Clinical Evolution and Prognostic Factors of Cancer Patients with COVID-19 in Mechanical Ventilation

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Evolução Clínica e Fatores Prognósticos de Pacientes Oncológicos com Covid-19 em Ventilação Mecânica

Evolución Clínica y Factores Pronósticos de Pacientes Oncológicos con COVID-19 en Ventilación Mecánica

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ABSTRACT

Introduction: Cancer patients were at risk of developing severe respiratory conditions when affected by COVID-19, requiring intensive support and invasive mechanical ventilation (IMV). **Objective:** Evaluate the factors associated with death of cancer patients by COVID-19 who developed respiratory failure and need of IMV. **Method:** Retrospective cohort study of cancer patients in an oncology intensive care unit (ICU), with COVID-19 and on IMV was carried out from April 2020 to December 2021. All patients with cancer admitted to the ICU on IMV or who developed IMV due to worsening of COVID-19 were sequentially included, excluding those who had been in follow-up of the oncological disease for more than five years. For statistical analysis, measures of central tendency and dispersion were used, as well as absolute and relative frequencies. Multiple logistic regression was applied to evaluate factors associated with mortality, considering statistically significant values of $p < 0.05$. **Results:** 85 patients were included in the study. Death was higher for patients with solid tumors (OR= 3.64; 95% CI, 1.06-12.52; $p = 0.04$), in addition to those who required renal support while in ICU (OR = 6.88; 95% CI, 1.82-25.98; $p = 0.004$), those who could not be extubated (OR= 8.00; 95% CI, 2.16-29.67; $p = 0.002$) and who presented an alveolar distension pressure value greater than 15cmH2O for at least one day (OR= 5.9; 95% CI, 1.76-19.80; $p = 0.004$). **Conclusion:** Clinical and IMV characteristics were associated with death in cancer patients with COVID-19 and IMV.

Key words: Neoplasms/epidemiology; COVID-19; Respiratory Distress Syndrome; Critical Care; Ventilators, Mechanical.

RESUMO

Introdução: Pacientes com câncer apresentaram risco de desenvolver quadros respiratórios graves quando acometidos por covid-19, com necessidade de suporte intensivo e de ventilação mecânica invasiva (VMI). **Objetivo:** Avaliar os fatores associados ao óbito em pacientes oncológicos que tiveram covid-19 e evoluíram com insuficiência respiratória e necessidade de VMI. **Método:** Estudo de coorte retrospectivo de pacientes com câncer em uma unidade de terapia intensiva (UTI) oncológica, com covid-19 e em VMI de abril de 2020 a dezembro de 2021. Foram incluídos de forma sequencial todos os pacientes com câncer admitidos na UTI em VMI ou que evoluíram com VMI por agravamento da covid-19, sendo excluídos aqueles em controle da doença oncológica há mais de cinco anos. Para a análise estatística, foram utilizadas medidas de tendência central e dispersão, assim como frequências absolutas e relativas. A regressão logística múltipla foi aplicada para a avaliação dos fatores associados à mortalidade, considerando estatisticamente significante valores de p<0,05. **Resultados:** Foram incluídos no estudo 85 pacientes. O óbito foi maior entre os pacientes com tumores sólidos (OR= 3,64; IC 95%: 1,06-12,52; p=0,04), entre os que necessitaram de suporte renal durante a internação na UTI (OR= 6,88; IC 95%: 1,82-25,98; p=0,004), os que não puderam ser extubados (OR= 8,00; IC 95%: 2,16-29,67; p=0,002) e os que apresentaram o valor de pressão de distensão alveolar maior do que 15cmH_2O por pelo menos um dia (OR= 5,9; IC 95%: 1,76-19,80; p=0,004). **Conclusão:** Características clínicas e de VMI estavam associadas à morte de pacientes oncológicos com covid-19 e em VMI.

Palavras-chave: Neoplasias/epidemiologia; covid-19; Síndrome do Desconforto Respiratório; Cuidados Críticos; Ventiladores Mecânicos.

