Morning Brief : Scientific Review

03 June 2020

The purpose of the Morning Brief is to summarize and present key information, research articles and other relevant publications pertaining to critical care and COVID-19.

Stellenbosch University Research Response Team

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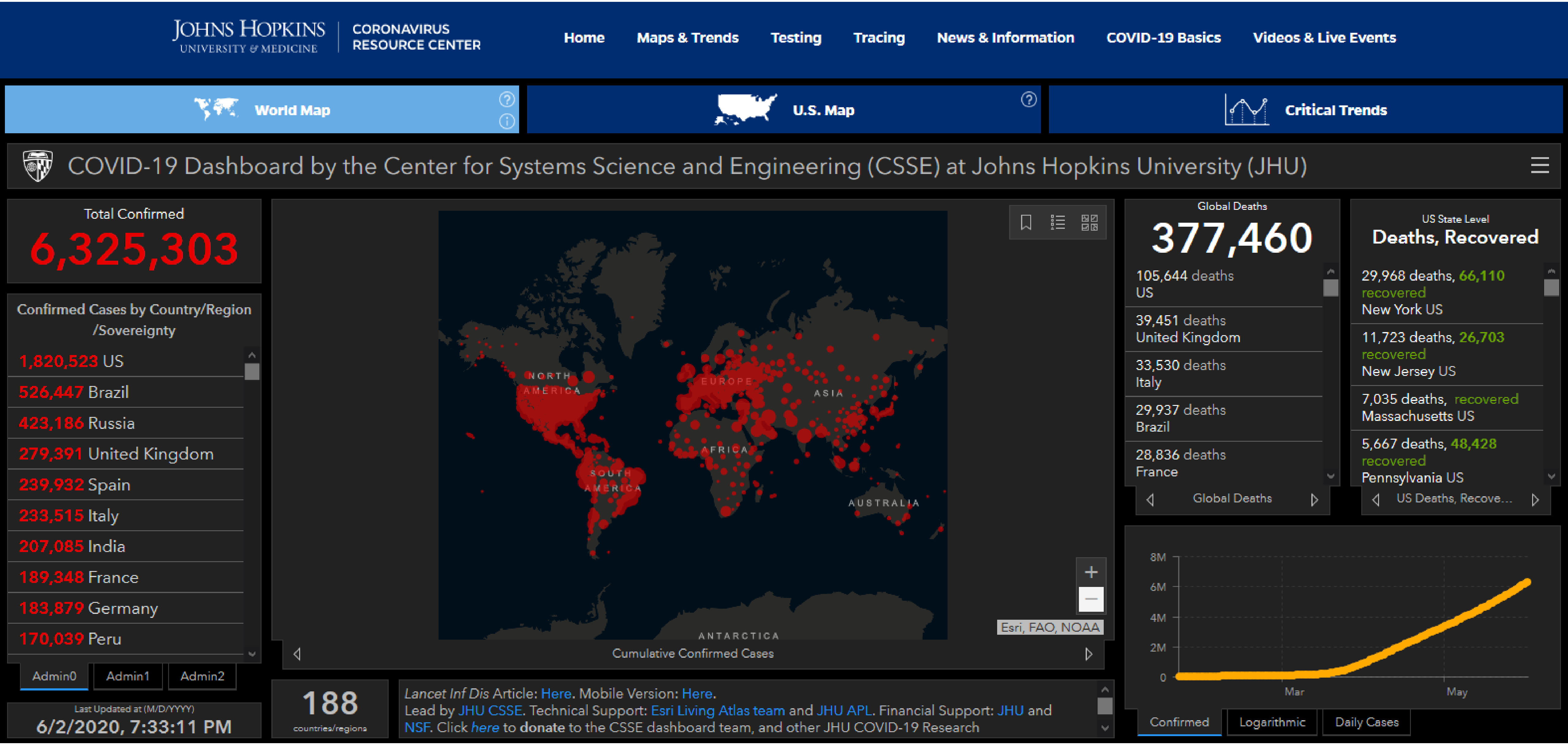
Content of the brief

