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.

Poor clinical outcomes for patients with cancer during the COVID-19 pandemic

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According to global cancer statistics, there were an estimated 18·1 million new cancer cases and 9·6 million cancer deaths worldwide in 2018.[1] In the ongoing COVID-19 pandemic, these millions of patients with cancer seem to be more susceptible to the viral disease than the general population. Indeed, they could be more likely to develop severe complications of COVID-19, owing to their immunosuppressed status caused by both the cancer and anticancer therapies, such as radiotherapy, chemotherapy, and surgery.[2] In this urgent situation, it is crucial to characterise the clinical features, risk factors, and outcomes of patients with cancer and COVID-19.

In *The Lancet Oncology*, results from two independent, multicentre studies on patients with cancer and COVID-19 have been published—both done in Hubei, China, the initial epicentre of the pandemic. Kunyu Yang and colleagues investigated the clinical characteristics, outcomes, and risk factors for mortality in 205 patients with cancer and COVID-19.[3] 30 (15%) patients were transferred to an intensive care unit and 40 (20%) died while in hospital. Receipt of chemotherapy within 4 weeks of symptom onset was a risk factor for in-hospital death (odds ratio [OR] 3·51 [95% CI 1·16–10·59]; p=0·026). Yang and colleagues also highlighted that compared with patients with solid tumours, those with haematological malignancies had a higher case-fatality rate (nine [41%] of 22 patients *vs* 31 [17%] of 183 patients) and had more severe events such as acute respiratory distress syndrome (six [27%] of 22 *vs* 17 [10%] of 177) and acute renal failure (four [18%] of 22 *vs* nine [5%] of 177). Faster disease progression, more frequent hospital admissions for chemotherapy, increased susceptibility to bacterial coinfection, and greater myelosuppression and immunosuppression could explain the poorer prognosis in patients with haematological malignancies compared with those with solid tumours. In the second study in *The Lancet Oncology*, Jianbo Tian and colleagues included 232 patients with cancer and COVID-19 during the same period, who were statistically matched to patients with COVID-19 without cancer.[4] Tian and colleagues found that patients with cancer had increased risk of developing severe or critical COVID-19 than patients without cancer (OR 3·61 [2·59–5·04]; p<0·0001). They also identified several novel predictors for poor prognosis, such as advanced tumour stage (OR 2·60 [95% CI 1·05–6·43]; p=0·039), elevated tumour necrosis factor α (1·22 [1·01–1·47]; p=0·037) and N-terminal pro-B-type natriuretic peptide (1·65 [1·03–2·78]; p=0·032), and reduced CD4+ T cells (0·84 [0·71–0·98]; p=0·031).

It should be noted that the two studies have inherent limitations. Because both studies enrolled patients from hospitals designated for COVID-19 treatment, there is overlap in the hospitals involved and thus possibly in the patients enrolled. Both studies were retrospectively designed, with incomplete documentation, recall bias, and a lack of dynamic clinical and laboratory data. The sample sizes were not large enough to support the results with high confidence. Neither study was able to analyse the relationship between clinical outcomes and treatment strategies. Moreover, the authors did not analyse the frequent thrombophilic complications in cancer as well as in COVID-19: deep vein thrombosis and pulmonary embolism. Despite these limitations, the two groups have provided information that can help to provide more appropriate care for patients with cancer and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and monitor reliable markers during the infection course.

A few other short reports with small sample sizes have also focused on patients with cancer, describing clinical characteristics of patients with cancer and investigating their prognosis.[5–7] The studies found higher risk of SARS-CoV-2 infection in patients with cancer compared with the general population in Wuhan,[5] and higher risk of severe events in patients with cancer and COVID-19,[6] particularly those who had received antitumour treatment recently.[7] When taking all studies into consideration, patients with cancer and COVID-19 in China have a case fatality rate of up to 20%, which is much higher than that of the community (1·8–7·2%), as reported in various countries (figure). Moreover, patients with cancer who had received chemotherapy, targeted therapy, or immunotherapy, or had undergone surgery 2–4 weeks before presenting with COVID-19 were found to have an approximately 4-times higher risk for in-hospital death than patients who had not been recently treated with anticancer therapies

(figure). Targeted therapy and immunotherapy are of particular concern during the pandemic. In multivariable logistic regression analysis in the study by Tian and colleagues, these therapies were found to confer a 3·29 times (95% CI 1·26–8·61; p=0·015) increased risk of developing severe COVID-19.[4] Therefore, oncology teams should pay close attention to immunotherapy-related adverse effects, such as severe neurotoxicity, myocarditis, and pneumonitis, which might negatively affect survival of patients with COVID-19.

