



SPECIAL REPORT

Guidance regarding COVID-19 for survivors of childhood, adolescent, and young adult cancer: A statement from the International Late Effects of Childhood Cancer Guideline Harmonization Group

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Abstract

Childhood, adolescent, and young adult (CAYA) cancer survivors may be at risk for a severe course of COVID-19. Little is known about the clinical course of COVID-19 in CAYA cancer survivors, or if additional preventive measures are warranted. We established a working group within the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) to summarize existing evidence and worldwide recommendations regarding evidence about factors/conditions associated with risk for a severe course of COVID-19 in CAYA cancer survivors, and to develop a consensus statement to provide guidance for healthcare practitioners and CAYA cancer survivors regarding COVID-19.

KEYWORDS

childhood adolescent and young adult (CAYA) cancer survivors, COVID-19, late effects of cancer treatment

1 | INTRODUCTION

COVID-19 is an infectious disease caused by a coronavirus (SARS-CoV-2) that emerged in December 2019 in Wuhan, China.¹ The coronavirus has spread rapidly across the globe, and on March 11, 2020, COVID-19 was declared a pandemic by the World Health Organization (WHO). The clinical presentation of COVID-19 ranges from asymptomatic to life-threatening infection requiring hospitalization and critical care.² Emerging evidence in the general population indicates that individuals with comorbidities such as cardiopulmonary disease, diabetes, and obesity, or those with advanced age have an increased risk of severe infection and death.³⁻⁶

Long-term survival of childhood, adolescent, and young adult (CAYA) cancer has improved remarkably due to advances in treatment strategies and supportive care over the past decades. Approximately 80% of children diagnosed with cancer achieve five-year survival, which has resulted in growing numbers of CAYA cancer survivors worldwide.⁷ Numerous studies have highlighted that CAYA cancer survivors have a higher risk of chronic health conditions such as subsequent cancers, diabetes mellitus, heart failure, and pulmonary disease,⁸⁻¹³ compared with the general population. There is further evidence to suggest that some survivors treated with intensive multimodality approaches (e.g., chemotherapy plus radiation, hematopoietic stem cell transplantation) are at risk for

accelerated physiological aging.¹⁴ That said, there is very little known about the incidence of COVID-19 and its clinical course in CAYA cancer survivors, or whether preventive measures are warranted above and beyond those recommended for the general population. The high burden of chronic comorbidities experienced by CAYA cancer survivors raises concern that they may be at increased risk for severe COVID-19.

Establishing a statement to guide healthcare providers (HCPs), long-term follow-up clinics, and CAYA cancer survivors about how a history of cancer may affect the course of COVID-19 is key to ensuring that survivors take optimal precautions during the current pandemic. With this in mind, we organized an international working group within the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG).¹⁵ We aimed (1) to summarize existing evidence and worldwide recommendations regarding relevant factors and conditions associated with risk for a severe course of COVID-19 and (2) to develop a consensus statement to provide guidance for HCPs and CAYA cancer survivors regarding COVID-19.

2 | METHODS

For this report, CAYA cancer survivors were defined as individuals of any age who were diagnosed with cancer before age 25 years and were at least one year following completion of primary cancer therapy.

2.1 | The IGHG COVID-19 working group

IGHG is an international collaboration focused on developing widely applicable guidance for the long-term follow-up of CAYA cancer survivors. The main goal of the IGHG is to establish a common vision and integrated strategy for the surveillance of chronic health conditions in CAYA cancer survivors.¹⁵⁻²¹ The IGHG COVID-19 working group was assembled by the co-chairs of the IGHG (MH and LK), and currently consists of pediatric oncologists, late effects clinicians, supportive care specialists, infectious disease specialists, psychologists, patient representatives, and survivorship researchers from the following 15 countries: Australia, Austria, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Japan, Sweden, Switzerland, the Netherlands, the United Kingdom, and the United States. We used a stepwise approach to summarize the existing evidence and recommendations, and to develop recommendations for the IGHG COVID-19 statement.

2.2 | Summary of the evidence

We defined two clinical questions: "What is the evidence on COVID-19 infections in survivors of CAYA cancer?" and "Which factors are associated with severe course among patients with confirmed/suspected COVID-19 in the general population?"

