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ADVANCES IN Cancer IMMUNOTHERAPY™

COVID-19 in Cancer Immunotherapy

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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I will NOT be discussing non-FDA approved indications during my presentation

Between Scylla & Charybdis

PERSPECTIVE

BETWEEN SCYLLA AND CHARYBDIS

Between Scylla and Charybdis — Oncologic Decision Making in the Time of Covid-19

Mark A. Lewis, M.D.

"Doctor, should we activate the sepsis protocol?" my medical assistant asked with obvious concern. I triaged the patient in question. The metrics that had caused alarm at intake were tachycardia and tachypnea, but there was no fever or hypotension in this middle-aged woman. On exam, she was indeed breathing quickly and had a rapid, regular pulse, but there were clues beyond the vital signs as to the cause of her distress. Her eyes were as wide as her dilated pupils. Her skin was diaphoretic, and her feet tapped percussively on the tile floor. After some questioning, all evidence pointed to a hyperadrenergic response to extreme anxiety.

I am a medical oncologist. With distressing frequency, I tell people they have cancer, adding a brutal coda for many that their condition is incurable. A consultation with me is often accompanied by the tinnitus of terror — the patient hears the declarative confirmation of malignancy and then nothing else. In my professional capacity, I am used to witnessing primal fear, but I have never seen such widespread panic in my patient population as during the advent of SARS-CoV-2.

As an oncologist, I am also accustomed to framing danger in terms of proportions. In the calculus of difficult judgments, I try to demonstrate to my patients that the well-known side effects of chemotherapy are worth hazarding, presenting a risk–benefit ratio that I hope will not seem unacceptably top-heavy. When administering cytotoxic drugs, I carry in my head a repository of percentages — a 37% chance of neutropenia with a certain combination regimen versus only a 13% chance when a single agent is deployed, for instance — whereas my patients are understandably less empirical. Their choices often stem from their amygdala, their fear center, more than any other part of their brain. And so theirs becomes a relative assessment of threats to their person. In the ledger of horrors, for them to proceed with myelosuppressive treatment, their natural revulsion to "poison" must be superseded by their dread of an unopposed cancer.

Every patient's balance sheet looks different. For some, no chance of therapeutic benefit is too slim to lose its seductiveness, still enticing even when hope for a positive outcome looks razor-thin. In my career I have been astonished at how many patients have been willing to accept nearly inevitable toxicity for the vanishingly small possibility that they will be one of a select few "exceptional responders."

At least, that is, until now. While the worldwide health community grapples with the novel contagion, the starkest end point in the outbreak has been the rising tally of lives claimed by Covid-19. As the deaths have mounted, it has also been common for the case fatality rate to be reported to the public; I have seen many patients under my care struggle to process that grim fraction in the context of all the other statistics I already cite to them. Chemotherapy, hardly desirable at the best of times, may never have been less appealing.

Although this pandemic poses danger in the most global sense, certain subgroups appear particularly vulnerable to critical illness and death. Chinese investigators reported that patients with cancer affected by Covid-19 had a risk of the composite end point of invasive ventilation, admission to the intensive care unit, or death as high as five times that among patients without cancer.[1] Even a remote history of cancer seemed to multiply the risk of severe events, possibly owing to protracted immunodeficiency,[2] although that association may be correlative at best, and the increased risk might be more closely tied to older age.[3] Confounding factors notwithstanding, most people with cancer, in comparing themselves with their healthy peers, perceive themselves as at greater risk from Covid-19, especially if they are actively undergoing therapy.

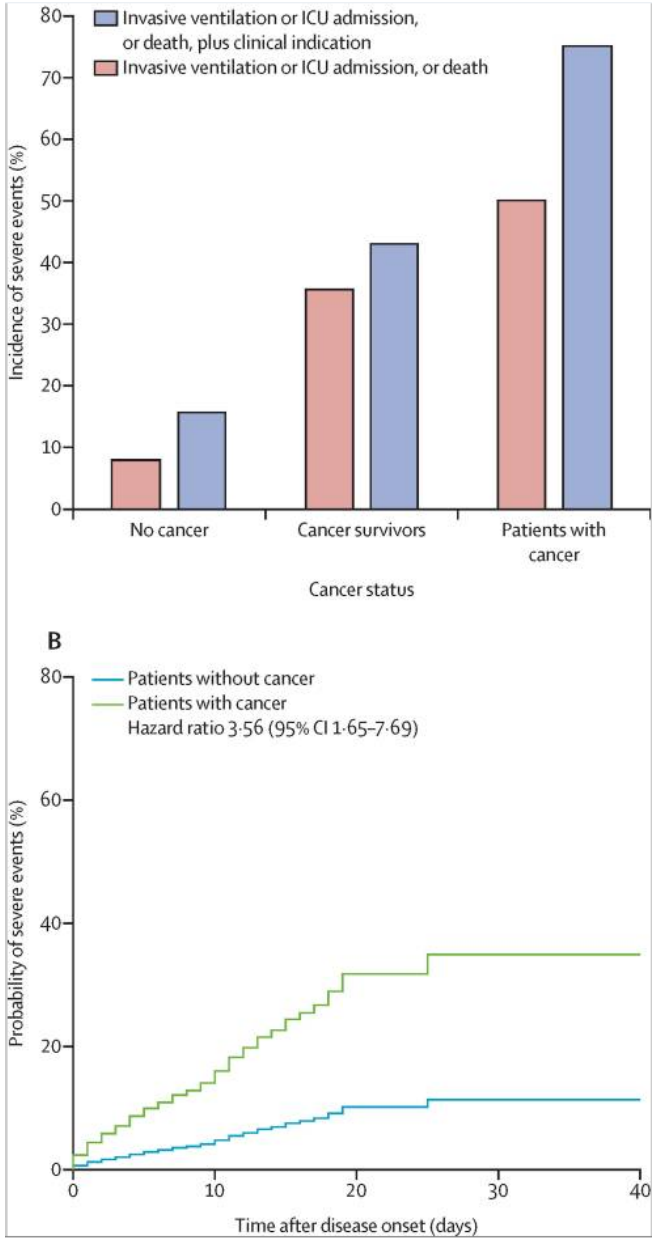
"Are we still friends?" is the half-joking question I have long asked any patient to whom I've administered chemotherapy for the first time. The initial treatment is instructive and clarifying