- Global Statistics
- South African Statistics
- Topics:
  - Brief reports



Source: https://coronavirus.jhu.edu/map.html

South African Statistics

Sources: https://sacoronavirus.co.za

Articles of Interest

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Anakinra for severe forms of COVID-19: a cohort study

Thomas Huet, Hélène Beaussier, Olivier Voisin, Stéphane Jouveshomme, Gaëlle Dauriat, Isabelle Lazareth, Emmanuelle Sacco, Jean-Marc Naccache, Yvonnick Bézie, Sophie Laplanche, Alice Le Berre, Jérôme Le Pavec, Sergio Salmeron, Joseph Emmerich, Jean-Jacques Mourad, Gilles Chatellier, Gilles Hayem

- SARS-CoV-2 cytokine storm involves pro-inflammatory interleukins (IL-1β and IL-6) and tumour necrosis factor. IL-1β is a mediator of fever, lung inflammation, and fibrosis
- Anakinra is a human IL-1 receptor antagonist with a good safety profile
- Anakinra was found to have some beneficial effects in severe sepsis, but only in the subgroup of patients with multiple organ dysfunction syndrome, in which the inflammasome pathway is involved

Hypothesis:

Anakinra could represent an efficient treatment for severe forms of COVID-19, predominantly involving the inflammasome pathway

Aim:

To assess the off-label use of anakinra in patients who were admitted to hospital for severe COVID-19 with symptoms indicative of worsening respiratory function

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Methods

A prospective cohort of patients who received anakinra and a historical comparison group who received standard of care

- Inclusion criteria:
  - Aged older than 18 years, with severe COVID-19-related bilateral pneumonia
  - SARS-CoV-2 infection confirmed by either a positive result from an RT-PCR assay or a typical aspect on CT scan of the lungs (multiple ground-glass abnormalities with crazy paving, absence of lymphadenopathy, and pulmonary nodules)
  - Bilateral lung infiltrates on a lung CT scan or chest x-ray
  - Oxygen saturation of 93% or less under 6 L/min of oxygen or more; or oxygen saturation of less than 93% on 3 L/min with a saturation on ambient air decreasing by 3% in the previous 24 h

- Exclusion criteria:
  - Refusal of the patient to participate
  - Patients who were bedridden and near the end of life
  - Patients with respiratory failure explained by an alternative aetiology, and patients already admitted to the ICU

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Methods

- Anakinra dose:
  - Subcutaneous anakinra 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days, in addition to the standard treatment and supportive care
  - Renal patients (on dialysis or GFR < 30 mL/min) – 100 mg daily for 72 hours followed by 100 mg every alternate day for 7 days

- Standard treatment
  - Oral HCQ 600 mg/day for 10 days, oral AZM 250 mg/day for 5 days, and intravenous ceftriaxone 1 g per day or intravenous amoxicillin 3 g per day for 7 days
  - Some patients received an IV bolus of methylprednisolone (500 mg)

- Supportive care
  - Included low-flow oxygen therapy (≤6 L/min through low-flow nasal cannula) or high-flow oxygen therapy (>6 L/min with high-flow nasal cannula or face mask)

None of the patients had invasive or non-invasive mechanical ventilation at baseline

Methods

Sample size calculated at 50 patients per group for 86% power to detect a 50% risk reduction of the primary endpoint, at significance level α=0.05, assuming a 60% incidence of the primary endpoint

- Primary outcome
    - The composite of either need for admission to the ICU with invasive mechanical ventilation or death

- Secondary outcomes
    - Death
    - Need for invasive mechanical ventilation,
    - Difference in the mean oxygen therapy requirements between day 0 and day 7
    - Changes in CRP concentration from day -4 until discharge from hospital or death

- Safety outcomes
    - Increase in liver aminotransferase enzymes
    - Thromboembolic events
    - Bacteraemia
    - Premature discontinuation of treatment

52 consecutive patients were included in the anakinra group and 44 historical patients were identified in the Groupe Hospitalier Paris Saint-Joseph COVID cohort study

