COVID-19 Evidence Update

COVID-19 Update from SAHMRI, Health Translation SA and the Commission on Excellence and Innovation in Health

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The risk of severe COVID in patients undergoing immunosuppressive cancer treatment

Executive Summary

There is concern that people who are immunocompromised, such as those being treated for cancer, may be at increased risk of contracting COVID-19 and increased risk of more severe infection.

Prevalence and severity: There are multiple reports of increased prevalence of COVID-19, and increased severity in people with cancer. However, these studies are small and do not adequately control for confounders including age. Overall this evidence is inconclusive. Reports of severity or case fatality for cancer are not higher than for other medical comorbidities.

There is currently insufficient evidence on the relationship between people having treatment for cancer and severity of COVID-19, due to lack of data. As cancers vary considerably in their biology, prognosis and treatment, it is likely that evidence will be slow to accumulate.

Immunosuppression in people with conditions other than cancer: Research is ongoing regarding the relationship between immune responses and disease severity for COVID-19. There is interest in the role of for **immune-suppressing or -stimulating drugs** in COVID-19 and their potential to reduces the chance of a damaging immune response to the virus.

Context

- There is concern that people who are immunocompromised, such as those being treated for cancer, may be at increased risk of contracting COVID-19 and increased risk of more severe infection. This has resulted in debate about the pros and cons of postponing cancer treatment during the COVID-19 pandemic.
- There is reason for concern based on broader research indicating that patients with cancer are more susceptible to bacterial and viral infections than individuals without cancer because malignancy and anticancer treatments such as chemotherapy or surgery can lead to systemic immunosuppression [1-3]
- Commentators have also pointed out that cancer patients may be at increased risk of contracting the disease because of disruptions to social distancing due to visiting hospitals and clinics for check-ups and treatment [4-7].
- *Note: we refer to the virus as SARS-CoV-2 and the disease as COVID-19*

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Resources for health professionals and consumers

- **Cancer Australia** has developed an online resource for Australians affected by cancer, as well as a repository of up-to-date, evidence-based resources from Australia and International organisations for health professionals and researchers [8].
- **Ecancer.org** is publishing the latest research, expert opinions, and latest cancer-related news on their website [9].

Summary of Key Evidence

Statistics on COVID-19 in cancer patients (incidence/prevalence)

- Two meta-analyses have been published; the first included 7 articles available up to the 16 Feb 2020 [10], and the second included 11 articles (including the 7 reported on in the first study) available up to 14 March 2020 [11].
    - In the more recent meta-analysis [11], **the overall pooled prevalence of cancer in patients with COVID-19 was 2%**. Of the 11 articles, 5 studies had a population less than 100, 4 studies had a population of between 100 and 201, and the remaining 2 studies had a population of 1099, and 1590, respectively. The prevalence was slightly higher when the sample size was <100 (3%) than when the sample size was greater than 100 (2%).
    - The authors suggest that patients with cancer and cancer survivors remain an important at-risk population for COVID-19, but the **evidence on the association between cancer and COVID-19 remains inconclusive**.
- Studies published since the meta-analyses:
    - A study reporting on patients (n=1524) who were being treated at a tertiary cancer institution in Wuhan, China [12] found an infection (i.e. tested positive for SARS-CoV-2) rate of 0.79% (n=12), of which 3 patients developed COVID-19 and 1 patient required intensive care. The authors suggest that the **infection rate was higher in cancer patients** than the general population in the same region during the same time period (0.37%). Note: only 5 of the infected patients were undergoing active treatment for their cancers.
    - A study [13] reported on a single centre experience on infection control measures undertaken to minimise cross transmission between cancer patients (n=209) undergoing radiotherapy and between patients and healthcare workers. The results indicate a 0.48% infection rate (n=1) among cancer patients with the infection control protocol in place. Despite 70 radiotherapy patients being deemed to have a contact history with the SARS-CoV-2 positive patient, none contracted SARS-CoV-2.
    - The incidence of COVID-19 among patients hospitalised for gynaecologic oncology surgery was 1.59% (3 of 189 patients undergoing surgeries in the ward). Two were discharged and one remained in treatment. Comorbidities (diabetes, hypertension) were present in all three patients [14].