RESUMEN

Introducción: Los pacientes con cáncer corrían riesgo de desarrollar afecciones respiratorias graves al ser afectados por la COVID-19, requiriendo soporte intensivo y ventilación mecánica invasiva (VMI). **Objetivo:** Evaluar los factores asociados a la muerte en pacientes con cáncer que tuvieron COVID-19 y que desarrollaron insuficiencia respiratoria y necesidad de VMI. **Método:** Estudio de cohorte retrospectivo en pacientes oncológicos internados en una unidad de cuidados intensivos (UCI) de oncología, con COVID-19 y en VMI de abril de 2020 a diciembre de 2021. Se incluyeron secuencialmente todos los pacientes con cáncer ingresados en UCI con VMI o que necesitaron VMI por empeoramiento de la COVID-19, excluyendo a aquellos que llevaban más de cinco años bajo control de la enfermedad oncológica. Para el análisis estadístico se utilizaron medidas de tendencia central y dispersión, así como frecuencias absolutas y relativas. Se aplicó regresión logística múltiple para evaluar los factores asociados a la mortalidad, considerando valores de p<0,05 estadísticamente significativos. **Resultados:** Se incluyeron en el estudio 85 pacientes. La muerte fue mayor entre los pacientes con tumores sólidos (OR= 3,64; IC 95%, 1,06-12,52; p=0,04), entre los que requirieron soporte renal durante la estancia en UCI (OR = 6,88; IC 95%, 1,82-25,98; p= 0,004), entre los que no pudieron ser extubados (OR= 8,00; IC 95%, 2,16-29,67; p= 0,002) y entre los que presentaron un valor de presión de distensión alveolar mayor a 15cmH2O durante al menos un día (OR = 5,9; IC 95%, 1,76-19,80; p=0,004). **Conclusión:** Las características clínicas y de VMI se asociaron con la muerte en pacientes oncológicos con COVID-19 y en VMI.

Palabras clave: Neoplasias/epidemiología; COVID-19; Síndrome de Dificultad Respiratoria; Cuidados Críticos; Ventiladores Mecánicos.

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INTRODUCTION

Patients with cancer account for nearly 15% to 20% of all the patients admitted to intensive care units (ICU)[1,2]. The admission to the ICU is guided by the evaluation of clinical and oncologic prognosis with complex and multiprofessional approach[3,4].

Acute respiratory failure associated with infections is among the multiple causes of admission of patients with cancer to the ICU[5,6]. Viral and bacterial pneumonias are the main triggering causes of the acute respiratory distress syndrome (ARDS) in immunocompromised individuals such as cancer patients. In the last years, the epidemic provoked by emerging viruses as SARS-CoV-2 in 2019, was responsible for the biggest incidences of ARDS in the whole world[7,8].

When affected by COVID-19, cancer patients were in the group of individuals with risk of developing severe respiratory conditions needing intensive support care and invasive mechanic ventilation (IMV)[9]. Studies have shown that these patients presented worse outcomes than other group of patients affected by COVID-19 with high risk of evolving to the severe form of the disease and cancer diagnosis is an independent risk of death[10]. In addition, patients with cancer tend to be older with more comorbidities than the general population. For this group, the main comorbidities described are hypertension, diabetes and obesity[11].

The great number of ARDS triggered by SARS-CoV-2 associated viral pneumonia brought new discussions about clinical presentation, diagnosis, treatment and outcome of the syndrome[12]. One of the relevant topics was that for patients with associated COVID-19 acute respiratory distress syndrome (CARDS), the period since the diagnosis of viral infection and diagnosis of ARDS can be greater than earlier defined by the Berlin classification[12].

Another important discussion was the understanding that patients with CARDS presented different respiratory mechanic patterns and heterogeneous responses to alveolar recruitment by increased pressure applied to airways, leading to the concept of different phenotypes in patients with ARDS[12,13].

The thorough management of mechanic ventilation is one of the main non-pharmacological approaches for patients with ARDS and is the target of efforts to ensure improved care to these patients.

It is relevant to know the profile of patients with cancer needing IMV as a result of COVID-19 due to the substantial number of patients admitted to the ICU and the specificities of cancer patients. The objective of this study is to evaluate the factors associated with death of cancer patients diagnosed with COVID-19 in 30 days who evolved to acute respiratory failure and needed IMV at an oncologic ICU.

METHOD

Retrospective cohort study of patients with any type of cancer, older than 18 years admitted to the ICU for adults of "*Hospital do Câncer I (HCI)*" of the National Cancer Institute (INCA) in Rio de Janeiro, diagnosed with COVID-19 and who needed mechanic ventilation from April 2020 to December 2021. All cancer patients admitted to the ICU who had COVID-19 and evolved to respiratory failure and needed IMV during the study period were enrolled sequentially.

The Institutional Review Board (IRB) approved the study, report number 4,176,866 on July 28, 2020 (CAAE (submission for ethical review) 35200820.0.0000.5274), in compliance with ethical guidelines of Directive 466/2012[14] of the National Health Council.

