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Assessment of case fatality rate and survival in cancer patients with and without COVID-19, according to cancer topography: a retrospective cohort study

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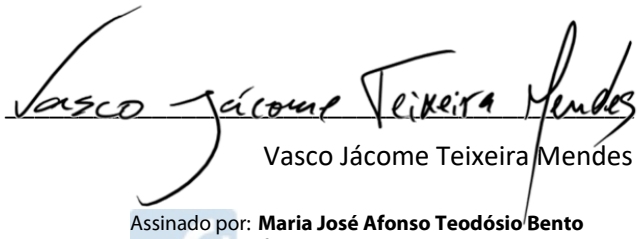

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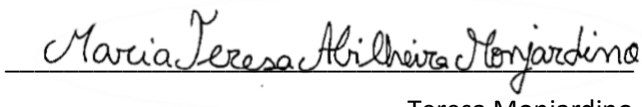
Maria José Bento



Teresa Monjardino

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"A saúde pública é um capital da Nação, que esta tem o dever de vigiar e auxiliar com o mesmo carinho e zelo com que protege todas as suas outras riquezas.

A saúde dos povos interessa às nações, pois sem os homens fortes de alma e corpo estas não podem suportar os esforços que a história lhes impõe."

Corino de Andrade

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nascimento até ao dia de hoje e para sempre. A tua sensibilidade, empatia e compaixão são valores que aprendi contigo e farão de mim um médico melhor.

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Resumo

Introdução: A doença do Coronavírus foi detetada pela primeira vez em 2019 (COVID-19) e pouco tempo depois, a Organização Mundial de Saúde declarou uma pandemia. A taxa de letalidade de doentes com diferentes subtipos de cancro é relatada como sendo mais elevada nos cancros pulmonares e hematológicos. No IPO-Porto, os doentes submetidos a tratamentos e exames invasivos foram obrigatoriamente submetidos a rastreio para o Síndrome Respiratória Aguda Grave por Coronavírus 2 (SARS-CoV-2).

Objetivos: Os principais objetivos deste estudo foram avaliar a taxa de letalidade e a probabilidade de sobrevivência dos doentes com cancro de acordo com o resultado do teste SARS-CoV-2.

Metodologia: Foi realizado um estudo de coorte retrospetivo, incluindo todos os doentes adultos com um primeiro tumor maligno primário diagnosticado entre 2018-2021, codificado no Registo Oncológico e com um resultado conclusivo do teste SARS-CoV-2, realizado entre 24 de Março de 2020 e 31 de Março de 2022. Foram recolhidas características demográficas, comorbilidades doentes e as características dos tumores malignos, tendo sido confirmado o estado vital de cada doente. As variáveis foram agrupadas conforme apropriado e pacientes com cancro e COVID-19 foram comparados com pacientes com cancro e sem COVID-19, através do teste t ou qui-quadrado de Student. Foi calculada a taxa de letalidade e a análise de sobrevivência foi feita utilizando o método de Kaplan-Meier. Para a comparação das curvas de sobrevivência, foi utilizado o teste de log-rank. Foi realizada uma análise univariável e multivariável, aplicando o método de regressão de Cox para calcular o Hazard Ratio (HR) e o intervalo de confiança a 95%. Valores de P inferiores a 0.05 foram considerados estatisticamente significativos. Todas as análises foram realizadas utilizando o software STATA 14®.

Resultados: De todos os pacientes com cancro, 3,774 tiveram resultados negativos no teste SARS-CoV-2 e 203 tiveram pelo menos um teste positivo. As características demográficas e comorbilidades eram semelhantes entre os dois grupos, exceto no que diz respeito à idade. Os doentes infetados que tinham cancro de pulmão ou lábio, cavidade oral e faringe apresentaram as taxas de letalidade mais elevadas (62,5% e 60,0%, respetivamente). O risco de morte em doentes infetados foi maior do que nos não infetados, mas este resultado não foi estatisticamente significativo (HR: 1,07; IC 95%: 0,79-1,44). O sexo masculino, idade avançada e os estadios III/IV são fatores significativamente associados a um maior risco de morte na população global (HR: 1.22, 1.02, 5.87, respetivamente)

Conclusões: Na população agora estudada, os doentes com cancro e infetados com COVID-19 não tinham maior risco de morte, ao contrário do que foi encontrado noutra meta-análise. Globalmente, o sexo masculino, a idade avançada e os estadios III/IV eram variáveis independentes para um maior risco de morte. A taxa de letalidade estimada na nossa coorte corrobora estudos anteriores, exceto para os cancros hematológicos e o linfoma. Esta análise mostrou que, em geral, os doentes tiveram intervalos de tempo mais curtos desde o diagnóstico até ao primeiro tratamento durante a pandemia, em comparação com os anos anteriores

Palavras-chave: Doentes oncológicos; COVID-19; Taxa de fatalidade; Hazard Ratio; Análise de sobrevivência.

Abstract

Introduction: Corona Virus Disease was firstly detected in 2019 (COVID-19) and shortly after a pandemic was declared by the World Health Organization (WHO). The case-fatality rate (CFR) of patients with different cancer subtypes is reported to be higher in lung and hematological cancers. At IPO-Porto, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) screening was mandatory for patients undergoing treatments and invasive exams.

Purpose: The main objectives of this study were to evaluate the CFR and survival probability of cancer patients by SARS-CoV-2 test result.

Methods: We conducted a retrospective cohort study including all adult patients with a first primary malignant tumor diagnosed between 2018-2021, coded at the Cancer Registry and with a conclusive SARS-CoV-2 test result performed between 24th of March 2020 and 31st of March 2022. Demographic characteristics, comorbidities and features of cancer diagnosis data was collected, and vital status was confirmed. Variables were grouped as appropriate and were compared between COVID-19 positive and negative patients with two-sample Student's t or chi-squared tests. The CFR was calculated, and survival analysis was done using the Kaplan-Meier method. For comparison of the survival curves, the log-rank test was used. A univariable and multivariable analysis was done applying the Cox regression method to calculate the Hazard Ratio (HR) and 95% confidence interval. P-values less than 0.05 were considered statistically significant. All analyses were performed using STATA 14® software.

Results: From all included cancer patients, 3,774 had negative SARS-CoV-2 test result and 203 had at least one positive test. The demographic characteristics and comorbidities were similar between the two groups, except for age. Infected patients that had lung or lip, oral cavity and pharynx cancers had higher CFR than their counterparts (62.5% and 60.0%, respectively). The risk of death in infected patients was higher than in non-infected ones but this result was not statistically significant (HR: 1.07; 95% CI: 0.79-1.44). Male sex, older age and III/IV stage were significantly associated with a higher risk of death (HR: 1.22, 1.02, 5.87, respectively).

Discussion and conclusions: COVID-19 infected cancer patients didn't have higher risk of death, contrary to what was found in other meta-analysis. Globally, male sex, older age and III/IV stage were independent variables for higher risk of death. The CFR estimated in our cohort corroborates previous studies, except for hematological cancers and lymphoma. This analysis showed that overall patients had shorter time gaps from diagnosis until the first treatment during the pandemic, compared to previous years.

Keywords: Cancer patients; COVID-19; Case-fatality rate; Hazard ratio; Survival analysis.

Abbreviation List

ACE2 – Angiotensin Converting Enzyme 2

AFRO – African Region

ALT – Alanine Aminotransferase

ARDS – Acute Respiratory Distress Syndrome

AST – Aspartate Aminotransferase

BMI – Body Mass Index

CEC – Comissão de Ética Competente

CFR – Case Fatality Rate

CI – Confidence Interval

COPD – Chronic Obstructive Pulmonary Disease

COVID-19 – Coronavirus Disease 2019

CRRT – Continuous Renal Replacement Therapy

DE – Department of Epidemiology

ECMO – Extracorporeal Membrane Oxygenation

ECOG PS – Eastern Cooperative Oncology Group Performance Status

ELISA – Enzyme-linked Immunosorbent Assay

EMRO – Eastern Mediterranean Region

EURO – European Region

HR – Hazard Ration

ICD-10 – International Classification of Diseases and Related Health Problems, 10th Revision

ICU – Intensive Care Unit

IPO-Porto – Instituto Portugês de Oncologia

IT – Immunological Tests

LAMP – Loop-mediated Isothermal Amplification

LFIA – Lateral Flow Immunochromatographic Assays

NAAT – Nucleic Acid Amplification Testing

NICE – National Institute for Health and Care Excellence

PAHO – Region of the Americas

RIC – Integrated Knowledge Repository

RNA – Ribonucleic Acid

RNU – National Health Service Database

RON – National Cancer Registry

RORENO – Portuguese Northern Region Cancer Registry

RT-PCR – Reverse Transcription Polymerase Chain Reaction

SARS-CoV – Severe Acute Respiratory Syndrome

SARS-CoV-2 - Severe Acute Respiratory Syndrome 2

SEARO – South-East Asia Region

SP – Survival Probability

WHO – World Health Organization

WPRO – Western Pacific Region

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Introduction

I. COVID-19

I.I Chain of events

In 2019, a new infectious human-to-human disease outbreak erupted from a local seafood market in Wuhan. The full-length genome obtained from five patients at an early stage of the outbreak identified a virus with significant similarity with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Coronaviruses belong to the family *Coronaviridae,* and order *Nidovirales,* and are broadly distributed in humans and other mammals [1]. This new Coronavirus identified in 2019 (2019-nCoV) is almost identical at the whole-genome level to a bat coronavirus [2]. The zoonotic origin of 2019-nCoV was determined to be bats acting as the reservoir host and pangolins possibly acting as one of intermediate amplifying host transmitting it to humans through butchering and consumption of meat [3].

On the 31st of December 2019, the World Health Organization's (WHO) Country Office in the People's Republic of China picked up a media statement by the Wuhan Municipal Health Commission from their website on cases of "viral pneumonia" in Wuhan [4]. Shortly after, on the 9th of January 2020, the WHO reported that the Chinese authorities had determined that the outbreak was caused by a novel coronavirus and on the 13th of January, the first protocol for a Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay by a WHO partner laboratory to diagnose the novel coronavirus was published [5]. Then, WHO issued the official taxonomy and name for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), namely for Coronavirus Disease 2019 (COVID-19) [6].