Lewis MA. Between Scylla and Charybdis. New Engl J Med. 11 Jun 2020.

Navigating the strait

A warning sign

Among patients with cancer, older age was the only risk factor for severe events (OR 1·43, 95% CI 0·97–2·12; p=0·072)



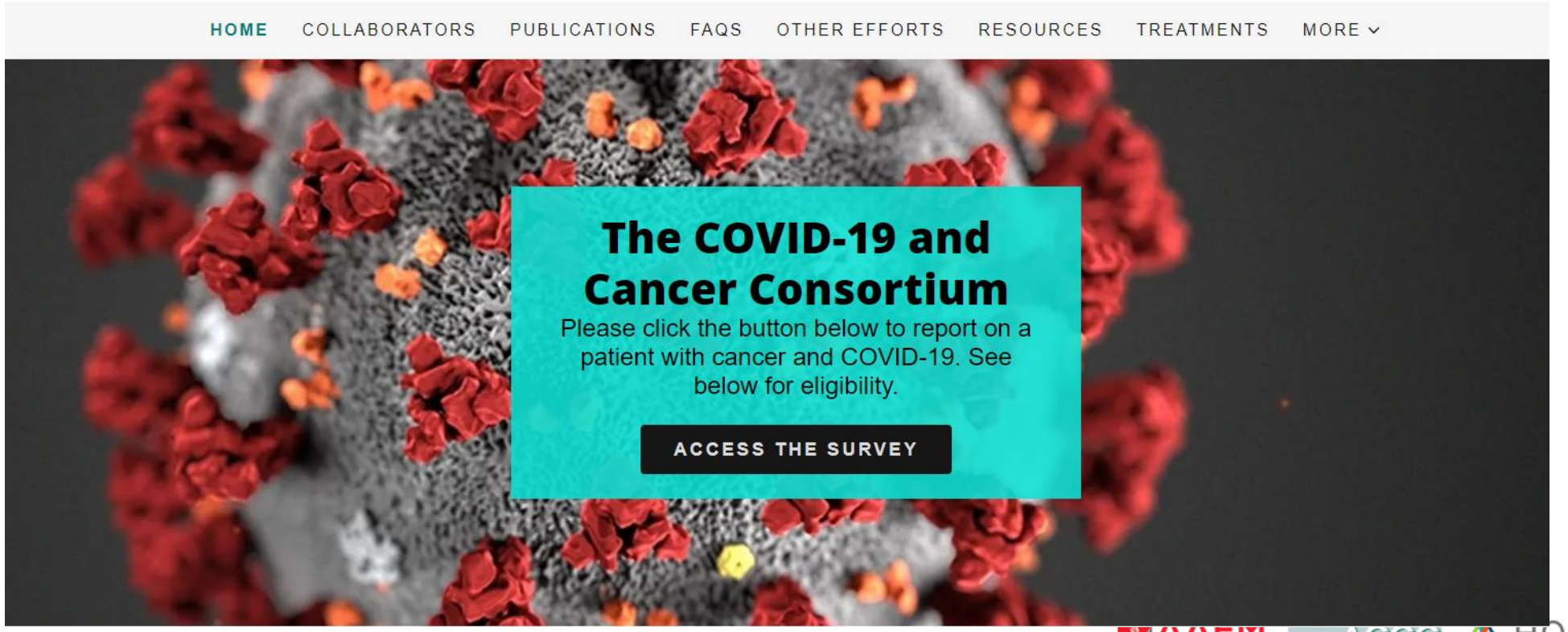
Liang *et al*. Lancet Oncol. 2020 Mar; 21(3): 335–337.

Recommendations as of March 2020:

- First, an intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer should be considered in endemic areas.
- Second, stronger personal protection provisions should be made for patients with cancer or cancer survivors.
- Third, more intensive surveillance or treatment should be considered when patients with cancer are infected with SARS-CoV-2, especially in older patients or those with other comorbidities.

CCC19 consortium

The COVID-19 & Cancer Consortium



ccc19.org

Formation to publication time = <3 months!

Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study

Nicole M Kuderer, Toni K Choueiri*, Dimpy P Shah*, Yu Shyr*, Samuel M Rubinstein, Donna R Rivera, Sanjay Shete, Chih-Yuan Hsu, Aakash Desai, Gilberto de Lima Lopes Jr, Petros Grivas, Corrie A Painter, Solange Peters, Michael A Thompson, Ziad Bakouny, Gerald Batist, Tanios Bekaii-Saab, Mehmet A Bilen, Nathaniel Bouganim, Mateo Bover Larroya, Daniel Castellano, Salvatore A Del Prete, Deborah B Doroshow, Pamela C Egan, Arielle Elkrief, Dimitrios Farmakiotis, Daniel Flora, Matthew D Galsky, Michael J Glover, Elizabeth A Griffiths, Anthony P Gulati, Shilpa Gupta, Navid Hafez, Thorvardur R Halfdanarson, Jessica E Hawley, Emily Hsu, Anup Kasi, Ali R Khaki, Christopher A Lemmon, Colleen Lewis, Barbara Logan, Tyler Masters, Rana R McKay, Ruben A Mesa, Alicia K Morgans, Mary F Mulcahy, Orestis A Panagiotou, Prakash Peddi, Nathan A Pennell, Kerry Reynolds, Lane R Rosen, Rachel Rosovsky, Mary Salazar, Andrew Schmidt, Sumit A Shah, Justin A Shaya, John Steinharter, Keith E Stockerl-Goldstein, Suki Subbiah, Donald C Vinh, Firas H Wehbe, Lisa B Weissmann, Julie Tsu-Yu Wu, Elizabeth Wulff-Burchfield, Zhuoer Xie, Albert Yeh, Peter P Yu, Alice Y Zhou, Leyre Zubiri, Sanjay Mishra, Gary H Lyman*, Brian I Rini*, Jeremy L Warner*, on behalf of the COVID-19 and Cancer Consortium*

Summary

Background Data on patients with COVID-19 who have cancer are lacking. Here we characterise the outcomes of a cohort of patients with cancer and COVID-19 and identify potential prognostic factors for mortality and severe illness.

Methods In this cohort study, we collected de-identified data on patients with active or previous malignancy, aged 18 years and older, with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from the USA, Canada, and Spain from the COVID-19 and Cancer Consortium (CCC19) database for whom baseline data were added between March 17 and April 16, 2020. We collected data on baseline clinical conditions, medications, cancer diagnosis and treatment, and COVID-19 disease course. The primary endpoint was all-cause mortality within 30 days of diagnosis of COVID-19. We assessed the association between the outcome and potential prognostic variables using logistic regression analyses, partially adjusted for age, sex, smoking status, and obesity. This study is registered with ClinicalTrials.gov, NCT04354701, and is ongoing.

Findings Of 1035 records entered into the CCC19 database during the study period, 928 patients met inclusion criteria for our analysis. Median age was 66 years (IQR 57–76), 279 (30%) were aged 75 years or older, and 468 (50%) patients were male. The most prevalent malignancies were breast (191 [21%]) and prostate (152 [16%]). 366 (39%) patients were on active anticancer treatment, and 396 (43%) had active (measurable) cancer. At analysis (May 7, 2020), 121 (13%) patients had died. In logistic regression analysis, independent factors associated with increased 30-day mortality, after partial adjustment, were: increased age (per 10 years; partially adjusted odds ratio 1·84, 95% CI 1·53–2·21), male sex (1·63, 1·07–2·48), smoking status (former smoker *vs* never smoked: 1·60, 1·03–2·47), number of comorbidities (two *vs* none: 4·50, 1·33–15·28), Eastern Cooperative Oncology Group performance status of 2 or higher (status of 2 *vs* 0 or 1: 3·89, 2·11–7·18), active cancer (progressing *vs* remission: 5·20, 2·77–9·77), and receipt of azithromycin plus hydroxychloroquine (*vs* treatment with neither: 2·93, 1·79–4·79; confounding by indication cannot be excluded). Compared with residence in the US-Northeast, residence in Canada (0·24, 0·07–0·84) or the US-Midwest (0·50, 0·28–0·90) were associated with decreased 30-day all-cause mortality. Race and ethnicity, obesity status, cancer type, type of anticancer therapy, and recent surgery were not associated with mortality.

Interpretation Among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general risk factors and risk factors unique to patients with cancer. Longer follow-up is needed to better understand the effect of COVID-19 on outcomes in patients with cancer, including the ability to continue specific cancer treatments.

Funding American Cancer Society, National Institutes of Health, and Hope Foundation for Cancer Research.

Lancet 2020 Jun 20;395(10241):1907-1918. Epub 2020 May 28.

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Table 1 from CCC19:

Median age = 66
Preponderance of solid tumors
Majority not on treatment in 4 weeks before COVID dx

	Analysable population (n=928)
Age, years*	
Median	66 (57–76)
Range	18 to >90
<65	412 (44%)
65–74	237 (26%)
≥75	279 (30%)
Sex	
Female	459 (49%)
Male	468 (50%)
Not specified	1 (<1%)
Race and ethnicity†	
Non-Hispanic white	460 (50%)
Non-Hispanic black	148 (16%)
Hispanic	150 (16%)
Other or unknown	128 (14%)
Data missing	42 (5%)
Region of patient residence‡	
US-Northeast	375 (40%)
US-Midwest	203 (22%)
US-South	117 (13%)
US-West	116 (13%)
Canada	49 (5%)
Spain	68 (7%)
Smoking status†	
Never smoked	469 (51%)
Former smoker	326 (35%)
Current smoker	43 (5%)
Unknown	57 (6%)
Data missing	33 (4%)
Obesity status†	
Not specified	720 (78%)
Obese	172 (19%)
Data missing	36 (4%)
Number of comorbidities†	
0	132 (14%)
1	202 (22%)
2	231 (25%)
3	117 (13%)
≥4	192 (21%)
Unknown	23 (2%)
Data missing	31 (3%)
Type of malignancy§	
Solid tumours	758 (82%)
Breast	191 (21%)
Prostate	152 (16%)
Gastrointestinal	108 (12%)
Thoracic	91 (10%)
Gynaecological	49 (5%)
Renal cell carcinoma	45 (5%)
Endocrine	39 (4%)
Melanoma	38 (4%)