In collaboration with Cochrane Childhood Cancer, we first performed a literature search to examine the published data on

COVID-19 in CAYA cancer survivors (Supporting Information Table S1a), and a second literature search on factors that are associated with severe course among patients with confirmed/suspected COVID-19 in the general population (Supporting Information Table S1b). For the first question, we planned to include all published studies. For the second question, we included studies that used multivariable analysis to evaluate factors or comorbidities associated with a severe course of disease, including hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and death. We excluded all case reports, reviews, and articles not written in English. We checked the reference lists of systematic reviews to find additional studies. The searches were performed in PubMed from December 1, 2019, and April 20, 2020. Two independent reviewers first screened titles and abstracts to identify potentially eligible articles. Two independent reviewers then screened full-text articles. For all included articles, evidence tables were prepared. The evidence was organized in summary tables and conclusions of evidence were formulated. We defined a high level of evidence as having a risk factor or comorbidity associated with a specific outcome based on multivariable analyses in three or more studies, a moderate level of evidence if this factor was identified in two studies, and a low level of evidence if only one study identified the risk factor or comorbidity.¹⁵

2.3 | Summary of existing recommendations for high-risk groups for a severe course of COVID-19 in the general population

We collected information from the websites of national health institutions and the WHO about recommendations for risk factors and comorbidities associated with higher risk of a severe course of COVID-19 in the general population (Supporting Information File S2). We summarized the risk factors and comorbidities associated with higher risk for a severe course of COVID-19 and identified (dis)concordances.

2.4 | Development of recommendations for the IGHG COVID-19 statement

During weekly working group discussion sessions, we evaluated the results of the conclusions of evidence and summary of recommendations on risk groups for the general population, and the relevance of the identified risk factors and comorbidities in the general population for CAYA cancer survivors. Consensus was reached to designate comorbidities and risk factors that were identified in recommendations for the general population by > 70% of the organizations as high risk. We extrapolated these risk factors to CAYA cancer survivors and assumed that same conditions, even when cancer treatment-related (e.g., radiation-related cardiovascular disease), may similarly increase the risk for a severe course of COVID-19 in CAYA cancer survivors. Subsequently, we formulated recommendations for measures that all CAYA cancer survivors should take to reduce the risk of infection, the additional measures that survivors at high risk should take, and what

should be done if a survivor at high risk develops symptoms suggestive of COVID-19.

The websites of the national health organizations of the involved countries were consulted weekly between March 20 and May 14, 2020. New information was discussed on a weekly basis and the statement was modified accordingly.

The statement and updates are published at the IGHG website (www.ighg.org), and working group members disseminated the IGHG COVID-19 statement on the Cochrane Childhood Cancer website and to societies such as the American Society of Pediatric Hematology Oncology, the Japanese Society of Pediatric Hematology/Oncology, the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer, the Childhood Cancer International–Europe organization, and the European branch of the International Society of Pediatric Oncology Europe (SIOPE) to reach as many CAYA cancer survivors as possible. The IGHG COVID-19 statement was developed in English and translated into the following languages: Chinese, Croatian, Czech, Dutch, French, German, Greek, Italian, Japanese, Polish, Portuguese, Spanish, and Turkish. Translations of the latest statement are available at www.ighg.org. Additional translations will also be posted on the website as they become available.

3 | RESULTS

3.1 | Summary of the evidence

In the systematic literature search concerning COVID-19 among cancer survivors, there were only three studies identified and none reported on the effects of COVID-19 on CAYA cancer survivors. The systematic literature search on severe course among patients with confirmed/suspected COVID-19 in the general population identified 14 studies that were included after full text review. Supporting Information File S3 shows the flow chart of inclusion of articles and the summary of evidence. The conclusions of evidence from identified studies and reporting of risk factors for a severe course of disease are presented in Table 1. No studies examined risk factors or comorbidities with increased risk of hospitalization as an outcome. For ICU admission and mechanical ventilation, only low level of evidence was identified (e.g., older age, male sex, and body mass index ≥ 35). For mortality, high level of evidence was identified for older age and moderate evidence for male sex and heart disease. For a combined outcome (i.e., ICU admission, mechanical ventilation, and mortality) moderate level of evidence was identified for older age, hypertension, diabetes, chronic obstructive pulmonary disease, and malignancies.

3.2 | Summary of existing recommendations for high-risk groups for a severe course of COVID-19 in the general population

Sixteen conditions have been reported to be associated with a higher risk of a severe course of COVID-19 in the general population (Table 2 and Supporting Information Table S4). Among these, older

age, endocrine disease, heart disease, lung disease, oncologic disease, immune disorders, or organ transplantation were mentioned by more than 70% of the organizations.

