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FACULDADE DE MEDICINA
MESTRADO EM SAÚDE DA CRIANÇA E DO ADOLESCENTE

MARIANA CRISTINA MORAES CORSO

**REPERCUSSÃO DA INFECÇÃO POR SARS-CoV-2 EM CRIANÇAS TRATADAS
EM SERVIÇOS DE ONCOLOGIA, HEMATOLOGIA OU TRANSPLANTE DE
MEDULA ÓSSEA NO BRASIL: ESTUDO MULTICÊNTRICO**

Porto Alegre

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A apresentação desta dissertação é requisito parcial para título de mestre do Programa de Pós-Graduação em Saúde da Criança e do Adolescente, da Universidade Federal do Rio Grande do Sul.

Orientadora: Prof.^a Dr^a Mariana Bohns Michalowski

Coorientadora: Dr^a Ciliana Rechenmacher

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BANCA EXAMINADORA:

Prof.^a Dr.^a Cláudia Caceres Astigarraga
Universidade Federal do Rio Grande do Sul / UFRGS

Prof.^a Dr.^a Estela Maria Novak
Universidade de São Paulo / USP

Prof. Dr. Lauro José Gregianin
Universidade Federal do Rio Grande do Sul / UFRGS

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...essa conquista também é de vocês!!!

*"Conheça todas as teorias, domine todas as técnicas,
mas ao tocar uma alma humana, seja apenas outra
alma humana".*

(Carl Jung)

RESUMO

Introdução: No final do ano de 2019, um novo Coronavírus foi identificado por cientistas chineses em Wuhan, na China. Denominado como SARS-CoV-2, em razão da sua grande semelhança com a já conhecida Síndrome Respiratória Aguda Grave, o vírus se propagou rapidamente para outros países incluindo o Brasil. Devido a suas dimensões continentais e diferenças regionais significativas, o país tem enfrentado um grande desafio em estabelecer estratégias adequadas para mitigar o forte impacto causado pela chegada da COVID-19, doença causada pelo SARS-CoV-2, no território nacional. Poucos relatos descrevem o impacto desse vírus na população de pacientes pediátricos com câncer ou submetidos ao transplante de células-tronco hematopoiéticas (TCTH). Menos frequentes ainda são as descrições das situações dessas crianças em países de baixa ou média renda. **Objetivo:** descrever a apresentação clínica e a evolução de crianças com câncer e pacientes submetidos a transplante de células-tronco hematopoiéticas acometidos pela COVID-19. **Métodos:** estudo nacional multicêntrico retrospectivo. Centros foram convidados a participar através da Sociedade Brasileira de Oncologia Pediátrica (SOBOPE) e Associação Brasileira de Hematologia e Hemoterapia (ABHH). Com a utilização do software Redcap® foram registrados, nos 35 centros participantes, pacientes adultos e pediátricos em acompanhamento com suspeita de infecção por SARS-CoV-2 ou que tenham sido expostos à pessoa contaminada. As variáveis registradas incluíram sintomas clínicos, método diagnóstico, medidas terapêuticas e local de tratamento. Além disso, as repercussões da infecção no tratamento inicial e no prognóstico geral também foram avaliadas. Esse estudo foi aprovado pelo Comitê de Ética do HCPA. **Resultados:** Cento e setenta e nove crianças com câncer foram diagnosticadas com SARS-CoV-2. Crianças com IMC baixo ou alto para a idade apresentaram sobrevida global menor 71,4% e 82,6%, respectivamente, do que aquelas com IMC adequado à idade (92,7%) ($p= 0,007$). A gravidade da apresentação ao diagnóstico foi significativamente associada ao pior desfecho ($p < 0,001$). A mortalidade geral na presença de infecção foi de 12,3% ($n=22$). Entre os 86 pacientes receptores de TCTH e diagnosticados com SARS-CoV-2 acompanhadas neste estudo, 24 eram crianças e 62 eram adultos. Desse total, 26 pacientes morreram. A sobrevida global estimada (SG) no dia 40 foi de 69%. Os adultos apresentaram SG inferior às crianças (66% vs 79%, $p= 0,03$). A gravidade dos sintomas no momento do diagnóstico, escore ECOG, exames laboratoriais (proteína C reativa, valores de ureia) foram maiores nos pacientes que foram a óbito ($p < 0,05$). **Conclusões:** Em crianças com câncer e COVID-19, o menor IMC foi associado a um pior prognóstico. A mortalidade neste grupo de pacientes (12,3%) foi significativamente maior do que a descrita na população pediátrica em geral (~1%). No que se refere aos receptores de TCTH infectados com SARS-CoV-2 também foi observada uma alta taxa de mortalidade principalmente em adultos e pacientes com apresentação inicial crítica de COVID-19. Esses achados mostram a fragilidade de ambos os grupos estudados à infecção por SARS-CoV-2 e evidencia a importância da adesão dessas populações às medidas preventivas, além da vacinação dos familiares e equipe assistencial.

Palavras-chave: SARS-CoV-2. COVID-19. Oncologia. Transplante de células-tronco hematopoiéticas. Câncer.

ABSTRACT

Introduction: In late 2019, a new coronavirus was identified by Chinese scientists in Wuhan, China. Named SARS-CoV-2, for its great similarity to the already known Severe Acute Respiratory Syndrome, the virus quickly spread to other countries, including Brazil. Due to its continental dimensions and significant regional differences, the country has faced a great challenge in establishing adequate strategies to mitigate the strong impact caused by the arrival of COVID-19, a disease caused by SARS-CoV-2, in the national territory. Few reports describe the impact of this virus in the population of pediatric patients with cancer or undergoing hematopoietic stem cell transplantation (HSCT). Even less frequent are descriptions of the situation of these children in low- and middle-income countries. **Objective:** to describe the clinical presentation and evolution of children with cancer and patients undergoing hematopoietic stem cell transplantation affected by COVID-19. **Methods:** national multicenter retrospective study. The centers were invited to participate through the Brazilian Society of Pediatric Oncology (SOBOPE) and the Brazilian Association of Hematology and Hemotherapy (ABHH). Using Redcap® software, follow-up adult and pediatric patients with suspected SARS-CoV-2 infection or who were exposed to an infected person were enrolled from 35 participating centers. The variables recorded included clinical symptoms, diagnostic method, therapeutic measures, and treatment site. In addition, the repercussions of infection on initial treatment and overall prognosis were also evaluated. This study was approved by the HCPA Ethics Committee. **Results:** One hundred and seventy-nine children with cancer were diagnosed with SARS-CoV-2. Children with a low or high BMI for their age had 71.4% and 82.6% lower overall survival, respectively, than those with an age-appropriate BMI (92.7%) ($p=0.007$). Severity of presentation at diagnosis was significantly associated with worse outcome ($p < 0.001$). Overall mortality in the presence of infection was 12.3% ($n=22$). Among the 86 HSCT recipients diagnosed with SARS-CoV-2 followed up in this study, 24 were children and 62 were adults. Of this total, 26 patients died. The estimated overall survival (OS) at day 40 was 69%. Adults had lower OS than children (66% vs 79%, $p=0.03$). Symptom severity at diagnosis, ECOG score, laboratory tests (C-reactive protein, urea values) were higher in patients who died ($p < 0.05$). **Conclusions:** In children with cancer and COVID-19, lower BMI was associated with worse prognosis. Mortality in this group of patients (12.3%) was significantly higher than that reported in the general pediatric population (~1%). Regarding HSCT recipients infected with SARS-CoV-2, a high mortality rate was also observed, mainly in adults and patients with critical initial presentation of COVID-19. These findings show the fragility of both groups studied for SARS-CoV-2 infection and highlight the importance of these two populations adhering to preventive measures, in addition to vaccinating family members and care teams.

Keywords: SARS-CoV-2. COVID-19. Oncology. Hematopoietic Stem Cell Transplantation. Cancer.

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LISTA DE ABREVIATURAS E SIGLAS

ABHH	Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular
ACM	Análise de Correspondência Múltipla
ANOVA	Análise de Variância
BMI	Body mass index
CAAE	Certificado de Apresentação de Apreciação Ética
CAR	Chimeric antigen receptor
CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
COVID-19	Coronavirus disease of 2019
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
GVHD	Graft Versus - host disease
HCPA	Hospital de Clínicas de Porto Alegre
HSCT	Hematopoietic stem-cell transplantation
ICU	Intensive care unit
IgM	Imunoglobulina M / Immunoglobulin M
IgG	Imunoglobulina G / Immunoglobulin G
IMC	Índice de Massa Corporal
IV	Intravenous
Kg	Kilograma

LMIC	Low- and middle-income countries
m	Metro
MCA	Multiple Correspondence Analysis
MERS-CoV	Middle East respiratory syndrome coronavirus
MIS-C	Multisystem inflammatory syndrome
OMS	Organização Mundial da Saúde
OS	Overall survival
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase-polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SBTMO	Sociedade Brasileira de Transplante de Medula Óssea
SD	Standard deviation
SDRA	Síndrome do desconforto respiratório agudo
SG	Sobrevida Global
SOBOPE	Sociedade Brasileira de Oncologia Pediátrica
SUS	Sistema Único de Saúde
TCTH	Transplante de células-tronco hematopoiéticas
UTI	Unidade de tratamento intensivo
WHO	World Health Organization

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1 INTRODUÇÃO

Um novo Coronavírus foi identificado por cientistas chineses após um surto de pneumonia de causa desconhecida em dezembro de 2019 na cidade de Wuhan, na China (WANG *et al.*, 2020). Este novo vírus (RNA-betacoronavírus) foi denominado posteriormente de SARS-CoV-2 devido à sua grande semelhança com a já conhecida Síndrome Respiratória Aguda Grave. Devido à suscetibilidade da maior parte da população, houve uma rápida disseminação para outros países desafiando a infraestrutura econômica e de saúde pública em todo o mundo (WEAVER & WIENER, 2020). Em 11 de março de 2020, a Organização Mundial da Saúde (OMS) classificou a situação como emergência de saúde pública internacional.

A chegada da COVID-19, doença causada por esse microrganismo, ao Brasil em fevereiro de 2020 representou um grande desafio no estabelecimento de estratégias adequadas para mitigar o forte impacto causado pela doença, uma vez que o país possui dimensões continentais e diferenças regionais significativas. Assim como em outros países, após enfrentar um período crítico com altas taxas de transmissão do SARS-CoV-2 entre a sua população, o Brasil apresentou uma breve estabilização e princípio de queda nos registros de contaminações. Contudo, a flexibilização das ações de isolamento social, associada a novas variantes mais contagiosas e letais do coronavírus, geraram um crescimento exponencial de novos casos, ocasionando um colapso no sistema de saúde e um alarmante número de mortes diárias (DE SOUZA *et al.*, 2021; DIAZ; VERGARA, 2021).

É importante destacar que o Brasil possui o Sistema Único de Saúde (SUS), um dos maiores e mais complexos sistemas públicos de saúde do mundo, que garante a universalização da saúde por meio da atenção básica, bem como atendimento de média e alta complexidade. Porém, apesar de possuir esse importante diferencial no combate à pandemia, a difícil situação econômica e social enfrentada por parte de sua população pode aumentar os riscos de exposição ao SARS-CoV-2 e também causar um pior prognóstico. A grande proporção de trabalhadores informais no Brasil exprime a importância da implementação de medidas públicas de proteção social e apoio a segmentos vulneráveis para que se garantam medidas de contenção eficazes e sustentáveis, como o distanciamento social (AQUINO *et al.*, 2020).

Nesse cenário, o desenvolvimento de diferentes vacinas vem contribuindo de forma significativa no combate a esse vírus. Entretanto, devido à alta demanda, limitada capacidade de produção desses imunizantes e equivocadas estratégias governamentais, a pandemia no Brasil já se apresenta como a maior crise de saúde pública já enfrentada nesse país (BOSCHIERO *et al.*, 2021; CARNUT; MENDES; GUERRA, 2021). Até o presente momento, o Brasil possui 76,9% da população com o esquema vacinal completo (aplicação de 2 doses), 39,9% dose de reforço (3º dose) e acumula a marca de 662.185 vidas perdidas. (BRASIL. Ministério da Saúde).

Enquanto a imunização coletiva é realizada, vários estudos abordando o impacto da COVID-19 na população mundial são publicados. Informações sobre a suscetibilidade dos indivíduos a este novo vírus, faixas etárias mais vulneráveis, formas de contágio, diferentes manifestações clínicas e medidas terapêuticas adotadas são geradas e contribuem de forma significativa no estabelecimento de estratégias para amenizar o impacto dessa doença. Porém, poucos estudos abordaram a repercussão da COVID-19 em pacientes imunocomprometidos como oncológicos ou submetidos à transplante de células-tronco hematopoiéticas (TCTH) e ainda menos em pacientes que residem em países de baixa e média renda (*LMICs*) (MONTROYA *et al.*, 2020; VASQUEZ *et al.*, 2020). Diante desse quadro, após apresentar um breve panorama sobre o cenário da COVID-19 na oncologia pediátrica e TCTH, o presente trabalho buscou descrever a repercussão desta infecção nesta população de pacientes através de um estudo de registro nacional multicêntrico (CORSO *et al.*, 2020).

2 REVISÃO DA LITERATURA

2.1 ONCOLOGIA

O câncer é a principal causa de morte por doença entre crianças e adolescentes. Compreendendo cerca de 3% de todas as neoplasias malignas, abrange um amplo espectro de doenças com diferentes características clínicas, biológicas e histológicas. O diagnóstico precoce e preciso e o rápido acesso a tratamentos de qualidade são fatores determinantes para a boa evolução e cura dos pacientes (JANEIRO, 2019).

As principais terapias adotadas são cirurgia, quimioterapia, radioterapia, imunoterapia, terapia-alvo e TCTH. Sendo necessário, em muitos casos, combiná-los. Devido ao amplo espectro de neoplasias, os tratamentos são direcionados de acordo com o tipo e estágio da doença. A cirurgia oncológica atua, ao lado da quimioterapia e radioterapia, como parte do tripé de tratamento da doença e consiste na remoção total ou parcial de tumores. Já os compostos quimioterápicos, por sua vez, visam destruir diretamente as células tumorais agindo de forma sistêmica enquanto a radioterapia busca um melhor controle local. Além disso, outros tratamentos surgem como boas alternativas. Como exemplo, recentemente há o advento das imunoterapias que buscam estimular o sistema imunológico do paciente a diferenciar células saudáveis de cancerígenas, combatendo-as e eliminando o câncer, e as terapias-alvo moleculares que surgem como tratamentos inovadores desenvolvidos para atuar em alvos específicos do tumor, como em proteínas ou receptores de superfície (INSTITUTO NACIONAL DO CÂNCER, 2021). Os avanços nos tratamentos vêm apresentando reflexos diretos na sobrevida dos pacientes. Em países desenvolvidos, a sobrevida global de crianças com câncer é de aproximadamente 80%, já no Brasil, essa estimativa é de 64% (JANEIRO, 2019).

Apesar dos grandes avanços em relação a diagnósticos mais precisos e tratamentos direcionados, o câncer ainda gera grandes preocupações quanto à vulnerabilidade dos pacientes imunocomprometidos. Dessa forma, a chegada do SARS-CoV-2 e a COVID-19, despertou um alerta sobre a suscetibilidade destes pacientes frente à pandemia.

Conforme citado anteriormente, poucos estudos abordaram o impacto da COVID-19 na população pediátrica com câncer e ainda menos em crianças de LMICs

(MONTROYA *et al.*, 2020; VASQUEZ *et al.*, 2020). No que se refere às pessoas saudáveis, todas as faixas etárias são suscetíveis ao SARS-CoV-2 (HOANG *et al.*, 2020). Porém, diferentes estudos indicam que crianças e adolescentes apresentam um menor risco de desenvolver quadros graves quando comparados com adultos, principalmente idosos (CLARK *et al.*, 2020; DING; YAN; GUO, 2020). O mesmo parece se apresentar em pacientes oncológicos. Liang *et al.* sugerem que adultos com câncer têm um risco aumentado de infecção por este vírus (LIANG *et al.*, 2020). No entanto, Boulad, Rojas e Ferrari e seus respectivos coautores acreditam que pacientes pediátricos com câncer, embora tratados como de alto risco, podem não ser mais vulneráveis à infecção ou morbidade resultante de SARS-CoV-2 do que outras crianças (BOULAD *et al.*, 2020; DE ROJAS *et al.*, 2020; FERRARI *et al.*, 2020). Isso, contudo, não pode ser generalizado. O câncer não só pode predispor o indivíduo a novas infecções como também dificultar o processo de convalescência. Além disso, outro obstáculo enfrentado por esses pacientes está relacionado ao possível comprometimento do acesso aos centros de oncologia pediátrica localizados em regiões urbanizadas, como capitais ou centros econômicos (GRABOIS, DE OLIVEIRA, SÁ CARVALHO, 2013).