The information were collected from physical and electronic charts and entered into the data management software Research Electronic Data Capture (REDCap)[15].

The patients were not approached directly. Sociodemographic data and information about the oncologic disease as type of neoplasm, staging, cancer treatment performed and performance status (PS) were collected one week before the admission to the ICU. The types of cancer were divided in solid tumors and hematological neoplasms to analyze the results.

Polymerase Chain Reaction Test (PCR-RT) for coronavirus, hemoglobin, D-dimer, C-reactive protein (CRP) and albumin were the lab tests collected. At admission to ICU, the prognostic Simplified Acute Physiology Score (SAPS-3) was collected and the diagnosis of sepsis or ARDS has been performed.

Information about interventions during hospitalization to the ICU as use of neuromuscular blockers, kidney support and tracheostomy have also been obtained, in addition to ventilatory support at admission, reason and date of intubation and extubation, whether pronation maneuvers have been performed, parameters of mechanic ventilation, arterial blood gas and discontinuation of mechanic ventilation were collected as well, further to the date of discharge or death during hospitalization and death within 30 days.

The software SPSS[16] (Statistical Package for Social Science for Windows, São Paulo, Brazil) version 24.0 was utilized for statistical analyzes. The Kolmogorov Smirnov normality test was applied with $p > 0.05$ for normal distribution. Measures of central tendency and dispersion for the continuous variables and absolute and

relative frequencies for categorical variables were utilized to analyze the data.

Stepwise-forward univariate and multiple logistic regression was calculated to evaluate mortality associated factors. In the crude model, the variables had level of significance of $p \leq 0.20$. The variables with $p < 0.05$ were included in the adjust model in logistic regression. The measure of effect utilized was odds ratio (OR) with confidence interval (CI) of 95%.

RESULTS

In the study period, 85 patients met the inclusion criteria: males (55.3%), older than 60 years of age (55.3%) and body mass index (BMI) > 25 (63.1%). The main comorbidities found were systemic arterial hypertension (49.4%) and diabetes *mellitus* (21.2%) (Table 1).

Most of them had solid tumors (55.3%): gastrointestinal system (11.8%), head and neck (11.8%), lung cancer (8.2%), primary tumor/metastasis to the central nervous system (7.1%), prostate cancer (7.1%) and others (9.4%). The hematologic neoplasms detected were: lymphomas (18.8%), leukemias (17.6%) and multiple myeloma (8.2%).

The majority had functional status little affected with PS from zero to two (75.1%), active disease (83.3%) and in cancer treatment at the enrollment (76.5%) (Table 1). Chemotherapy (61.4%), surgery (22.4%) and radiotherapy (14.3%) performed within 12 months before admission were counted combined.

Most of the patients was admitted to the ICU with sepsis or septic shock (82.4%), severity grade SAPS-3 ≥ 65 (52.4%), diagnosed with ARDS (72.9%) and needed neuromuscular blocker (84.7%). Nearly half of the patients needed kidney support (47.1%). More than one third of the patients (38.8%) was submitted to at least one pronation maneuver during hospitalization.

Approximately two thirds (68.2%) of the patients were hospitalized for 15 days or more. Most of them needed mechanic ventilation for more than 15 days with IMV (65.5%). Extubation was performed in 27.1% of the cases and tracheostomy, in 37.6% of the patients (Table 2).

The median time of hospitalization to the ICU was 20 days (interquartile range – IQR –11.50-30.50) and the median time of mechanic ventilation was 21 days (IQR – 11.50-30.00). The time of mechanic ventilation up to extubation and tracheostomy was 10.04 (±5.23) days and 15.50 (±4.63) days, respectively. And the time of mechanic ventilation in patients tracheostomized was 32.50 (IQR 24.00-40.25) days.

The multivariate analysis of mechanic ventilation (Table 3) revealed that values of driving pressure higher than 15 cmH_2O (49.9%) and peak pressure (P peak) higher than 30 cmH_2O (47.1%) at least for one day was statistically significant associated with death. Most of the patients (78.8%) kept the tidal volume (Vt) higher than 6 ml/kg of predicted individual weight in the first 72 hours of IMV. Positive end-expiratory pressure (PEEP) higher than 11 cmH_2O for two days or more were found in 56.55% of the patients.

The overall median Vt of the population was 7.42 (IQR 7.20-7.50) ml/kg and mean of DP in the initial 72 hours was 14.0 (±2.8) cmH_2O in patients who died and 11.7 (±3.0) cmH_2O in survivors with $p = 0.002$.