3.3 | Development of recommendations for the IGHG COVID-19 statement

The IGHG statement advises that all CAYA cancer survivors adhere to their local and/or national authorities' recommendations for the general population regarding social distancing, frequent handwashing, and wearing masks in specific situations.

Based on the recommendations of (inter)national organizations, we concluded that survivors who have the following characteristics or comorbidities may be at increased risk for a severe course of COVID-19: (1) age ≥ 60 years; (2) cardiovascular disease (e.g., following anthracycline therapy and/or chest radiation); (3) chronic lung disorders (e.g., following chest radiation); (4) diabetes (e.g., following radiation to abdomen or pancreas); and (5) conditions or active treatments that affect the immune system (e.g., CAYA cancer survivors undergoing treatment for new adult-onset cancer, history of organ transplantation, chronic graft versus host disease). Original studies supported this conclusion, with evidence that these conditions have an increased risk of a severe course of COVID-19 in the general population. For these high-risk survivors, we recommend additional precautionary measures to reduce risk of COVID-19 exposure/infection in the workplace or home (see Figure 1 for the v3.0 IGHG COVID-19 statement). Moreover, survivors who develop symptoms consistent with COVID-19 or those who test positive for COVID-19 are advised to seek medical advice early and alert HCPs about their cancer history and other health conditions that may increase their risk for a severe course of disease.

Recognizing that the impact of the pandemic extends beyond physical health, IGHG also provides guidance about measures to take to cope with stress, anxiety, and the emotional effects of COVID-19 and refers survivors to local mental health services.

The IGHG COVID-19 statement has been updated each time new information has emerged (Supporting Information Figure S5: version 1.0; Supporting Information Figure S6: version 2.0; Figure 1: current version 3.0). The latest version is posted at www.ighg.org and is available in 14 languages. As of July 1, 2020, the website has been viewed 9024 times since April 6, 2020.

4 | DISCUSSION

The IGHG COVID-19 working group developed harmonized COVID-19 recommendations for CAYA cancer survivors within a relatively short period of time, through an internationally collaborative approach that utilized methods that balanced the paucity of information regarding the incidence and clinical course of COVID-19 in CAYA cancer survivors with the rapidly emerging need for guidance within the survivorship community and beyond. Information was then disseminated to the public through the IGHG website and a variety of national/institutional

TABLE 1 Conclusions of identified evidence for comorbidities and risk factors associated with increased risk for severe course of disease in the general population based on a systematic search (see Supporting Information File S3 for the complete table of all risk factors and outcomes)

What are risk factors or comorbidities with increased risk of hospitalization?		
	Studies	Level of evidence
	No studies	No evidence
What are risk factors or comorbidities with increased risk of ICU admission?		
	Studies	Level of evidence
Increased risk of <i>older age</i> vs younger age	Reported in 1 study ²⁵	Low
No significant effect of male vs female	Reported in 1 study ²⁵	Low
No significant effect of any comorbidity vs no comorbidity	Reported in 1 study ²⁵	Low
What are risk factors or comorbidities with increased risk of mechanical ventilation?		
	Evidence	Level of evidence
No significant effect of older age vs younger age	Reported in 1 study ⁴	Low
Increased risk of <i>male</i> vs female	Reported in 1 study ⁴	Low
No significant effect of BMI 25-35 vs < 25	Reported in 1 study ⁴	Low
Increased risk of BMI ≥ 35 vs < 25	Reported in 1 study ⁴	Low
No significant effect of hypertension vs no hypertension	Reported in 1 study ⁴	Low
No significant effect of diabetes vs no diabetes	Reported in 1 study ⁴	Low
What are risk factors or comorbidities with increased risk of mortality?		
	Studies	Level of evidence
Increased risk of <i>older age</i> vs younger age	Reported in 7 studies ^{6,26-31} out of 8 (1 study reported no significant result ³²)	High
Increased risk of <i>male</i> vs female	Reported in 2 studies ^{30,33} out of 6 (4 studies reported no significant results ^{6,26,27,32})	Moderate
Increased risk of <i>heart disease</i> vs no heart disease	Reported in 2 studies ^{26,29} out of 5 (3 studies reported no significant result ^{6,31,32})	Moderate
Increased risk of <i>hypertension</i> vs no hypertension	Reported in 1 study with univariable analyses ⁶ out of 5 (4 studies reported no significant results ^{26,28,31,32})	Low
Increased risk of <i>cerebrovascular disease</i> vs no cerebrovascular disease	Reported in 1 study ²⁹ out of 3 (2 studies reported no significant results ^{26,28})	Low
Increased risk of <i>diabetes</i> vs no diabetes	Reported in 1 study with univariable analyses ⁶ out of 4 (3 studies reported no significant results ^{26,31,32})	Low
Increased risk of <i>COPD</i> vs no COPD	Reported in 1 study ²⁶ out of 3 (2 studies reported no significant results ^{6,32})	Low
No significant effect of malignancy vs no malignancy	Reported in 1 study with univariable analyses ²⁶	Low
Increased risk of smoking vs no smoking	Reported in 1 study with univariable analyses ⁶	Low
No significant effect of liver disease vs no liver disease	Reported in 1 study with univariable analyses ²⁶	Low
No significant effect of any comorbidity vs no comorbidity	Reported in 2 studies ^{27,33}	Moderate
No significant effect of kidney disease vs no kidney disease	Reported in 1 study with univariable analyses ²⁶	Low
No significant effect of autoimmune disease vs no autoimmune disease	Reported in 1 study with univariable analyses ²⁶	Low