Nesse cenário, uma outra população de risco são os receptores de TCTH. Isso porque as infecções virais são uma causa importante de morbidade e mortalidade para esses pacientes devido a mielossupressão profunda e prolongada.

2.2 TRANSPLANTE DE CÉLULAS-TRONCO HEMATOPOIÉTICAS

O TCTH alogênico consiste na substituição de medula óssea doente por células-tronco hematopoiéticas saudáveis, provenientes de um doador aparentado ou não aparentado. Já o TCTH autólogo é o transplante de células do próprio paciente, permitindo assim a recuperação hematológica mais rápida após a realização de altas doses de quimioterapia. O objetivo é a reconstituição do processo de formação de novas células sanguíneas. Essa terapia é alternativa disponível para o tratamento de diferentes doenças. Sua indicação é apropriada quando a sobrevida global e qualidade de vida do paciente se apresentam como uma opção significativamente melhor quando comparado ao tratamento convencional. Porém, as indicações do transplante devem ser regularmente reavaliadas, considerando os avanços científicos de ambas as áreas (SEBER, 2009).

Assim como no cenário da oncologia pediátrica, até o momento, poucos dados foram publicados sobre as manifestações clínicas e resultados de receptores de transplantes em pacientes com COVID-19 em países de média e baixa renda. Porém, devido ao potencial risco envolvido, a Sociedade Brasileira de Transplante de Medula Óssea preparou diretrizes visando o auxílio nas decisões clínicas com o objetivo de proteger receptores e doadores neste cenário pandêmico. Como principais medidas recomendadas estão a criopreservação de produtos de células-tronco antes de iniciar o regime de condicionamento ou dispor de um doador alternativo caso seja necessário, realização de *RT-PCR* COVID-19 antes do transplante para o paciente e doador, adiamento de transplantes não urgentes, especialmente no contexto de doenças não malignas, além da adesão estrita aos protocolos de controle de infecção durante a internação do TCTH (ALGWAIZ *et al.*, 2020; LJUNGMAN *et al.*, 2020; MACHADO, 2020). As recomendações propostas vêm auxiliando a tomada de decisões referente a esse público, porém, devido ao alto risco de contágio, alguns pacientes foram infectados.

Frente a estes questionamentos, este trabalho visou descrever o impacto da COVID-19 na população pediátrica em tratamento contra o câncer, assim como pacientes adultos e crianças submetidos à TCTH. Por meio de um registro nacional multicêntrico buscamos identificar potenciais fatores de risco objetivando contribuir para o entendimento da incidência, manifestações clínicas e a evolução da COVID-19 nessas populações (CORSO *et al.*, 2020).

3 JUSTIFICATIVA

O momento que estamos vivendo em função da pandemia pode afetar os cuidados prestados para pacientes em tratamento onco-hematológico não apenas no Brasil, como em outros países. Ainda são escassas as publicações que relatam o impacto da COVID-19 na oncologia pediátrica ou em pacientes submetidos a TCTH, principalmente em países de média e baixa renda. Através do estudo proposto, poderemos entender a incidência, as manifestações clínicas e a evolução da COVID-19 em pacientes oncológicos pediátricos ou submetidos a TCTH em todo o país e comparar os resultados observados com os relatos descritos na literatura internacional.

4 HIPÓTESE

A manifestação e evolução clínica de crianças e adolescentes com câncer, assim como pacientes submetidos a transplante de medula óssea acometidas por SARS-CoV-2 é mais grave e com maior risco de mortalidade quando comparada com a população.

5 OBJETIVO

5.1 OBJETIVO GERAL

Descrever a manifestação e a evolução clínica de crianças e adolescentes com câncer, assim como pacientes submetidos à transplante de células tronco hematopoiéticas no Brasil acometidos pelo vírus SARS-CoV-2.

5.2 OBJETIVOS ESPECÍFICOS

- a) descrever os primeiros sintomas de pacientes portadores do vírus SARS-CoV-2 em tratamento oncológico e TCTH;
- b) acompanhar a evolução clínica dos pacientes durante o processo infeccioso;
- c) comparar a sobrevida destes pacientes com os dados descritos na literatura internacional;
- d) avaliar fatores de risco relacionados à mortalidade nesta população;
- e) descrever os principais desfechos observados nestes pacientes durante o desenvolvimento deste estudo.

6 METODOLOGIA

6.1 DELINEAMENTO

Estudo de coorte multicêntrico observacional.

6.2 LOCAL

Centros de tratamento oncológico, hematológico ou de transplante de medula óssea localizados no Brasil.

6.3 POPULAÇÃO

Os pacientes registrados neste estudo foram analisados em dois grupos distintos:

6.3.1 Oncologia pediátrica

Pacientes de 0 a 18 anos completos (BRASIL,1990) portadores do vírus SARS-CoV-2 em acompanhamento ou remissão em centros de oncologia e hematologia localizados no Brasil.

6.3.2 TCTH

Pacientes submetidos à TCTH autólogo ou alogênico portadores do vírus SARS-CoV-2, atendidos em centros de oncologia, hematologia e transplante de medula óssea localizados no Brasil.

6.4 AMOSTRA

Dois grupos de pacientes foram incluídos conforme critérios de inclusão descritos abaixo no período de março 2020 a março 2021.

6.4.1 Critérios de inclusão

6.4.1.1 Oncologia pediátrica (Coorte 1)

a) Paciente de 0 a 18 anos completos que apresentaram e/ou:

- Diagnósticos de tumores tratados por quimioterapia, radioterapia, imunoterapia ou terapia-alvo;

- Tratamento oncológico em curso ou terminado há menos de 12 meses;
- b) Diagnóstico de COVID-19 através de PCR para SARS-CoV-2

6.4.1.2 TCTH (Coorte 2)

a) Pacientes que apresentaram

- Antecedente de transplante alogênico ou autólogo de células hematopoiéticas há menos de 24 meses;
- Diagnóstico de COVID-19 a partir de PCR SARS-CoV-2 positivo

Em ambos os estudos, os pesquisadores poderiam incluir pacientes que preenchem os critérios de inclusão durante a pandemia mesmo que anterior à aprovação do comitê de ética com dados oriundos de prontuário médico, desde que assinado o Termo de Consentimento Livre e Esclarecido.

Os pacientes puderam ser incluídos a partir de suspeita de diagnóstico de COVID-19, porém a confirmação foi realizada por meio do teste molecular (*RT-PCR*) e/ou sorologia (IgM e/ou IgG).

6.4.2 Critério de exclusão

Para ambas as pesquisas:

Diagnóstico de COVID-19 baseado apenas em critérios clínicos e/ou radiológicos cujos exames de diagnóstico molecular (*RT-PCR*) e/ou sorologia (IgM e IgG) apresentaram resultados negativos.

Na coorte 1 (oncologia pediátrica) participaram 17 centros distribuídos nas cinco regiões do Brasil. Já na coorte 2 (TCTH) participaram 21 centros distribuídos nas cinco regiões do Brasil.

6.4.3 Tamanho da amostra

O cálculo amostral não foi realizado por se tratar de um estudo com amostra por conveniência.

6.5 COLETA E PROCESSAMENTO DE DADOS

Os dados foram coletados através do formulário unificado para ambos os estudos, elaborado pelo grupo coordenador e registrado no software Redcap®, garantindo, assim, o sigilo das informações e permitindo a integração com as demais

instituições nacionais participantes. Uma formação para o uso do aplicativo foi realizada de forma remota antes do início da inserção dos dados. A cada centro foi permitido acesso às informações de sua própria unidade. Somente o centro coordenador teve acesso aos dados globais. Os registros foram avaliados regularmente quanto a sua conformidade pela equipe do centro coordenador.

6.6 CENTROS DE TRATAMENTO ONCOLÓGICO, HEMATOLÓGICO OU DE TRANSPLANTE DE MEDULA ÓSSEA

Por meio da divulgação pela Sociedade Brasileira de Oncologia Pediátrica (SOBOPE), Associação Brasileira de Hematologia e Hemoterapia (ABHH), 35 centros distribuídos nas cinco regiões do Brasil se vincularam ao projeto.

6.6.1 Centros colaboradores:

- **Centro coordenador**

Hospital de Clínicas de Porto Alegre (HCPA) - Porto Alegre/RS - (Oncologia Pediátrica e TCTH);

- **Região Centro-Oeste**

Hospital da Criança de Brasília José Alencar - Brasília/DF - (Oncologia Pediátrica);

- **Região Nordeste**

Centro de Oncologia de Sergipe Dr. Oswaldo Leite - Aracaju/SE - (Oncologia Pediátrica e TCTH);

Hospital Infantil Albert Sabin - Fortaleza/CE - (Oncologia Pediátrica e TCTH);

Hospital Martagão Gesteira - Salvador/BA - (Oncologia Pediátrica);

Hospital São Rafael - Salvador/BA - (TCTH);

Hospital Universitário Professor Edgar Santos - Salvador/BA - (TCTH);

Hospital Universitário Walter Cantídio - Fortaleza/CE - (TCTH);

Instituto de Medicina Integral Professor Fernando Figueira - IMIP - Recife/PE - (Oncologia Pediátrica);

REAL Hospital Português de Beneficência em Pernambuco - Recife/PE - (TCTH);

- **Região Norte**

Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas - Manaus/AM - (Oncologia Pediátrica);

Hospital Oncológico Infantil Octávio Lobo- Belém/PA - (Oncologia Pediátrica);

- **Região Sudeste**

Hospital Amaral Carvalho - Jaú/SP - (Oncologia Pediátrica e TCTH);

Hospital das Clínicas de Ribeirão Preto, Ribeirão Preto/SP - (Oncologia Pediátrica);

Hospital de Câncer de Barretos - Fundação Pio XII - Barretos/SP – (Oncologia Pediátrica);

Hospital de Clínicas de São Paulo - São Paulo/SP - (TCTH);

Hospital Infantil Darcy Vargas - São Paulo/SP - (Oncologia Pediátrica);

Hospital Israelita Albert Einstein - São Paulo/SP - (Oncologia Pediátrica e TCTH);

Hospital Nove de Julho - São Paulo/SP - (TCTH);

Hospital São Paulo - São Paulo/SP - (TCTH);

Hospital Sírio-Libanês - São Paulo/SP - (TCTH);

Instituto Brasileiro de Controle do Câncer - São Paulo/SP - (TCTH);

Instituto da Criança do Hospital das Clínicas - FMUSP - São Paulo/SP - (TCTH);

Instituto de Oncologia Pediátrica – GRAACC/UNIFESP - São Paulo/SP - (Oncologia Pediátrica e TCTH);

Instituto de Tratamento do Câncer Infantil - ITACI, São Paulo/SP - (Oncologia Pediátrica);

- **Região Sul**

Associação Hospitalar Beneficente São Vicente de Paulo - Passo Fundo/RS - (Oncologia Pediátrica);

Hospital Criança Conceição - Porto Alegre/RS - (Oncologia Pediátrica);

Hospital de Clínicas da Universidade Federal do Paraná - Curitiba/PR - (TCTH)

Hospital do Câncer de Cascavel - UOPECCAN - Cascavel/PR - (Oncologia Pediátrica);

Hospital Erasto Gaertner - Curitiba/PR - (Oncologia Pediátrica e TCTH);

Hospital Infantil Joana de Gusmão – Florianópolis/SC - (Oncologia Pediátrica);

Hospital Nossa Senhora das Graças - Curitiba/PR - (TCTH);

Hospital Oncopediátrico Erastinho – Curitiba/PR - (Oncologia Pediátrica e TCTH);

Hospital Pequeno Príncipe - Curitiba/PR - (Oncologia Pediátrica e TCTH);

Hospital Universitário de Londrina / UEL – Londrina/PR - (TCTH).

6.6.2 Organização entre os centros

Semanalmente os centros participantes receberam resultados parciais do projeto via e-mail (APÊNDICE A), além de participarem de reuniões remotas para discussão do andamento do estudo.

Foram nomeados em publicações todos os centros que realizaram inclusões no projeto e participaram ativamente das atividades. A ordem das citações foi realizada a partir do número de pacientes incluídos, respeitando o primeiro e últimos autores de acordo com a atividade desenvolvida, envolvimento no projeto e colaboração na análise e redação.

6.7 VARIÁVEIS UTILIZADAS

As variáveis registradas incluíram idade, índice de massa corporal (IMC), método diagnóstico, sintomas clínicos, Status de Desempenho Eastern Cooperative Oncology Group (ECOG) (OKEN, MM. *et al.*, 1982) no momento do diagnóstico da COVID-19, medidas terapêuticas e ambiente de tratamento. Além disso, foram incluídas as repercussões da infecção no tratamento inicial e no prognóstico geral. O IMC de todos os pacientes foi calculado dividindo-se a massa corporal (Kg) pelo quadrado da altura (m). A interpretação dos resultados foi baseada nos parâmetros definidos pela Organização Mundial da Saúde (OMS). Considerou-se a idade e o sexo com seus respectivos parâmetros pré-estabelecidos para pacientes pediátricos e, no caso de pacientes adultos, parâmetros descritos na Tabela 1.

Quadro 1 - Classificação Índice Massa Corporal (pacientes adultos)

IMC	Classificação
Abaixo de 18,5	Baixo Peso
Entre 18,6 e 24,9	Peso Adequado
Entre 25,0 e 29,9	Sobrepeso
Acima de 29,9	Obesidade

Fonte: Organização Mundial da Saúde

A gravidade da apresentação clínica ao diagnóstico foi baseada em critérios estabelecidos por Qiu *et al.* e pode ser verificada na Tabela 2.

Quadro 2 - Classificações de gravidade a partir de sintomas clínicos

Leve	<ul style="list-style-type: none"> • Sintomas respiratórios superiores (congestão faríngea, dor de garganta, febre) por um curto período; <ul style="list-style-type: none"> • Ausência de suplementação de oxigênio; • Sem apresentação radiográfica e séptica anormal.
Moderada/ Severa	<ul style="list-style-type: none"> • Características clínicas moderadas, além de quaisquer manifestações que sugerem progressão da doença; <ul style="list-style-type: none"> • Pneumonia leve; • Hipoxemia (algum grau); • Oxigênio suplementar; • Sem complicações e manifestações relacionadas a condições críticas; <ul style="list-style-type: none"> • Lesão miocárdica; • Elevadas enzimas hepáticas; <p>Disfunção de coagulação e quaisquer outras manifestações que sugerem lesões em órgãos vitais.</p>
Crítica	<ul style="list-style-type: none"> • Progressão rápida da doença, além de quaisquer outras condições como: insuficiência respiratória com necessidade de ventilação mecânica (SDRA, hipóxia persistente que não pode ser aliviada por inalação através de cateteres nasais ou máscaras); <ul style="list-style-type: none"> • Choque séptico; • Internação na UTI; • Falência de órgãos (necessidade de monitoramento na UTI).

Abreviações: SDRA, síndrome do desconforto respiratório agudo; UTI, unidade de terapia intensiva

Os pacientes adultos foram classificados clinicamente pelo Status de Desempenho *ECOG* (Tabela 3).

Quadro 3 - Status de desempenho *ECOG*

0	Assintomático - totalmente ativo, capaz de realizar todo o desempenho pré-doença sem restrição.
1	Sintomático, mas completamente ambulatorial - restrito a atividades fisicamente extenuantes. Capaz de realizar trabalhos de natureza leve e sedentária (trabalho doméstico leve, trabalho de escritório).
2	Sintomático, <50% na cama durante o dia - ambulatorial e capaz de cuidar de si, mas incapaz de suportar todas as atividades de trabalho. Acima ou cerca de 50% das horas de vigília.
3	Sintomático, >50% na cama, mas não confinado a ela. Capacidade de autocuidado limitado. Confinado à cama ou cadeira mais de 50% das horas de vigília.
4	Acamado (completamente incapacitado). Incapacidade de autocuidado. Totalmente confinado à cama ou cadeira.
5	Morto

Fonte: Status de Desempenho *ECOG*

No estudo TCTH, o desfecho primário considerado se referiu à sobrevida global de 40 dias após a confirmação da infecção por SARS-CoV-2.

6.8 ANÁLISES ESTATÍSTICAS

As análises estatísticas foram realizadas de acordo com as variáveis selecionadas para cada estudo.