	Analysable population (n=928)
(Continued from previous column)	
Head and neck	30 (3%)
Sarcoma	24 (3%)
Nervous system	12 (1%)
Solid tumour, not otherwise specified	43 (5%)
Haematological malignancies	204 (22%)
Lymphoid neoplasms	102 (11%)
Multiple myeloma	55 (6%)
Low-grade non-Hodgkin lymphoma	54 (6%)
Myeloid neoplasms	42 (5%)
High-grade non-Hodgkin lymphoma	27 (3%)
Acute myeloid leukaemia	13 (1%)
Acute lymphoblastic leukaemia	6 (1%)
Haematological malignancy, not otherwise specified	6 (1%)
Cancer status†	
Remission or no evidence of disease	422 (45%)
Present, stable, or responding to treatment	294 (32%)
Present, progressive disease	102 (11%)
Unknown	59 (6%)
Data missing	51 (5%)
ECOG performance status†	
0 or 1	614 (66%)
2	72 (8%)
3 or 4	46 (5%)
Unknown	167 (18%)
Data missing	29 (3%)
Type of anticancer therapy§	
None in the 4 weeks before COVID-19 diagnosis	553 (60%)
Non-cytotoxic therapy	206 (22%)
Targeted therapy	75 (8%)
Endocrine	85 (9%)
Immunotherapy¶	38 (4%)
Radiotherapy	12 (1%)
Surgery‖	2 (<1%)
Cytotoxic systemic therapy	160 (17%)
Unknown	9 (1%)
Recent surgery†	
None in the 4 weeks before COVID-19 diagnosis	811 (87%)
Yes‖	32 (3%)
Unknown	42 (5%)
Data missing	43 (5%)

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Endpoints from CCC19:

The primary endpoint was all-cause mortality within 30 days of diagnosis of COVID-19.

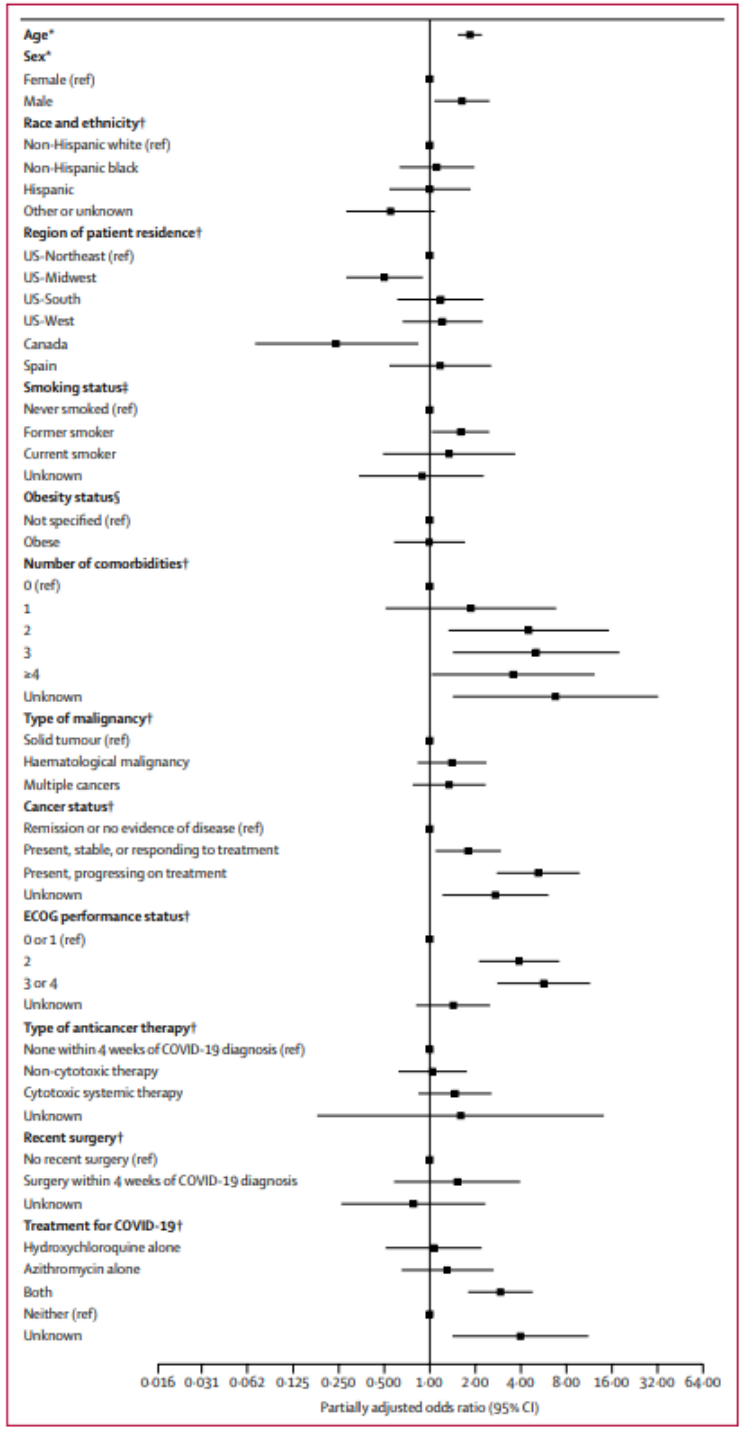
Secondary outcomes were: a composite of severe illness (death, severe illness requiring admission to hospital, admission to an intensive care unit [ICU], mechanical ventilation, or a combination of these); admission to hospital; admission to an ICU; mechanical ventilation; and need for supplemental oxygen during the course of COVID-19.