I.II Epidemiology

The first report of human-to-human transmission was published in early January 2020 and described a group of family members who ate game meat in Wuhan markets. The family had no direct zoonotic involvement with animals. Nevertheless, a super-spreading event of COVID-19 infections throughout family homes, hotels, and hospitals was recognized to have potential origin in this episode [7].

A few months later, on the 11th of March 2020, WHO declared COVID-19 a pandemic due to the alarming levels of spread and severity of the disease [5]. Available data between the 22nd of January 2020 and the 31st of December 2021 showed that more than 288.69 million confirmed cases and 5.44 million deaths had occurred worldwide [8].

I.III Transmission

The initial reproductive number (R_0) of SARS-CoV-2 was estimated to vary between 2-3 with a median of 2.79, classifying it as a highly transmissible disease [9]. The S glycoproteins of SARS-CoV-2 are used to link with the host by covalent bond to the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is present in the respiratory and the digestive tract, and transmission occurs once this glycoprotein bonds with an ACE2 receptor. Droplets are the primary transmission route of infection, but respiratory secretions, direct contact, fecal matter, and blood represent alternative routes of infection due to ACE2 receptor expression by enterocytes in the small intestine [2, 10-13]. After transmission, an incubation period occurs, and the virus may be present in the throat or nose a few days before and after symptoms onset. Therefore, asymptomatic individuals are a threatful source of infection as they are unaware of their positive infection status [14].

I.IV Mechanism of action

SARS-CoV-2 mainly invades alveolar epithelial cells, resulting in respiratory symptoms [15]. Its mechanism of action is mainly based on the binding of S-glycoprotein to an ACE2 receptor and replication of the virus in alveolar cells, inducing damage and inflammatory response. Consequently, several molecules including interferons, cytokines, chemokines, and arachidonic acid metabolites like leukotrienes and prostaglandins are released. Altogether, proinflammatory cytokines with inflammatory cells lead to a cytokine storm, organ damage and multi-organ failure [15, 16].

Initial symptoms, like dry cough, are provoked by nerve endings stimulation while fever and fatigue are associated to prostaglandins and leukotrienes release [17-19]. Symptoms like dyspnea and hypoxemia are caused by the ventilation/perfusion mismatch and the increase in vascular permeability induces fluid leakage and pulmonary edema causing this physiopatological phenomena. Higher vascular permeability also increases adhesion molecule expression and recruitment of more immune cells that damage alveolar cells and overstimulate the cytokine storm. With the damage of these cells, less surfactant is produced and the alveoli collapse. This collapse of the airway and the bronchoconstriction caused by leukotrienes magnifies the ventilation/perfusion mismatch [20, 21]. Subsequently, low oxygen levels stimulate the cardiopulmonary center in the brain to induce tachypnea and tachycardia [22, 23]. Nevertheless, there is increasing evidence that some patients with a competent immune system may be asymptomatic or develop only minor symptoms [24].

I.V Clinical presentation

Several studies played a key role in the characterization of clinical presentation and symptoms at the outburst of cases related the novel coronavirus [25-27]. At the onset of illness, the most common symptoms are fever, fatigue, dry cough, myalgia, and dyspnea. However, headache, dizziness, abdominal pain, nausea, vomiting, confusion, chest pain, diarrhea, sputum production, and hemoptysis represent less common symptoms [25-27]. A systematic review on July 2020, updated on May 2022, concluded that neither absence nor presence of symptoms are accurate enough to include or exclude COVID-19 because of their very low sensitivity. Although, the presence of anosmia or ageusia may be useful as a red flag and, additionally, cough supports further testing. This review supports clinicians search for symptoms like cough, sore throat, high temperature or fever, diarrhea, headache, myalgia or arthralgia, fatigue, anosmia, and ageusia and signs like lung sounds, blood pressure, blood oxygen level and heart rate. [28].

The laboratory profile of COVID-19 patients can reveal high frequency of leukocytosis with neutrophilia, lymphopenia, lower than normal hemoglobin, higher than normal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with severe liver function damage, elevated urea, nitrogen, or serum creatinine with renal function damage and prolonged pro-thrombin time. These abnormalities suggest that SARS-CoV-2 infection is associated with cellular immune deficiency, coagulation activation, myocardial, hepatic, and kidney injury, septic shock, and multi-organ failure [26, 27]. Non-survivors are more likely to have developed severe leukocytosis, lymphopenia, neutrophilia, and more severe changes in D-dimer, blood urea and creatinine levels when compared with survivors [26].

In hospital care setting, most patients show bilateral involvement on the X-ray or CT-Scan with multiple lobular and subsegmental areas of consolidation [25-27].

I.VI Diagnosis

COVID-19 diagnosis can only be confirmed with complementary laboratorial tests and the two main types of tests for SARS-CoV-2 detection are Nucleic Acid Amplification Testing (NAAT) and Immunological Tests (IT) [24].

The RT-PCR and the Loop-mediated Isothermal Amplification (LAMP) are two types of NAAT. Both RT-PCR and LAMP are based on the principle of amplification Nucleic Acid and detecting viral Ribonucleic Acid (RNA) in a nasopharyngeal swab, sputum, or stool. Nonetheless, RT-PCR is the most sensitive (> 95%) and specific (> 97%) test and, therefore, gold standard for SARS-CoV-2 detection [29, 30].

The Lateral Flow Immunochromatographic Assays (LFIA) and the Enzyme-linked Immunosorbent Assay (ELISA) are both IT. Both LFIA and ELISA are based on the principle of detection of Immunoglobulin M and Immunoglobulin G (IgM/IgG) in nasopharyngeal swab or serum. Although LFIA delivers the result in 15 minutes and requires little or almost no training and can even be performed by the patient, it is less sensitive (> 80%) and less specific (> 96%) than ELISA or NAAT techniques [31, 32].

I.VII Treatment

Until this new pandemic, there was no specific treatment for other coronavirus infections other than supportive care [33]. Accordingly, health care centers used resources as specialized care in intensive care unit (ICU), oxygen therapy (nasal canula and high-flow oxygen mask), mechanical ventilation (noninvasive and invasive), extracorporeal membrane oxygenation (ECMO), blood dialysis, continuous renal replacement therapy (CRRT), corticosteroids when appropriate, antivirals, antibiotic or antifungal therapies to eliminate secondary infections whenever required by the patient' clinical status [25-27].

I.VIII Clinical outcome

A meta-analysis published in mid-2020 assessed potential determinants of severe disease and adverse prognostic endpoints such as: cardiac abnormality, acute respiratory distress syndrome (ARDS), disease progression, disease severity, invasive ventilation, admission to the ICU, composite endpoint and/or death. Male sex and older age were reported to be associated with worst adverse prognostic endpoints [34].

The comorbidities significantly associated with COVID-19 severity were chronic obstructive pulmonary disease (COPD), respiratory system disease, and cerebrovascular disease. Other comorbidities such as arterial hypertension, diabetes, malignancy, cardiovascular disease, coronary heart disease, cardiovascular/cerebrovascular disease, chronic kidney disease, hepatitis B infection, and digestive disease were also significantly associated with adverse prognostic endpoints in COVID-19 patients. Drinking and smoking were shown not to be relevant risk factors to disease severity [34].

Regarding risk for contracting SARS-CoV-2 virus, it was reported that individuals with or without specific comorbidities and behaviors such as alcohol and tobacco consumption seems to have equal distribution of COVID-19 infection in patients, and these are equally susceptible to virus infection regardless their clinical characteristics. Any of the previously referred risk factors must be interpreted as severe COVID-19 prognosis risk factor only [34].

I.IX Prognosis

Two different studies have described similar median time estimates of 5 days, from SARS-CoV-2 transmission to hospitalization and of 10 days, from transmission to ICU admission [26, 35]. Figure 1 shows a more detailed analysis of the occurrence of each symptom since the disease onset [35].

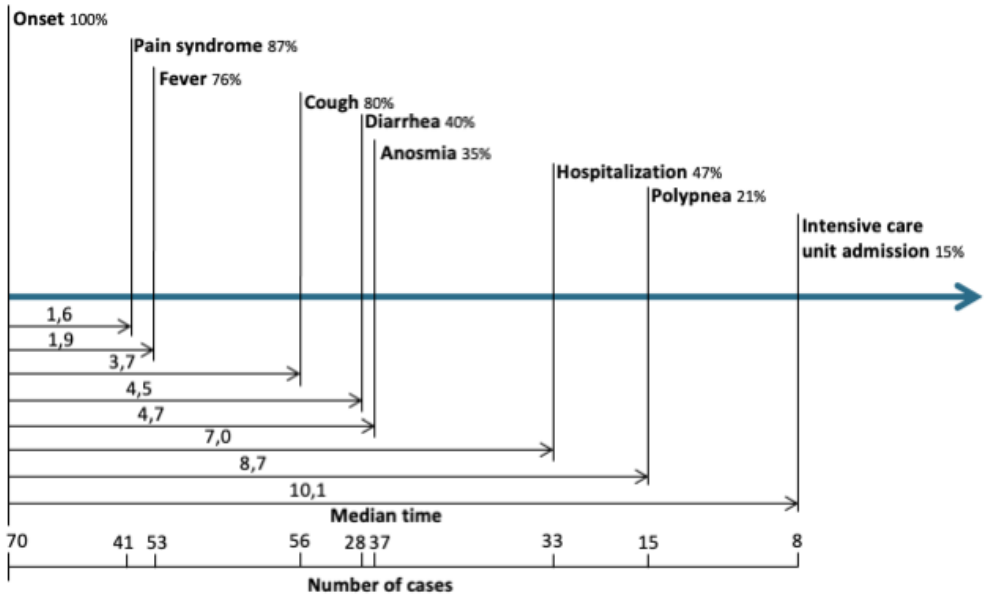

FIGURE 1. Timeline of COVID-19 after onset of illness (adapted from Zayet, et. al. [35]).