As variáveis contínuas foram avaliadas com o teste de normalidade de Shapiro-Wilk; aqueles com distribuição assimétrica foram expressos em medianas e intervalos interquartis. As variáveis qualitativas foram resumidas em frequências absolutas e relativas. O nível de significância adotado foi de 0,05. Os dados foram compilados em planilha do Microsoft Excel® e analisados no PASW Statistics® versão 18.0 e WinPepi versão 11.65. O teste exato de Fisher e o teste do qui-quadrado de Pearson foram usados para variáveis categóricas e o teste U de Mann-Whitney para variáveis quantitativas. A análise de variância (ANOVA) foi utilizada para verificar a distribuição dos dados entre três ou mais grupos. Testes de log rank

(Mantel-Cox) foram usados para comparar as curvas de sobrevida de Kaplan-Meier entre dois ou mais grupos. Foi realizada análise multivariada comparando variáveis significativas na análise univariada. A relação entre as variáveis foi realizada por meio da Análise de Correspondência Múltipla (ACM), considerando apenas os casos completos. Para selecionar as variáveis para o modelo de melhor ajuste, foram utilizados o teste de confiabilidade e a variância explicada dos critérios das duas primeiras dimensões.

6.9 CONSIDERAÇÕES ÉTICAS

Este projeto foi aprovado pelo Comitê de Ética do AGHUse e submetido à Plataforma Brasil - CAAE 30983320.4.1001.5327 e GPPG N°2020-0183. Os participantes ou responsáveis pelos participantes menores assinaram um Termo de Consentimento Livre e Esclarecido (APÊNDICE B), em duas vias, no qual foram informados sobre os objetivos dos respectivos estudos, bem como os procedimentos, riscos e benefícios.

Os autores declaram não haver conflito de interesses.

REFERÊNCIAS

ALGWAIZ, G. *et al.* Real-world issues and potential solutions in hematopoietic cell transplantation during the COVID-19 pandemic: Perspectives from the worldwide network for blood and marrow transplantation and Center for International Blood and Marrow Transplant Research He. **Biology of Blood and Marrow Transplantation**, [S. l.], v. 26, n. 12, p. 2181–2189, 2020. Disponível em: <https://doi.org/10.1016/j.bbmt.2020.07.021>

AQUINO, E. M. L. *et al.* Social distancing measures to control the COVID-19 pandemic: Potential impacts and challenges in Brazil. **Ciencia e Saude Coletiva**, [S. l.], v. 25, p. 2423–2446, 2020. Disponível em: <https://doi.org/10.1590/1413-81232020256.1.10502020>

BOSCHIERO, M. N. *et al.* One year of coronavirus disease 2019 (Covid-19) in brazil: A political and social overview. **Annals of Global Health**, [S. l.], v. 87, n. 1, p. 1–27, 2021. Disponível em: <https://doi.org/10.5334/AOGH.3182>

BOULAD, F. *et al.* COVID-19 in children with cancer in New York city. **JAMA Oncology**, [S. l.], v. 6, n. 9, p. 1459–1460, 2020. Disponível em: <https://doi.org/10.1001/jamaoncol.2020.2028>

BRASIL. Decreto-lei nº. 8.069, de 13 de julho de 1990. **Estatuto da Criança e do Adolescente**. Disponível em: http://www.planalto.gov.br/ccivil_03/leis/l8069.htm.

CARNUT, L.; MENDES, Á.; GUERRA, L. Coronavirus, capitalism in crisis and the perversity of public health in Bolsonaro's Brazil. **International Journal of Health Services**, [S. l.], v. 51, n. 1, p. 18–30, 2021. Disponível em: <https://doi.org/10.1177/0020731420965137>

CLARK, A. *et al.* Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. **The Lancet Global Health**, [S. l.], v. 8, n. 8, p. e1003–e1017, 2020. Disponível em: [https://doi.org/10.1016/S2214-109X\(20\)30264-3](https://doi.org/10.1016/S2214-109X(20)30264-3)

CORSO, M. *et al.* RECOV-Brasil : COVID-19 in children undergoing cancer treatment or HSCT in Brazil. [S. l.], p. 1–3, 2020. Disponível em: <https://doi.org/10.1002/pbc.28410.3>

DE ROJAS, T. *et al.* COVID-19 infection in children and adolescents with cancer in Madrid. **Pediatric Blood and Cancer**, [S. l.], v. 67, n. 7, p. 19–21, 2020. Disponível em: <https://doi.org/10.1002/pbc.28397>

DE SOUZA, F. S. H. *et al.* Second wave of COVID-19 in Brazil: younger at higher risk. **European Journal of Epidemiology**, [S. l.], v. 36, n. 4, p. 441–443, 2021. Disponível em: <https://doi.org/10.1007/s10654-021-00750-8>

DIAZ, R. S.; VERGARA, T. R. C. The COVID-19 second wave: a perspective to be explored. **Brazilian Journal of Infectious Diseases**, [S. l.], v. 25, n. 1, p. 101537, 2021. Disponível em: <https://doi.org/10.1016/j.bjid.2020.101537>

DING, Y.; YAN, H.; GUO, W. Clinical characteristics of children with COVID-19: a meta-analysis. **Frontiers in Pediatrics**, [S. l.], v. 8, n. July, p. 1–10, 2020. Disponível em: <https://doi.org/10.3389/fped.2020.00431>

FERRARI, A. *et al.* Children with cancer in the time of COVID-19: an 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy. **Pediatric Blood and Cancer**, [S. l.], n. April, p. 3–5, 2020. Disponível em: <https://doi.org/10.1002/pbc.28410>

GRABOIS, MF.; DE OLIVEIRA, EXG; SA CARVALHO, M. Assistência ao câncer entre crianças e adolescentes: mapeamento dos fluxos origem-destino no Brasil. **Revista Saúde Pública**. [S. l.] v. 47, n. 2, p.368-378, 2013

HOANG, A. *et al.* COVID-19 in 7780 pediatric patients: a systematic review. **E Clinical Medicine**, [S. l.], v. 24, p. 100433, 2020. Disponível em: <https://doi.org/10.1016/j.eclinm.2020.100433>

INSTITUTO NACIONAL DO CÂNCER (Brasil). Tratamento [Brasília, DF]: **Instituto Nacional do Câncer**, 2021. Disponível em: <https://www.inca.gov.br/tratamento>. Acesso em: 02 set. 2021

JANEIRO, R. I. O. D. E. **Panorama de Oncologia Pediátrica**, v. 6, n. 6, ISSN 2594-6846, 2019.

LIANG, W. *et al.* Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. **The Lancet Oncology**, [S. l.], v. 21, n. 3, p. 335–337, 2020. Disponível em: [https://doi.org/10.1016/S1470-2045\(20\)30096-6](https://doi.org/10.1016/S1470-2045(20)30096-6)

LJUNGMAN, P. *et al.* The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. **Bone Marrow Transplantation**, [S. l.], v. 55, n. 11, p. 2071–2076, 2020. Disponível em: <https://doi.org/10.1038/s41409-020-0919-0>

MACHADO, C. M. COVID-19 and hematopoietic stem cell transplantation: recommendations from the Brazilian Society of Bone Marrow Transplantation (SBTMO). **Journal of Bone Marrow Transplantation and Cellular Therapy**, [S. l.], v. 1, n. 1, p. 67–72, 2020. Disponível em: <https://doi.org/10.46765/2675-374x.2020v1n1p67-72>

MONTOYA, J. *et al.* COVID-19 in pediatric cancer patients in a resource-limited setting: national data from Peru. **Pediatric Blood and Cancer**, [S. l.], v. 7, n. July, p. 1–2, 2020. Disponível em: <https://doi.org/10.1002/pbc.28610>

OKEN, MM. *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. **American Journal of Clinical Oncology**. p.649-655, 1982.

QIU, H. *et al.* Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. **Lancet Infect Dis.** 2020;20:689–96

SEBER, Adriana. Hematopoietic stem cell transplantation in childhood: current status and perspectives. **Revista Brasileira de Hematologia e Hemoterapia**, [S. l.], v. 31, n. SUPPL. 1, p. 59–67, 2009. Disponível em: <https://doi.org/10.1590/S1516-84842009005000035>

VACINAÇÃO, Governo Federal, **Ministério da Saúde-Coronavírus, 2022.** Disponível em: < <https://www.gov.br/saude/pt-br/coronavirus/informes-diarios-covid-19> >. Acesso em: 17 abr. e 2022.

VASQUEZ, L. *et al.* Early impact of the COVID-19 pandemic on pediatric cancer care in Latin America. **The Lancet Oncology**, [S. l.], v. 21, n. 6, p. 753–755, 2020. Disponível em: [https://doi.org/10.1016/S1470-2045\(20\)30280-1](https://doi.org/10.1016/S1470-2045(20)30280-1)

WANG, C. *et al.* A novel coronavirus outbreak of global health concern. **The Lancet**, [S. l.], v. 395, n. 10223, p. 470–473, 2020. Disponível em: [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9)

WEAVER, M. S.; WIENER, L. Applying palliative care principles to communicate with children about COVID-19. **Journal of Pain and Symptom Management**, [S. l.], v. 60, n. 1, p. e8–e11, 2020. Disponível em: <https://doi.org/10.1016/j.jpainsymman.2020.03.020>

7 RESULTADOS

7.1 ARTIGO 1

SARS-CoV-2 in children with cancer in Brazil: results of a multicenter national registry

Mariana Cristina Moraes Corso¹; Victor Jablonski Soares²; Anna Maria Prado Amorim, MD³; Rosana Cipolotti, MD, PhD^{4,5}; Isis Maria Quezado Magalhães, MD, PhD⁶; Mecneide Mendes Lins, MD, PhD⁷; Silvana Forsait, MD⁸; Luciana Nunes Silva, MD, MSc⁹; Ana Virginia Lopes de Sousa, MD, MSc¹⁰; Nádia Gurgel Alves, MD¹¹; Seila Israel do Prado, MD¹²; Klerize Anecely de Souza Silva, MD, MSc¹³; Edna Kakitani Carbone, MD, MSc¹⁴; Melina Brumatti, MD¹⁵; Pablo Santiago, MD¹⁶; Kaline Maria Maciel de Oliveira Pereira, MD, MSc⁷; Fabianne Altruda de Moraes Costa Carlesse, MD, PhD¹⁰; Marina Gondim Aguiar, MD¹¹; Rebeca Ferreira Marques, MD¹⁷; Ciliana Rechenmacher, PhD^{1,17}; Liane Esteves Daudt, MD, PhD^{1,17,18}; Mariana Bohns Michalowski MD, PhD^{1,17,19}

¹ Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Departamento de Pediatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;

² Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;

³ Hospital Oncológico Infantil Octávio Lobo, Belém, Brazil;

⁴ Universidade Federal de Sergipe, São Cristóvão, Brazil;

⁵ Centro de Oncologia de Sergipe Dr. Oswaldo Leite, Aracaju, Brazil;

⁶ Hospital da Criança de Brasília José Alencar, Brasília, Brazil;

- ⁷ Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil;
- ⁸ Instituto de Tratamento do Câncer Infantil - ITACI, São Paulo, Brazil;
- ⁹ Hospital Martagão Gesteira, Salvador, Brazil;
- ¹⁰ Universidade Federal de São Paulo/ Instituto de Oncologia Pediátrica – GRAACC, São Paulo, Brazil;
- ¹¹ Hospital Infantil Albert Sabin, Fortaleza, Brazil;
- ¹² Hospital de Câncer de Barretos - Fundação Pio XII, Barretos, Brazil;
- ¹³ Hospital Criança Conceição, Porto Alegre, Brazil;
- ¹⁴ Hospital Pequeno Príncipe, Curitiba, Brazil;
- ¹⁵ Hospital Israelita Albert Einstein, São Paulo, Brazil;
- ¹⁶ Associação Hospitalar Beneficente São Vicente de Paulo, Passo Fundo, Brazil;
- ¹⁷ Laboratório de Pediatria Translacional, Serviço de Pesquisa Experimental, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil;
- ¹⁸ Unidade de Hematologia e Transplante de Medula Óssea Pediátrica, Serviço de Hematologia Clínica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil;
- ¹⁹ Serviço de Oncologia Pediátrica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

CLINICAL INVESTIGATORS

The authors listed below have actively contributed through data collection:

Sandra Emília Almeida Prazeres, MD¹; Maristella Bergamo Francisco dos Reis, MD, PhD²; Carmem Maria Costa Mendonça Fiori, MD, PhD³; Marcelo Otsuka, MD, MSc⁴; Mara Albonei Dudeque Pianovski, MD, PhD^{5,6}; Tatiana El Jaick Bonifacio Costa, MD⁷; Maria do Perpétuo Socorro Sampaio Carvalho, MD⁸; Larissa Bueno Polis Moreira, MD, MSc⁹

¹ Hospital Infantil Albert Sabin, Fortaleza, Brazil; ² Hospital das Clínicas de Ribeirão Preto, Ribeirão Preto, Brazil; ³ Hospital do Câncer de Cascavel - UOPECCAN, Cascavel, Brazil; ⁴ Hospital Infantil Darcy Vargas, São Paulo, Brazil; ⁵ Hospital Erasto Gaertner, Curitiba, Brazil; ⁶ Hospital Oncopediátrico Erastinho, Curitiba, Brazil; ⁷ Hospital Infantil Joana de Gusmão, Florianópolis, Brazil; ⁸ Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas, Manaus, Brazil; ⁹ Hospital Amaral Carvalho, Jaú, Brazil

Abbreviations

ABHH	Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease of 2019
HCPA	Hospital de Clínicas de Porto Alegre
ICU	Intensive care unit
IQR	Interquartile range
IV	Intravenous
LMIC	Low- and middle-income countries
MIS-C	multisystem inflammatory syndrome
OS	Overall survival
RT-PCR	Reverse transcriptase-polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SBTMO	Sociedade Brasileira de Transplante de Medula Óssea
SD	Standard deviation
SOBOPE	Sociedade Brasileira de Oncologia Pediátrica
SUS	Sistema Único de Saúde
WHO	World Health Organization

ABSTRACT

Background: Strategies to mitigate the impact of COVID-19 in special populations are complex and challenging. Few studies have addressed the impact of COVID-19 on pediatric patients with cancer in low- and middle-income countries.

Methods: multicenter observational cohort study with prospective records and retrospective analyzes starting in April 2020 in 21 pediatric oncology centers distributed throughout Brazil. **Participants:** Patients under 18 years of age who are infected by the SARS-CoV-2 virus (confirmed diagnosis through RT-PCR) while under treatment at pediatric oncology centers. The variables of interest included clinical symptoms, diagnostic and therapeutic measures. The repercussions of SARS-CoV-2 infection on cancer treatment and general prognosis were monitored.

Results: One hundred and seventy-nine patients were included (median age 6 [4-13] years, 58% male). Of these, 55.9% had acute leukemia and 34.1% had solid tumors. The presence of SARS-CoV-2 was diagnosed by RT-PCR. Various laboratory markers were analyzed, but showed no correlation with outcome. Children with low or high BMI for age had lower overall survival 71.4% and 82.6%, respectively) than those with age-appropriate BMI (92.7%) ($p= 0.007$). The severity of presentation at diagnosis was significantly associated with outcome ($p<0.001$). Overall mortality in the presence of infection was 12.3% ($n=22$).

Conclusion: In children with cancer and COVID-19, lower BMI was associated with worse prognosis. The mortality in this group of patients (12.3%) was significantly higher than that described in the pediatric population overall (~1%).

INTRODUCTION

In late 2019, a novel coronavirus was identified by Chinese scientists in Wuhan, China.¹ Named Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), due to its phylogenetic proximity to the already known causative agent of severe acute respiratory syndrome (SARS) first identified in 2003, the virus spread quickly to other countries². The arrival of coronavirus disease of 2019 (COVID-19) in Brazil in February 2020 represented a great challenge in establishing adequate strategies to mitigate the impact caused by the disease, since the country has continental dimensions and significant regional differences. One of these obstacles is the possibility of compromising access by children and adolescents with cancer to pediatric oncology centers, which is already constrained by the fact that these facilities are almost exclusively located in urban regions such as state capitals and regional economic centers.³ Although Brazil has one of the world's largest and most complex publicly funded, free-at-the-point-of-care, universal health system, the *Sistema Único de Saude* (SUS),⁴ the economic and social challenges faced by large segments of the population can increase the risk of exposure to SARS-CoV-2, as well as cause a worse prognosis.⁵

Few studies have addressed the impact of COVID-19 on the pediatric population with cancer, and even fewer have been conducted with children from low- and middle-income countries (LMICs).^{6,7} It is already known that all age groups are susceptible to SARS-CoV-2.⁸ In the oncology setting, Liang *et al.* suggest that adults

with cancer have an increased risk of infection with this virus.⁹ However, Boulad, Rojas, and Ferrari and their respective coauthors believe that pediatric cancer patients, although managed as high risk, may be no more vulnerable to infection or morbidity resulting from SARS-CoV-2 than are other children.^{10,11,12}

Given this scenario, the present study describes the impact of COVID-19 on this population. Through a nationwide multicenter registry,¹³ we identified factors related to worse prognosis in children with cancer, such as body mass index (BMI), age, and initial clinical presentation. In addition, we evaluated the mortality/fatality rate in comparison with the general pediatric population.