The arterial blood gas in the initial 72 hours of mechanic ventilation for 25.9% of the patients still kept the ratio of $PaO_2/FiO_2 \leq 200$, being this a variable statistically associated with death. Potential of hydrogen (pH) lower than 7.35 for at least four days (47.1%) and partial pressure of CO_2 (pCO_2) higher than 45 cmH_2O for at least seven days (60%) were also associated with death according to the univariate analysis (Table 3).

In addition, patients who died presented mean of 7.4 (±0.9) of pH in the initial 72 hours and survivors, mean of 7.3 (±0.8).

The lab tests (Table 4) show the patients who presented median values of D-dimer of 4,645 (2,212-8,644), hemoglobin of 8.78 (8.07-9,98), and mean values of CRP of 12.93 (±6.08) and CRP/albumin index of 6.20 (±4.13). The median of days with CRP > 10 mg/L was four days (2-5). However, no statistically significant difference was found among these characteristics and death.

The adjusted analysis (Table 5) revealed that patients with solid tumors had 3.64 more odds of dying than patients diagnosed with hematological neoplasms when admitted with severe COVID-19 and submitted to mechanic ventilation (CI 95%, 1.06-12.52; $p = 0.04$). Patients submitted to kidney support during hospitalization had 6.88 more odds of death than those who didn't (CI 95%, 1.82-25.98; $p = 0.004$). Those patients who were unable to be extubated had eightfold more odds of dying than those who were extubated during hospitalization (CI 95%, 2.16-29.67; $p = 0.002$). And the patients who remained at least one day with DP higher than 15 cmH_2O had 5.9 more odds of dying than those with DP lower than 15 cmH_2O during the first 15 days of mechanic ventilation (CI 95%, 1.76-19.80; $p = 0.004$).

DISCUSSION

The objective of the article was to describe the profile of patients with cancer who evolved to COVID-19 related respiratory failure and needed IMV. Death was higher

Table 1. Sociodemographic and clinic characteristics and association with death of cancer patients with COVID-19 who evolved to acute respiratory failure and needed mechanic ventilation from April 2020 to December 2021 at the ICU of HCI/INCA (n=85)

Sociodemographic and clinic characteristics	n (%)	Death		OR (CI 95%)	*p*
		Yes n (%)	No n (%)		
Age					
≥60 years	47 (55.3)	33 (61.1)	14 (45.2)	1.00	0.155*
<60 years	38 (44.7)	21 (38.9)	17 (54.8)	0.52 (0.21-1.28)	
Sex					
Male	47 (55.3)	31 (57.4)	16 (51.6)	1.00	
Female	38 (44.7)	23 (42.6)	15 (48.4)	0.79 (0.33-1.92)	0.605
Race/skin color[1]					
White	36 (44.4)	23 (44.2)	13 (44.8)	1.00	
Non-white	45 (55.6)	29 (55.8)	16 (55.2)	1.02 (0.41-2.55)	0.959
BMI[1]					
< 25	31 (36.9)	17 (31.5)	14 (46.7)	1.00	
≥ 25	53 (63.1)	37 (68.5)	16 (53.3)	1.90 (0.76-4.77)	0.167*
SAH					
No	43 (50.6)	26 (48.1)	17 (54.8)	1.00	
Yes	42 (49.4)	28 (51.9)	14 (45.2)	1.31 (0.54-3.17)	0.553
Diabetes *mellitus*					
No	67 (78.8)	41 (75.9)	26 (83.9)	1.00	
Yes	18 (21.2)	13 (24.1)	5 (16.1)	1.65 (0.53-5.17)	0.388
Type of cancer					
Hematologic neoplasm	38 (44.7)	20 (37.0)	18 (58.1)	1.00	0.063*
Solid tumors	47 (55.3)	34 (63.0)	13 (41.9)	2.35 (0.95-5.80)	
Activity of the disease					
No evidence	14 (16.7)	11 (20.4)	3(10.3)	1.00	0.211
Active disease	70 (83.3)	43 (79.6)	26 (89.7)	0.42 (0.11-1.63)	
Cancer treatment					
No	20 (23.5)	14 (25.9)	6 (19.4)	1.00	0.493
Yes	65 (76.5)	40 (74.1)	25 (80.6)	0.69 (0.23-2.02)	
Performance status[1]					
Up to two	61 (75.3)	39 (75.0)	22 (75.9)	1.00	0.931
Above two	20 (24.7)	13 (25.0)	7 (24.1)	1.04 (0.36-3.01)	

Captions: OR = odds ratio; CI = confidence interval; BMI = body mass index; SAH = systemic arterial hypertension.
[1]Valid cases.
*Variable included in the multivariate analysis (p < 0.20).

in patients with solid tumors, needing kidney support during hospitalization to the ICU, patients unable to be extubated and those who presented alveolar distending pressure higher than 15 cmH_2O at least for one day in the first 15 days of mechanic ventilation.