(Continues)

TABLE 1 (Continued)

What are risk factors or comorbidities with increased risk of combined outcome severe events including hospitalization, ICU admission, mechanical ventilation, and/or mortality?		
	Studies	Level of evidence
Increased risk of <i>older age</i> vs younger age	Reported in 2 studies ^{3,34} out of 3 (1 study reported no significant results ²⁵)	Moderate
Increased risk of <i>male</i> vs female	Reported in 1 study ³⁴ out of 2 (1 study reported not significant results ³⁵)	Low
Increased risk of <i>hypertension</i> vs no hypertension	Reported in 2 studies ^{3,34}	Moderate
Increased risk of <i>diabetes</i> vs no diabetes	Reported in 2 studies ^{3,34}	Moderate
Increased risk of <i>COPD</i> vs no COPD	Reported in 2 studies ^{3,34}	Moderate
Increased risk of <i>malignancy</i> vs no malignancy	Reported in 2 studies ^{3,34}	Moderate
Increased risk of <i>last antitumor treatment</i> ≤14 days vs last antitumor treatment ≥14 days	Reported in 1 study ³⁵	Low
Increased risk of <i>smoking</i> vs no smoking	Reported in 1 study ³	Low
Increased risk of <i>any comorbidity</i> vs no comorbidity	Reported in 1 study ³	Low

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

TABLE 2 Conclusions for comorbidities and risk factors associated with increased risk for severe course of disease in the general population according to recommendations in 15 national health organizations and the WHO^a

Comorbidity or risk factor associated with increased risk for severe course of disease of COVID-19	Number of organizations that mentioned this risk factor
Older age	16 ^a
Endocrine disease	14 ^a
Heart disease	14 ^a
Lung disease	14 ^a
Oncologic disease	13 ^a
Immune disorders or organ transplantation	11 ^a
Kidney disease	10
High blood pressure	9
Liver disease	8
Pregnancy	6
Overweight	6
Neurological condition	5
Hematological (blood) disease	4
Problems with the spleen	3
Smoking	3
Males	1

^aThe following 15 countries and the WHO are involved: Australia, Austria, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Japan, Sweden, Switzerland, the Netherlands, the United Kingdom, and the United States. Selected comorbidity or risk factor for the high-risk group of survivors for a severe course of disease of COVID-19 because more than 70% of the organizations mentioned these factors as comorbidity or risk factor associated with increased risk for severe course of disease of COVID-19.

pediatric cancer forums. This effort was facilitated by the existing IGHG collaborative platform, and the recognition by its members of the urgent need to summarize existing knowledge during a time of great uncertainty. Because evidence about the course of COVID-19 in CAYA cancer survivors was lacking, we extrapolated knowledge from evidence on risk factors for a severe course of COVID-19 in the general population, as well as recommendations from national health organizations and the WHO about relevant risk factors and comorbidities associated with a severe course of COVID-19 in the general population to CAYA cancer survivors. As shown in Table 1, the evidence for risk factors for a severe outcome in the general population was also very limited; only older age and a higher risk of mortality were identified in three or more studies. The recommendations of the different (inter) national organizations varied substantially among the different sources (Table 2). References to original studies underpinning many of the national recommendations were often lacking, and recommendations were frequently based on expert consensus. This is likely due to the rapidly emerging nature of the pandemic and subsequent lack of large cohort studies characterizing the magnitude of risk for comorbidities and risk factors associated with a severe course of COVID-19 in either CAYA cancer survivors or the general population. The IGHG COVID-19 working group will continue to monitor the literature quarterly and update recommendations as new data emerge.