METHODS

During the one-year period (from April 2020 to March 2021), pediatric patients (age 0 to 18 years) with cancer and infected by the SARS-CoV-2 virus seen at pediatric oncology centers were registered. All patients in this study were tested and had their confirmed diagnosis by reverse transcriptase-polymerase chain reaction (RT-PCR). Patients with suspected COVID-19 based on clinical and/or radiological criteria whose molecular diagnostic tests were negative were excluded from the analysis. Children and adolescents who died due to causes unrelated to COVID-19 were also excluded from the study.

Twenty-one centers located in all five regions of Brazil registered patients in this study during the period of analysis. Data was recorded prospectively through Redcap® software, thus ensuring confidentiality and allowing integration with other participating national institutions. Each center had access only to the information of its unit. Only the coordinating center had access to global data. The records were

regularly assessed for compliance by the coordinating center team (Hospital de Clínicas de Porto Alegre (HCPA) - Porto Alegre / RS).

The recorded variables include clinical symptoms, diagnostic method, therapeutic measures, and treatment setting. In addition, the repercussions of the infection on the initial treatment and on general prognosis are evaluated. BMI for age and sex was calculated, and nutritional status (underweight ($< -2DP$), adequate weight, overweight ($> +1SD$ - equivalent to BMI 25Kg/m^2 at 19 years) or obesity ($> +2SD$ - equivalent to BMI 30Kg/m^2 at 19 years)), was defined for each child according to the World Health Organization (WHO) classification.¹⁴

The severity of the clinical presentation at diagnosis was based on the parameters established by Qiu *et al.*¹⁵ Briefly, mild disease is defined as the absence of the need for oxygen therapy; moderate or severe, there is hypoxemia that requires supplemental oxygen; and in critical condition, there is a need for mechanical ventilation and / or the presence of hemodynamic instability.

Statistical analysis

Continuous variables were assessed with the Shapiro-Wilk test of normality; those with asymmetric distribution were expressed as medians and interquartile ranges (IQR). Qualitative variables were summarized as absolute and relative frequencies. The significance level adopted was 0.05. Data was compiled in a Microsoft Excel® spreadsheet and analyzed in PASW Statistics® Version 18.0 and WinPepi version 11.65. Fisher's exact test and Pearson's chi-square test were used for categorical variables and the Mann-Whitney *U* test for quantitative variables. Analysis of variance (ANOVA) was used to verify the distribution of data between three or more groups. Log rank tests (Mantel-Cox) were used to compare Kaplan-Meier survival curves between two or more groups.

Ethical statement and consent to participate

Ethical approval to conduct this study has been granted by the Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA). The legal guardians of all participating minors provided written informed consent in duplicate, keeping one copy of the consent form for themselves.

RESULTS

One hundred and seventy-nine pediatric patients were included (Table 1) in 21 pediatric oncology centers, of whom 55.9% had acute leukemia, 8.4% had lymphoma, and 34.1% had solid tumors. Diagnosis of COVID-19 was confirmed by RT-PCR for all patients registered in this study. One hundred and forty-five (81%) had undergone some cancer treatment up to 30 days before diagnosis (85.5% chemotherapy, 8.3% surgery, and/or 6.2% radiotherapy).

Sixty-six (36.9%) children were asymptomatic or had mild symptoms, 72 (40.2%) had moderate to severe symptoms, and 41 (22.9%) had a critical condition during the study. At the time of diagnosis, 34 (19.0%) were admitted to an intensive care unit and 109 (60.9%) to a regular ward, while 35 (19.6%) remained at home; the disposition of 1 (0.5%) patient was not reported. Among the patients who did not require hospitalization, 19 (54.3%) were asymptomatic or had mild symptoms, 8 (22.9%) were treated with antibiotics. The median follow-up time was 44 [23-78.5] days. No asymptomatic patient or with mild symptoms died.

Type of neoplasm, lymphocyte count, inflammatory markers (ferritin, C-reactive protein, and fibrinogen), and sex were not associated with severity or mortality. However, nutritional status defined by the BMI characterized 3 different prognostic groups. Children classified as underweight (<-2 standard deviation (SD)) had the worst

prognosis, with overall survival (OS) in the presence of infection of 71.4%, followed by children with overweight or obesity (>+1SD) (OS 82.6%); those who had an adequate BMI had an OS of 92.7% ($p=0,007$; Fig. 1).

We also observed that the group of patients whose initial severity was considered critical experienced worse outcomes when compared to the other groups ($p < 0.001$); Fig 2).

Information on management of COVID-19 was available for 122 children. Of these, 40.2% received antivirals ($n=49$), 9.0% systemic antifungals, 95.1% antibiotics, and 17.2% corticosteroids. Oseltamivir was the most prescribed antiviral (42.9%). With regard to antibiotics, azithromycin was prescribed to 72 patients (62.1.0%), followed by cefepime (40.5%), vancomycin (25.9%), piperacillin/tazobactam (19.02%) and amoxicillin/clavulanate (3.4%). Corticosteroids were administered to 21 (17.2%) patients. Heparin (8.2%), intravenous (IV) immunoglobulin (2.5%), and hydroxychloroquine (2.5%) were also prescribed.

Information on the continuity of cancer treatment was available for 178 children. Of these, 65 (36.5%) experienced a delay of treatment (median 16 [10-28] days of delay), mainly in chemotherapy 42 (64.6%).

The overall lethality rate in the presence of infection for this sample was 12.3%, with a total of 22 deaths. The diagnosis of leukemia was presented in 10 (45.5%) of the cases, 8 (36.4%) with a solid tumor, 2 (9.1%) with lymphoma and 2 (9.1%) another. The median time to death was 19.5 [6.5-39] days and 8 (36.4%) patients had some change in the underlying treatment of the disease due to SARS-CoV-2 infection.

DISCUSSION

Comparatively little data are available on the pediatric population with COVID-19 in developing countries. There is even less information about children with cancer infected with SARS-CoV-2 in these countries. The present study described the clinical presentation and course of these patients in a middle-income country, seeking to provide clues about possible risk factors for a less favorable prognosis. In the present national registration study, a high lethality rate was observed in children with cancer and factors such as severity of the condition at the time of presentation as well as nutritional status were associated with the final prognosis.

Combating COVID-19 represents a major challenge for health authorities. Different protocols have been tested in order to find the best treatment to combat this disease. Thus, the fact that the patients in this study are treated in a heterogeneous manner was expected. Initiatives led by the International Pediatric Oncology Society (SIOP), Child Oncology Group (COG), the St Jude Global and Childhood Cancer International program and the Brazilian Society of Pediatric Oncology (SOBOPE) can allow a more uniform management of these patients.¹⁶

Our data indicated a relationship between the severity of COVID-19 at diagnosis and the likelihood of death in these patients. Children classified as critically ill at diagnosis had a higher mortality rate when compared to groups of children classified as asymptomatic or with mild or moderate/severe symptoms. This finding is unsurprising, since the critical classification is reserved for patients at advanced stages of COVID-19, requiring intensive care unit (ICU) admission or mechanical ventilation and, often, with septic conditions.

Regarding biological markers, in a recent meta-analysis ElGohary *et al.*, evaluated 22 studies with a total of 1018 adult patients and found that C-reactive protein, D-dimer, and prothrombin time were significantly higher in those with cancer.¹⁷

In the pediatric population, a study conducted by Whittaker *et al.*, evaluated 58 children admitted to 8 hospitals in England. The objective was to seek clinical and laboratory characteristics of critically ill patients who developed a multisystem inflammatory syndrome (MIS-C) during the COVID-19 pandemic, and compare these data with other pediatric inflammatory diseases. The authors suggested that MIS-C differs from other known pediatric inflammatory entities.¹⁸ To date, we are not aware of a study that sought to describe inflammatory markers in children with cancer who developed COVID-19. In our sample, there was no correlation between the evaluated markers and severity or prognosis.

Data on prognosis and outcome of pediatric cancer patients infected with SARS-CoV-2 remain scarce. A study carried out with 523 adult patients with COVID-19 in four hospitals in Wuhan established an association of low BMI and protein levels with higher risk of death. In that study, patients with BMI under 20.5 kg/m² were more prevalent among ICU non-survivors than those with a normal BMI.¹⁹ In addition, obesity and overweight were described as risk factors in a meta-analysis by Hussaim *et al.* In 14 studies selected for quantitative analysis, BMI >25 was directly associated with higher mortality, as were factors such as advanced age (> 70 years), severe comorbidities, and requiring advanced respiratory support.²⁰ Some studies in Brazil have addressed the impact of nutritional status on the survival of acute leukemias and found that low weight for age at diagnosis is associated with a worse prognosis due to a higher rate of recurrences.²¹ In a cohort that analyzed obesity in lymphoblastic leukaemia, the 5-year event-free survival in patients was significantly lower than that of the non-overweight/obesity patients.²² In this context, we observed that pediatric cancer patients with a BMI below the value considered appropriate for their age were also significantly more likely to die acutely when infected with SARS-CoV-2. Likewise,

the group of patients classified as overweight/obese had a worse prognosis than patients with adequate nutritional status. Considering these analyses, our data suggest that the nutritional situation may have an impact on the clinical response and prognosis related to SARS-CoV-2 acute infection.

It can be observed that 49 (40.2%) patients of our sample (n= 122) received antiviral treatment, especially Oseltamivir. Due to lack of evidence regarding effective treatments for COVID-19 in the first few months of pandemic, it is believed that some treatment centers appealed to these antivirals in off-label use. To the present day, Oseltamivir is not recommended against SARS-CoV-2 infection.²³ Also, evidences of proven benefit from the use of corticosteroids was not clear until June 2020, when the preliminary data from the RECOVERY Trial was published.²⁴

Our study has some limitations, mostly inherent to the conduct of a multicenter registry in a country of continental dimensions with major regional differences. As the questionnaire was completed by local teams at each facility rather than centrally, some data required careful monitoring to ensure uniformity and consistency; despite our best efforts, some data could not be obtained for all patients. Another important point refers to the short follow-up period. We were able to identify acute repercussions such as hospitalizations and survival. Only through continuous monitoring of these patients will we be able to understand the long-term repercussions of infection in these children. In addition, it is possible that not all children diagnosed with COVID-19 in the period of interest entered the register or there was a variation in systematic screening between institutions, causing a selection bias and, consequently, leading to a higher proportion of most serious patients. It is also important to mention that due to the small number of events, results of a multivariable analysis could be biased and therefore have not been performed.^{25,26}

Despite these, a very striking result is the case fatality rate in our sample. Unfortunately, it is similar to what was previously described by Montoya *et al.*, who observed 10% of deaths in a pediatric cancer population with COVID-19 (ages ranging from 0 to 16) from six tertiary centers in Peru⁶, but very different from what was described in other pediatric studies. In a nationwide register-based study conducted in Brazil, it was found a rate of 0.7% of the deaths related to COVID-19 in the healthy pediatric population.²⁷ In a systematic review that evaluated 131 studies across 26 countries, the case-fatality rate was less than 1%.⁸ It shows that, despite socioeconomic differences between high-income and low-income countries, the mortality rate of COVID-19 in healthy children is similar and very lower than those with cancer. In this context, the reasons why children with cancer in LMICs are at greater risk of developing severe forms of COVID-19 and progressing to death remain to be clarified. It is possible that immunosuppression associated with treatment or underlying disease plays a role, but the relationship between survival and BMI found in our study suggests that social issues leading to a more precarious nutritional status may be important in the origin of this result. With the continuity of the record, we hope to be able to better understand how variables related to the socioeconomic context can interfere in the prognosis, as well as to determine the long-term impact of SARS-CoV-2 infection in these children.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395(10223):470-473. doi:10.1016/S0140-6736(20)30185-9
2. Gorbalenya AE, Baker SC, Baric RS, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 2020;5(4):536-544. doi:10.1038/s41564-020-0695-z
3. Grabois MF, de Oliveira EXG, Sa Carvalho M. Assistência ao cancer entre crianças e adolescentes: mapeamento dos fluxos origem-destino no Brasil. *Rev Saude Publica*. 2013;47(2):368-378. doi:10.1590/S0034-8910.2013047004305
4. Castro MC, Massuda A, Almeida G, et al. Brazil's unified health system: the first 30 years and prospects for the future. *Lancet*. 2019;394(10195):345-356. doi:10.1016/S0140-6736(19)31243-7
5. Demenech LM, Dumith S de C, Vieira MECD, Neiva-Silva L. Desigualdade econômica e risco de infecção e morte por COVID-19 no Brasil. *Rev Bras Epidemiol*. 2020;23. doi:10.1590/1980-549720200095
6. Montoya J, Ugaz C, Alarcon S, et al. COVID-19 in pediatric cancer patients in a resource-limited setting: National data from Peru. *Pediatr Blood Cancer*. 2020;7(July):1-2. doi:10.1002/pbc.28610
7. Vasquez L, Sampor C, Villanueva G, et al. Early impact of the COVID-19 pandemic on paediatric cancer care in Latin America. *Lancet Oncol*. 2020;21(6):753-755. doi:10.1016/S1470-2045(20)30280-1
8. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine*. 2020;24:100433. doi:10.1016/j.eclinm.2020.100433
9. 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. doi:10.1016/S1470-2045(20)30096-6

10. Boulad F, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in Children With Cancer in New York City. *JAMA Oncol.* 2020;382(17):1663-1665. doi:10.1001/jamaoncol.2020.2028
11. de Rojas T, Pérez-Martínez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. *Pediatr Blood Cancer.* 2020;67(7):19-21. doi:10.1002/pbc.28397
12. Ferrari A, Zecca M, Rizzari C, et al. Children with cancer in the time of COVID-19: An 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy. *Pediatr Blood Cancer.* 2020;(April):3-5. doi:10.1002/pbc.28410
13. Corso M, Rechenmacher C, Jablonski V, Marques R, Daudt L, Michalowski M. RECOV-Brasil: COVID-19 in children undergoing cancer treatment or HSCT in Brazil. Preprint posted online July, 2020:1-3. doi: 10.22541/au.159415243.34937767
14. WHO Child Growth Standards. Geneva: World Health Organization, 2006
15. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis.* 2020;20(6):689-696. doi:10.1016/S1473-3099(20)30198-5
16. 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):1-12. doi:10.1002/pbc.28409
17. ElGohary GM, Hashmi S, Styczynski J, et al. The risk and prognosis of COVID-19 infection in cancer patients: A systematic review and meta-analysis. *Hematol Oncol Stem Cell Ther.* Published online July 2020. doi:10.1016/j.hemonc.2020.07.005
18. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA.* 2020;324(3):259. doi:10.1001/jama.2020.10369
19. Li G, Zhou C, Ba Y, et al. Nutritional risk and therapy for severe and critical COVID-19 patients: A multicenter retrospective observational study. *Clin Nutr.* Published online October 2020. doi:10.1016/j.clnu.2020.09.040
20. Hussain A, Mahawar K, Xia Z, Yang W, EL-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. *Obes Res Clin Pract.* 2020;14(4):295-300. doi:10.1016/j.orcp.2020.07.002
21. Viana MB, Murao M, Ramos G, et al. Malnutrition as a prognostic factor in lymphoblastic leukaemia: A multivariate analysis. *Arch Dis Child.* 1994;71(4):304-310. doi:10.1136/adc.71.4.304

22. Gelelete CB, Pereira SH, Azevedo AMB, et al. Overweight as a prognostic factor in children with acute lymphoblastic leukemia. *Obesity*. 2011;19(9):1908-1911. doi:10.1038/oby.2011.195
23. Falavigna M, Colpani V, Stein C, et al. Guidelines for the pharmacological treatment of COVID-19. The task force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology. *Rev Bras Ter Intensiva*. 2020;32(2):166-196. doi:10.5935/0103-507X.20200039
24. Horby P, Lim WS, Emberson J, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/nejmoa2021436
25. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis I. Background, goals, and general strategy. *J Clin Epidemiol*. 1995;48(12):1495-1501. doi:10.1016/0895-4356(95)00510-2
26. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. *J Clin Epidemiol*. 1995;48(12):1503-1510
27. Martins-Filho PR, Quintans-Júnior LJ, de Souza Araújo AA, et al. Socio-economic inequalities and COVID-19 incidence and mortality in Brazilian children: a nationwide register-based study. *Public Health*. 2021;190(September 2020):4-6. doi:10.1016/j.puhe.2020.11.005

TABLE 1 Characteristics of patients

Variable		N= 179 (%)	
Age in years, median (IQR)		6.0 (4-13)	
Sex	Male	103 (58)	
BMI	Underweight	14 (8)	
	Normal weight	110 (62)	
	Overweight	22(12)	
	Obese	24(13)	
	Not reported	9(5)	
Oncological Diagnosis		AML	22 (12)
	Leukemia/MDS	B	69 (38)
		T	8 (4)

	MDS	1 (1)	
Lymphoma	Hodgkin	4 (2)	
	Not Hodgkin	10 (6)	
	Not reported	1 (1)	
Solid tumor	Neuroblastoma	10 (6)	
	Wilm's Tumor	9 (5)	
	Bone tumors	8 (4)	
	Others	34 (19)	
Other		1 (1)	
	Not reported	2 (1)	
Symptoms related to COVID-19*	Absence of symptoms	25 (14)	
	Cough	64 (36)	
	Fever	57 (32)	
	Rhinorrhea	40 (22)	
	Respiratory Dysfunction	37 (21)	
	Diarrhea	21 (12)	
	Headache	10 (6)	
	Ageusia and/or Anosmia	10 (6)	
	Vomit	5 (3)	
Severity	Asymptomatic	25 (14)	
	Mild	41 (23)	
	Moderate/Severe	72 (40)	
	Critical	41 (23)	
Initial oxygen therapy	Nasal catheter	22 (12)	
	High-flow oxygen therapy	2 (1)	
	Noninvasive ventilation	7 (4)	
	Immediate invasive ventilation	10 (6)	
	None	137 (76)	
	Not reported	1 (1)	
Laboratory tests – diagnosis		n	Median (IQR)
	Lymphocytes (/mL)	137	691 (220 - 2071)
	C-reactive protein (ng/mL)	96	46 (10 - 161)
	D-dimers (mg / L)	33	639 (306 - 1500)
	Ferritin (mcg / L)	36	1165 (669 - 2633)
	Fibrinogen (mg / dL)	35	403 (270 - 511)
	Creatinine	121	0.4 (0.3 - 0.6)

Urea	118	21 (14 - 27)
GOT	102	32 (25 - 49)

*Some patients had more than one symptom.