A meta-analysis of the case fatality rate (CFR) of patients with COVID-19 requiring invasive mechanical ventilation described a CFR between 43-64%. This estimation shown to be higher in the elderly population and in early COVID-19 epicenters like Wuhan and New York [36].

Worldwide, the peak of COVID-19 struck during the 17th epidemiological week. Before that, the weekly mean cumulative CFR was 3.6% with a 95% confidence interval (CI) of 2.5-4.6%. During the peak, CFR reached 7.2% and, after the peak, CFR dropped to 3.8% (95%CI: 3.3 to 4.3%). In December 2020, CFR stabilized at 2.2%. Time variation of CFR, by WHO member states grouping regions, can be observed in Figure 2. It has been reported that CFR varies widely not only between regions but also within them and within countries [37].

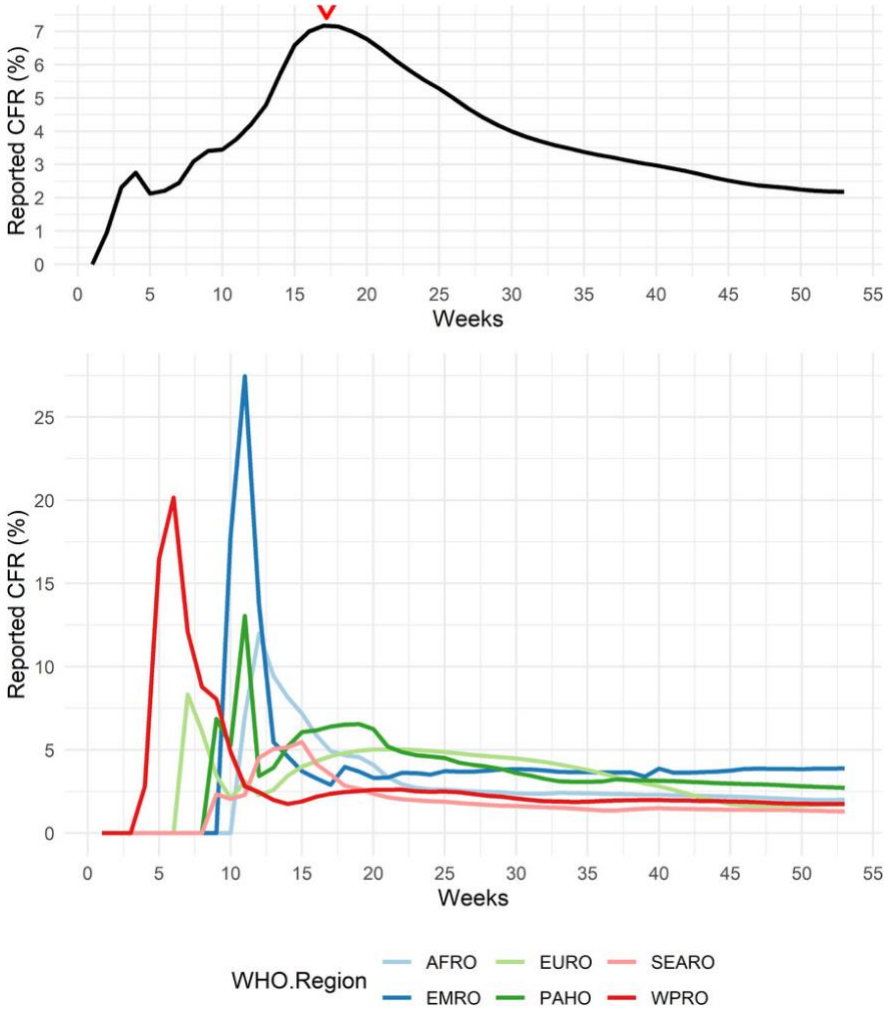

FIGURE 2. The changes of global weekly cumulative reported CFR of COVID-19 (top) with the weekly cumulative reported CFR in different WHO regions. Adapted from Hassan, et. al. [37]. WHO member states grouping regions: African Region (AFRO), Region of the Americas (PAHO), South-East Asia Region (SEARO), European Region (EURO), Eastern Mediterranean Region (EMRO), and Western Pacific Region (WPRO).

I.X Prevention

A preventive approach to COVID-19 infection control is based on testing, case tracing, isolation, social distancing, and personal hygiene strategies.

The WHO recommended the use of personal protective equipment (PPE) in healthcare and informal care. Specifically, medical/surgical masks, gowns, gloves, and face shields are recommended when treating infected patients or collecting samples. The use of surgical mask in social interactions reduces infection, mortality, and ICU admissions as well as hand hygiene, crowd avoidance, social distancing, isolation, school/workspace/business and event measures or closures, quarantine, and travel restrictions [38-52]. In highly infectious settings, quarantine decreased the rate of infected cases from 81% to 44% and mortality from 61% to 31%, as assessed in 29 COVID-19 related studies [52].

II. COVID-19 and Cancer

II.I The impact of COVID-19 in patients with cancer

Patients with cancer are a population of particular interest in COVID-19 research since they could not only be vulnerable to direct impact of COVID-19 infection, but also to the effects of healthcare reprioritization during the peak of the pandemic, where subsequent delays in cancer diagnosis and treatment happened [53].

Regarding mortality risk of individuals that get infected with SARS-CoV-2, it was estimated at 0.7-3.6%, in individuals younger than 65 years and no comorbidities, while the risk in individuals with cancer is higher and estimated at between 9 and 20% [54, 55]. Likewise, a meta-analysis of mortality-related risk factors of COVID-19 estimated a pooled HR of patients with cancer and COVID-19, of 1.33 (95% CI: 1.09-1.56), as compared to cancer-free patients [56].

II.II Effects of COVID-19 pandemic on delay on cancer diagnosis, treatment, and follow-up

During the years of 2020 and 2021 many countries underwent through several confinement periods. Many concerns were raised due to obstacles imposed by COVID-19 pandemic regarding less cancer diagnosis, less treatment efficacy or higher mortality. Medical staff redeployment to ICU and Emergency Wards caused shortage in non-COVID-19 clinical activities. Despite the broadening of telemedicine, the number of medical appointment and surgical procedures decreased. Cancer screening programs were interrupted or individual participation in screening declined, and patients feared going to the doctor or emergency department [57].

Medical entities in China quickly published recommendations (February 2020) to protect patients with cancer and soon, other institutions across the world followed with further precautions [58, 59]. The United Kingdom's National Institute for Health and Care Excellence (NICE) advised clinicians to discuss with all patients the risks and benefits of starting, continuing, or deferring systemic anticancer treatment once it was unclear whether these patients had an increased risk of becoming severely ill with COVID-19. Additionally, clinicians were also advised to select the continuity of anticancer systemic treatments for some patients since those with hematological cancers and immunosuppressive systemic anticancer treatments could have a greater risk of poor outcomes from COVID-19. NICE also stated that patients with curative treatments with low and very low chances of success and non-curative treatments were also considered last in priority for systemic anticancer treatment. At last, shorter treatment regimens, decreased frequency of immunotherapy regimens, at-home treatments instead of in-hospital treatments and treatment breaks up to 6 weeks were also recommended to avoid hospital-acquired SARS-CoV-2 infection [60]. These precautions took in consideration the confirmed risk of hospital acquired SARS-CoV-2 infection and high prevalence of COVID-19 in healthcare workers [26, 61].

A study in Portugal comparing data from the first 3 months following the pandemic with the same time period that on the previous year was published in March 2021. Results showed an increase in the short-term mortality among patients diagnosed with cancer. In more detail, higher HR of risk for death in males and individuals aged

between 65 and 74 years old diagnosed and treated in the 3 months after the COVID-19 pandemic outbreak when compared with patients with the same characteristics diagnosed and treated on the same period of the prior year.

It was reported that after the COVID-19 outbreak, there were less cancer diagnosis. Less patients referred from cancer screening or other hospital and more patients referred by a doctor or after an appointment directly at IPO-Porto were also associated with the pandemic. There was also lower proportion of cervical and prostate cancers and a higher proportion of pancreas and lung cancers diagnosed in the period after the outbreak, comparing to the same period in the previous year. Both cervical and prostate cancer are subjected to screening, organized and opportunistic, respectively. A proportional increase in cancer stage, mainly for stage III, and in the number of symptomatic patients at diagnosis was also reported. Comparing patients treated between March and July 2020, HR of dying was higher for patients who received any treatment than in patients treated in the same period of 2019, suggesting that changes in timely diagnosis, treatment and follow-up of cancer cases, inevitably impacted in the prognosis of these patients [62, 63].

Some of these results are also reflected in studies from other countries, just like the Netherlands, where less cancers were diagnosed, or in the United States of America, where a meta-analysis showed higher HR for cancer treatments subjected to delays [64, 65]. A modelling study in the English population reported an increased number of deaths in all cancer subtypes analyzed, associated to the reported delays in diagnosis observed during the COVID-19 pandemic, of 7.9 to 9.6% in breast cancer, of 15.3 to 16.6% in colorectal cancer, 4.8 to 5.3% in lung cancer, and 5.7 to 6.0% in esophageal cancer [66]. In Sweden, few colorectal cancers were diagnosed between April and June 2020 when compared with the 4 previous years. Although, no overall differences were found when comparing colon cancer diagnosis, treatment, and short time outcomes (any surgical treatments in the same year) in all 2020 period with previous years [67].

Overall, these results reflect the impact that delays in diagnosis, treatment and follow-up during COVID-19 pandemic had in patients with cancer, in populations across the world.

II.III COVID-19 effects in cancer subtypes

The analysis of CFR and HR for death in patients with different cancer subtypes and SARS-CoV-2 infection is poorly described in the literature. Several studies have mentioned prevalence of cancer subtypes and describe the overall mortality in cancer patients with COVID-19, not specifying by cancer subtype [27, 68-74]. Although, patients with cancer are a very distinct and heterogeneous population and it is expected that different cancer subtypes contribute differently for disease outcomes when infected with COVID-19.