	Died	Met composite endpoint	Admitted to an ICU	Required mechanical ventilation
(Continued from previous page)				
Cancer status				
Remission or no evidence of disease (n=422)	39 (9%)	95 (23%)	63 (15%)	55 (13%)
Present, stable, or responding to treatment (n=294)	41 (14%)	80 (27%)	40 (14%)	38 (13%)
Present, progressive disease (n=102)	25 (25%)	36 (35%)	12 (12%)	11 (11%)
Unknown (n=59)	11 (19%)	23 (39%)	14 (24%)	11 (19%)
Data missing (n=51)	5 (10%)	8 (16%)	3 (6%)	1 (2%)
ECOG performance status				
0 or 1 (n=614)	54 (9%)	135 (22%)	81 (13%)	81 (13%)
2 (n=72)	23 (32%)	31 (43%)	16 (22%)	8 (11%)
3 or 4 (n=46)	19 (41%)	22 (48%)	6 (13%)	5 (11%)
Unknown (n=167)	22 (13%)	51 (31%)	28 (17%)	21 (13%)
Data missing (n=29)	3 (10%)	3 (10%)	1 (3%)	1 (3%)
Type of anticancer therapy				
None in the 4 weeks before COVID-19 diagnosis (n=553)	75 (14%)	156 (28%)	91 (16%)	79 (14%)
Non-cytotoxic therapy (n=206)	23 (11%)	50 (24%)	24 (12%)	24 (12%)
Cytotoxic systemic therapy (n=160)	22 (14%)	35 (22%)	17 (11%)	12 (8%)
Unknown (n=9)	1 (11%)	1 (11%)	0	1 (11%)
Recent surgery				
None in the 4 weeks before COVID-19 diagnosis (n=811)	108 (13%)	212 (26%)	118 (15%)	104 (13%)
Yes (n=32)	6 (19%)	12 (38%)	6 (19%)	7 (22%)
Unknown (n=42)	4 (10%)	14 (33%)	6 (14%)	3 (7%)
Data missing (n=43)	3 (7%)	4 (9%)	2 (5%)	2 (5%)
Treatment of COVID-19				
Hydroxychloroquine alone (n=89)	11 (12%)	32 (36%)	18 (20%)	14 (16%)
Azithromycin alone (n=93)	12 (13%)	26 (28%)	15 (16%)	14 (15%)
Azithromycin plus hydroxychloroquine (n=181)	45 (25%)	86 (48%)	53 (29%)	51 (28%)
Neither (n=486)	41 (8%)	80 (16%)	39 (8%)	29 (6%)
Unknown (n=22)	7 (32%)	8 (36%)	2 (9%)	4 (18%)
Data missing (n=57)	5 (9%)	10 (18%)	5 (9%)	4 (7%)

Data are n (%). Due to rounding, not all variables might add up to 100%. The composite endpoint was a combination of death, severe illness requiring admission to hospital, admission to an ICU, or mechanical ventilation. ECOG=Eastern Cooperative Oncology Group. ICU=intensive care unit. *Data not shown for one patient, with sex not specified. †US regions are census-tract defined. ‡Any patient with two or more cancers reported, which could be solid, haematological, or both.

Forest plot of factors associated with 30-day mortality in CCC19:

"In our cohort, patients with progressive cancer died at a numerically higher rate without ICU admission than among those who were admitted to an ICU, and the reverse pattern was seen for patients in remission. This finding, and the numerically higher rate of deaths without ICU admission in patients aged 75 years and older and those receiving treatment with palliative intent, suggests that aggressive interventions might have already been reduced in these subpopulations."



Post hoc analysis of CCC19:

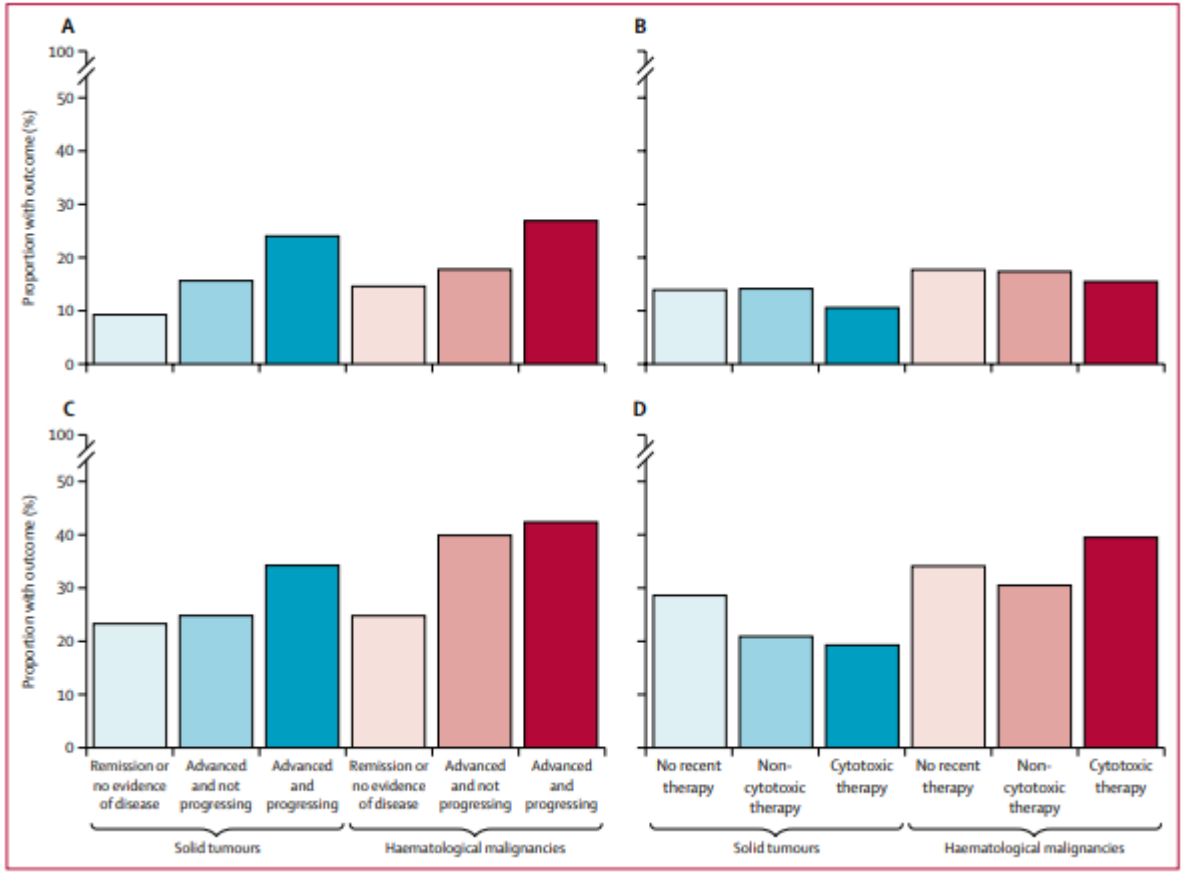
The following factors were associated with an increased rate of the composite outcome:

- Increasing age
- Number of comorbidities
- Hematological malignancy
- Progressing cancer or unknown cancer status
- ECOG performance status of 2 or higher
- Treatment with azithromycin, hydroxychloroquine, or both

CCC19 conclusions

Patients with cancer appear to be at increased risk of mortality and severe illness due to SARS-CoV-2 infection, regardless of whether they have active cancer, are on anticancer treatment, or both.

"Most members of our cohort had symptoms compatible with COVID-19, and the overall rate of complications was high."



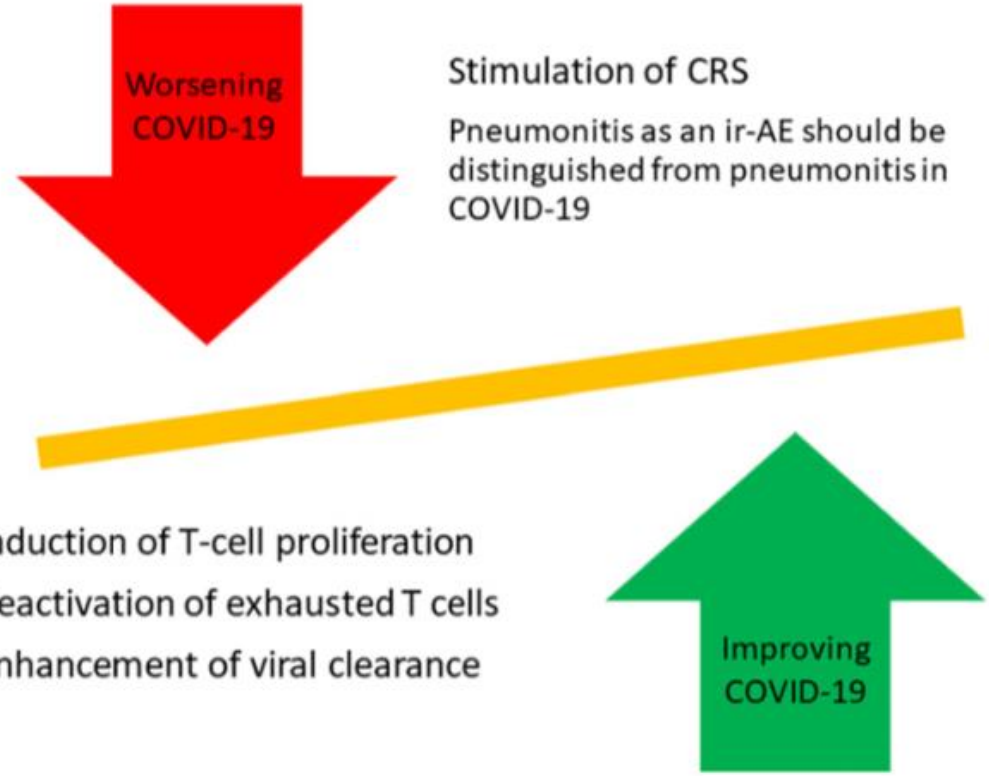
IO in COVID-19: the past as prologue?

- Patients with chronic viral infections were conventionally excluded from trials of immunotherapy due to concern for exacerbation/reactivation
- However, in a systematic review[1] on 73 cancer patients infected with HIV, fewer than 10% of patients experienced grade III or higher irAEs
- In more than 90% of patients, HIV was suppressed and CD4+ cell count was improved; moreover, the efficacy of ICI in these patients was reported to be acceptable
- *Post hoc* ASCO recommended[2] enrolling HIV patients with CD4+ counts > 350 cells/µL in clinical trials of anti-cancer therapy, including IO studies

[1]Cook MR, Kim C. Safety and Efficacy of Immune Checkpoint Inhibitor Therapy in Patients With HIV Infection and Advanced-Stage Cancer: A Systematic Review. JAMA Oncol. 2019 Jul 1;5(7):1049-1054.
[2]Uldrick TS, Ison G, Rudek MA, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research HIV Working Group. J Clin Oncol. 2017 Nov 20;35(33):3774-3780.