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Results

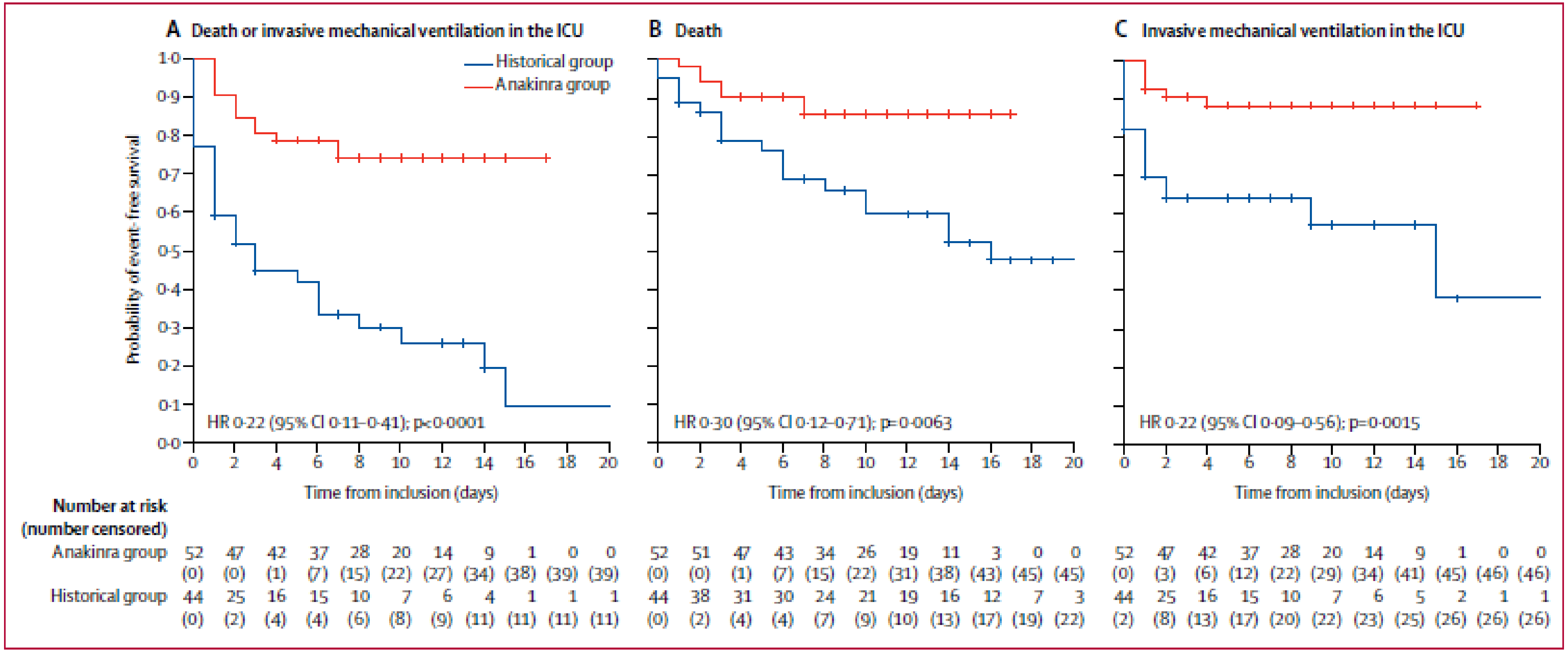

Figure 1: Kaplan-Meier cumulative estimates of probability of death or invasive mechanical ventilation in the ICU (A), death (B) and invasive mechanical ventilation in the ICU (C) in the anakinra group compared with the historical group

HR=hazard ratio. ICU=intensive care unit.