The IGHG COVID-19 working group also identified a critical knowledge gap regarding the impact of COVID-19 on CAYA cancer survivors. Registration of CAYA cancer patients and CAYA cancer survivors with COVID-19 will increase our knowledge on the clinical course of COVID-19 in these populations.²² Toward this end, registries have been organized by institutional, national, and pediatric cooperative groups. Among these, the open registry established by the International Society of Pediatric Oncology and the St. Jude Children's Research Hospital provides a forum to share resources and experiences about COVID-19 and to collect data on both CAYA cancer

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for survivors of childhood, adolescent and young adult cancer

The IGHG and Cochrane Childhood Cancer are carefully monitoring the rapidly emerging medical information about COVID-19 and will update this guidance as new information becomes available. See www.ighg.org for future updates of this statement.

Purpose



The purpose of this statement is to provide guidance to childhood, adolescent and young adult cancer survivors related to risk and additional preventive measures for Coronavirus Disease 2019 (COVID-19). For this guidance, childhood, adolescent and young adult (CAYA) cancer survivors are defined as individuals of any age who were diagnosed with cancer before age 25 years and are at least one year following completion of primary cancer therapy.

Knowledge



Survivors, their caregivers, and health care providers should be mindful that the risk and course of COVID-19 in childhood, adolescent and young adult cancer survivors is not currently known. Thus, the information provided in this guidance is largely extrapolated from medical information from national health services and the World Health Organization (WHO) about COVID-19 in the general population.

Recommendation 1

Who



is at
higher risk?

Based on medical information about COVID-19 in the general population, cancer survivors with the specific health conditions below may have a higher risk for a severe course of COVID-19, especially if they have more than one of these conditions.

In addition to these comorbid conditions, a more severe course has been observed in older individuals, especially those 60 years of age or older, which may be because older individuals are more likely to have the chronic health conditions listed in the table. Individuals with conditions and/or use of drugs that affect immune system function may also be at risk for a more severe course of COVID-19 because of their overall higher risk of infection.

Conditions ¹ most frequently identified by national health services and WHO to increase risk for a severe course of COVID-19	Examples of cancer treatment-related conditions that may increase a CAYA cancer survivor's risk for a severe course of COVID-19
Heart disease, including but not limited to: <ul style="list-style-type: none"> Heart failure requiring medication History of myocardial infarction (heart attack) 	Heart disease, including but not limited to: <ul style="list-style-type: none"> Cardiomyopathy (heart muscle disease) following anthracycline therapy Coronary artery disease following chest radiation
Chronic lung disorders, including but not limited to: <ul style="list-style-type: none"> Chronic obstructive pulmonary disease (COPD) Severe asthma Any lung disease causing chronic shortness of breath, difficulty breathing or requiring oxygen therapy 	Chronic lung disorders, including but not limited to: <ul style="list-style-type: none"> Lung fibrosis (scarring) following bleomycin or chest radiation Chronic lung disease after bone marrow transplant
Diabetes	Diabetes following radiation to abdomen or pancreas
Conditions and/or use of drugs that affect immune system function, including but not limited to: <ul style="list-style-type: none"> Anticancer treatment Organ transplantation Immune disorders 	Conditions and/or use of drugs that affect immune system function, including but not limited to: <ul style="list-style-type: none"> Ongoing treatment for a new or recurrent adult-onset cancer History of organ transplant because of cancer or damage from cancer treatment (for heart, kidney or liver) Chronic graft versus host disease

¹ The following conditions/factors, which have been reported to increase risk for a severe course of COVID-19, were less frequently mentioned by national health services or medical reports: kidney disease, hypertension, liver disease, obesity, pregnancy, blood disorders, neurological dysfunction, asplenia, hyposplenia, high BMI, male sex, and use of ACE inhibitors or ibuprofen. The IGHG and Cochrane Childhood Cancer will monitor the medical literature about all of these conditions/factors and revise recommendations as new information becomes available. The higher risk of secondary bacterial infections should be considered for survivors with asplenia and hyposplenia.