IO in COVID-19: risk vs. benefit?

- By interfering with the transduction of inhibitory signals through PD-1/PD-L1 or CTLA-4 or other inhibitory receptors, ICI can improve the number and function of T cells in patients with COVID- 19 and subsequently enhance the rate of viral clearance by T cells
- However, there is still a probability of inflammatory cytokine release exacerbation by reactivation of the exhausted T cells in the immune system



Pezeshki PS & Rezaei N. Immune Checkpoint Inhibition in COVID-19: Risks and Benefits. Expert Opinion on Biological Therapy, DOI: 10.1080/14712598.2021.1887131

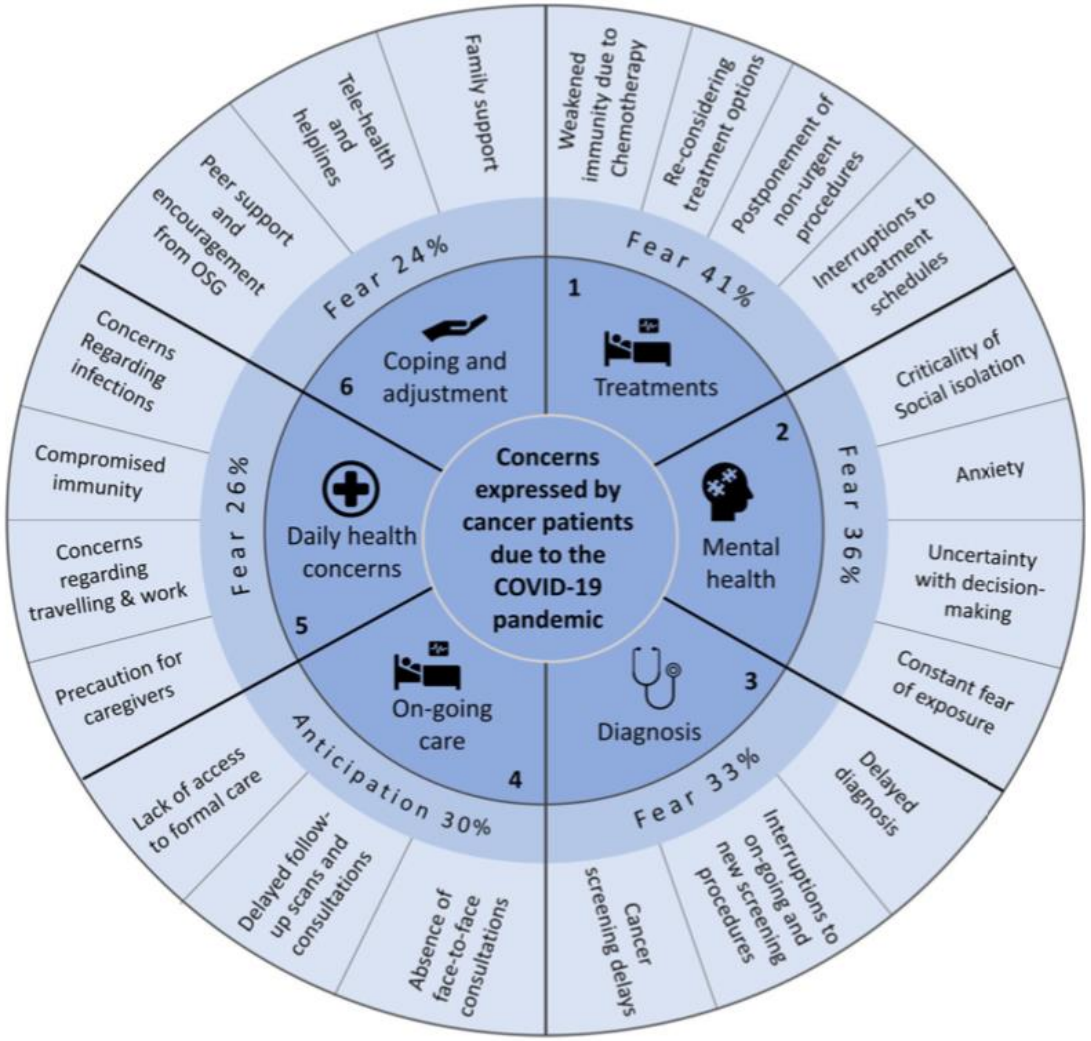
Impact on patients

Abstract

The lockdown measures of the ongoing COVID-19 pandemic have disengaged patients with cancer from formal health care settings, leading to an increased use of social media platforms to address unmet needs and expectations. Although remote health technologies have addressed some of the medical needs, the emotional and mental well-being of these patients remain underexplored and underreported. We used a validated artificial intelligence framework to conduct a comprehensive real-time analysis of two data sets of 2,469,822 tweets and 21,800 discussions by patients with cancer during this pandemic. Lung and breast cancer are most prominently discussed, and the most concerns were expressed regarding delayed diagnosis, cancellations, missed treatments, and weakened immunity. All patients expressed significant negative sentiment, with fear being the predominant emotion. Even as some lockdown measures ease, it is crucial that patients with cancer are engaged using social media platforms for real-time identification of issues and the provision of informational and emotional support. *The Oncologist* 2021;26:e342–e344