A set of studies describing CFR in patients with different cancer subtypes and COVID-19. For instance, CFR is reported to be lower in breast cancer and COVID-19 co-diagnosis, varying from 14% to 21% and higher in lung cancer and COVID-19 co-diagnosis varying from 33% to 75%. All other cancer subtypes have CFR values in between these two examples and include lip, oral cavity and pharynx cancer, digestive organs cancer,

colorectal cancer, respiratory and intrathoracic organs cancer, bone, articular cartilage, and soft tissue cancer, skin cancer, genitourinary organs cancer, female and male genital organs cancer, central nervous system cancer, endocrine glands cancer, or hematological cancer [53, 55, 67, 75-82].

II.IV COVID-19 and cancer treatments

The impact of COVID-19 in anticancer treatments has been subject of analysis from different researchers around the world. A meta-analysis of Liu et al. published in 2020 demonstrated that anticancer treatments do not lead to worst prognosis in patients with solid tumors diagnosed with COVID-19. However, the same was not found in patients with hematological malignancies. In these patients, chemotherapy administered three months prior to COVID-19 infection increased the risk of death [83]. This may be explained by the immunosuppressed/immunodepressed status of these patients, and the cytokine storm triggered by COVID-19.

Results of the effect of targeted therapy on mortality of cancer patients with COVID-19 were similar to those observed for chemotherapy [83].

There was found a reduce in mortality rate in patients who underwent through surgery. The fact that admission dates for surgery vary between studies and that some of these cancer centers had elective surgeries postponed or cancelled may influence mortality rates for these patients [83].

With respect to radiotherapy, researchers hypothesized that this treatment often leads to lymphopenia, which may mitigate the cytokine storm [84-86]. Hence results from this meta-analysis showed better prognosis in patients with cancer diagnosed with COVID-19 receiving radiotherapy [83].

Amongst all anticancer treatments, immunotherapy was associated to the highest risk of mortality in COVID-19 infected patients [83]. Indeed, uncontrolled inflammatory response of individuals who received immunotherapy when diagnosed with COVID-19 is thought to explain this mechanism [87]. Under the scope of the associations between immunotherapy and increased mortality risk, a risk assessment scoring system has been developed to help clinicians decide whether a patient with cancer and a COVID-19 infection should receive immunotherapy.

III. COVID-19 in Portugal

III.I Chain of events and IPO-Porto response

The Portuguese Oncology Institute of Porto (IPO-Porto) is in the city of Porto and belongs to the Portuguese National Health Service. It is the largest cancer-dedicated hospital in Portugal, admitting patients from all over the country, though mainly from the Northern region. IPO-Porto provides the entire cancer care continuum that allow the disease management from diagnosis to treatment (surgery, radiotherapy, systemic therapy, and supportive care) and follow-up. A cancer-specific emergency service operating 24 hours a day, assist and provide care to cancer patients registered at IPO-Porto, with acute situations derived from the disease itself or induced by treatment, and patients with an acute oncological pathology referred from other healthcare

institutions. More than 45 000 patients are covered by this cancer continuum care and over 7500 new cancer cases are admitted every year in the institution, corresponding to nearly half of all the cases diagnosed in the Northern region and one-fifth of those diagnosed in the country.

During the COVID-19 pandemic, following the Portuguese government and scientific community recommendations, IPO-Porto published a series of recommendations and held several measures to protect patients with cancer from the impact of COVID-19.

Shortly after the report of the first cases of COVID-19 by the Wuhan Municipal Health Commission, the WHO's Country Office in the People's Republic of China (31 December 2019) and the Chinese authorities (9 January 2020), IPO-Porto published a COVID-19 Contingency Plan with a guide on procedures to be followed with any suspected COVID-19 case on the 18th of February.

The first confirmed COVID-19 cases in Porto, Portugal, were reported on the 2nd of March. The highest level of alert due to COVID-19 was declared by the Portuguese Government on the 12th of March, a day after the declaration of a global pandemic by the WHO. On the 16th of March, the first confirmed death due to COVID-19 was recorded in the country, as the country entered the Mitigation Phase and community transmission was detected [5, 88-90].

All services at IPO-Porto had to undergo major reorganization due to several recommendations issued to surgical interventions, outpatient appointments, diagnostic tests and medical procedures, ambulatory care, and cancer-specific emergency service. On the 17th of March, inclusion of new patients in clinical trials was suspended.

National State of Emergency was declared by the Portuguese Government on the 18th of March and a COVID-19 Crisis Office was created. The Contingency Plan at IPO-Porto was revised on the 19th of March [91].

The SARS-CoV-2 screening procedures were introduced at different timings for groups of patients, IPO-Porto workers, and visitors. Firstly, on the 27th of March, asymptomatic patients with a scheduled surgery and symptomatic workers were subject to test. Secondly, on the 6th of April, asymptomatic patients with scheduled hospitalizations were included in the screening. Thirdly, on 28th of May, patients undergoing chemotherapy in the Ambulatory Service were also screened. Finally, on the 5th of June, overnight visitors of hospitalized cancer patients also had to be tested.

The Portuguese Government did not renew the state of emergency on the 2nd of May, entering in a state of contingency. On the 7th of May, a second cancer-specific emergency service for the evaluation of suspected COVID-19 patients was settled at IPO-Porto to allow surgeries, outpatient appointments, diagnostic tests and medical procedures, day hospital, hospitalizations, and the clinical research unit to return, gradually and progressively, to normal activity [92, 93]. This special service was opened until the 2nd of June and guidelines for telemedicine appointments and face-to-face appointments at IPO-Porto were published on the 15th of June.

Finally, State of Alert, the lowest exceptional status of the Portuguese Republic, was declared on the 1st of July. From the 1st of July onwards mandatory confinement for patients and those under active surveillance rules on physical distancing, mask use,

respiratory hygiene, limited indoor and outdoor space capacity, and restricted hours of operation were maintained. Additionally, gathering limits were increased but alcohol consumption in public outdoor spaces (e.g.: beach, parks) continued to be prohibited [94].

From the 6th of November 2020 until the 30th of April 2021 a new State of Emergency was applied to all Portuguese territory [95-104]. Published official governmental data showed that in January 2021 the country attained the highest number of confirmed deaths, reaching 29.80 deaths per million inhabitants [8]. On the 28th of December 2020 the first vaccines for COVID-19 were administered to healthcare workers at IPO-Porto [105]. After the end of the State of Emergency, on the 23rd of August 2021, visitors were allowed back into IPO-Porto [106].

Selected key events, described from 2019 until 2021, are summarized and represented in Figure 3.

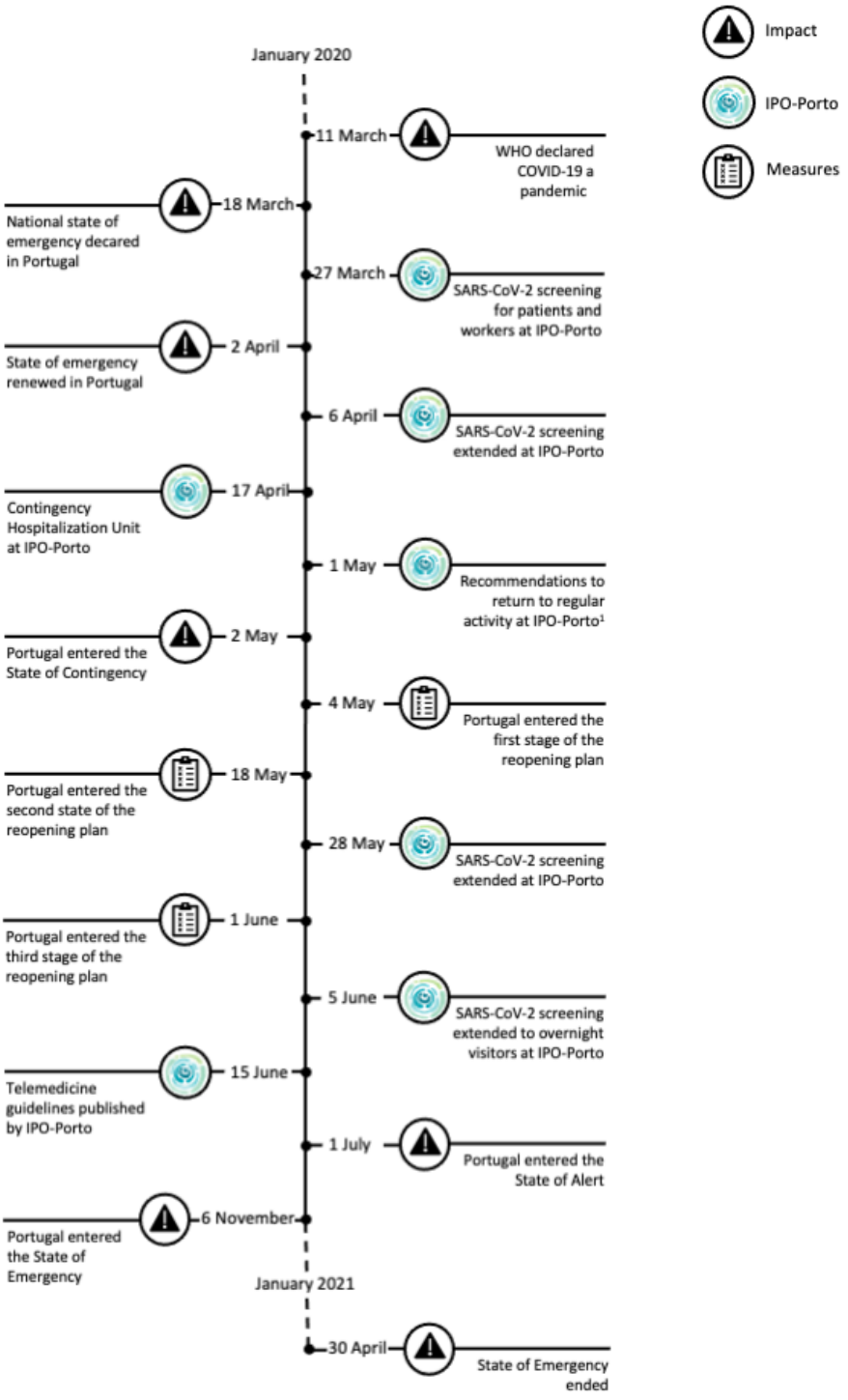

FIGURE 3. Timeline of selected key events and recommendations by the Portuguese Oncology Institute of Porto (IPO-Porto) during the COVID-19 pandemic (adapted from Morais et al. [62])

However, important issues regarding the CFR of COVID-19 in patients with cancer remain to be clarified. There is not robust support in literature for measures of disease lethality for different cancer subtypes. No study could be found which reported HR for death in patients with different types of cancer and COVID-19, compared with patients with the same cancer subtype but without COVID-19.