Abbreviations: MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; BMI, body mass index; COVID-19, coronavirus disease 2019; GOT, Glutamic-Oxalacetic Transaminase; IQR, interquartile range

FIGURES

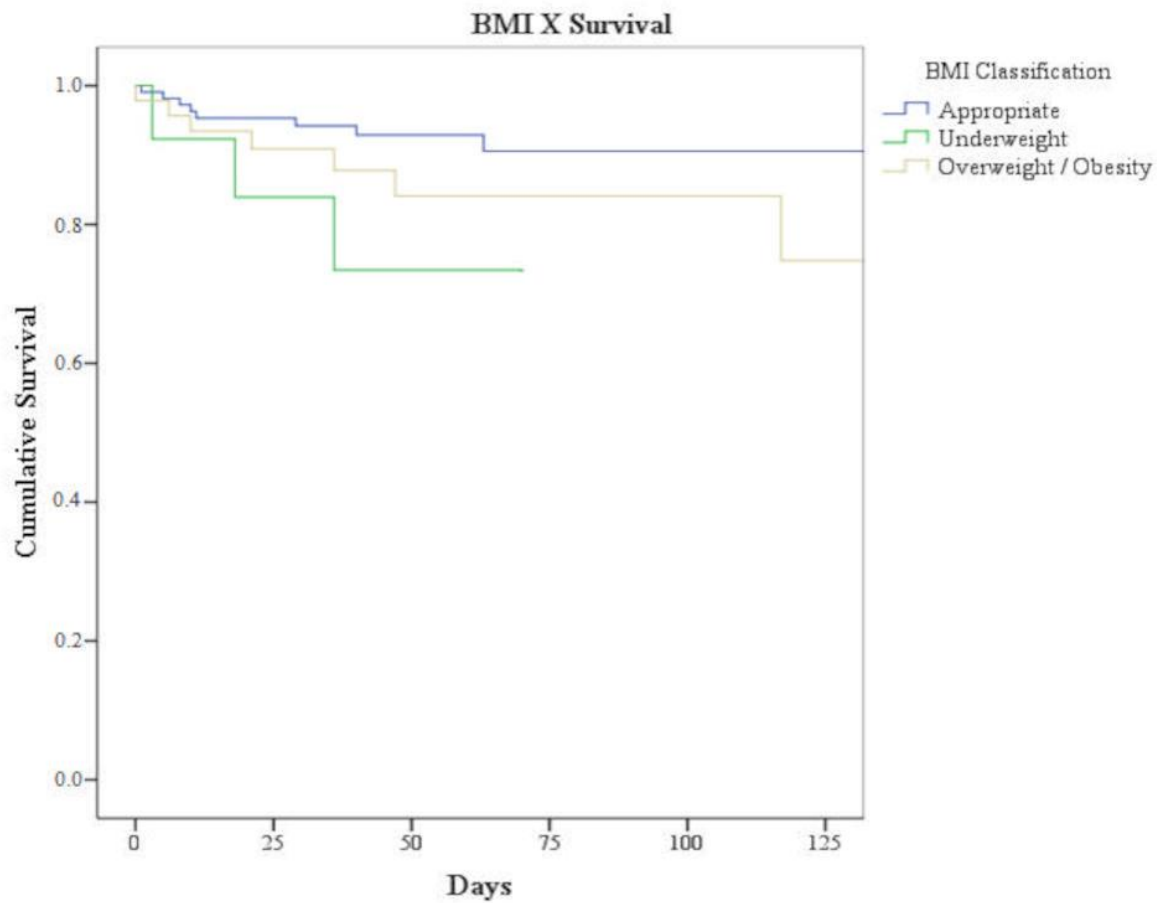


FIGURE 1 Survival according to body mass index (BMI). Underweight: $<-2SD$; overweight: $>+1SD$ (equivalent to BMI 25 kg/m² at 19 years); obesity: $>+2SD$ (equivalent to BMI 30 kg/m² at 19 years) ($p=0.007$).

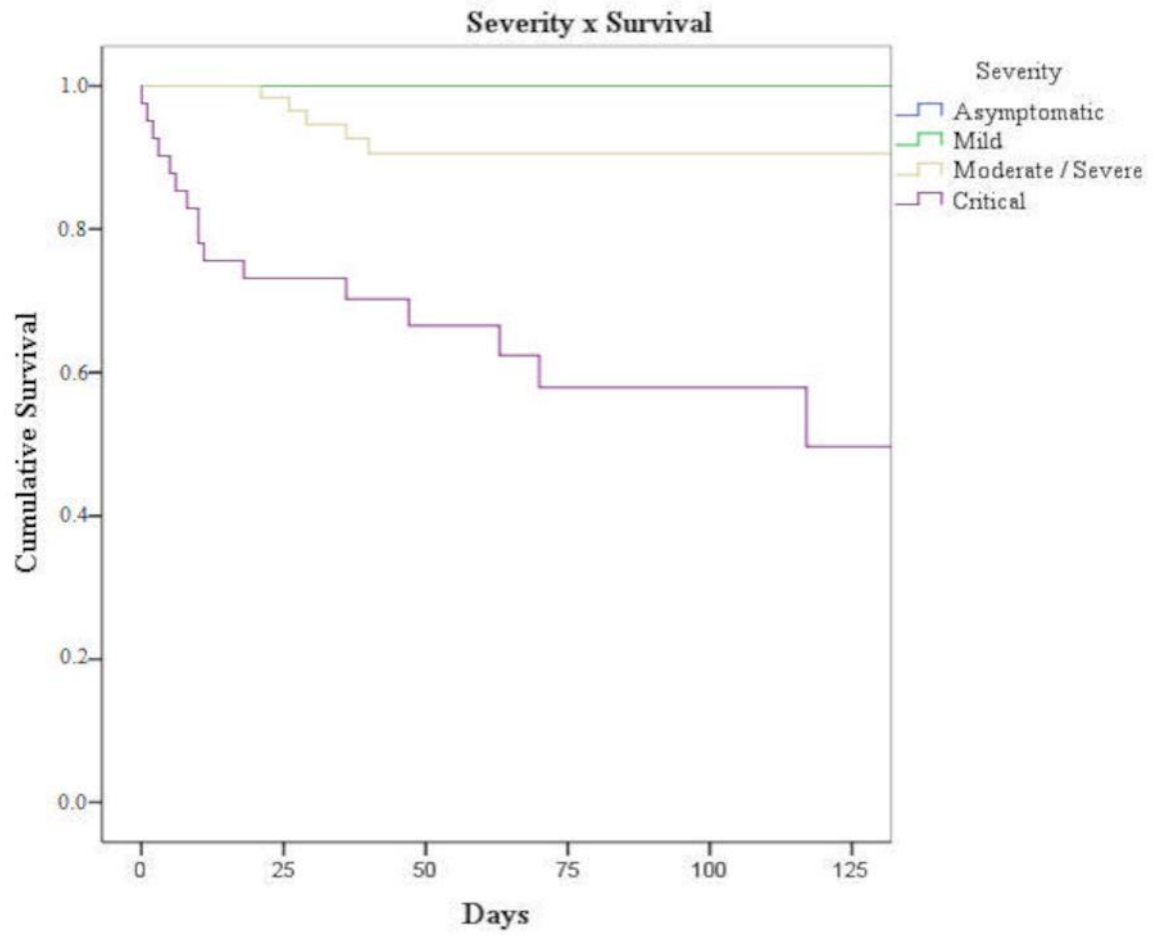


FIGURE 2: Survival according to clinical severity at diagnosis ($p < 0.001$).

7.2 ARTIGO 2

COVID-19 in HSCT recipients: a collaborative study of the Brazilian Society of Marrow Transplantation (SBTMO)

Liane Esteves Daudt, MD, PhD^{*1,2,3}; Mariana Cristina Moraes Corso¹; Mariana Nassif Kerbauy, MD⁴; Luiz Henrique dos Santos de Assis, MD⁵; Ciliana Rechenmacher, PhD^{1,2}; Iago Colturato, MD⁶; Fernanda Rodrigues Barbieri, MD⁶; Vanderson Rocha, MD, PhD^{7,8,9}; Livia Mariano, MD⁷; Julia Lopes Garcia, MD⁴; Vanessa Esther Cavalcanti Barreto Dantas, MD¹⁰; Gisele Loth, MD¹¹; Vaneuza Araujo Moreira Funke, MD, MSc¹¹; Polliany Roberta Dorini Pelegrina, MD,¹²; Fernando Barroso Duarte, MD, PhD¹³; Roberto Luiz da Silva, MD, MSc¹⁴; Marco Aurelio Salvino Araújo MD, PhD^{5,15}; Fabianne Altruda de Moraes Costa Carlesse, MD PhD^{16,17}; Ana Virginia Lopes de Sousa, MD, MSc¹⁷; Luana Azevedo Maia¹⁸; Juliana Folloni Fernandes, MD¹⁹; Celso Arrais Rodrigues, MD, PhD²⁰; Carmem Bonfim, MD, PhD²¹; Leticia Navarro Gordan Ferreira Martins, MD²²; Rosana Cipolotti, MD, PhD²³; Erick Menezes Xavier, MD^{8,9}; Alessandra Araújo Gomes, MD⁹; Hugo Manuel Paz Morales^{24,25}; Anderson J. Simioni⁶; Victor Jablonski Soares²⁶; Mariana Bohns Michalowski, MD, PhD^{1,2,27}; Nelson Hamerschlak, MD, PhD⁴; Clarisse Martins Machado, MD, PhD^{*4,6,28}

¹ Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Departamento de Pediatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; ² Laboratório de Pediatria Translacional, Serviço de Pesquisa Experimental, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; ³ Unidade de Hematologia e Transplante de Medula Óssea Pediátrica, Serviço de Hematologia Clínica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; ⁴ Hospital Israelita Albert Einstein,

São Paulo, Brazil; ⁵ Hospital São Rafael, Salvador, Brazil; ⁶ Hospital Amaral Carvalho, Jaú, Brazil; ⁷ Service of Hematology, Transfusion and Cell Therapy, and Laboratory of Medical Investigation in Pathogenesis and Directed Therapy in Onco-Immuno-Hematology (LIM-31). Hospital das Clínicas, Faculty of Medicine, Sao Paulo University (FM-USP), Brazil; ⁸ Hospital Nove de Julho, São Paulo, Brazil; ⁹ Hospital Sírio-Libanês, São Paulo, Brazil; ¹⁰ REAL Hospital Português de Beneficência em Pernambuco, Recife, Brazil; ¹¹ Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, Brazil; ¹² Hospital Pequeno Príncipe, Curitiba, Brazil; ¹³ Hospital Universitário Walter Cantídio, Fortaleza, Brazil; ¹⁴ Instituto Brasileiro de Controle do Câncer, São Paulo, Brazil; ¹⁵ Hospital Universitário Professor Edgar Santos, Universidade Federal da Bahia, Salvador, Brazil; ¹⁶ Universidade Federal de São Paulo, São Paulo, Brazil; ¹⁷ Instituto de Oncologia Pediátrica - GRAACC/UNIFESP, São Paulo, Brazil; ¹⁸ Hospital Infantil Albert Sabin, Fortaleza, Brazil; ¹⁹ Instituto da Criança do Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; ²⁰ Hospital São Paulo. Universidade Federal de São Paulo, São Paulo, Brazil; ²¹ Hospital Nossa Senhora das Graças, Curitiba, Brazil; ²² Hospital Universitário de Londrina, Universidade Estadual de Londrina, Londrina, Brazil; ²³ Centro de Oncologia de Sergipe Dr. Oswaldo Leite, Aracaju, Brazil; ²⁴ Hospital Erasto Gaertner, Curitiba, Brazil; ²⁵ Hospital Oncopediátrico Erastinho, Curitiba, Brazil; ²⁶ Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; ²⁷ Serviço de Oncologia Pediátrica, Unidade de Hematologia Pediátrica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; ²⁸ Laboratório de Virologia (LIM 52), Instituto de Medicina Tropical, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Abstract

In the COVID-19 scenario, patients undergoing hematopoietic stem cell transplantation (HSCT) infected with SARS-CoV-2 may have an increased risk of death. Through a national multicenter study, we aimed to describe the impact of COVID-19 on the survival of HSCT recipients in Brazil. Eighty-six patients with a confirmed diagnosis of SARS-CoV-2 (92% by RT-PCR) were included. There were 24 children and 62 adults receiving an autologous (n=25) and allogeneic (n=61) HSCT for malignant (n=72) and non-malignant (n=14) disorders. Twenty-six patients died, (10 on autologous (38%) and 16 patients (62%) on allogeneic group). The estimated overall survival (OS) at day 40 was 69%. Adults had decreased OS compared to children (66% vs 79%, $p=0.03$). The severity of symptoms at the time of diagnosis, ECOG score, laboratory tests (C-reactive protein, urea values) were higher in patients who died ($p<0.05$). In conclusion, HSCT recipients infected with SARS-CoV-2 have a high mortality rate mainly in adults and patients with critical initial COVID-19 presentation. These findings show the fragility of HSCT recipients with SARS-CoV-2 infection. Therefore, the importance of adherence to preventive measures is evident, in addition to prioritizing the vaccination of family members and the HSCT team.

Introduction

COVID-19 respiratory syndrome is caused by an RNA-betacoronavirus called SARS-CoV-2 and was classified as a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO). Until June 29, 2021, there were more than 3.9 million documented deaths worldwide.^{1,2}

Although there is a spectrum of clinical manifestations of SARS-CoV-2 infection, the majority of patients are asymptomatic or have only mild symptoms of the

upper respiratory tract and about 6-14% evolve with a severe pulmonary syndrome, requiring admission to the intensive care unit (ICU), with respiratory failure, and death.³⁻⁶ Some risk factors for the occurrence of severe cases have been reported. In a retrospective study that evaluated 1590 hospitalized patients, those who died, had, more often, chronic comorbidities, advanced age, dyspnea and laboratory abnormalities.⁷ Comorbidities such as hypertension, diabetes, obesity and coronary heart disease have been reported as risk factors for disease severity in different studies.^{3,6,8}

Infections are an important cause of morbidity and mortality for hematopoietic stem cell (HSCT) transplant recipients due to chemotherapy effects such as myelosuppression and mucositis. Moreover, in the allogeneic HSCT setting, the occurrence of viral infection is even higher due to immunosuppressive therapy, graft-versus-host disease (GVHD) and its treatment. Due to the risk involved with symptomatic SARS-CoV-2 infection in the HSCT scenario, a collaborative effort by Bone Marrow Transplant Societies has prepared guidelines to assist the clinical call decision to protect recipients and donors in this pandemic scenario. Recommended measures include postponing non-urgent transplants, especially in the setting of non-malignant diseases, performing real-time reverse-transcriptase polymerase chain reaction exams (RT-PCR) for SARS-CoV-2 before transplantation to the recipient and donor, cryopreserving the stem cell product before starting the conditioning regimen or having an alternative donor as backup, in addition to strict adherence to infection control protocols during HSCT hospitalization.⁹⁻¹¹

Despite protective recommendations for transplant planning and management, transplant patients remain subject to infection. Few data have been published to date on the clinical manifestations and results of transplant recipients infected with COVID-

19, including patients from middle-income countries. In a study conducted at the Memorial Sloan Kettering Cancer Center, 77 patients who were positive for COVID-19 and had previously received allogeneic or autologous HSCT and CD19-directed chimeric antigen receptor T cell (CAR T) had a high rate of hospitalizations (44%), and 15% with severe disease died. Secondary infections were formally documented in 12%, and 43% required supplemental oxygen.¹²In another study Sharma *et al.* analyzed 318 HSCT recipients diagnosed with COVID-19 with a median time from HSCT to COVID-19 diagnosis of 17 and 23 months for allogeneic and autologous HSCT recipients, respectively. In 45 (14%) of the cases the disease was classified as severe and 30 days after the diagnosis of COVID-19, the OS was 68% for allogeneic HSCT recipients and 67% for autologous HSCT recipients.¹²

The present study describes the main clinical findings and complications of COVID-19 in HSCT patients in Brazil. In this national multicenter cross-sectional study, we aimed to identify the variables associated with OS after COVID-19.