The data described above raise an important issue: should anticancer treatment be postponed during the COVID-19 pandemic? We should keep in mind that the primary risk for patients with cancer during the pandemic is reduced access to hospitals and inability to receive necessary medications in a timely fashion. This pandemic is putting unprecedented pressure on health-care services worldwide, which have become increasingly focused on caring for patients with COVID-19. All aspects of cancer treatment have been affected: not only screening, referral, and clinical testing in symptomatic cancer diagnosis, but also treatment and follow-up of patients with cancer.[8] A report from the Netherlands has shown a decrease in cancer diagnoses during the COVID-19 pandemic, with the overall rate of cancer diagnosis decreasing by 27% from Jan 6 to March 2, 2020.[9] Patients might be anxious about being exposed to SARS-CoV-2 in a health-care setting, and might struggle to consult with a general practitioner in the midst of strict social distancing and lockdown policies. In this context, treatments for people living with and beyond cancer are being delayed. Some patients with cancer—especially those with haematological malignancies—are at increased risk of disease progression, tumour relapse, and death while waiting for treatment. Therefore, it is likely that postponing cancer care without consideration of its implications could cost more lives among patients with cancer than COVID-19 itself. Extreme caution is required in delaying life-saving cancer therapies.

Some preliminary recommendations have been proposed to guide decisions on delaying or continuing cancer treatment during the COVID-19 pandemic. They are based mainly on categorising patients into low, moderate, or high risk of disease progression without anticancer treatment. For some types of tumour including lung and pancreatic cancer, acute leukaemia, and highly aggressive lymphoma, timely diagnosis and management are warranted. For others such as breast and thyroid cancer, delaying therapeutic interventions might be considered. Such a modification might not affect long-term outcomes, whereas their potential exposure to COVID-19 could be risky or even fatal. These recommendations can be cautiously applied in current clinical practice until evidence-based guidelines are available.[10]

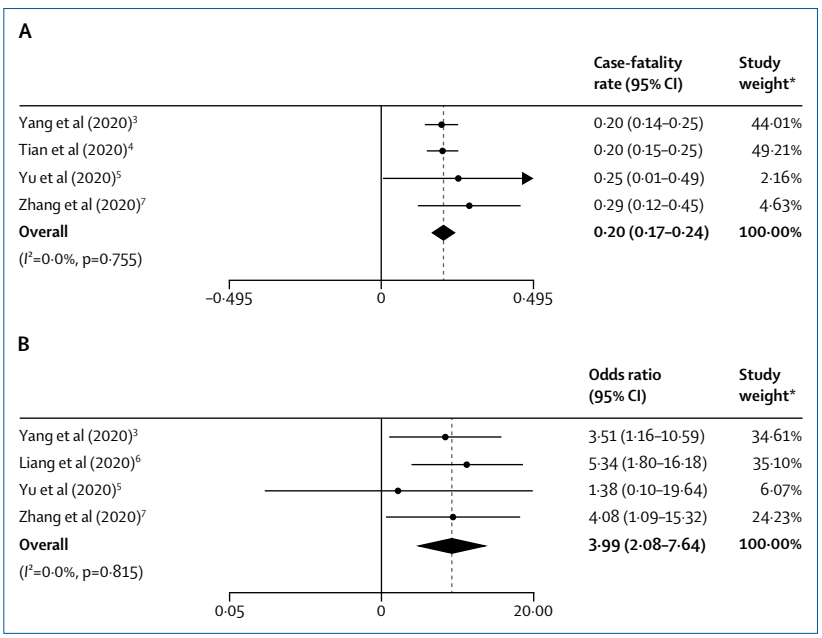

Figure: **Pooled analysis from the current published evidence**
(A) Case-fatality rate of patients with cancer and COVID-19. (B) Odds ratio for in-hospital death for patients receiving anticancer therapies within 2–4 weeks before onset of COVID-19 versus those who did not receive such anticancer therapies. *Weights are from random-effects analysis.