Primarily, for being an exclusive cohort of individuals with cancer, all of them presented high risk of being admitted to the ICU, invasive mechanic ventilation and possibility of death by COVID-19 due to immunocompromise and cancer treatment than the general population[10,17,18].

The total percent of deaths was 63.5%, a result higher than the numbers found by Chang et al.[19] in COVID-19-infected patients with several clinical etiologies and need of mechanic ventilation (43%), but close to the value found by Zylberman et al.[18], with 72.2% of deaths in patients with cancer and COVID-19 who needed

Table 2. Characteristics of admission to ICU and association with death of cancer patients diagnosed with COVID-19 who evolved to acute respiratory failure and needed mechanic ventilation from April 2020 to December 2021 at the ICU of HCI/INCA (n=85)

Variable	n (%)	Death		OR (CI 95%)	p
		Yes n (%)	No n (%)		
SAPS-3					
<65	39 (47.6)	23 (44.2)	16 (53.5)	1.00	0.427
≥65	43 (52.4)	29 (55.8)	14 (46.7)	1.44 (0.58-3.55)	
Severity of the infection at admission					
No sepsis	15 (17.6)	7 (13.0)	8 (25.8)	1.00	0.237
Sepsis/Septic shock	70 (82.4)	47 (87.0)	23 (74.2)	3.06 (0.48-19.64)	
ARDS					
No	23 (27.1)	12 (22.2)	11 (35.5)	1.00	0.442
Yes	62 (72.9)	42 (77.8)	20 (64.5)	1.55 (0.50-4.83)	
Moderate/severe ARDS					
No	50 (58.8)	29 (53.7)	21 (67.7)	1.00	0.480
Yes	35 (41.2)	25 (46.3)	10 (32.3)	1.47 (0.50-4.29)	
Hospitalization (days)					
Up to 14 days	27 (31.8)	18 (33.3)	9 (29.0)	1.00	0.682
15 days or more	58 (68.2)	36 (66.7)	22 (71.0)	0.89 (0.31-2.13)	
Mechanic ventilation (days)					
Up to 14 days	31 (36.5)	17 (31.5)	14 (45.2)	1.00	0.209
15 days or more	54 (65.5)	37 (68.5)	17 (54.8)	1.79 (0.72-4.48)	
Extubation					
Yes	23 (27.1)	7 (13.0)	16 (51.6)	1.00	<0.001*
No	62 (72.9)	47 (87.0)	15 (48.4)	7.16 (2.48-20.72)	
Tracheostomy at ICU[1]					
No	53 (62.4)	35 (64.8)	18 (58.1)	1.00	0.537
Yes	32 (37.6)	19 (35.2)	13 (41.9)	0.75 (0.30-1.86)	
Use of neuromuscular block					
No	13 (15.3)	4 (7.4)	8 (26.7)	1.00	0.012*
Yes	72 (84.7)	50 (92.6)	22 (73.3)	5.11 (1.42-18.4)	
Kidney support at ICU					
No	45 (52.9)	22 (40.7)	23 (74.2)	1.00	0.004*
Yes	40 (47.1)	32 (59.3)	8 (25.8)	4.18 (1.58-11.03)	
Pronation maneuver					
Yes	33 (38.8)	24 (44.4)	9 (29.0)	1.00	0.160*
No	52 (61.2)	30 (55.6)	22 (71.0)	0.51-1.31	

Captions: OR = odds ratio; CI = confidence interval; ICU = intensive care unit; SAPS-3 = Simplified Acute Physiology Score; ARDS = acute respiratory distress syndrome

*Variable included in the multivariate analysis ($p < 0.20$).