Objetives

The main objectives of this study were:

- to evaluate the case-fatality of cancer patients with or without COVID-19, according to their cancer subtype;
- to assess the survival probability of cancer patients with a positive or a negative SARS-CoV-2 test result and the risk of death, adjusting for important prognostic variables as sex, age, and stage;
- to estimate the time in days from diagnosis until first treatment in the two groups of patients.

Methods

Study design and data collection

We conducted a retrospective analysis of cancer cases diagnosed at IPO-Porto to assess the influence of SARS-CoV-2 infection on cancer patients' survival. Two different cohort groups were created: SARS-CoV-2 positive test result and SARS-CoV-2 negative test result patients.

As previously mentioned, IPO-Porto adopted early strategies to diagnose SARS-CoV-2 in symptomatic healthcare workers and screening for asymptomatic patients on a regular basis as soon as the first cases appeared. Systematically, patients were submitted to a SARS-CoV-2 RT-PCR test in every occasion they were admitted to the hospital for treatments, invasive exams or if an outbreak surged in the hospital's wards.

Information on cases regarding the following variables was retrieved from the cancer registry database, as applicable: sex, age at diagnosis, date of diagnosis, body mass index (BMI), tobacco consumption, alcohol consumption, Eastern Cooperative Oncology Group performance status (ECOG PS), Charlson comorbidity index, arterial hypertension, myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, cancer topography (according to the International Classification of Diseases for Oncology (ICD-O-3), 3rd Edition, 1st Revision [107] and to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [108]), histologic type, cancer stage, date of each type of treatment received (surgery, chemotherapy, radiotherapy, hormone therapy immunotherapy, and other treatments, as applicable), date and result of SARS-CoV-2 test detection, vital status, date and cause of death.

Cancer patients were grouped by topography according to the ICD-10, as follows:

1. Lip, oral cavity, and pharynx (codes C00-C14);
2. Digestive organs (C15-C26);
3. Colorectal (C18-C21);
4. Respiratory and intrathoracic organs (C30-C39);
    a. Lung (C34);
5. Bone, articular cartilage and soft tissue (C40-C41, C45-C49);
6. Skin (C43-C44);
7. Breast (C50);
8. Genitourinary organs (C51-C68);
    a. Female genital organs (C51-C58);
    b. Male genital organs (C60-C63);
9. Central nervous system (C69-C72);
10. Endocrine glands (C73-C75);
11. Malignant neoplasm without specification of the site (C80);
12. Hematological (C81-C86, C88, C90-C96, D46-D47, D71, D73-D74);
13. Lymphoma (C81-C86).

Vital status and date of death, if applicable, were assessed for all patients through the National Health Service database (RNU) up to the 30th of April 2022, in May 2022. The ultimate date of follow-up for all cases was 30th of April 2022.

Study sample

Patients with a first primary malignant tumor diagnosed between 2018 and 2021 and subjected to SARS-CoV-2 tests at IPO-Porto from 24th of March 2020 until the 31st of March 2022 were selected from the cancer registry database.

All 12,153 adult patients diagnosed between the 1st of January 2018 and 31st December 2021 at IPO-Porto with a first primary malignant tumor, other than basal cell carcinoma, with at least one SARS-CoV-2 test performed at IPO-Porto were eligible to the study. Cases of basal cell carcinomas were excluded from this analysis since these are very numerous and have low lethality [109]. We excluded 6,920 patients with tumors not yet validated by the IPO-Porto registrars, i.e., that have not gone through the entirety of the cancer coding process, because of limited information on the variables of interest to answer this study objectives. Also, 1,246 patients with the first oncological treatment outside IPO-Porto were excluded since the treatment protocol has been planned differently from those treated initially at IPO-Porto. Moreover, 11 patients with inconclusive SARS-CoV-2 test result were excluded from this study sample, leaving 3,977 cases of cancer for this study analysis. The flow-chart of patients included and excluded for this analysis is showed by Figure 4.

We defined as positive cases of COVID-19 all oncological patients with a positive result in at least one SARS-CoV-2 test performed in IPO-Porto (accordingly to the Portuguese diagnosis norm published by the Directorate-General for Health [110-113]). The negative control group included patients with negative results for all SARS-CoV-2 laboratory tests performed at IPO-Porto.

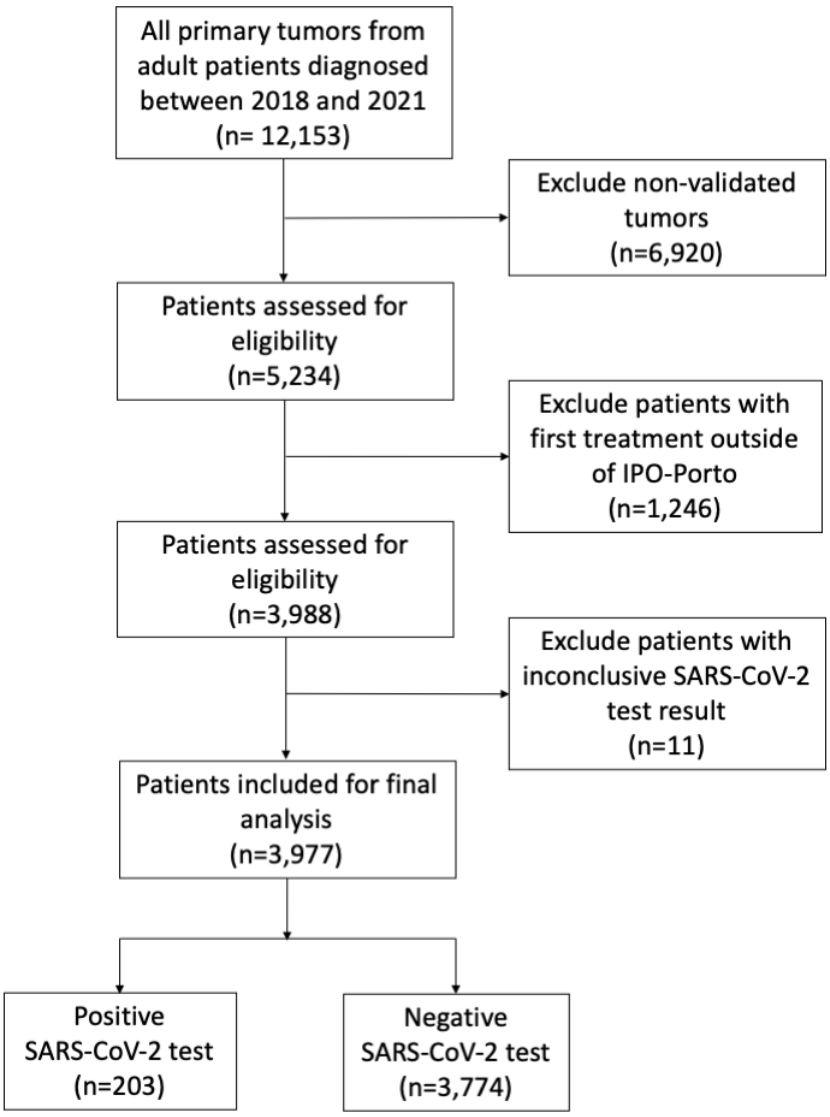

FIGURE 4. Flow-chart of patients suitable for descriptive and survival analysis

Statistical analysis

Descriptive analyses with calculation of absolute frequencies and proportions, for categorical variables, or central tendency and dispersion measurements, for continuous variables, were performed as appropriate.

Some variables were grouped posteriorly to data collection, for instance, BMI was firstly grouped considering WHO's recommended categories and then divided into 3 subcategories: Underweight (<18,5kg/m^2); Normal weight (≥18,5kg/m^2 and >25kg/m^2); Overweight/Obese (≥25kg/m^2) [114]. Tobacco consumption was grouped considering Ever smoked (Smoker at the moment/Previous smoker); Never smoked (Passive smoker/Never smoked). The use of alcohol was grouped considering: Current consumer (Excessive/Moderate/frequent); Sporadic consumer/Never consumed; Previous consumer. Those with an ECOG PS of I were grouped in a distinct category from all others with an ECOG PS of II/III/IV. Patients with a 0 score on the Charlson comorbidity index were grouped distinctly of those with an index equal or greater than 1. The initial time of follow-up began from the moment that the first primary tumor was diagnosed, rulling out basocelular tumors. This analysis focused on the survival of these patients accordingly to their first primary tumor subtype but patients with more than one tumor were also described regarding their SARS-CoV-2 test result in descriptive analysis. Cancer stage was estimated and grouped for patients with stage I/II and patients III/IV. Every first treatment was specified considering surgery, chemotherapy, immunotherapy, hormone therapy, radiotherapy, and other treatments such as: cis-retinoic acid; CAR T-Cells; cryotherapy; electrotherapy; laser therapy; nuclear medicine with strontium-89, phosphorus-32, iodine-131, yttrium-90, radiolabeled peptides, radium-223, samarium-153; and others.