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Results

<u>Significant differences between the two cohorts</u>

- Lower BMI (mean difference –3.5 kg/m^2 [95% CI –5.5 to –1.5]; p=0.0009) and longer duration of symptoms before inclusion (2.2 days [0.6 to 3.9]; p=0.0088) in the anakinra group

	Hazard ratio	95% CI	p value
Anakinra group vs historical group	0·22	0·10–0·49	0·0002
Male vs female	1·34	0·69–2·62	0·38
Symptom duration >7 days vs ≤7 days	1·12	0·51–2·43	0·78
Body-mass index (per kg/m²)	0·99	0·94–1·05	0·75
Number of comorbidities ≥2 vs 0–1	0·82	0·41–1·66	0·58
Hydroxychloroquine: treated vs untreated	1·35	0·57–3·17	0·50
Azithromycin: treated vs untreated	0·82	0·34–1·99	0·66

ICU=intensive care unit.

Table 2: Estimation of anakinra effect on the composite of invasive mechanical ventilation in the ICU or death, after adjustment for potential confounding factors, using a multivariable Cox proportional hazards model

- Higher proportion of patients treated with HCQ (29% [12 to 45]; p=0.0007) and AZM (17% [3 to 32]; p=0.015) in the anakinra group than in the historical group
- Higher platelet count in the anakinra group (58 × 10^9 cells per L [16 to 99]; p=0.0071)

Safety

- 13% in the anakinra group and 9% in the historical group had an increase in liver aminotransferase (> 3x ULN)
- 19% in the anakinra group and 11% in the historical group developed a thromboembolic event during the hospital stay

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Conclusion and limitations

Conclusion: *In severe forms of COVID-19-related pneumonia requiring oxygen therapy, a 10-day treatment with subcutaneous anakinra was associated with the reduction of both need of mechanical ventilation and mortality*

- Limitations
  - Historical group differed from the anakinra group for several potentially confounding variables
  - Historical group had a greater percentage of patients with obesity and slightly higher percentage of patients with co-morbidities
  - Greater percentage of patients on HCQ and azithromycin in the anakinra group
  - Not a randomized control trial
  - Sample size of the prospective cohort study was arbitrarily set at 50 patients in the absence of information on treatment effect

COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study

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Lennard Y W Lee*, Jean Baptiste Cazier*, T Starkey, C D Turnbull, UK Coronavirus Cancer Monitoring Project Team, Rachel Kerr†, Gary Middleton†

- Introduction
  - Patients with cancer receiving systemic anticancer treatments have been assumed to be at a higher risk of SARS-CoV-2 than their counterparts are who are not receiving anticancer treatment
  - This hypothesis led to widespread global changes to patterns of prescribing chemotherapy and anticancer treatment
  - UK Coronavirus Cancer Monitoring Project (UKCCMP) generated the largest prospective database of COVID-19 in patients with cancer

Aim: To describe the clinical and demographic characteristics and COVID-19 outcomes in this cohort of patients with cancer and symptomatic COVID-19, and attempted to assess how the presence of cancer and the receipt of cytotoxic chemotherapy and other anticancer treatments affects the COVID-19 disease phenotype

Methods

- UKCCMP database was used to generate information on 800 patients from 55 cancer sites
- Inclusion:
  - Patients with a positive COVID-19 RT-PCR assay test
- *Active cancer* defined as, those with metastatic cancer, or on anticancer treatment in any setting (curative, radical, adjuvant, or neoadjuvant setting) or treated within the past 12 months with surgery cytotoxic chemotherapy, or radiotherapy
- Outcomes:
  - Assessed whether the patient died or eventually achieved discharge, and observed the effect of anticancer treatment on outcomes

A *primary endpoint of all-cause mortality* was defined a priori. This definition included deaths described as related to COVID-19 during admission, as well as deaths reported as a consequence of any other cause during admission, such as due to cancer progression or treatment toxicity

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Results

Adjustment for clinically relevant potential confounders of age, gender, diabetes, hypertension, chronic obstructive pulmonary disease, or other comorbidities at admission