FIGURE 1 IGHG statement for COVID-19 V3.0 14 May 2020 (updated v1.0 published 7 April 2020)

Recommendation 2

What Measures

should be taken by survivors?



All CAYA cancer survivors should adhere to recommendations, like social distancing, frequent hand washing, etc, as advised by national and/or local authorities.

Recommendation 3

What additional measures

should be taken by survivors at high risk?



Survivors at higher risk of a severe course of COVID-19 (as described in the above list) should:

- Continue to practice strict social distancing, frequent handwashing, etc, as advised by national and/or local authorities.
- For a small number of survivors, this may necessitate continuing social isolation or shielding as advised by your doctor and/or national and/or local authorities.
- Request reassignment to remote work activities (for you and for household members if possible) if your work is typically performed in public spaces.
- Encourage household members who are visiting or working in public spaces to take extra care to avoid exposure and transmission of COVID-19.
- Take extra care to avoid exposure to household members who have symptoms or have been diagnosed with COVID-19.
 - Isolate ill household members in the home or move to another location if possible.
 - If isolation or relocation is not possible, have ill household members wear masks.
 - Increase the frequency of hand washing and cleaning of hard surfaces with disinfectants.
 - Clean shared toilet and bathroom surfaces after every use.

Recommendation 4

What should be done by a survivor at high risk, who is ill?



Survivors at higher risk of a severe course of COVID-19 should:

- Seek medical advice early if you develop symptoms that could be related to COVID-19.
- Alert health care providers about your cancer history and other health conditions that have been linked to higher risk for a severe course of COVID-19.
- Call your doctor or emergency department for instructions if your symptoms worsen (e.g., fever, shortness of breath, difficulty breathing, confusion, etc...) and you feel you need to be evaluated.

Recommendation 5

What are other effects of the COVID-19 pandemic?



Survivors, parents and siblings :

- Be aware that changes and uncertainty caused by the pandemic may cause increased stress, anxiety, and other emotional effects.
- Follow coping strategies recommended by national/local health organizations f.e. <https://www.gov.uk/government/publications/covid-19-guidance-for-the-public-on-mental-health-and-wellbeing/guidance-for-the-public-on-the-mental-health-and-wellbeing-aspects-of-coronavirus-covid-19> Or <https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/managing-stress-anxiety.html>
- Contact local mental health services if you need help dealing with distress, anxiety, or other emotional concerns.

IGHG: International Late Effects of Childhood Cancer Guideline Harmonization Group (www.ighg.org)

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FIGURE 1 Continued

patients receiving cancer treatment and CAYA cancer survivors across different age groups who have completed therapy.²³ This registry will facilitate a global observatory where the data of CAYA cancer survivors with COVID-19 can be updated in real time.

The COVID-19 pandemic has challenged the delivery of healthcare across the world and will also have consequences for long-term follow-up services for CAYA cancer survivors. Off therapy clinical evaluations have been limited to increase availability of medical and nursing staff for frontline clinical care at many cancer centers.²⁴ Consequently, this has resulted in deferral of elective long-term follow-up and primary care appointments for CAYA cancer survivors, who as a group represent a medically vulnerable population. At this point, the long-term impact of these disruptions for CAYA cancer survivors is unclear. To begin to address this concern, a global survey of survivorship clinics is planned to evaluate the impact of COVID-19 on long-term follow-up services and identify ongoing initiatives to facilitate CAYA cancer survivors' access to health resources and services during the current pandemic. It remains to be seen whether recent efforts to expeditiously implement novel healthcare delivery platforms such as telehealth and remote patient monitoring can adequately address healthcare access gaps created by this global pandemic.

In conclusion, the IGHG COVID-19 working group provides guidance to CAYA cancer survivors, who in many cases may have comorbid conditions linked to a high risk of a severe course of COVID-19. Our ongoing monitoring of emerging COVID-19 data and recommendations will facilitate modification of guidance relevant to the survivor population.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

ACKNOWLEDGMENTS

We gratefully acknowledge the kind help of Luisa Basset-Salom, Tiago Costa, Agnes Dumas, Menia Koukougiani, Aslihan Mantici, Anna Panasiuk, Jelena Roganovic, Ziqin Tang, and Zhijun Yu in the translation of the IGHG COVID-19 statement.