Table 3. Characteristics of mechanic ventilation, arterial blood gas and association with death in patients diagnosed with COVID-19 who evolved with acute respiratory failure and need of mechanic ventilation from April 2020 to December 2021 at the ICU of HCI/INCA (n = 85)

Variable	n (%)	Death		OR (CI 95%)	*p*
		Yes n (%)	No n (%)		
P peak > 30 cmH_2O (days)					
None	45 (52.9)	21 (38.9)	24 (77.4)	1.00	0.001*
One day or more	40 (47.1)	33 (61.1)	7 (2.6)	5.39 (1.97-14.70)	
PEEP > 11 cmH_2O (days)					
Less than two days	37 (43.5)	18 (33.3)	19 (61.3)	1.00	0.140*
Two days or more	48 (56.5)	36 (66.7)	12 (38.7)	3.16 (1.26-7.93)	
Mean Vt (6)					
Up to 6 ml/kg	18 (21.2)	13 (24.1)	5 (16.1)	1.00	0.391
>6 ml/kg	67 (78.8)	41 (75.9)	26 (83.9)	0.61 (0.19-1.90)	
DP > 15 cmH_2O (days)					
None	43 (50.6)	19 (35.2)	4 (77.4)	1.00	< 0.001*
One day or more	42 (49.4)	35 (64.8)	7 (22.6)	6.31 (2.3-17.35)	
PaO2/FiO2 initial 72 hours					
>200	63 (74.1)	34 (63.0)	29 (93.5)	1.00	0.006*
≤200	22 (25.9)	20 (37.0)	2 (6.5)	8.53 (1.84-39.61)	
pH initial 72 hours					
>7.35 mmHg	45 (52.9)	24 (44.4)	21 (67.7)	1.00	0.380
≤7.35 mmHg	40 (47.1)	30 (55.6)	10 (32.3)	2.62 (1.04-6.61)	
pH < 7.35 (days)					
Less than four days	42 (49.4)	19 (35.2)	23 (74.2)	1.00	0.001*
Four days or more	43 (50.3)	35 (64.8)	8 (25.8)	5.29 (1.99-14.10)	
PCO2 initial 72 hours					
≤ 45 mmHg	20 (24.4)	11 (20.4)	9 (32.1)	1.00	0.240
> 45 mmHg	62 (75.6)	43 (79.6)	19 (67.9)	1.85 (0.66-5.20)	
pCO_2 > 45 mmHg (days)					
Less than seven days	34 (40.0)	15 (27.8)	19 (61.3)	1.00	0.003*
Seven days or more	51 (60.0)	39 (72.2)	12 (38.7)	4.11 (1.61-10.50)	

Captions: OR = odds ratio; CI = confidence interval; P peak = peak airway pressure; DP = driving pressure; PEEP = positive end-expiratory pressure; Vt = tidal volume; PaO_2/FiO_2 = ratio of arterial O2 partial pressure to fraction of inspired O2; pH = potential hydrogen; pCO_2 = partial pressure of CO_2.
[1]Data of the first 15 days in mechanic ventilation.
*Variable included in the multivariate analysis ($p < 0.20$).

mechanic ventilation from May to November 2020. In that study[18], death was associated with older than 65 years of age and tobacco use. In the current investigation, the majority of the patients were males, older than 60 years of age and these characteristics were associated with worst outcomes either in the general populations[20] or specific populations of patients with cancer[21,22]. However, age and sex were not associated with death, possibly due to the small number of patients.

The patients with solid tumors had 3.64-fold higher odds of dying than those with hematological neoplasms (OR = 3.64, CI 95%:1.06-12,52; $p = 0.04$) in the final adjusted model, contrary to other studies: Lee et al.[23] found 2.09-fold higher odds of death in hematologic patients submitted to chemotherapy recently than all the others without this condition (OR: 2.09, CI95%: 1.06-4.08; $p = 0.028$). In a recent retrospective population-based cohort study, Hosseini-Moghaddam et al.[17] described a risk 1.65-fold higher of death in patients with hematologic neoplasms than those with solid tumors (Hazard ratio 2.08, CI 95% , 1.74-2.49)[14].

The first hypothesis was that the patients with solid tumors investigated in the present study would be older than those with hematological neoplasms. However, it was not confirmed in the adjusted analysis. Another justification would be the variety of types of neoplasms,

Table 4. Lab tests and association with death of cancer patients diagnosed with COVID-19 who evolved with acute respiratory failure and needed mechanic ventilation from April 2020 to December 2021 at the ICU of HCI/INCA (n=85)

Variables	Total	Death		*p*
		Yes	No	
D-dimer (n = 80)[1]	4.645 (2.212-8.644)	4.754 (2.098-8.962)	4.631 (2.356-8.074)	0.905
D-dimer maximum (n = 80)[1]	7.109 (3.505-15.515)	6.778 (3.470-15.075)	7.469 (4.304-19.150)	0.327
Hemoglobin (n = 85)[1]	8.75 (8.07-9.98)	8.70 (8.06-9.80)	8.78 (8.11-10.33)	0.62
CRP (n = 84)[2]	12.93 (±6.08)	13.88 (±6.24)	11.30 (±5.54)	0.612
CRP/albumin (n = 58)[2]	6.28 (±4.13)	6.21 (±3.94)	6.33 (±4.46)	0.917

[1]median (IQR); [2]mean (standard deviation).
Caption: CRP = C-reactive protein.