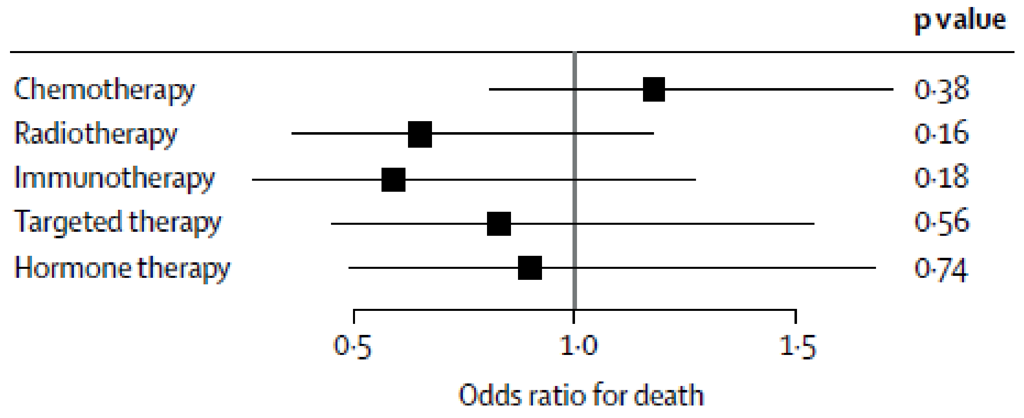

***Figure 4*: Forest plots showing effect of anticancer treatments and mortality from COVID-19**

Odds ratios were adjusted for age, gender, and comorbidities. Whiskers indicated 95% CI.

	Odds ratio (95% CI)	p value	Adjusted p value
Cancer treatment within 4 weeks of COVID-19 diagnosis			
Chemotherapy	0·78 (0·55–1·11)	0·173	1·000
Hormone therapy	1·16 (0·64–2·06)	0·659	1·000
Immunotherapy	0·60 (0·27–1·24)	0·179	1·000
Radiotherapy	0·66 (0·37–1·17)	0·178	1·000
Surgery	0·83 (0·32–2·15)	0·825	1·000
Targeted treatment	0·56 (0·30–1·01)	0·058	0·525

	Odds ratio (95% CI)	p value
Anticancer treatment within 4 weeks of COVID-19 diagnosis		
Chemotherapy vs no chemotherapy	1·18 (0·81–1·72)	0·380
Hormone therapy vs no hormone therapy	0·90 (0·49–1·68)	0·744
Immunotherapy vs no Immunotherapy	0·59 (0·27–1·27)	0·177
Radiotherapy vs no radiotherapy	0·65 (0·36–1·18)	0·159
Targeted treatment vs no targeted treatment	0·83 (0·45–1·54)	0·559
Cytotoxic chemotherapy		
Non-palliative chemo vs palliative chemo	0·40 (0·17–0·96)	0·040
Palliative first-line chemotherapy vs other line	0·84 (0·36–1·98)	0·690
Palliative chemotherapy vs no chemotherapy	1·48 (0·93–2·36)	0·102
Palliative chemotherapy vs no treatment	1·05 (0·63–1·76)	0·854

Multivariate analysis was done correcting for age, sex, and patient comorbidities.

***Table 3*: Multivariate regression analysis and odds of death based recent anticancer treatment in patients in the UK Coronavirus Cancer Monitoring Project**

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Conclusion and Limitations

Study concluded that withholding effective cancer treatments from many cancer patients during the pandemic runs the very real risk of increasing cancer morbidity and mortality, perhaps much more so than COVID-19 itself

Limitations:

- A retrospective review of cases
- Only UK data presented and COVID-19 testing policy is less permissive in the UK than that of other nations
- Project might therefore, under-report total COVID-19 cases in patients with cancer
- A selection bias might exist, in that those patients who were not on chemotherapy might have stopped chemotherapy because of a poor performance status, thus increasing the risk of death from COVID-19 disease

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References

1. Huet, T. *et al.* (2020) ‘Anakinra for severe forms of COVID-19: a cohort study’, *The Lancet Rheumatology*, 9913(20), pp. 1–8. doi: 10.1016/S2665-9913(20)30164-8.
2. Lee, L. Y. W. *et al.* (2020) ‘COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study’, *The Lancet*. Elsevier Ltd, 6736(20). doi: 10.1016/S0140-6736(20)31173-9.

This summary was prepared by Dr Veshni Pillay-Fuentes as part of the daily brief to the TBH ICU team.