In conclusion, patients with cancer have worse clinical outcomes of COVID-19 than those without cancer. Further studies regarding comprehensive management of patients with cancer and COVID-19 are urgently needed to provide better health care to this patient population.

We declare no competing interests.

*Liang V Tang, *Yu Hu*
dr_huyu@126.com

Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

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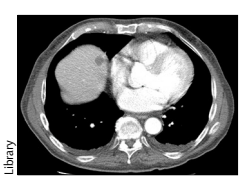
A new approach to refractory gastrointestinal stromal tumours with diverse acquired mutations



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Molecular targeted therapy has improved the prognosis for patients with advanced cancers with driver mutations as seen in lung adenocarcinomas, leukaemia, and gastrointestinal stromal tumours. Targeted agents include antibodies or small molecules that specifically bind to proteins coded by driver alterations. The clinical efficacy of these drugs, however, can be limited by the emergence of refractory clones with resistant mutations. These mutations have typically been seen in patients with gastrointestinal stromal tumours. Gastrointestinal stromal tumours are rare cancers that develop mainly in the gastrointestinal tract. The discovery of driver mutations in the *KIT* and *PDGFRA* genes has led to clinical development of three tyrosine kinase inhibitors (TKIs)—imatinib, sunitinib, and regorafenib—and has revolutionised treatment and prognosis of patients with advanced gastrointestinal stromal tumours. However, primary and secondary resistance to these drugs limit their activity and, eventually, almost all gastrointestinal stromal tumours progress, mainly due to acquired mutations.[1] These TKIs inhibit KIT and PDGFRA tyrosine kinases by competitively binding to their ATP-binding domains with ATP, thus, most acquired mutations are found in the ATP-binding pocket or activation loop of the *KIT* or *PDGFRA* gene, resulting in reactivation of the corresponding kinase.[2] Acquired mutations after TKI therapy are highly variable and are heterogeneous in a patient, even within a single lesion. Furthermore, refractory gastrointestinal stromal tumours might potentially have different resistance mechanisms other than acquired mutations.[3] Hence, the activities of TKIs with similar mode of action are limited after imatinib; median progression-free survival of sunitinib in the second-line is 6·8 months and that of regorafenib in the third-line is 4·8 months.[4,5] Since the approval of regorafenib in 2012, many agents have been evaluated for fourth-line therapy, but none of them were approved for patients with gastrointestinal stromal tumours that were refractory to three TKIs until the end of 2019.

Ripretinib is designed to stabilise KIT and PDGFRA tyrosine kinases in an inactive conformation by binding to switch pocket regions and is shown to specifically inhibit the wide spectrum of primary and secondary resistant mutations found in the ATP-binding pocket or activation loop of *KIT* and *PDGFRA*, and also other mutated kinases (eg, *BRAF* in in-vitro experiments and mouse models).[6] In *The Lancet Oncology*, Jean-Yves Blay and colleagues[7] report the results of the INVICTUS study, which examined the efficacy of ripretinib in patients with gastrointestinal stromal tumours that were refractory or intolerant to three available TKIs in a placebo-controlled, double-blind, randomised phase 3 study. Median progression-free survival, the primary endpoint, was longer in the ripretinib group than in the placebo group (6·3 months [95% CI 4·6–6·9] *vs* 1·0 month [0·9–1·7], hazard ratio 0·15, 95% CI 0·09–0·25, p<0·0001) and the objective response rate, the key secondary endpoint, was higher in the group that received ripretinib (9%, 95% CI 4–18) than in the group that received placebo (0%, 0–8) by the central review, although this difference was not statistically significant (p=0·050). Moreover, ripretinib had an improved overall survival, with a median overall survival of 15·1 months compared with 6·6 months in the placebo group despite crossover to riprecinib from placebo, which was permitted after disease progression. However, due to hierarchal testing, overall survival could not be formally tested