Methods

Study design, settings and participants

Patients undergoing autologous or allogeneic HSCT and diagnosed with COVID-19 infection from March 29 to September 1, 2020 admitted to 21 hospitals in 5 regions of Brazil were included. We considered only patients with positive results in molecular diagnostic tests (RT-PCR) and/or serology (presence of at least one of the immunoglobulins M or G and clinical signs). Patients with suspected COVID-19 disease based only on clinical or radiological findings were excluded.

Variables analyzed

The data were recorded through Redcap® software, and included variables such as: age, Body Mass Index (BMI), diagnostic method, clinical symptoms, performance status at COVID-19 diagnosis, therapeutic measures and ICU recovery. Children were defined as those under 18 years old. BMI was calculated and nutritional status (thinness, adequate weight or overweight/obesity) was defined for each child based on age and sex according to the WHO classification.¹³ The severity of the clinical presentation at diagnosis was adapted from the classification proposed by Qiu et al.¹⁴ Briefly, mild disease was defined as no oxygen supplemented; moderate and severe, were placed together for any degree of hypoxemia and supplemental oxygen; and critical, mechanical ventilation and or hemodynamic instability. Adult patients were clinically classified by ECOG Performance Status.¹⁵

The primary outcome was overall survival of 40 days^{9,12} after SARS-CoV-2 infection was confirmed.

Statistical analysis

We use descriptive statistics to analyze patient, transplantation and disease variables and the impact of SARS-CoV-2 infections in our HSCT population. Continuous variables were assessed for their distribution with the Shapiro-Wilk test and asymmetric distribution were expressed as medians and 25th and 75th percentiles. Qualitative variables were summarized as absolute and relative frequencies. The significance level adopted was 0.05. Fisher's exact test and Pearson's chi-square test were used for categorical variables and the Mann-Whitney *U* test for quantitative variables. Clinical symptoms and laboratory results were considered after 7 days of evolution. Median values were used to study the effect of associations in a univariable test. Analysis of variance (ANOVA) was used to verify the distribution of data between three or more groups. Log rank tests (Mantel-Cox)

were used to compare Kaplan–Meier survival curves between two or more groups. Multivariate analysis comparing significant variables in univariate analysis were performed. The relationship between variables was performed using Multiple Correspondence Analysis (MCA) considering only the cases with all the complete data. In order to select variables for the best fitting model, the reliability test and the explained variance of the criteria of the first two dimensions were used. SPSS® version 18.0 and Winpepi version 11.65 were used for statistical analyses.

Results

A total of 86 patients (61 allogeneic and 25 autologous HSCT recipients) were included from March 29th to September, 1st 2020. Twenty-four (28%) were children and adolescents (median 6.5 [1-17] years) and 62 (72%) were adults (median 44 [18-74] years). 58% of the patients were male. COVID-19 occurred at a median of 7 [0-216] months after HSCT. The median follow-up time was 43 days (0-161 days). The diagnosis of COVID-19 was confirmed by RT-PCR in 79 (92%) patients and by serology (IgM/IgG) in the remaining patients. Among children, 16 (67%) were asymptomatic (screening according to their own institutional policies) or had mild symptoms, 1 (4%) was classified as having a moderate/severe condition and 7 (29%) were considered critical. For the 62 adult patients, 36 (58%) were asymptomatic or with mild symptoms, 6 (10%) were moderate or severe and 20 (32%) were critical.¹⁶ Among the 86 patients in this cohort, 61 required hospitalization, 12 of them in ICU. Other relevant clinical data in adult and pediatric HSCT recipients are described in Table 1.

Twenty-one patients (24%) were included in institutional treatment protocols for COVID-19 and 2 (2%) in a clinical trial. The remaining patients underwent other

treatments that included antivirals for 24%, where 19 (22%) were treated with Oseltamivir and 2 (2%) received Ganciclovir. No patient received the drug Remdesivir despite its approval and use in other countries during the period of observation. 43 (50%) patients were treated with antibiotics (azithromycin, amoxicillin, cefepime). Corticosteroids were administered to 24 patients, prophylactic heparin to 22 and full anticoagulation to 2. Medicines such as hydroxychloroquine (14%); tocilizumab (1%); immunoglobulin (1%) and treatment with convalescent plasma (2%) were also used. Twenty-six patients required intensive care (13 days of hospitalization on average), 12 were discharged and 22 of them died. The clinical evolution of the patients can be seen in Figs 1 and 2.

The mortality in this cohort was 30% with a total of 26 deaths. Eighteen patients died due to COVID-19. In the remaining 8 patients, the causes of death were 3 fungal infections, 2 bacterial sepsis, 1 sinusoidal obstruction syndrome, 1 relapse of underlying malignancy and 1 GVHD. The overall COVID-19 lethality rate was 21% (15% and 36% in allogeneic and autologous HSCT recipients, respectively).

Overall survival (OS) estimated at day 40 was 69%. Patients whose initial presentation was considered critical had decreased OS when compared to patients with less severe symptoms (Critical 31% vs Others 70%; $p < 0.001$; IC=95%) (Fig. 3A). Children and adolescents showed an increased OS compared to adults (81% vs 66%, $p = 0.034$) (Fig. 3B). In addition, boys had decreased survival rates when compared to girls (62% vs 100%; $p = 0.049$) (Fig. 3C). In adult patients, gender was not associated with survival. Regarding ECOG Performance Status, patients with higher scores (3 e 4) presented worse OS (14% vs 76%, $p = 0.003$) (Fig. 3D).

BMI, ABO blood typing, type of transplant (allogeneic versus autologous), conditioning regimens or presence of comorbidities were not associated with survival.

Laboratory tests were also analyzed at diagnosis and after 7 days hospital admission. The values of C-reactive protein (CRP) and urea at diagnosis were statistically higher in patients who died. Seven days after diagnosis, practically all the laboratory values evaluated were worse for patients who died than for those who survived (Table 2).

Through multivariate analysis, we evaluated the variables severity (mild, moderate/severe, critical vs asymptomatic), age (groups of adults between 41-60 years and >60 years vs <41 years), HSCT (autologous vs allogeneic) and ECOG (score (0,1,2) vs (3,4)). The variables age and HSCT were not significant in this analysis despite being significant in univariate test. However, we observed a difference between the two categories of ECOG ($p=0.01$) and between patients with mild symptoms vs asymptomatic ($p=0.008$) (other classifications of severity were not significant in this analysis).

The MCA model represented 75% of explained variance, and reliability analysis measured by Cronbach's alpha 0.706 (95% CI 0.499, 0.820) was adequate for exploratory purposes. A cluster of patients classified as severe and critical at clinical presentation and with urea higher than 50 mg/dL was observed in deceased patients. Instead, creatinine ≤ 2 mg/dL, urea lower than 50 mg/dL, and a clinical mild or asymptomatic presentation are associated with OS. Figure 4 also shows a trend towards allogeneic recipients and with an ECOG score of 0 to 2 for better survival.

Discussion

Viral infections are among the main causes of morbidity and mortality in HSCT populations. For this reason, there is great concern regarding immunosuppressed patients infected with SARS-CoV-2. After the conditioning regimen (mainly in allogeneic settings) these populations become especially vulnerable due to delayed

immune reconstitution. This picture is potentially aggravated by the use of immunosuppressive therapy and other complications, such as GVHD and transplantation-related morbidities. Community-acquired viral respiratory infections can affect at least 50% of transplanted patients, with varied outcomes.¹⁶ Historically, the Coronavirus family (with regard to SARS-CoV-1 and MERS-CoV) has not been associated with more severe disease in severely immunosuppressed populations (transplants, chemotherapy or immunosuppressants). The risk of contracting this disease was comparable to the general population.¹⁷ There is little data of COVID-19 in HSCT recipients and our study is the first to describe the presentation of COVID-19 in the HSCT population on a national scale in Latin America.

Regarding the clinical symptoms, the most frequent respiratory symptoms were cough and signs of respiratory dysfunction. The asymptomatic condition observed in children was significantly higher than that diagnosed in adults ($p < 0.001$). These results are very similar to those previously described by Felsenstein *et al.*, where children were also more frequently asymptomatic. According to them, one of the possible explanations for mild presentation in childhood may be the frequent contact to seasonal coronaviruses, as a result, the presence of antibodies with cross-reactivity and co-elimination with other viral infections. The authors also hypothesized that vaccinations and associated heterologous immune responses, and a more diverse memory T cell may provide advantages over the elderly population.¹⁸

Our results are similar in comparison with other case series recently published. In the present study, the estimated OS at day 40 was 69.8% (children 79% vs adults 66%). Considering the type of HSCT, we observed an OS of 72.9% among patients undergoing allogeneic transplantation and 60% in the autologous transplantation group. The outcome in autologous HSCT recipients was slightly inferior to what was

previously described in the study conducted by the European Society for Blood and Marrow Transplantation (EBMT), where approximately 500 transplant patients in 22 countries were included. At 6 weeks, mortality rate was 19% and 24% in autologous and allogeneic HSCT, respectively.⁹ Likewise, in a study by Akshay Sharma et al., with 318 patients, from the Center of International Blood and Marrow Transplant Research (CIBMTR), the OS observed 30 days after the diagnosis of COVID-19 was 68% for allogeneic and 67% for autologous. The latter study also showed an association between the diagnosis of COVID-19 and mortality in the following 12 months in allogeneic HSCT recipients¹². We did not observe any significant association between mortality and time of occurrence of COVID-19 after HSCT during a follow-up of 7 months. In our study, we were not able to individualize differences to explain this finding, however, it is worth emphasizing that mean age tended to be higher in patients in the autologous group and possibly associated with other comorbidities, although no statistical difference was found. In this study, we also did not explore differences in measures of protection or care between the evaluated groups.

According to data provided by the Ministry of Health, on June 30, 2021, Brazil accumulated the number of deaths related to COVID-19 above 515,900 and a fatality rate of 2.8%.¹⁹ Although Brazil has a Unified Health System (SUS) that guarantees assistance to all, the rapid and progressive increase in cases of COVID-19, especially in low-income populations, put a lot of pressure on hospital care, leading to the saturation of hospital and ICU beds, which certainly impacted final outcomes. Such premise was reinforced by the results obtained by Baqui *et al.*, where 11,321 Brazilian patients with COVID-19 admitted to hospitals with severe acute conditions were analyzed. Higher mortality rates were observed in the northern region of the country in comparison to the central-south region (65% vs 41%), the so-called “regional effect”.

The authors also demonstrated that comorbidities were more common in Brazilians admitted to hospitals in the northern region. The study theorizes that the regional effect is driven by an increase in the burden of comorbidities in regions with lower levels of socioeconomic development and that the ethnic effect is possibly related to differences in the susceptibility of COVID-19 and access to health care.²⁰

We also show that the initial clinical presentation was decisive in the prognosis. As noted in the EBMT record, patients with impaired performance status at COVID-19 diagnosis, and worsening inflammatory tests and kidney function had worse prognosis. Due to the absence of specific therapies, the early identification of patients with higher risk of unfavorable evolution and the prompt introduction of supportive therapy can determine the evolution of the infection in this specific group of patients.

Few data exist in the literature on characteristics of patients after HSCT with COVID-19. Garnica *et al.* described a total of 11 patients, all with hematological neoplasms, but only two after the transplant. Of these, 5 died. 45% had neutropenia, 73% had lymphocyte count below 1,000/mm³.²¹ Shah *et al.*, when analyzing 77 patients with SARS-CoV-2 who were recipients of cellular therapy found that neutropenia, comorbidities and presence of infiltrates on initial imaging were associated with more severe disease and death (25 of 77)²². In our study, neutropenia was present in 26% of the subjects, and lymphopenia in 53%, (data available for 72 and 70 patients, respectively) Variables such as urea, C-reactive protein, fibrinogen, d-dimers, creatinine, lymphocytes and hemoglobin (evaluated 7 days after hospitalization) showed significant difference between survival groups. The qualitative MCA (Fig. 4) analysis carried out also showed that variables such as urea and creatine, as well as the severity of the clinical presentation, seem to be related to the outcome. Also showed a tendency for allogeneic recipient patients to survive longer

than the group of autologous recipients, although this was not significant in other analyzes carried out in this study. Although the analysis is limited due to the small sample size, these findings are relevant as they point to indicators that may be related to worse outcomes.

Our study has some limitations. First, Brazil is a country of continental dimensions and significant regional differences. Thus, our group of patients is heterogeneous including children and adults, allogeneic and autologous HSCT for malignant and non-malignant diseases. Second, since patients' follow-up was short, it was not possible to assess long-term consequences of COVID-19 in these patients. Finally, although some laboratory results may indicate a worse prognosis, biomarkers could not be robustly evaluated due to the lack of data. Despite this, it is a representative sample of post-transplant patients treated in 21 centers in our country and the largest series of cases published so far in a middle-income country.

Even with the protective measures generally applied to these patients and many changes imposed by the pandemic in the BMT centers, infection by SARS-CoV-2 represents a great challenge for the team and the patients. Despite advances in the understanding of pathophysiology and therapeutic measures, prevention remains the main measure to minimize its impact and should be strongly recommended.²³ Understanding the delayed sequelae in surviving patients, the impact of new mutations and worldwide mass vaccination on the persistence of circulating SARS COV-2, and the efficacy of current COVID-19 vaccines in HSCT recipients will be the challenges for years to come.

