**4,84 (4,02–5,66)**	**< 0,001**	**3,05 (2,19–3,91)**	**0,05**
SARS-COV2 RT-PCR+ pts	**55 (100%)**	**8 (14%)**				
Age > 60	**40**	**8 (20%)**	**33,9(27,4–40,5)**	**0,026**		
Male gender	**26**	**7 (26,9%)**	**8,19 (6,09–10,3)**	**0,014**		
KPS < 60	**17**	**6 (35,2%)**	**7,7 (6,09–9,31)**	**0,005**		
Fever & respiratory symptoms	**36**	**8 (22,2%)**	**36,9 (30,5–43,3)**	**0,017**		
Lung cancer	7	3 (42,9%)	4,69 [3,24-6,14]	0,16	**ND**	
Covid-19 suspect CT scan	27	7 (25,9%)	0,89 (−0,64–2,42)	0,072		
Relapsing cancer	31	7 (22,5%)	5,29 (3,19–7,39)	0,061		
CRP > 50	**18**	**6 (66,6%)**	**6,87 (4,75–8,99)**	**0,039**		
Ly < 700/µL	**13**	**3 (23,1%)**	**8,98 [6,71-11,3]**	**0,037**		
SARS-COV2 RT-PCR neg. pts	**247**	**22 (8%)**				
Age>60	139	14 (10.1%)	1,4 (0,54–2,26)	0,43		
Male gender	118	14 (11.9%)	1,97 (1,11–2,83)	0,11		
KPS < 60	**97**	**19 (19.6%)**	**10,6 (9,38–11,82)**	**< 0,001**	**6,64 (5,41–7,87)**	**0,003**
Relapsing cancer	**146**	**20 (13.7%)**	**7,5 (6,05–8,95)**	**< 0,001**	**4,26 (2,79–5,73)**	**0,053**
Fever & respiratory symptoms	**94**	**17 (18.1%)**	**5,78 (4,78–6,78)**	**< 0,001**	**4,9 (3,90–5,90)**	**0,002**
Covid-19 suspect CT scan	32	2 (6.2%)	0,89 (−0,64–2,42)	0,87		
CRP>50	115	16 (13.9%)	2,67 (1,67–3,67)	0,05		
Ly < 700/µL	**78**	**15 (19.2%)**	**4,39 [3,49-5,29]**	**0,001**	**2,16 (1,24–3,08)**	**0,09**

HR, hazards ratio; CI, confidence interval; CT, computed tomography; KPS, Karnofsky performance status.

along with elderly patients, patients with overweight, diabetes, hypertensive disease and other associated conditions [1–10]. This death rate of cancer patients is higher to that observed in large series of cancer patient consulting in emergency reported from this and other institutions, most often <5% [14–19]. This death rate is also higher than that reported for seasonal influenza in large historical series (9%) and close to that reported with H1N1 (16%) [20,21].

The description of COVID-19 mortality is further complexified by the limited sensitivity of the diagnostic tests [11–13,22]. Biological diagnostic tests of COVID-19 are based on the detection of the virus using RT-PCR from biological (nasopharyngeal samples) or on the detection of specific antibodies [11–13,22]. Both types of tests have limits in sensitivity, leading to false negative testing in a significant proportion of patients, even in the acute phase of the disease. For RT-PCR, the sensitivity has been reported to be inferior to 40% for the first testing, increasing up to 50% on repeated testing [12]. A large proportion of patients with COVID-19 are therefore not detected by this test, and clinical as well as CT scans symptoms are important to identify COVID-19 patients. Serological test also lack sensitivity, in particular in cancer patients [22].

The objective of the present PRE-ONCOVID-19 study was to analyse the characteristics, symptoms and outcome of the exhaustive population of cancer patients presenting with clinical or radiological symptoms of COVID-19 in this comprehensive cancer centre, from March 1st to April 25th. This study served as the first step to build the prospective multicentre national prospective study open since April 2020 (ONCOVID-19, NCT04363632) investigating in a multicentric setting and in more details the presentation and outcome of cancer patient with documented or suspected COVID-19.

The results obtained in the PRE-ONCOVID-19 study show that only a minority, 18.2% (55/302) cancer patients presenting with clinical symptoms of COVID-19, had demonstrated SARS-COV-2 with RT-PCR performed on nasopharyngeal samples. RT-PCR–positive patients were slightly older, more frequently affected with haematological malignancies and frequently presenting with clinical respiratory symptoms, anosmia/ageusia, diarrhoea and COVID-19 suspect images on CT scan, but these symptoms were also observed in a large proportion of RT-PCR-patients: close to 40% of patients presented with respiratory symptoms and/or CT scan images of COVID-19. Comorbidities (smoking

history, obesity, COPD, diabetes and hypertension) were similar in RT-PCR–positive and –negative patients in the present series.

The biological characteristics of the RT-PCR–positive and RT-PCR–negative patients were also similar: both populations presented similar major lymphopenia and a major inflammatory syndrome with increased CRP levels, and an accurate surrogate of circulating interleukin (IL)-6 levels [22–24] reported to be increased in severe COVID-19 [25,26].

The majority (24/30) of cancer patients who died, in both groups, had a cancer in relapse. This parameter was retained in the multivariate analysis as a risk factor for death with a high hazard ratio in the whole series and in the two subgroups, whereas comorbidities of SARS-COV-2 detection on RT-PCR were not. Indeed, the risk of death of SARS-COV-2 RT-PCR–positive and RT-PCR–negative patients was not found significantly different in this series in univariate or in multivariate analysis. It was high in both subgroups, close to that reported in previous studies for the SARS-COV-2 RT-PCR–positive subgroup [2–5]. It was also found to be high (10% at 30 days) for SARS-COV-2 RT-PCR–negative patients, higher than that of COVID-19 patients in general [1] and also higher than expected from large series of patients with cancer emergencies from the same and other institutions [14–19]. It was conversely close to the mortality reported in cancer patients with seasonal influenza and H1N1 [20,21].

Extreme lymphopenia and increased inflammatory syndrome, as evidenced by high CRP levels, are well known risk factors for early death in cancer [23–25]. Still, the death rate of SARS-COV-2 RT-PCR–negative cancer patients is unusually high in this series. Actually, 22 (73%) of the 30 deaths observed occurred in cancer patients with respiratory symptoms without detected SARS-COV-2 on RT-PCR. These observations strongly suggest an underdiagnosis of COVID-19 in this population of cancer patients and an major underestimation of SARS-COV-2 contribution as a cause of death in cancer patients. The management of cancer patients with febrile respiratory symptoms in this period of epidemic should therefore be particularly careful even in the absence of SARS-COV-2 detection. Dedicated clinical trials for this patient population are ongoing, testing immunotherapies, chloroquine analogues or anti-IL-6 (Immunoncovid-20, NCT04333914).

In conclusion, this retrospective series of cancer patients presenting with suspicion of COVID-19 indicates that the death rate at 30 days after diagnosis is high both in patients with and without documented SARS-COV-2 on RT-PCR, the latter group representing 80% of patients. This subgroup of cancer patients presenting with COVID-19 symptoms without documented SARS-COV-2 gathers also 73%, of the observed deaths at 30 days. Specific therapeutic procedures suggested to improve COVID-19 patient survival, e.g. anti-IL-6 Ab [23,25,27,28], chloroquine analogues [29], remdesivir [30], should be investigated also in this SARS-COV-2–negative cancer patient population presenting with severe symptoms suggestive of COVID-19.

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Conflict of interest statement

The authors declare no conflict of interest.

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