Socio-demographic and cancer's clinical and treatment characteristics were compared between COVID-19 positive and negative patients with two-sample Student's t or chi-squared tests, as appropriate. Using the Kaplan-Meier estimator overall survival time was calculated, and survival curves were plotted. The event considered will be death by any cause. The log-rank test was used to compare survival between COVID-19 positive and negative patients. P-values less than 0.05 were considered statistically significant.

The CFR was estimated for SARS-CoV-2 positive and negative test result for each cancer subtype, according to its topography. The Cox proportional method was used to calculate the crude HR and 95% CI was estimated for each cancer subtype. Adjustment was made for SARS-CoV-2 test result (negative vs. positive), age (continuous), sex (female vs. male), and stage (I/II vs. III/IV).

All analyses were performed using STATA 14 ® (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Setting - The Department of Epidemiology of Portuguese Oncology Institute of Porto (IPO-Porto)

The Department of Epidemiology (DE) of IPO-Porto has as its main responsibility the IPO-Porto's Cancer Registry management, as well as the management of the Portuguese Northern Region Cancer Registry (RORENO). Also, currently and until 2023, the National Cancer Registry (RON) is under DE of IPO-Porto coordination. At the same time, DE collaborates with other services of IPO-Porto, including IPO-Porto Research Center and the Hospital's Group of Coordination for the Program of Prevention and Control of Infections and Antimicrobial Resistance, and provides support in research methodology and statistics to investigators.

The main objectives of the DE of IPO-Porto are to promote epidemiological training and research in oncology. The use of advanced statistical methods has contributed to a better understanding of cancer epidemiology, namely geographical patterns of incidence, the influence of socio-economic characteristics, projection of incidence, and quantification of disease burden at the population level. Participation in national and international research projects, and publication in international peer-reviewed journals are some of the outputs of the DE activity. DE of IPO-Porto regularly publishes reports for dissemination of statistical information and survival evaluation on the most frequent oncologic diagnosis at IPO-Porto, at the IPO-Porto internet site.

The IPO-Porto Cancer Registry

Until 2019, cancer registry data collection was almost entirely manual, except for administrative data. From this date, a new platform was implemented for the IPO-Porto Cancer Registry - the Integrated Knowledge Repository (RIC). RIC allows the registration of a wide range of data, of great value for clinical and epidemiological research, but also automatically integrates a set of exams and treatments performed at IPO-Porto and the pathological diagnosis. This process allows to reduce the registration time of each clinical file in the registry.

With RIC, it is possible to consult the patients' pipeline of treatments and exams at the institution. This cancer registry along with the RNU and RORENO were essential to extract data and thus frame our database. Every patient's data used in this study was used with the supervision and coordination of the DE researchers.

Data protection and ethical considerations

The study protocol complies with the Ethical Principles expressed in the Declaration of Helsinki and was approved by the Ethics Committee of IPO-Porto (Ref. CES IPO: 76/022). Procedures were developed to guarantee data confidentiality and protection. All investigators involved in this study with access to the databases of the Integrated Repository of Oncology Knowledge, RORENO and National Health Service User Registry of Users, from which all mentioned data was extracted, are obliged to professional sigil. The data extracted from the cancer registry database, with no unique personal identifiers, was stored on a Microsoft ® Excel ® database, and only authorized research team members had access to this data.

All data collected for the purpose of the present dissertation analyses is of observational and retrospective nature, in accordance with the definition of “non-interventional clinical study”, present on Art.º2, line p) of Law n. º 21/2014, of April 16th on the Portuguese Diário da República. As present in the same law, “Comissão de Ética Competente” (CEC) dismisses the need for informed consent for non-interventional clinical studies (Art.º6, point nº2 of Law n. º 21/2014, of April 16th). Given the scientific interest of this study and pseudo-anonymization and protection of data storage, the need for informed consent is not met.

Results

Patient characteristics

The characteristics of IPO-Porto patients diagnosed with cancer and with a positive or negative SARS-CoV-2 test result are presented in Table 1. From a total of 3,977 patients, 3,774 had all SARS-CoV-2 test with negative results and 203 patients had at least one SARS-CoV-2 positive test between the dates of March 24th 2020 and March 31st 2022. In this sample, 2,195 of patients were females and 1,782 were males (55.2% vs. 44.8%). When we compare cancer patients with negative SARS-CoV-2 serology test with patients with positive serology test regarding demographic and behavioral characteristics, patients with a positive SARS-CoV-2 result were significantly younger (mean: 60.66 vs. 57.76 years; p-value=0.002) (Figure 5). There were no differences in the other analyzed characteristics by SARS-CoV-2 serology groups.

Overall, there was a greater proportion of overweight/obese patients when compared with underweight/normal weight patients (44.6% vs. 28.4%) and of patients who never smoked (passive smokers/never smoked) when compared to patients who had smoked (current/previous smokers) (46.3% vs. 31.5%). There were no differences in the prevalence of overweight/obese or smoking status between non-infected and infected patients. Although SARS-CoV-2 infected patients had higher proportion of alcohol excessive to moderate consumers (55.7% vs. 47.0%) this difference was not statistically significant (p=0.169).

Regarding ECOG PS and the prevalence of comorbidities also summarized in Table 1, most patients were completely active (59.1%) and had no comorbidities (44.5%) in conformity with the ECOG PS and Charlson comorbidity index. In this sample of patients with cancer, arterial hypertension, diabetes, and peripheral vascular disease were the most prevalent comorbidities (36.6%, 13.6% and 12.6%, respectively). There were no significant differences in the prevalence of these and other comorbidities, between groups accordingly to SARS-CoV-2 test results.

The follow-up of these patients in terms of mortality showed that between the 1st of January 2020 and the 30th of April 2022, about 21.5% of the non-infected patients (811 out of 3,774 patients) and 21.7% of the infected patients (44 out of 203 patients) had died.

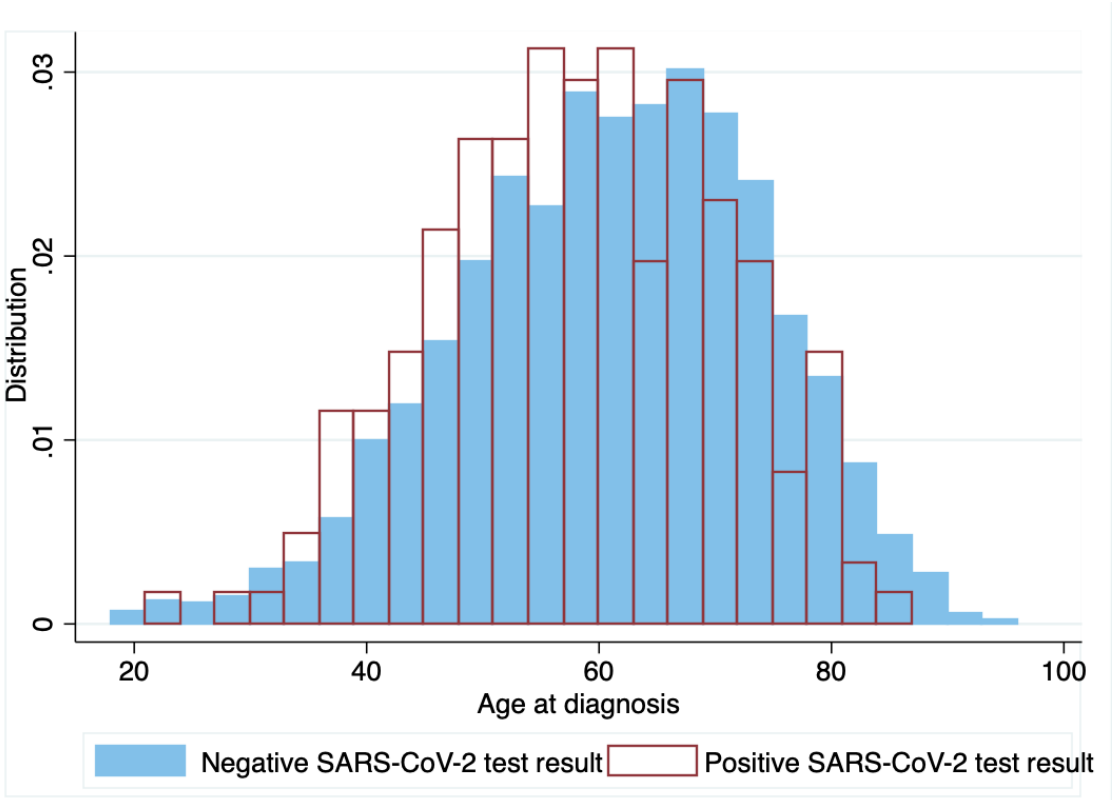

FIGURE 5. Patients' age distribution histogram by SARS-CoV-2 test result groups (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

TABLE 1. Characteristics of patients with cancer by SARS-CoV-2 test result groups (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Patient characteristics	Overall (n=3,977)	SARS-CoV-2 test result		P value
		Negative (n=3,774)	Positive (n=203)	
	n (%)	n (%)	n (%)	
Sex				
Female	**2,195** (55.2)	**2,082** (55.2)	**113** (55.7)	
Male	**1,782** (44.8)	**1,692** (44.8)	**90** (44.3)	0.889
Age				
Mean (SD); min-max	**60.51** (12.96); 18-95	**60.66** (12.99); 18-95	**57.76** (12.20); 21-85	0.002
Body mass index categories				
Underweight/Normal weight	**1,129** (28.4)	**1,070** (38.9)	**59** (38.1)	
Overweight/Obese	**1,775** (44.6)	**1,679** (61.1)	**96** (61.9)	0.831
Missing	**1,073** (27.0)			
Tobacco consumption				
Ever Smoked (Current/Previous smoker)	**1,252** (31.5)	**1,183** (40.3)	**69** (43.1)	
Never smoked (Passive/ Never smoked)	**1,843** (46.3)	**1,752** (59.7)	**91** (56.9)	0.479
Unknown	**92** (2.3)			
Missing	**790** (19.9)			
Alcohol consumption				
Excessive to moderate consumer	**1,115** (28.0)	**1,046** (47.0)	**69** (55.7)	
Low to any consumption	**1,107** (27.8)	**1,058** (47.5)	**49** (39.5)	
Previous consumption	**129** (3.4)	**123** (5.52)	**6** (4.8)	0.169
Unknown	**155** (3.9)			
Missing	**1,471** (37.0)			