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REFERENCES

- Mackenzie JS, Smith DW. COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't. *Microbiol Aust.* 2020;MA20013. <https://doi.org/10.1071/MA20013>.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020. <https://doi.org/10.1001/jama.2020.2648>.
- Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J.* 2020;55(5). <https://doi.org/10.1183/13993003.00547-2020>.
- Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring).* 2020;28(7):1195-1199.
- Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect.* 2020;26(6):767-772.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34.
- Chao C, Xu LF, Cannavale KL, et al. Risk of chronic comorbidities in survivors of adolescent and young adult cancer (AYA). *J Clin Oncol.* 2018;36(15):10015-10015.
- Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet.* 2017;390(10112):2569-2582.
- Feijen E, Font-Gonzalez A, Van der Pal HJH, et al. Risk and temporal changes of heart failure among 5-year childhood cancer survivors: a DCOG-LATER study. *J Am Heart Assoc.* 2019;8(1):e009122.
- Teepen JC, van Leeuwen FE, Tissing WJ, et al. Long-Term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: role of chemotherapy. *J Clin Oncol.* 2017;35(20):2288-2298.
- Meacham LR, Sklar CA, Li S, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. *Arch Intern Med.* 2009;169(15):1381-1388.
- Huang TT, Chen Y, Dietz AC, et al. Pulmonary outcomes in survivors of childhood central nervous system malignancies: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2014;61(2):319-325.
- Ness KK, Kirkland JL, Gramatges MM, et al. Premature physiologic aging as a paradigm for understanding increased risk of adverse health across the lifespan of survivors of childhood cancer. *J Clin Oncol.* 2018;36(21):2206-2215.
- Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer.* 2013;60(4):543-549.
- Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol.* 2015;16(3):e123-36.
- Skinner R, Mulder RL, Kremer LC, et al. Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Lancet Oncol.* 2017;18(2):e75-e90.
- Mulder RL, Kremer LC, Hudson MM, et al. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol.* 2013;14(13):e621-9.
- van Dorp W, Mulder RL, Kremer LC, et al. Recommendations for premature ovarian insufficiency surveillance for female survivors of childhood, adolescent, and young adult cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization

- Group in collaboration with the PanCareSurFup Consortium. *J Clin Oncol*. 2016;34(28):3440-3450.
20. Clement SC, Kremer LCM, Verburg FA, et al. Balancing the benefits and harms of thyroid cancer surveillance in survivors of childhood, adolescent and young adult cancer: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Cancer Treat Rev*. 2018;63:28-39.
 21. Clemens E, van den Heuvel-Eibrink MM, Mulder RL, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. *Lancet Oncol*. 2019;20(1):e29-e41.
 22. Bouffet E, Challinor J, Sullivan M, Biondi A, Rodriguez-Galindo C, Pritchard-Jones K. Early advice on managing children with cancer during the COVID-19 pandemic and a call for sharing experiences. *Pediatr Blood Cancer*. 2020;67(7):e28327.
 23. The global COVID-19 Observatory and Resource Center for Childhood Cancer. <https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer.html>. Accessed June 7, 2020.
 24. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. *Pediatr Blood Cancer*. 2020;67(7):e28409.
 25. Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect*. 2020;80(5):e1-e6.
 26. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80(6):639-645.
 27. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099.
 28. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020;55(5). <https://doi.org/10.1183/13993003.00524-2020>.
 29. Chen R, Liang W, Jiang M, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. *Chest*. 2020. <https://doi.org/10.1016/j.chest.2020.04.010>.
 30. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol*. 2020;146(1):110-118.
 31. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med*. 2020;201(11):1380-1388.
 32. Gao L, Jiang D, Wen XS, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res*. 2020;21(1):83.
 33. Chen T, Dai Z, Mo P, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study. *J Gerontol A Biol Sci Med Sci*. 2020. <https://doi.org/10.1093/gerona/glaa089>.
 34. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337.
 35. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. 2020;31(7):894-901.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Verbruggen LC, Wang Y, Armenian SH, et al. Guidance regarding COVID-19 for survivors of childhood, adolescent and young adult cancer: a statement from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer*. 2020;e28702. <https://doi.org/10.1002/pbc.28702>