In summary, this is the first multicenter retrospective study that evaluated the impact of SARS-CoV-2 on survival of HSCT recipients in Latin America. Long term

outcomes should be evaluated in the future, such as the impact of COVID-19 sequelae and the influence of infections on the quality of life of these patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical statement and consent to participate

Ethical approval to conduct this study has been granted by the Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA). Responsible for minors' signed informed consents in duplicate, keeping a copy for themselves.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao Jet, Hu Y *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497-506
2. World Health Organization - WHO. Coronavirus 2021 <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> Accessed 29 June 2021.
3. Gandhi RT, Lynch JB, del Rio C. Mild or Moderate Covid-19. *N Engl J Med.* 2020;383(18):1757-1766
4. Zhou F, Yu T, Du R, Du R, Fan G, Liu Y *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

5. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720
6. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson K *et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020;323(20):2052-2059.
7. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T *et al.* Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. *Chest* 2020;158(1):97-105
8. Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical Characteristics of Patients Who Died of Coronavirus Disease 2019 in China. *JAMA Netw open* 2020;3(4):e205619
9. Ljungman P, Mikulska M, de la Camara R, Basak G, Chabannon C, Corbacioglu S *et al.* The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. *Bone Marrow Transplant* 2020; 55:2071
10. Algwaiz G, Aljurf M, Koh M, Horowitz M, Ljungman P, Wiesdorf D *et al.* Real-World Issues and Potential Solutions in Hematopoietic Cell Transplantation during the COVID-19 Pandemic: Perspectives from the Worldwide Network for Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research Health Services and International Studies Committee. *Biol Blood Marrow Transplant* 2020;26(12):2181-2189
11. Machado CM. COVID-19 and hematopoietic stem cell transplantation: recommendations from the Brazilian Society of Bone Marrow Transplantation (SBTMO). *Jbmtct.* 2020;1(1):67-72
12. Sharma A, Bhatt NS, St Martin A, Abid MB, Bloomquist J, Chemaly RF, *et al.* Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol* [Internet]. 2021;3026(20):1–9
13. De Onis, M., Onyango, A. W., Borghi, E., Garza, C. & Yang, H. Comparison of the World Health Organization (WHO) Child Growth Standards and the National Center for Health Statistics/WHO international growth reference: Implications for child health programmes. *Public Health Nutr.* 2006;9:942–7.
14. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis.* 2020;20:689–96.
15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

16. Samaha R, Kattan J. Hematopoietic stem cell transplantation dilemma during the COVID-19 era. *Futur Oncol*. 2020;16(22):1569-1573
17. D'Antiga L. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transplant*. 2020;26(6):832-834
18. Felsenstein S, Hedrich CM. SARS-CoV-2 infections in children and young people. *Clin Immunol*. Sept 2020;220
19. Painel Coronavírus. Coronavírus Brasil. <https://covid.saude.gov.br/>. Published 2021. Accessed June 29, 2021
20. Baqui P, Bica I, Marra V, Ercole A, van der Schaar M. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. *Lancet Glob Heal* [Internet]. 2020;8(8):e1018–26
21. Garnica M, Valetim MR, Furtado P, Moreira MC, Bigni R, Vinhas S *et al*. COVID-19 in hematology: data from a hematologic and transplant unit. *Hematol Transfus Cell Ther* Oct-Dec 2020;42(4):293-299
22. Shah GL, DeWolf S, Lee YJ, Tamari R, Dahi PB, Lavery JA, *et al*. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *J Clin Investig*. 2020;130:6656–67.
23. Duarte FB, Moura ATG, Hallack Neto AE, Seber A, Vigorito AC, Lourenço ALG, *et al*. Comparative Analysis of the Data on the Influence of the Sars-Cov-2 Pandemic on Bone Marrow Transplantation and the Protocols Adopted in Brazil Between May and June 2020. *Jbmtct*. 2020;2(1):63–8

Table 1

Characteristic	COVID-19 (%)			p-value*
	Total (N= 86)	Children (N= 24)	Adults (N= 62)	
Median age (range)	33.5(0-74)	6.5 (0-17)	44 (18-74)	-
Sex (M/F)	50/36 (1.39:1)	14/10 (1.4:1)	36/26 (1.38:1)	1.000
Symptoms related to COVID-19				
Fever	20 (23%)	5 (21%)	15 (24%)	0.786
Upper respiratory tract symptoms	47 (55%)	10 (42%)	37 (60%)	0.153
Lower respiratory tract symptoms	19 (22%)	4 (17%)	15 (24%)	0.569
Headache	6 (7%)	2 (8%)	4 (7%)	0.670

Ageusia/Anosmia	4 (5%)	1 (4%)	3 (5%)	1.000
Diarrhea	14 (16%)	1 (4%)	13 (21%)	0.062
Asymptomatic	10 (12%)	8 (33%)	2 (3%)	0.001
Diagnosis				
Malignant disorders	72 (84%)	13 (54%)	59 (95%)	0.001**
Non malignant disorders	14 (16%)	11 (46%)	3 (5%)	
HSCT				
Allogeneic related	30 (35%)	7 (29%)	23 (37%)	0.006**
Haploidentical	17 (20%)	9 (38%)	8 (13%)	
Allogeneic unrelated	14 (16%)	6 (25%)	8 (13%)	
Autologous	25 (29%)	2 (8%)	23 (37%)	
Comorbidities				
Chronic Kidney Failure	1 (1%)	0 (0%)	1 (2%)	1.000
Diabetes (type 2)	8 (9%)	0 (0%)	8 (13%)	0.099
Heart disease	4 (5%)	1 (4%)	3 (5%)	1.000
Systemic arterial hypertension	12 (14%)	2 (8%)	10 (16%)	0.496
Outcome				
Alive	60 (70%)	19 (79%)	41 (66%)	0.034**
Deceased	26 (30%)	5 (21%)	21 (34%)	

*p-value refers to the comparison between children and adults.

**The p values related to two or more lines refer to analyzes performed using contingency tables. Underlying diseases included: malignant: germ tumor, multiple myeloma, myelodysplastic syndromes, Hodgkin lymphoma, non-Hodgkin lymphoma, chronic myeloid leukemia, acute myeloid leukemia, acute lymphoblastic leukemia,; non-malignant: primary immunodeficiency disease, Fanconi anemia, hemoglobinopathies, and aplastic anemia.

Table 2

Characteristics	Laboratory results at diagnosis				Laboratory results 7 days after diagnosis			
	Outcome				Outcome			
		Deceased	Alive	P-value		Deceased	Alive	P-value
Hemoglobin (g/ dL)								
n	74	26	48	0.058	56	19	37	0.004*
Median	10.2	9.1	10.65		9.7	8.5	10	

Min/Max	5.4 / 15.4	6.5 / 14.5	5.4 / 15.4		6.8 / 16.4	6.8 / 14.3	7 / 16.4	
Neutrophils (mL)								
n	72	25	47		55	18	37	
Median	2 588.5	3850	2310	0.401	1 753	1 989.5	1 753	0.590
Min/Max	0 / 13 637	0 / 13 637	0 / 8 152		0 / 9 048	0 / 5 000	0 / 9 048	
Lymphocyte (mg/ L)								
n	70	24	46		65	22	43	
Median	890	700	1061	0.608	690	452	858	0.042*
Min/Max	0 / 7 424	0 / 3 334	0 / 7 424		0 / 10 210	0 / 2 615	0 / 10 210	
Platelet (mL)								
n	73	26	47		55	18	37	
Median	84 000	83 300	88 000	0.080	67 000	37 000	89 000	0.007*
Min/Max	291 / 565 000	9 000 / 242 000	291 / 565 000		10 000 / 474 000	10 000 / 136 000	11 000 / 474 000	
Creatinine (mg/ dL)								
n	72	25	47		65	23	42	
Median	0.84	0.91	0.80	0.435	0.86	0.98	0.71	0.007*
Min/Max	0.1 / 17	0.10 / 17	0.10 / 2.01		0.1 / 56	0.1 / 56	0.13 / 2.78	
Urea (mg/dL)								
n	66	25	41		62	21	41	
Median	31	43	27	0.003*	34	59	30	0.001*
Min/Max	5 / 138	5 / 138	10 / 76		7 / 140	11 / 140	jul/74	
D-dimer (mg/ L)								
n	56	20	36		29	9	20	
Median	614	909.5	536	0.054	655	890	421.5	0.038*
Min/Max	0.1/17 350	1.12/17 350	0.1 / 6 576		0.28 / 7 010	2.4 / 7 010	0.28 / 1 790	
Fibrinogen (mg/ dL)								
n	24	12	12		21	11	10	
Median	431	460.5	429	0.623	448	513	349	0.011*
Min/Max	5.3 / 791	5.3 / 791	60 / 774		80 / 780	275 / 660	80 / 780	
C-reactive protein (ng/ mL)								
n	67	24	43		49	20	29	
Median	24	59.55	15	0.028*	35.29	57.5	14.3	0.031*
Min/Max	0.13 / 339 000	1.21 / 248	0.13 / 339 000		0.15 / 243 000	3.9 / 355.2	0.15 / 243 000	

*Statistically significant difference (p < 0.05)

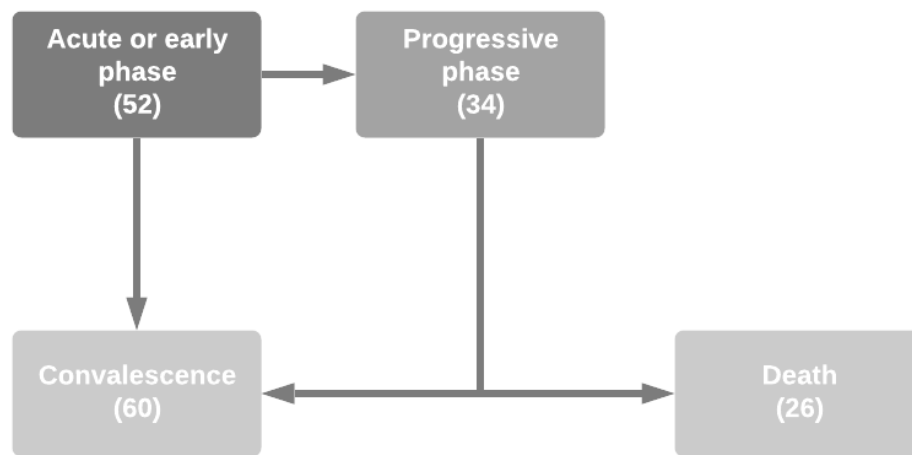


Fig. 1 Clinical evolutions of Hematopoietic Stem Cell Transplantation patients with COVID-19 diagnosis. The parentheses represent the number of patients in each stage of disease evolution.

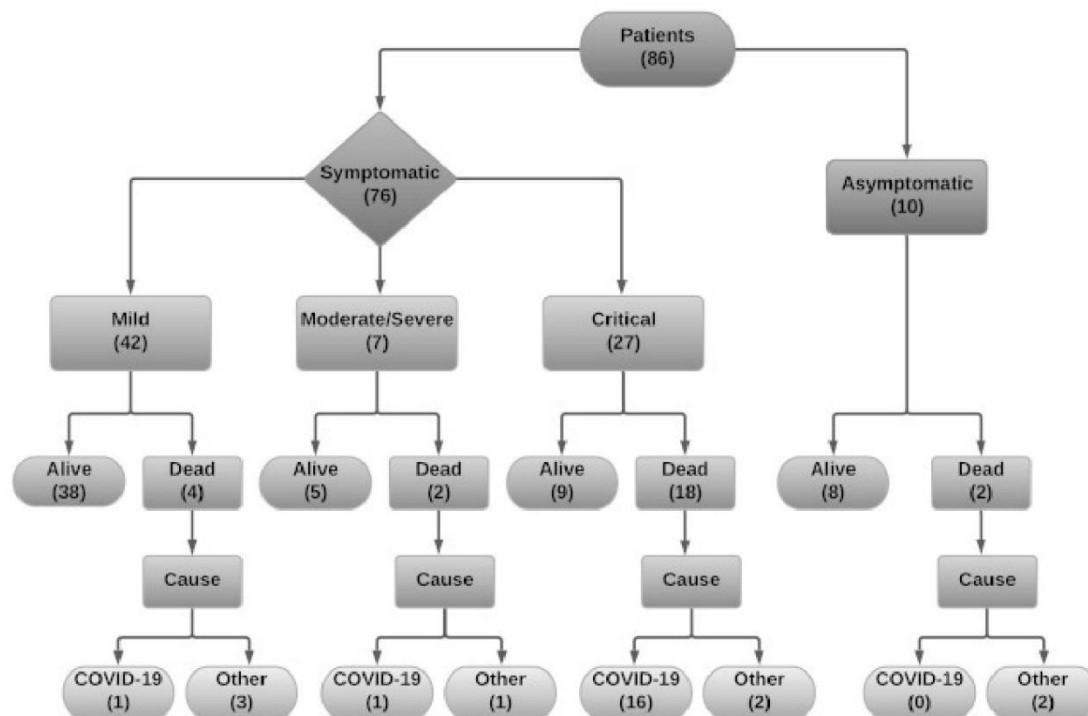


Fig. 2 Flowchart of COVID-19 clinical progression according to initial symptoms (number of patients). Mild disease: no oxygen supplemented; moderate and severe, any degree of hypoxemia and supplemental oxygen; and critical, mechanical ventilation and or hemodynamic instability.

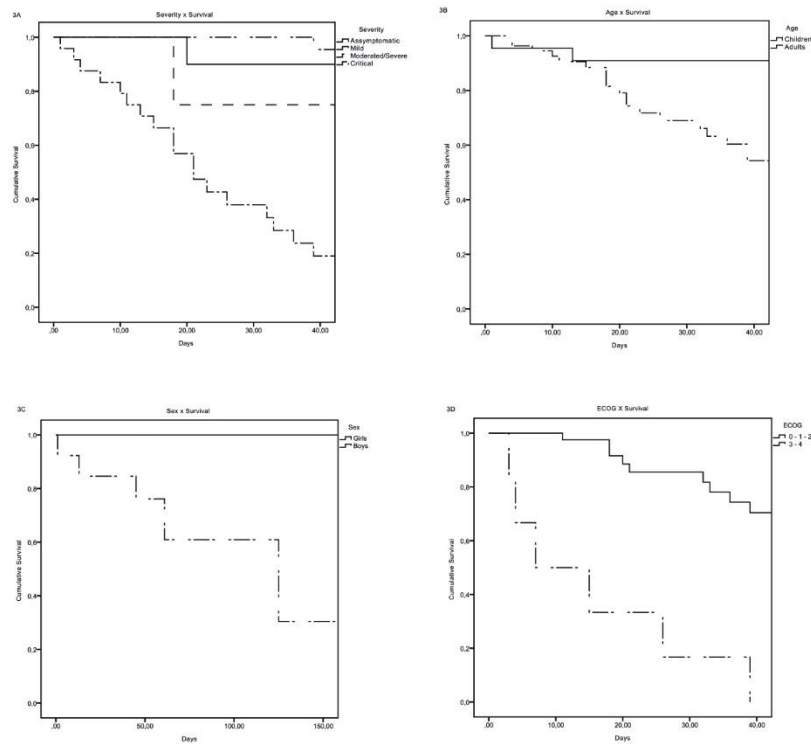


Fig. 3 Cumulative survival after COVID-19: A: Severity of the condition at diagnosis ($p < 0.001$); B: Age (Children \times Adults) ($p = 0.034$); C: Sex (pediatrics) ($p = 0.049$); D: ECOG (adult patients) ($p = 0.003$).

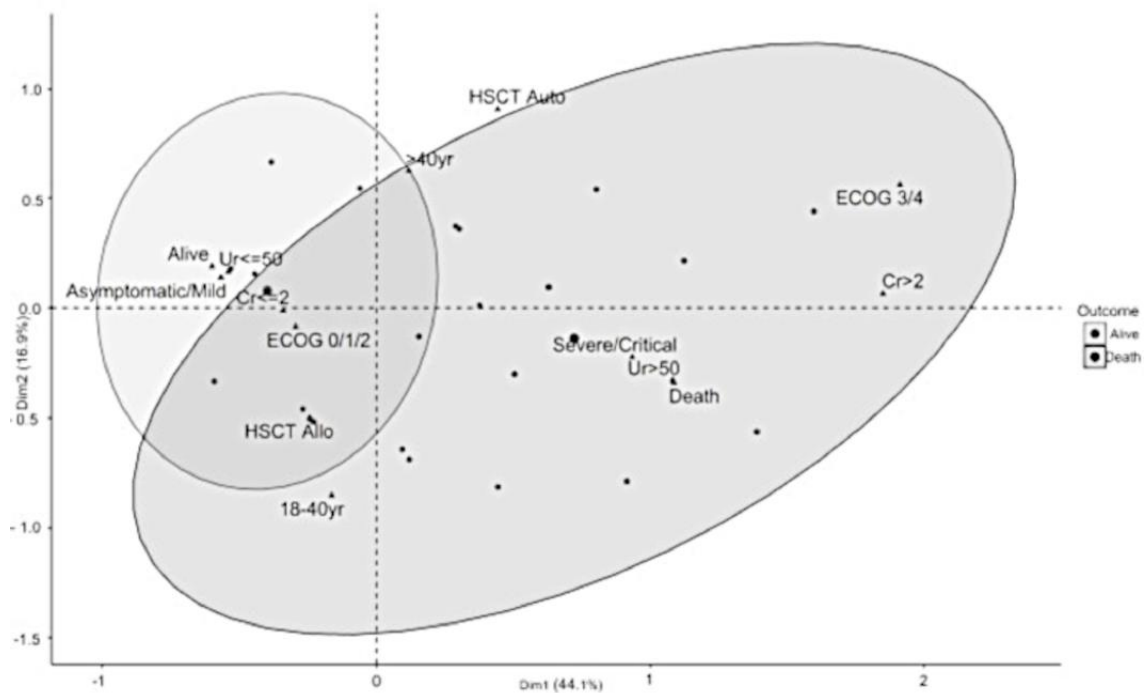


Fig. 4 Multivariate Correspondence Analysis between the main factors related to survival. MCA Multiple Correspondence Analysis, Dim Dimension, Cr serum creatinine mg/dL, Ur serum urea mg/dL, yr years old, HSCT Allo Allogeneic hematopoietic stem cell transplantation, HSCT Auto Autologous hematopoietic stem cell transplantation, ECOG: Eastern Cooperative Oncology Group Performance Status, Severity of clinical presentation: asymptomatic/mild and severe/critical (see text).