Comorbidities				
ECOG performance status				
0	**2,352** (59.1)	**2,225** (74.9)	**127** (77.4)	
I/II/III/IV	**781** (19.6)	**744** (25.1)	**37** (22.6)	0.587
Unknown	**53** (1.3)	**53**	**0**	
Missing	**791** (19.9)	**752**	**39**	
Charlson comorbidity index				
0	**1,771** (44.5)	**1,673** (55.0)	**99** (59.8)	
≥1	**1,436** (36.1)	**1,370** (45.0)	**66** (40.2)	0.231
Missing	**770** (19.4)			
Arterial hypertension				
Yes	**1,457** (36.6)	**1,386** (45.5)	**71** (43.3)	
No	**1,751** (44.0)	**1,658** (54.5)	**93** (56.7)	0.575
Unknown	**769** (19.3)			
Myocardial infarction				
Yes	**62** (1.6)	**58** (1.9)	**4** (2.4)	
No	**3,146** (79.1)	**2,986** (98.1)	**160** (97.6)	0.629
Unknown	**769** (19.3)			
Heart Failure				
Yes	**89** (2.2)	**84** (2.8)	**5** (3.0)	
No	**3,120** (78.5)	**2,961** (97.2)	**159** (97.0)	0.826
Unknown	**768** (19.3)			
Peripheral vascular disease				
Yes	**502** (12.6)	**476** (15.6)	**26** (15.8)	
No	**2,706** (68.0)	**2,568** (84.4)	**138** (84.2)	0.941
Unknown	**769** (19.3)			

Cerebrovascular disease				
Yes	**111** (2.8)	**106** (3.8)	**5** (3.0)	
No	**3,098** (7.9)	**2,939** (96.5)	**159** (97.0)	0.768
Unknown	**768** (19.3)			
Diabetes Melitus				
Yes	**540** (13.6)	**511** (16.8)	**29** (17.7)	
No	**2,669** (67.1)	**2,534** (83.2)	**135** (82.3)	0.764
Unknown	**768** (19.3)			
Chronic Obstrutive Pulmonary Disease				
Yes	**210** (5.4)	**204** (6.8)	**6** (3.6)	
No	**1,978** (76.0)	**2,818** (93.2)	**160** (96.4)	0.113
Unknown	**732** (18.7)			
Vital status				
Alive	**3,122** (78.5)	**2,963** (78.5)	**159** (78.3)	
Death	**855** (21.5)	**811** (21.5)	**44** (21.7)	0.95

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation

Cancer characteristics

Table 2 summarizes results concerning cancer subtypes by topography, (according to the ICD-O-3 and ICD-10), stage, first treatment, year of diagnosis and number of additional primary tumors diagnosed during the period in study.

The most prevalent cancers in the sample were located in the breast, digestive system and genitourinary organs (31.4%, 29.2% and 11.4%, respectively). While the most prevalent cancers in non-infected patients were also breast cancer, digestive organs cancer, and genitourinary organs cancer (31.3%, 29.1% and 11.8%, respectively), infected patients had higher prevalence of breast cancer, digestive organs cancer, and respiratory and intrathoracic organs (37.4%, 30.1% and 9.9%, respectively).

Specific subtypes were also considerably prevalent and colorectal, lung and cancer male genital organs cancer were the most prevalent in the overall sample (19.2%, 8.0% and 7.4%, respectively). In non-infected patients similar results were found with higher prevalence of colorectal, lung and male genital organs cancer (19.0%, 8.1% and 7.6%, respectively) while in infected patients colorectal, lung and lymphoma were more frequently diagnosed (22.2%, 7.9% and 5.9%, respectively).

SARS-CoV-2 infected patients were more likely to be diagnosed at later stages of cancer disease (stages III/IV) in comparison to non-infected patients (60.7% vs. 45.9%; p-value<0.001).

Analysis of treatment characteristics revealed that the first treatment was more likely to be surgery (53.9% of all patients), followed by chemotherapy (34.4% of all patients) or radiotherapy (13.5% of all patients) with no differences found between SARS-CoV-2 test result groups.

This sample included a higher proportion of patients diagnosed in 2018 and 2019 than in 2020 and 2021. Comparing patients by infection status, patients with more recent diagnoses (2020 and 2021) were more likely to have a positive SARS-CoV-2 test result than patients diagnosed before the COVID-19 pandemic (2018 and 2019) (40% of patients diagnosed during the COVID-19 pandemic had a negative SARS-CoV-2 test result vs. 49.8% of patients diagnosed during the COVID-19 pandemic had a positive SARS-CoV-2 test result; p-value=0.006).

A further analysis revealed that 7.1% of patients had more than one primary tumor diagnosed during the study period (from the 1st of January of 2018 until the 31st of December 2021) (283 out of 3,694 patients) but no differences in the prevalence of more than one primary tumor were found according to infection status.

TABLE 2. Cancer characteristics of patients diagnosed with cancer by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Cancer characteristics	Overall (n=3,977)		SARS-CoV-2 test result				P value
			Negative (n=3,774)		Positive (n=203)		
	n	(%)	n	(%)	n	(%)	
Subtype[a]							
Lip, oral cavity, and pharynx (C00-C14)	**180**	(4.5)	**170**	(4.5)	**10**	(4.9)	
Digestive organs (C15-C26)	**1,160**	(29.2)	**1,099**	(29.1)	**61**	(30.1)	
Colorectal (C18-C21) [a]	**762**	(19.2)	**717**	(19.0)	**45**	(22.2)	
Respiratory and intrathoracic organs (C30-C39)	**405**	(10.2)	**385**	(10.2)	**20**	(9.9)	
Lung (C34) [a]	**320**	(8.0)	**304**	(8.1)	**16**	(7.9)	
Bone, articular cartilage, and soft tissue (C40-C41, C45-C49)	**108**	(2.7)	**100**	(2.7)	**8**	(3.9)	
Skin (C43-C44)	**50**	(1.3)	**48**	(1.3)	**2**	(1.0)	
Breast (C50)	**1,247**	(31.4)	**1,171**	(31.3)	**76**	(37.4)	
Genitourinary organs (C51-C68)	**454**	(11.4)	**444**	(11.8)	**10**	(4.9)	
Female genital organs (C51-C58) [a]	**87**	(2.2)	**85**	(2.3)	**2**	(1.0)	
Male genital organs (C60-C63) [a]	**294**	(7.4)	**286**	(7.6)	**8**	(3.9)	
Central nervous system (C69-C72)	**4**	(0.1)	**4**	(0.1)	**0**	-	
Endocrine glands (C73-C75)	**109**	(2.7)	**109**	(2.9)	**0**	-	
Malignant neoplasm without specification of site (C80)	**12**	(0.3)	**12**	(0.3)	**0**	-	
Hematological (C81-C86, C88, C90-C96, D46-D47, D71, D73-D74)	**263**	(6.2)	**232**	(6.2)	**16**	(7.9)	
Lymphoma (C91-C95) [a]	**144**	(3.6)	**132**	(3.5)	**12**	(5.9)	

Stage								
	I	**1,163**	(9.2)					
I/II	II	**825**	(20.7)	**1,913**	(54.1)	**75**	(39.3)	
	III	**962**	(24.2)					
III/IV	IV	**775**	(19.5)	**1,621**	(45.9)	**116**	(60.7)	<0.001
Non-aplicable		**219**	(5.5)					
Unknown		**33**	(0.8)					
First treatment[b]								
Surgery		**2,145**	(53.9)	**2,058**	(54.5)	**87**	(42.7)	
Chemotherapy		**1,367**	(34.4)	**1,277**	(34.8)	**90**	(44.3)	
Immunotherapy		**296**	(7.4)	**283**	(7.5)	**13**	(6.4)	
Hormone therapy		**300**	(7.5)	**289**	(7.7)	**11**	(5.4)	
Radiotherapy		**538**	(13.5)	**514**	(13.6)	**24**	(11.8)	
Other		**136**	(3.4)	**134**	(3.6)	**2**	(1)	
None[c]		**106**	(2.7)	**104**	(2.8)	**2**	(1)	
Year of diagnosis								
	2018	**790**	(19.9)					
Previous to COVID-19 pandemic	2019	**1,578**	(39.7)	**2,266**	(60)	**102**	(50.2)	
	2020	**1,385**	(34.8)					
During COVID-19 pandemic	2021	**224**	(5.6)	**1,508**	(40)	**101**	(49.8)	0.006
Tumors								
Patients with 1 tumor only		**3,694**	(92.9)	**3,505**	(92.9)	**189**	(93.1)	
Patients with more than 1 tumor		**283**	(7.1)	**269**	(7.1)	**14**	(6.9)	0.982

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease 2019.

[a] Some specific cancer subtypes are specified, making sum of counts and proportions sum more than the total number of patients.

[b] Some patients did multiple first treatments, making the sum of first treatments sum more than the total number of patients.

[c] Some patients did a SARS-CoV-2 test while treating other than the first primary tumor, therefore, having no first treatment for the tumor in study.

Case Fatality Rate of COVID-19 in different cancer subtypes

The number of deaths and CFR of patients with cancer are described in detail in Table 3. In the overall sample, non-infected patients and infected patients had similar CFR (21.5% vs. 21.4%) and when considering all cancer subtypes, CFR was higher in COVID-19 infected patients than in non-infected patients except for colorectal (15.6% vs. 16.0%), bone, articular cartilage, and soft tissue (25.0% vs. 39.0%), hematological cancers (12.5% vs. 22.0%), and lymphoma (8.3% vs. 9.8%). This study found higher CFR in infected patients with lip, oral cavity, and pharynx cancers (60.0%), followed by infected patients with lung cancer (62.5%). Lower CFR were found for infected patients with lymphoma (8.3%) or with breast cancer (5.3%).