Table 5. Multiple model of factors associated with death in cancer patients diagnosed with COVID-19 who evolved with acute respiratory failure and need of mechanic ventilation from April 2020 to December 2021 at the ICU of HCI/INCA (n = 85)

Variable	OR crude (CI 95%)	*p*	OR adjusted (CI 95%)	*p*
Type of cancer				
Hematologic neoplasms	1.00	0.063	1.00	**0.040**
Solid tumors	2.35 (1.58-11.03)		3.64 (1.06-12.52)	
Renal support at ICU				
No	1.00	**0.004**	1.00	**0.004**
Yes	4.18 (1.58-11.03)		6.88 (1.82-25.98)	
Extubation				
Yes	1.00	**< 0.001**	1.00	**0.002**
No	7.16 (2.48-20.72)		8.00 (2.16-29.67)	
Days with DP > 15 cmH2O				
None	1.00	**< 0.001**	1.00	**0.004**
One days or more	6.31 (2.3-17.35)		5.91 (1.76-19.80)	

Captions: OR = odds ratio; CI = confidence interval; ICU = intensive care unit; DP = driving pressure.

different types of protocols utilized and the possibility of hematological patients being more propense to non-therapeutic limitation while at the ICU, but these variables were not addressed in this study.

A *post hoc* analysis of the EFRAIM study – a multicenter observational prospective study of immunocompromised patients with hypoxemic respiratory failure admitted to ICU – by Benguerfi et al.[24] identified that 45.7% of the patients with solid tumors who evolved to hypoxemic respiratory failure and died, was associated with the Sequential Sepsis-related Organ Failure Assessment (SOFA) at admission, the presence of heart failure and lung cancer[24].

Another *post hoc* analysis of the EFRAIM study by Secreto et al.[25] concluded that for patients with acute myeloid leukemia and associated respiratory failure, clinical characteristics and organ dysfunction at admission were predictors of death as well[25].

The diagnosis of ARDS is one of the organ dysfunctions which increases the risk of death in cancer patients[26]. However, in the present investigation, apparently, the outcome was more associated with the long period of

hospitalization than severity at admission. The main markers of severity at admission (diagnosis of sepsis or ARDS and elevated SAPS-3) were not associated with death. 41.2% of the patients presented moderate to severe ARDS at admission, but death was not different than those who were not diagnosed with ARDS or had mild ARDS at admission.

In a large cohort multicenter study, Li Bassi et al.[27] found that severity of hypoxemia during IMV was associated with mortality and prolonged hospitalizations in patients with COVID-19 but with considerable improvement of PaO_2/FiO_2 in the first 24 hours of mechanic ventilation[27]. PaO_2/FiO_2 lower than 200 in the first 72 hours of mechanic ventilation was associated with death in the crude analysis, being statistically different than the group whose PaO_2/FiO_2 was higher than 200 in the first 72 hours, suggesting the negative impact of prolonged hypoxemia in cancer patients with ARDS. However, this variable was not statistically significant in the adjusted model.

The impossibility of extubation was associated with death as the present investigation concluded. Spontaneous breathing and extubation trials depend on multiple factors as satisfactory level of consciousness, resolution or clinical improvement of established organ dysfunctions and capacity of respiratory muscle to support spontaneous ventilation[28].

The frequent use of deep sedation and neuromuscular blockers and persistent inflammatory conditions present in COVID-19 infection[29,30] may have contributed for prolonged mechanic ventilation and impediment of spontaneous breathing trials in tracheostomized patients and those who died still intubated. In addition, the patients maintained some inflammatory markers as D-dimer and CRP quite elevated while in mechanic ventilation, a clear sign of patients with cancer[31,32,] corroborating the hypothesis of perpetuation of the inflammatory process in this population.

Renal replacement therapy due to kidney insufficiency, resulting from direct lesion of the organ or secondary to the inflammation and secondary endothelial dysfunction to the infection[33] was associated with death of patients with COVID-19. Zampieri et al[34]. described a relation between the beginning of mechanic ventilation and renal insufficiency in patients affected by COVID-19 needing renal replacement therapy persisting as a factor associated with death of critically ill patients with and without cancer[35,36].