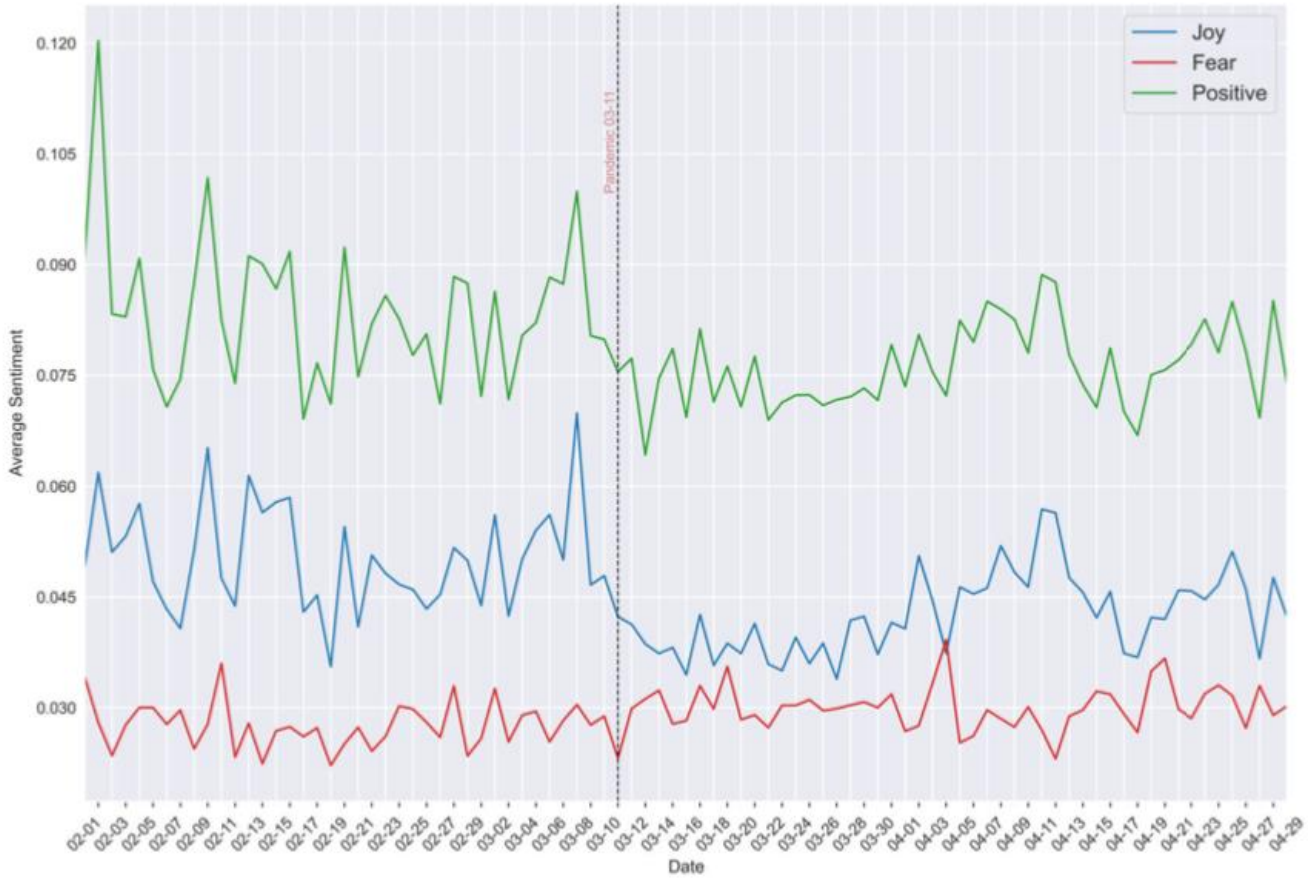
Moraliyage H, De Silva D, Ranasinghe W, Adikari A, Alahakoon D, Prasad R, Lawrentschuk N, Bolton D. Cancer in Lockdown: Impact of the COVID-19 Pandemic on Patients With Cancer. The Oncologist. 2021;26:e342–e344

A fearful sunburst



Moraliyage H, De Silva D, Ranasinghe W, Adikari A, Alahakoon D, Prasad R, Lawrentschuk N, Bolton D. Cancer in Lockdown: Impact of the COVID-19 Pandemic on Patients With Cancer. The Oncologist . 2021;26:e342–e344

Trading joy for fear



Moraliyage H, De Silva D, Ranasinghe W, Adikari A, Alahakoon D, Prasad R, Lawrentschuk N, Bolton D. Cancer in Lockdown: Impact of the COVID-19 Pandemic on Patients With Cancer. The Oncologist. 2021;26:e342–e344

A parting thought

We should admit, first to ourselves and then to our patients, the limitations of our gaze. In fact, in confessing our lack of prescience, we can begin to understand our patients' own precarious state. The best prognostic models available to us are still vulnerable to stochastic events. When we critically assess the evidence that guides our management, we apply the rigor of statistics and discard underpowered studies as insufficiently robust, but each individual patient with cancer partakes in an ongoing, irreproducible experiment where n = 1. A median overall survival measured in years does not preclude an unfortunate outlier from dying within weeks, and it is impossible to foresee each person's point on the probabilistic curve. But no matter how much time remains, and whether the goal of care is cure, control, or comfort, we can tell our patients with absolute certainty that we will not abandon them to the unknown.

Lewis MA. Gain of Function: Empathy for the Uncertain Patient with Cancer. J Clin Oncol. 4 Apr 2011.

Thank you!

I welcome questions or comments at:

Email at Mark.Lewis2@imail.org

or

Tweet @marklewismd