- Liang et al. [15] produced an early study which was frequently cited in commentary about the association between COVID-19 severity and cancer
    - Analysis of 1590 cases from 575 hospitals in China; all were diagnosed with laboratory-confirmed COVID-19 and were admitted to hospital [15]. Eighteen cases (1%) had a history of cancer, which was estimated as being **higher than the incidence of cancer in the overall Chinese population** (0.29%). Among the people with cancer, the most **common cancer was lung cancer** (28%). Four patients had received chemotherapy or surgery within the past month whereas 12 patients were cancer survivors in routine follow-up (2 patients had unknown treatment status). Compared to patients without cancer, **patients with cancer were older, more likely to have smoked, had more polypnea, and more severe baseline CT manifestation**. Patients with cancer, especially those who underwent chemotherapy or surgery in the past month, had **higher risk of severe events** compared to patients without cancer. Patients with cancer deteriorated more rapidly than patients without cancer. Among patients with cancer, older **age was the only risk factor for severe events**.
- A critique of the Liang et al. paper [16]
    - The authors offer the following criticisms to the above paper: comparing the general population is not sufficient, more informative to compare incidence of COVID-19 in patients with cancer. The eighteen cases had **significant heterogeneity in terms of cancer types**, highly variable disease courses (0-16 years) and diverse treatment strategies - this limits generalisability to all cancer patients. The results may also be confounded by surgical resection. With regard to severe events, cancer is usually associated with blunted immune status which is contradictory to the evidence suggesting that cytokine-associated lung injury is associated with severe disease progression. **Smoking history** may be a better explanation for the results. Overall, current **evidence remains insufficient** regarding the association between cancer and COVID-19.

Severity of COVID-19 in cancer patients

- Data from the Chinese Center for Disease Control and Prevention showed that the case fatality rate (CFR) among 44672 confirmed COVID-19 cases was 2.3%. The CFR was elevated among those with cancer (5.6%), as well as other comorbid conditions (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, and 6.0% for hypertension) [17]. *Note: these CFR were not adjusted for age*
- Numerous studies have published clinical data on cancer patients with COVID-19, most of which are studies of 1 or 2 patients only and cancer types and treatment varied across studies [18-24].
- Of 224 staff and 136 patients in 2 Wuhan haematological centres, there were 16 staff cases and 15 patient cases of COVID-19 (13 of which had haematological malignancies) [25]. All severe or critical cases (n=11) were patients and 10 of the 15 patient cases died while none of the staff cases died.
    - Among the 128 haematological malignancies patients in Wuhan, no significant difference in sex, age or previous comorbidities was found between the infected and uninfected groups.
- Clinical and laboratory data from 7 patients with lung cancer who underwent lung resection and were found to have severe SARS-CoV-2 infection (single department) [26]. Median age was 60 years and 5 were male. Two patients died (fatality rate 28.6%); Five patients had comorbidities, including chronic obstructive pulmonary disease (2 patients), coronary atherosclerosis (3), interstitial pneumonia (1), hyperlipidaemia (1), history of colorectal carcinoma (1).

- A study of 28 cancer patients with laboratory confirmed COVID-19 from three designated hospitals in Wuhan, China, found the median age was 65 years and 61% were male. Fifteen (53.6%) of the patients developed severe clinical events, 6 (21.4%) patients were admitted to ICU, 10 (35.7%) patients had life-threatening complications and 8 (28.6%) of the patients died. There was a significant increase in the risk of developing severe events if the last anti-tumour treatment was within 14 days. Note that 11 (39.2%) patients had one or more comorbidities [27].
- Clinical data and results from a cross-sectional survey of 392 Chronic Myeloid Leukemia (CML) patients in 29 centres were collected [28]. Twelve respondents had fever, cough or shortness of breath during the epidemic period and 9 of them did not go to the hospital because their symptoms were mild or remitted with oral medication. Of the three people that went to hospital for treatment, 2 tested positive for COVID-19, 1 (aged 47 years, male, no comorbidities) was treated and cured and the other (aged 89, female, also had coronary heart disease) died.
- The authors of a study conducted in Italy reported three immunocompromised children receiving treatment at a centre for paediatric liver transplants tested positive for SARS-CoV-2 but none developed clinical pulmonary disease; no mortality was reported [29].