Maintenance of DP higher than 15 cmH_2O for at least one day was a variable associated with death in the present study. Oliveira et al.[37] found that DP higher than 14 cmH_2O was an independent factor associated with death of patients with COVID-19. Demoule et al.[38], in a secondary analysis of the EFRAIM study, have also found significant association among variables of respiratory mechanic (DP, plateau pressure and compliance of respiratory system) and death, concluding that these are important predictors of mortality in immunocompromised patients[38].

These findings confirm the concept already established that the maintenance of an elevated alveolar distending pressure combined with other variables of the breather is one of the main etiologic agents of ventilation-induced lung injury (VILI). Overload on the lungs perpetuates the inflammatory process and tissue structural damage with gradual reduction of lung compliance, impacting the dependence on mechanical ventilation and mortality of patients with ARDS[39,40].

Although DP is a variable measured directly from the mechanic ventilator with well-defined cutoff value in intensive therapy practice, it is, actually, a function derived either from adjusted pressure, plateau pressure and PEEP or Vt and the mechanic properties of the respiratory system. Other variables as PEEP and Vt have not been associated with death in the present study, however, a consensus exists that, to minimize the risk of ventilator-induced lung injury in any patient, ventilatory monitoring should be comprehensive, frequent and thorough, including static parameters (plateau pressure and transpulmonary pressure) and dynamic parameters (respiratory frequency and flow)[41].

This study was one of the pioneers in analyzing factors associated with death of cancer patients with COVID-19 who evolved with acute respiratory failure and need of IMV at a reference oncology institution within the National Health System (SUS). In addition, it was possible to analyze multiple clinical variables and mechanic ventilation, which helped to design a more comprehensive prognostic profile of the population investigated.

The limitations of the study are inherent to the initial purpose and the atypical conditions of the period investigated but future and broader studies may address this issue.

One of them was that due to the reduced number of beds and the necessity of determining the oncologic treatment, the priority of ICU beds was for post-operation and oncologic emergencies. Some patients with COVID-19 in non-invasive mechanic ventilation or oxygen therapy were not admitted to the ICU, remaining in the institution's wards for this disease, unlike what happened in other COVID-19 reference ICUs which, in general, had patients in IMV or not.

Another limitation was not being possible to stratify the patients in relation to phenotypes of ARDS recently established in the literature. One of the most important

modifications post-COVID-19 pandemic was the identification of different phenotypes at the diagnosis of ARDS that allows better stratification of patients to provide patient-centered ventilatory support with dynamic parameters adjusted to the profile of respiratory mechanic and to the personal clinical characteristics either in ARDS by COVID-19 or other etiologies[12,42].

Data of patients of one institution were analyzed, but it is possible that cancer patients treated in other institutions have different profiles and are not comparable to the patients evaluated, in relation to external validity.

The death of cancer patients in intensive therapy should also be evaluated under the perspective of regular reassessments of clinical and oncologic prognosis[43,44], according to palliative care principles. Therefore, future studies can better stratify patients who have indication to receive full therapeutic resources and those with therapeutic limitations where intensive support becomes less invasive due to the imminent end of life.

The present study can aggregate scientific knowledge about this subgroup as a substantial portion of patients admitted to Brazilian ICU's, because of the scarcity of studies analyzing cancer patients in critical condition.

CONCLUSION

The diagnosis of solid tumors, the need of kidney support during the hospitalization to the ICU, the impossibility of extubation and maintenance of DP above 15 cmH_2O at least for one day were the variables associated with death of cancer patients diagnosed with COVID-19 who evolved to respiratory failure and need of IMV.

Thorough and patient-centered ventilatory monitoring of cancer patients in mechanic ventilation, particularly those with ARDS is an important non-pharmacological approach. Future studies about functional outcomes of these patients who needed mechanic ventilation can be relevant to evaluate the short and long-term impact on oncologic outcome.

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CONTRIBUTIONS

Michelle de Melo Queres dos Santos contributed substantially to the study design, acquisition, analysis and/or interpretation of the data and wording of the manuscript. Everton Araújo Cavalcante, Isabel Cid Taboada, Ana Cristina Machado Leão and Kelly Fireman contributed to the acquisition of the data. Monica Pena Quintão contributed to the study design. Anke Bergmann and Laura Augusta Barufaldi contributed substantially to the study design, analysis and/or interpretation of the data, wording and/or critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

The author Anke Bergmann, the scientific-editor of INCA's Revista Brasileira de Cancerologia declares potential conflict of interests. The other authors have no conflict of interests.

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