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Cancer and COVID-19

We read, with great interest, about the outcomes in a cohort of patients with cancer and COVID-19 by Nicole Kuderer and colleagues.[1] The authors showed that among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general and cancer-specific risk factors, with a mortality of 13·3%.

More data on the cause of mortality in the CCC19 cohort would have been useful. More specifically, how many patients died because of COVID-19-related issues (eg, acute respiratory distress syndrome or organ failure), and how many died because of background disease progression and relevant complications? Finally, how many of these deaths should be attributed to changes in the therapeutic plan caused by COVID-19, including access to care and delays in management?

Information on deaths caused by changes to a patient's care plan is of paramount clinical importance, since data on the incidence of avoidable mortality caused by the effect of the pandemic on health-care resources are scarce. During the pandemic, the management of patients with cancer has been affected at multiple stages, including the triage decisions, surgery, and neoadjuvant therapy as a bridge to reduce admissions and preserve health-care resources.[2] Also, when possible, oncologists are modifying or substituting oral for intravenous chemotherapy with oral agents to minimise admissions to hospital.

In the same vein, omissions, delays, or fragmentation of care can have clinically important adverse influence on quality of life or survival.[2] Unfortunately, the effect on the survival outcomes is not well described in the literature, and data from international cohorts and consortia can be useful.

Finally, the authors did not provide any data on the socioeconomic and insurance status of the patients included in their cohort. It would be interesting to know how many patients with cancer lost their insurance, dependent care, or employment, and how these changes affected their access to care and a treatment plan.

COVID-19 has caused unprecedented societal turmoil, triggering a rapid transformation of health-care systems on a global scale. Emerging data show that the COVID-19 pandemic has the potential to amplify pre-existing disparities, especially for patients with cancer.[3,4] Potential drivers of disparate cancer survival resulting from the pandemic can include variable access to telemedicine, timely diagnosis, and access to treatment. Despite oncology societies proposing guidelines on cancer care during the pandemic, the prioritisation in the delivery of cancer therapies is strongly influenced by the magnitude of potential treatment benefits, therapeutic intent, and the access to care.[5]

All in all, these changes can definitely affect the outcomes of patients with cancer. In this new landscape, when the cancer community is revising the optimal standards of cancer care, research should focus on identifying the factors that contribute to avoidable mortality and facilitate the implementation of strategies to benefit patients.

We declare no competing interests.

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Nicole Kuderer and colleagues[1] identified several independent prognostic factors to be conferring an increased risk of 30-day all-cause mortality: increased age, male sex, being a former smoker, multiple medical comorbidities, high Eastern Cooperative Oncology Group performance status score (≥2), and an active cancer. However, haematological malignancies, instead of increasing 30-day all-cause mortality, were associated with severe clinical outcomes, intensive care unit

admissions, and meeting composite severe illness endpoints.[1]

The findings raised concern for an increased risk of overall mortality in patients with cancer (13%). We believe that the uncertainties in the study[1] make the results difficult to interpret in subgroups of patients, particularly in patients with haematological malignancies.

928 patients met the inclusion criteria and 204 (22%) of the patients had haematological malignancies; however, the number of patients in each of the subtypes of haematological malignancies in total was 305 patients, not 204, and these patients were subdivided as follows: 102 with lymphoid neoplasms, 55 with multiple myeloma, 54 with low-grade non-Hodgkin lymphoma, 42 with myeloid neoplasms, 27 with high-grade non-Hodgkin lymphoma, 13 with acute myeloid leukaemia, six with acute lymphoblastic leukaemia, and six with unspecified cancers. These numbers mean that 101 cases of various haematological malignancies were unexplained. This discrepancy between the total reported number of patients with haematological malignancies (n=204) and the total number of patients reported in the subtypes (n=305) could be explained by the fact that several patients might have been in multiple subcategories.

Haematological malignancies might be associated with differential risks of infection and complications secondary to COVID-19, since myeloid and lymphoid neoplasms affect the immune systems differently; therefore, this factor should be evaluated in detail. The authors only mentioned patients who had multiple cancer types (n=107), solid tumours (n=654), and haematological malignancies alone (n=167) as they assessed for secondary and primary outcomes, with no additional details regarding the combination of cancers. For example, patients might have had a history of haematological neoplasms currently in remission (off chemotherapy) with another active solid cancer, or vice versa, which would have made a substantial difference in the treatment strategy and degree of immunodeficiency, thus resulting in the risk of severe COVID-19. In particular, patients with leukaemia are often immunosuppressed with possible hypogammaglobulinaemia, leading to further severe clinical outcomes associated with COVID-19. Furthermore, the authors did not follow the revised 2016 WHO classification when detailing the haematological malignancies.[2]

45% of the analysed population had a cancer status labelled as having remission with no evidence of disease.[1] However, no details were given regarding what types of malignancy were in remission. It is crucial to know the relative rates of remission between patients with solid tumours and haematological malignancies, and whether they were on maintenance therapy.

Finally, although the types of anticancer therapy used were described, the objective parameters for measuring the severity of resulting immunosuppression, such as white blood cell counts, absolute neutrophil counts, or absolute lymphocyte counts, were not. Additionally, it would have been informative to know the concentrations of inflammatory cytokine markers (eg, interleukin-6) in the patients reviewed. Ruan and colleagues[3] showed that lower absolute lymphocyte counts and increases in interleukin-6 concentrations were linked to a poor outcome in patients with COVID-19. Of interest, several studies calculated the ratios of neutrophils to lymphocytes and of lymphocytes to C-reactive protein to show systemic inflammation and predict more severe clinical outcomes in patients infected with COVID-19.[4]

The severity of COVID-19 infections in patients with cancer is an important clinical question. The analysis[1] would have benefited from enhanced subset disease evaluation, including more specific types of cancer, markers of immune status and inflammation, and type of treatment regimen.

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Authors' reply

We thank Dimitrios Moris and colleagues and Alexandre Malek and colleagues for their insightful commentary about the CCC19 study findings.[1] We value the opportunity to further characterise mortality outcomes beyond our initial report.[1]

With a median of 30 days (IQR 21–90) follow-up, as of Aug 21, 2020, 30-day all-cause mortality increased to 20% (154 of 754 patients who either died within 30 days or had at least 30 days of follow-up). Planned time-to-event analyses will refine these estimates. 121 (79%) deaths were attributed to respiratory failure (appendix). In our cohort,[1] the category of respiratory failure encompasses deaths from any respiratory failure syndrome. Although respiratory failure caused by cancer, its therapies, or other comorbidities could confound the cause of death attribution, this is unavoidable. Diagnostic procedures are challenging with COVID-19, autopsies are rare, and Vital Statistics Reporting Guidance specifically directs medical certifiers to


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See **Online** for appendix