8 CONCLUSÃO

A pandemia da COVID-19 se propagou rapidamente por todos os países do mundo. Devido ao limitado conhecimento a respeito dessa doença, sua chegada representou um grande desafio na vida de todos, especialmente para os grupos considerados mais vulneráveis. Os resultados obtidos a partir do desenvolvimento deste trabalho indicam uma vulnerabilidade dos grupos estudados em relação à população saudável. A relação entre um pior prognóstico e a gravidade da doença, se mostrou estatisticamente significativa em ambos os grupos. Porém, algumas características se apresentaram exclusivas a apenas uma das populações estudadas. Enquanto os pacientes da oncológica pediátrica apresentaram uma relação entre um pior desfecho e os valores de IMC (tanto inferiores como superiores aos parâmetros de referência), a população receptora de TCTH, não manifestou diferenças significativas para essa variável. Entretanto, este segundo grupo apresentou diferenças significativas para características como sexo, idade e *ECOG*, diferenças não encontradas entre os pacientes da oncologia pediátrica.

Em vista dos aspectos observados e conforme citado anteriormente, os resultados sugerem fortes indicativos de que o coronavírus é particularmente perigoso para pacientes pediátricos com câncer e para aqueles submetidos ao TCTH. Porém, as razões pelas quais essas populações correm maior risco de desenvolver formas graves da doença evoluindo para o óbito, bem como os riscos específicos de cada uma das populações estudadas ainda precisam ser esclarecidos.

De qualquer modo, acreditamos que os dados produzidos a partir desses estudos poderão agregar conhecimento a respeito desta infecção em subpopulações de risco principalmente no que se refere a esses habitantes imunocomprometidos de países de média e baixa renda. Ainda, pode vir a contribuir na identificação, acompanhamento e tratamento precoce de pacientes reconhecidamente mais suscetíveis. A compreensão referente aos riscos aos quais os pacientes estão expostos pode nos ajudar, enquanto sociedade, na elaboração de estratégias de mitigação dos impactos causados pela COVID-19.

Algumas limitações podem ser consideradas nesse estudo. Em primeiro lugar, a realização de um registro multicêntrico em um país de dimensões continentais com grandes diferenças regionais. Posteriormente, destacamos a impossibilidade de

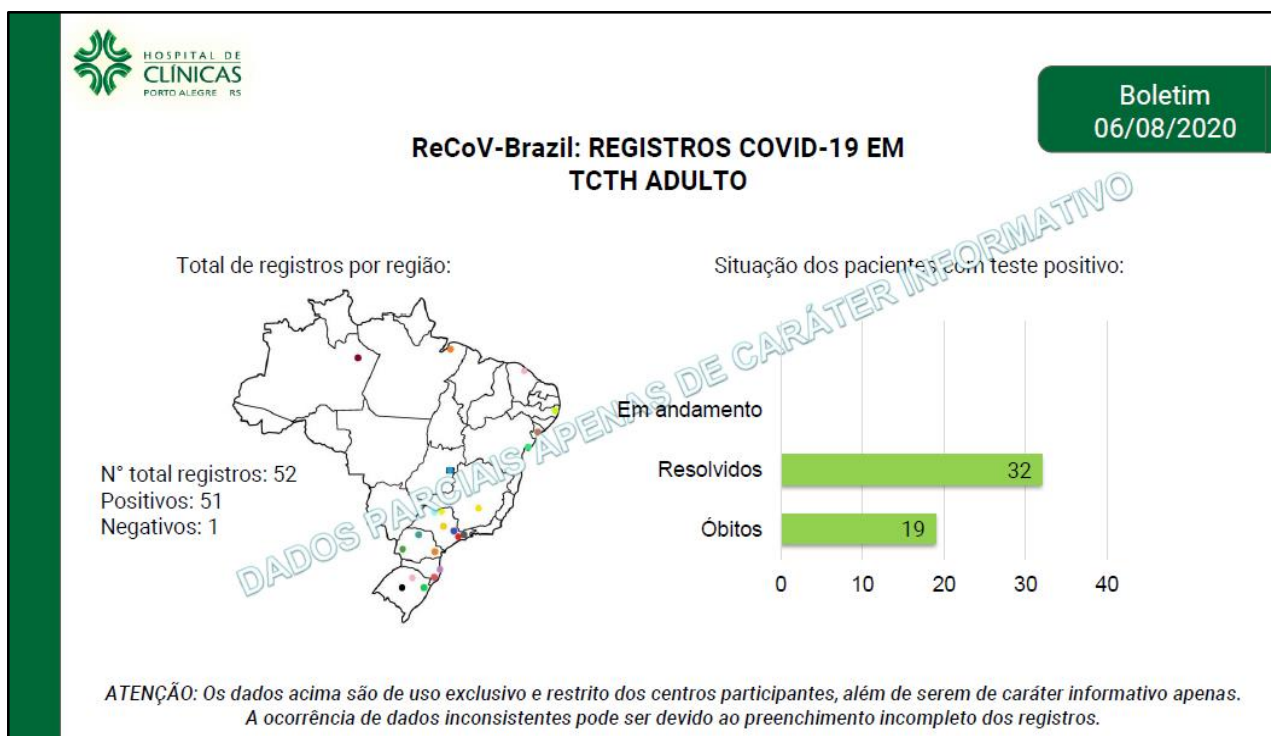
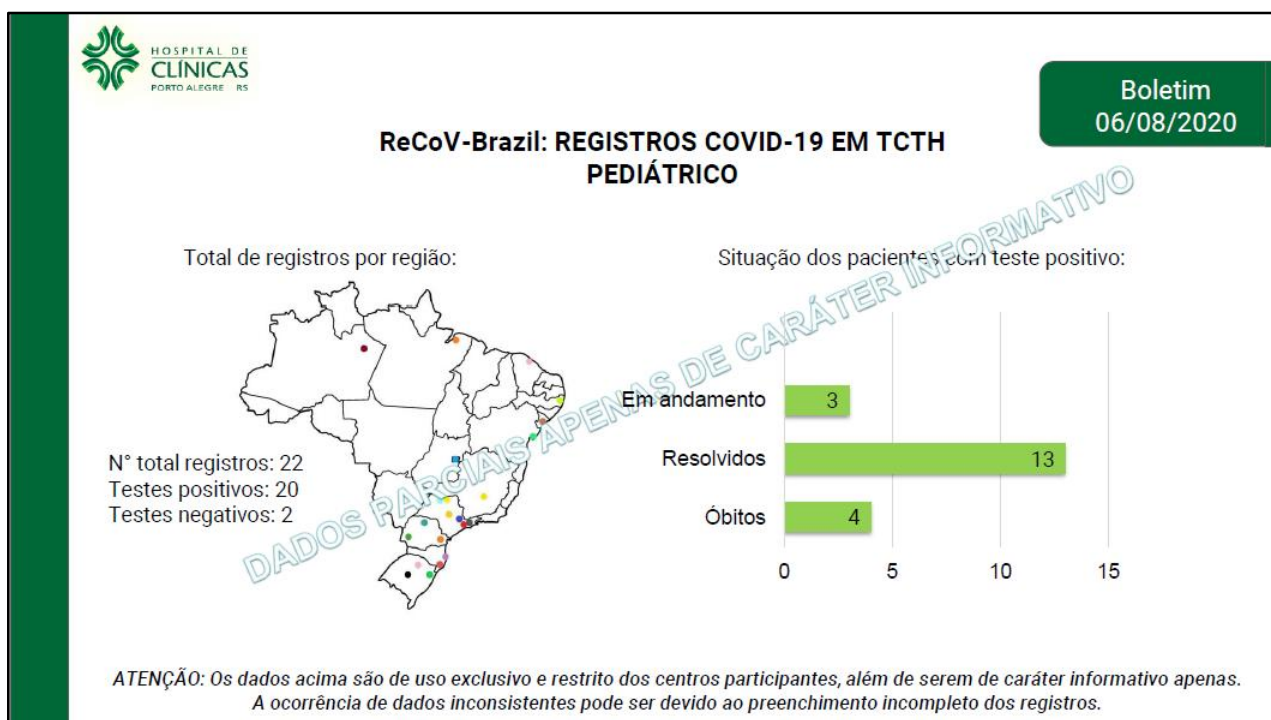
preenchimento dos questionários de forma centralizada necessitando do auxílio de equipes locais em cada centro. Alguns dados exigiram monitoramento cuidadoso para garantir uniformidade e consistência; apesar de nossos melhores esforços, algumas informações não puderam ser obtidas para todos os pacientes. Apesar de termos conseguido identificar repercussões agudas como hospitalizações e sobrevida, o curto período de acompanhamento deve ser destacado. Ademais, embora alguns resultados laboratoriais possam indicar um pior prognóstico, os biomarcadores não puderam ser avaliados de forma robusta devido à falta de dados. Finalmente, no que se refere ao estudo desenvolvido com pacientes receptores de TCTH, ganha destaque a heterogeneidade dos pacientes (crianças e adultos, TCTH alogênico e autólogo para doenças malignas e não malignas).

Apesar do progressivo conhecimento adquirido em relação à fisiopatologia, às medidas terapêuticas e eficazes protocolos empregados durante a pandemia para a proteção dessa população, a infecção pelo SARS-CoV-2 ainda representa um grande desafio para a equipe e para os pacientes. De qualquer modo, a prevenção e a vacinação em massa continuam sendo as principais medidas para minimizar seu impacto e devem ser fortemente recomendadas.

9 CONSIDERAÇÕES FINAIS

Este estudo multicêntrico prospectivo com análise retrospectiva avaliou o impacto do SARS-CoV-2 na sobrevivência a curto prazo de pacientes da oncologia pediátrica e de receptores de TCTH. Esperamos que os dados gerados a partir deste trabalho contribuam no estabelecimento de estratégias que possam mitigar o impacto dessa doença. Entretanto, a chegada de novas ondas da COVID-19 ao Brasil bem como o frequente surgimento de novas cepas do vírus SARS-CoV-2 indicam que somente por meio de um contínuo monitoramento dessas populações seremos capazes de compreender como variáveis relacionadas ao contexto socioeconômico podem interferir no prognóstico, bem como determinar o impacto a longo prazo da infecção pelo SARS-CoV-2 nessas crianças e no tratamento de suas patologias de base.

APÊNDICE A - Exemplo de Boletim Semanal



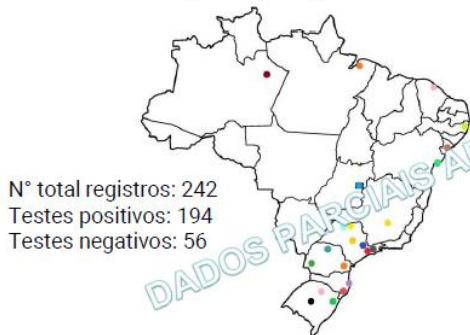


Boletim
13/08/2020

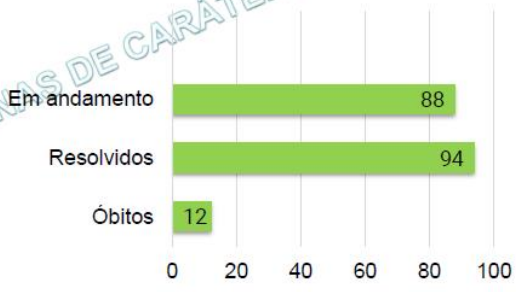
ReCoV-Brazil: REGISTROS COVID-19 EM PEDIATRIA ONCO-HEMATO

Total de registros por região:

Situação dos pacientes com teste positivo:



Nº total registros: 242
Testes positivos: 194
Testes negativos: 56



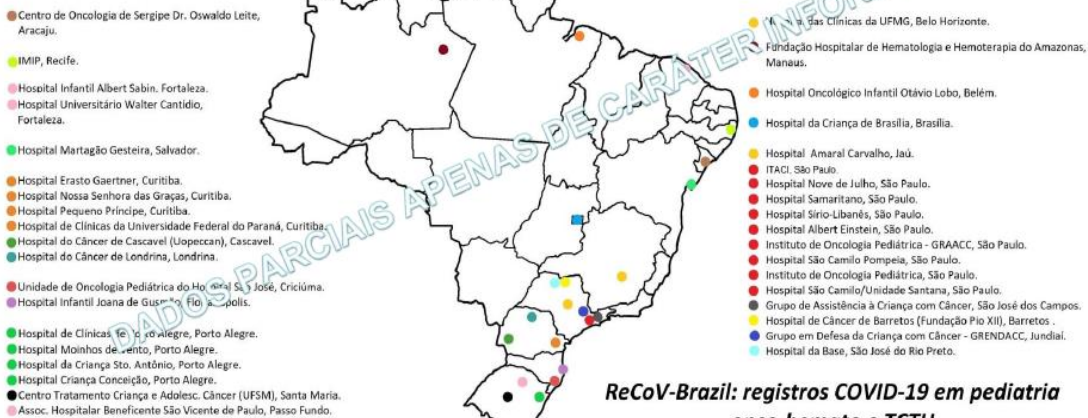
ATENÇÃO: Os dados acima são de uso exclusivo e restrito dos centros participantes, além de serem de caráter informativo apenas. A ocorrência de dados inconsistentes pode ser devido ao preenchimento incompleto dos registros.



Boletim
13/08/2020

ReCoV-Brazil: REGISTROS COVID-19 EM PEDIATRIA ONCO-HEMATO E TCTH

Centros cadastrados (37)



ReCoV-Brazil: registros COVID-19 em pediatria onco-hemato e TCTH

ATENÇÃO: Os dados acima são de uso exclusivo e restrito dos centros participantes, além de serem de caráter informativo apenas. A ocorrência de dados inconsistentes pode ser devido ao preenchimento incompleto dos registros.

APÊNDICE B

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – RESPONSÁVEIS

Projeto GPPG N°2020-0183

CAAE: 30983320.4.1001.5327

Título do Projeto: “Avaliação da repercussão da infecção por SARS-CoV-2 em crianças tratadas em serviços de Oncologia, Hematologia ou Transplante de Medula Óssea no Brasil: estudo multicêntrico”.

A pessoa pela qual você é responsável está sendo convidada a participar de uma pesquisa cujo objetivo é avaliar pacientes em acompanhamento em serviços de Oncologia ou Transplante de Células Hematopoiéticas que possuem suspeita ou fizeram investigação de COVID-19 no Brasil.

O COVID-19 é um novo vírus identificado no início de 2020, que tem se espalhado por muitos países e pode ter uma apresentação clínica variável desde não causar sintomas até quadros respiratórios graves. O estudo está sendo coordenado pelo Laboratório de Pediatria Translacional localizado no Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre - RS, mas engloba vários centros de tratamento de crianças e jovens do país. Se você aceitar que a pessoa pela qual você é responsável participe da pesquisa, o procedimento envolvido compreenderá: Apenas as coletas de informações relativas à consulta ambulatorial com equipe assistencial, a qual já está inserida dentro do planejamento de acompanhamento do paciente em tratamento neste serviço. Desta consulta serão coletados dados inseridos no prontuário do participante, como dados clínicos referentes a diagnóstico, resultados de exames, ressaltamos que não será realizado nenhum procedimento ou exame adicional além dos já recomendados conforme indicação da equipe assistente. Não são conhecidos riscos adicionais pela participação na pesquisa, apenas o risco mínimo de quebra de confidencialidade ao utilizar os dados, sendo que serão tomadas todas as medidas para preservar a privacidade do participante.

A participação na pesquisa não trará benefícios diretos aos participantes, porém, contribuirá para o aumento do conhecimento sobre o assunto estudado, e poderá beneficiar futuros pacientes. A participação na pesquisa é totalmente voluntária, ou

seja, não é obrigatória. Caso você decida não autorizar a participação, ou ainda, retirar a autorização após a assinatura deste Termo, não haverá nenhum prejuízo ao atendimento que o participante recebe ou possa vir a receber na instituição. Não está previsto nenhum tipo de pagamento pela participação na pesquisa e não terá nenhum custo com respeito aos procedimentos envolvidos. Caso ocorra alguma intercorrência ou dano, resultante da participação na pesquisa, o participante receberá todo o atendimento necessário, sem nenhum custo pessoal. Os dados coletados durante a pesquisa serão sempre tratados confidencialmente. Os resultados serão apresentados de forma conjunta, sem a identificação dos participantes, ou seja, o nome não aparecerá na publicação dos resultados. Caso você tenha dúvidas, poderá entrar em contato com a pesquisadora responsável Mariana Bohns Michalowski ou com a pesquisadora Liane Esteves Daudt, pelo telefone 51-3359-8019 ou com o Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre (HCPA), pelo telefone (51) 33597640, ou no 2º andar do HCPA, sala 2229, de segunda à sexta, das 8h às 17h. Esse Termo é assinado em duas vias, sendo uma para o participante e outra para os pesquisadores.

Nome do participante da pesquisa

Assinatura (se aplicável)

Nome do responsável

Assinatura

Nome do pesquisador que aplicou o Termo

Assinatura

Local e Data: _____