Modelling risk of chemotherapy treatment across a range of scenarios

- A modelling study of a range of scenarios which estimates the risk of death in patients who undergo chemotherapy and become infected with COVID-19 was undertaken [30]. Data comes from China, Italy and a cruise ship, and assumptions were derived from studies on influenza outbreaks. The results showed a clear relationship between age and risk of death. Furthermore, of the 9 scenarios, risk of death was higher than expected benefit in six, balanced in 1 and favoured chemotherapy in 2 scenarios. A caveat was that there is only limited data available on risks associated with cancer and COVID-19. More studies are needed.

Commentaries on risk of cancer treatment

- Authors raise 2 main issues 1) patients with cancer must leave their homes to visit cancer clinics, leading to potential exposure to others with COVID-19; 2) cancer treatments can predispose patients to the more serious harmful effects of COVID-19 [4]. Also makes the point that while the evidence is limited, the clear evidence that older age and higher levels of comorbidity is associated with more severe COVID-19 symptoms and outcomes is highly relevant to those with cancer. The authors also propose that:
    - The risk of transmitting SARS-CoV-2 can be mitigated through infection control policies.
    - The precautionary principle be used to weigh the risks of undergoing cancer therapy, which will vary according to a range of factors, including cancer and treatment type.
- Authors propose the following risks to consider: balance a delay in cancer diagnosis or treatment against risk for potential COVID-19 exposure, mitigate risks for care disruptions associated with social distancing, and manage appropriate allocation of limited health care resources [5].
    - Authors conclude that the quality of evidence in some cases is inadequate to support “one size fits all” statements applicable to every patient.
- Bersanelli [31] questions the recommendation to postpone cancer treatment and offers an in-depth analysis of the pathogenesis of COVID-19 and its relationship to immune checkpoint inhibitor treatment, which is increasingly used to restore cellular immunocompetence. The authors conclude that "Clinical

decisions about cancer patients deserving immunotherapy in the current context of the COVID-19 pandemic should be characterized by separated reflections, avoiding generalizations and remembering their deeply different immunological status compared with that of cancer patients undergoing chemotherapy or targeted agents."

Immunosuppressed non-cancer patients

- A study of patients with **chronic arthritis** treated with biological disease-modifying antirheumatic drugs (**bDMARDs**) or targeted synthetic disease-modifying antirheumatic drugs (**tsDMARDs**) in Italy did not find evidence of increased risk of complications from SARS-CoV-2 compared to the general population [32]. The authors were **unable to draw any conclusions** on the incidence rate of SARS-CoV-2 infection in patients with rheumatic diseases, nor on the overall outcome of immunocompromised patients affected by COVID-19.
- A narrative review [33] on the management of **solid organ transplant patients** found that "There is a **lack of data in the literature**, but three key-points are crucial: in the “pandemic era,” consider the symptomatic patient as positive for COVID-19 until proven otherwise; adjust/stop immunosuppressive agents; protect graft function with adequate route and dose administration of glucocorticoid and supportive measures".
- A case study of 1 patient with **systemic sclerosis (SSc)** who developed COVID-19 [34]. The patient had insulin-dependent type 2 diabetes mellitus and WHO grade I obesity and was successfully treated with tocilizumab.
- A case study of **2 deceased kidney transplant recipients** found that that the **course of COVID-19 did not significantly differ** from that of non-transplant individuals [35].
- A **systematic review** of the current evidence for **immune-suppressing or -stimulating drugs** synthesised findings from 89 studies [36]. The authors concluded that “**Low-dose prednisolone and tacrolimus may have beneficial impacts on COVID-19**. The **mycophenolate mofetil picture is less clear**, with conflicting data from pre-clinical studies. There is **no definitive evidence that specific cytotoxic drugs, low-dose methotrexate for auto-immune disease, NSAIDs, JAK kinase inhibitors or anti-TNFα agents are contraindicated**. There is clear evidence that IL-6 peak levels are associated with severity of pulmonary complications.”

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