TABLE 3. Number of deaths, case fatality rate, crude hazard ratio, and 95% confidence interval for each cancer subtype from the 1st of January 2020 until the 30th of April 2022, by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Cancer subtype	SARS-CoV-2 test result				HR [b]	95% CI
	Negative		Positive			
	Deaths (n)	CFR (%)	Deaths (n)	CFR (%)		
Overall [a]	**811**	(21.5)	**44**	(21.4)	**1.07**	0.79-1.44
Lip, oral cavity, and pharynx (C00-C14)	**84**	(49.4)	**6**	(60.0)	**1.31**	0.57-2.99
Digestive organs (C15-C26)	**270**	(23.3)	**15**	(24.5)	**1.07**	0.64-1.8
Colorectal (C18-C21)	**122**	(16.0)	**7**	(15.6)	**0.94**	0.44-2.02
Respiratory and intrathoracic organs (C30-C39)	**183**	(45.2)	**10**	(50.0)	**1.08**	0.57-2.04
Lung (C34)	**170**	(55.9)	**10**	(62.5)	**1.26**	0.67-2.39
Bone, articular cartilage, and soft tissue (C40-C41, C45-C49)	**39**	(39.0)	**2**	(25.0)	**NA**	NA
Skin (C43-C44)	**22**	(45.8)	**1**	(50.0)	**NA**	NA
Breast (C50)	**59**	(5.0)	**4**	(5.3)	**NA**	NA
Genitourinary organs (C51-C68)	**85**	(19.1)	**4**	(40.0)	**NA**	NA
Female genital organs (C51-C58)	**30**	(35.2)	**1**	(50.0)	**NA**	NA
Male genital organs (C60-C63)	**30**	(10.5)	**3**	(37.5)	**NA**	NA
Central nervous system (C69-C72)	**1**	(25.0)	**0**	NA	**NA**	NA
Endocrine glands (C73-C75)	**9**	(8.26)	**0**	NA	**NA**	NA
Malignant neoplasm without specification of site (C80)	**8**	(66.7)	**0**	NA	**NA**	NA
Hematological (C81-C86, C88, C90-C96, D46-D47, D71, D73-D74)	**51**	(22.0)	**2**	(12.5)	**NA**	NA
Lymphoma (C91-C95)	**13**	(9.8)	**1**	(8.3)	**NA**	NA

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; CFR, case fatality ratio; HR, hazard ratio; 95% CI, 95% confidence interval; NA, not applicable.

[a] Some specific cancer subtypes are specified, making sum of counts of deaths sum more than the total number of patients.

[b] Crude HR and 95% CI were estimated for cancer subtypes with a minimum of 5 deaths in each of the SARS-CoV-2 test result group.

Survival of cancer patients with COVID-19 in different cancer subtypes

In this cohort, cancer patients with SARS-CoV-2 infection had higher risk for death when compared with cancer patients without infection but with no statistical significance. Results were similar for specific cancer subtypes, except for colorectal cancer patients and can be found in Table 3.

The survival probability (SP) and the 95% CI at different time points (12, 24 and 36 months after the cancer diagnosis) was analyzed comparing different cancer subtypes by SARS-CoV-2 test result. All results are summarized in Table 4.

Over the follow-up period, both SP and 95% CI of patients with cancer and negative SARS-CoV-2 test result and patients with cancer and a positive SARS-CoV-2 test result overlapped several times for overall patients and several cancer subtypes.

Patients with cancer had different results regarding the follow-up time by SARS-CoV-2 test result (mean: 27.66 vs. 24.25; min-max: 0.62-51.91 vs. 1.87-51.22 months in non-infected and infected patients, respectively).

TABLE 4. Survival probability and 95% confidence interval of cancer patients 12, 24 and 36 months after cancer diagnosis, by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Cancer subtype	SARS-CoV-2 test result	Months after diagnosis					
		12		24		36	
		SP (%)	95% CI	SP (%)	95% CI	SP (%)	95% CI
Overall [a]	Negative	**95.3**	94.5-95.9	**86.0**	84.8-87.2	**73.6**	71.7-75.4
	Positive	**95.6**	91.7-97.7	**84.9**	78.8-89.4	**67.1**	57.0-75.3
Lip, oral cavity, and pharynx (C00-C14)	Negative	**94.1**	89.3-96.9	**78.2**	84.8-87.2	**52.0**	43.5-59.8
	Positive	**100**	NA	**70.0**	32.9-89.2	**48.0**	16.1-74.5
Digestive organs (C15-C26)	Negative	**94.0**	92.4-95.3	**82.6**	80.2-84.8	**73.0**	69.8-75.9
	Positive	**95.1**	85.5-98.4	**82.6**	70.0-90.3	**66.3**	48.8-79.0
Colorectal (C18-C21)	Negative	**93.4**	91.4-95.0	**86.2**	83.3-88.6	**80.8**	77.1-84.0
	Positive	**95.6**	83.4-98.9	**85.9**	71.1-93.5	**80.2**	60.4-90.8
Respiratory and intrathoracic organs (C30-C39)	Negative	**88.1**	84.4-90.1	**65.7**	60.7-70.2	**50.3**	44.5-55.8
	Positive	**85.0**	60.4-94.9	**60.0**	35.7-77.6	**46.7**	23.0-67.3
Lung (C34)	Negative	**85.7**	81.4-89.3	**58.4**	52.6-63.8	**40.6**	34.1-47.1
	Positive	**81.3**	52.5-93.5	**50.0**	24.5-71.1	**30.0**	8.4-55.7

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; SP, survival probability; 95% CI, 95% confidence interval.

Higher SP in non-infected cancer patients than infected patients is shown in Figure 6, although these results don't have statistical significance throughout all time due to overlapping 95% CI.

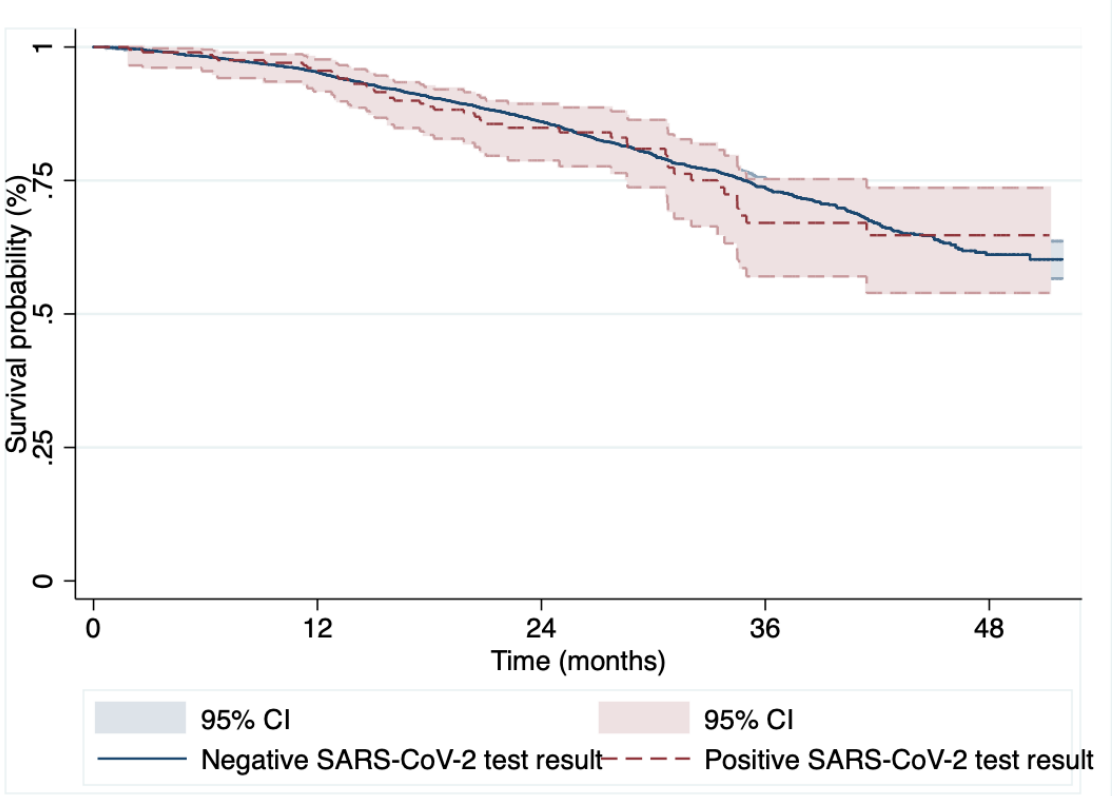

FIGURE 6. Survival curve (calculated using the Kaplan–Meier estimator) of overall patients with cancer, according to SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

In order to detect the significance independent variables associated with higher risk of death, a multivariable analysis was performed for these patients. The HR for death was adjusted by SARS-CoV-2 test result, for age as continuous variable, sex and cancer stage as shown in Table 5. While SARS-CoV-2 infection wasn't a significant risk factor for patients with cancer based on the multivariable analysis, male sex, older age and more advanced cancer stage were significantly associated with higher risk of death for patients in this cohort.

TABLE 5. Adjusted hazard ratio (95% confidence interval) for death by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result) in overall patients.

Parameters[a]	HR adjusted for covariates	95% CI
SARS-CoV-2 test result		
Negative	**1.00**	
Positive	**0.91**	0.66-1.25
Age (years)	**1.02**	1.02-1.03
Sex		
Female	**1.00**	
Male	**1.22**	1.06-1.42
Stage		
I/II	**1.00**	
III/IV	**5.87**	4.84-7.11

[a] SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result), age (continuous), sex (male vs. female), tumor stage (I/II vs. III/IV).
HR, hazard ratio; 95% CI, 95% confidence interval.

From the 12th month onward, patients with cancer of the lip, oral cavity, and pharynx and COVID-19 had lower SP than those without COVID-19. As Figure 7 and Table 4 demonstrate, results never achieved statistical significance.

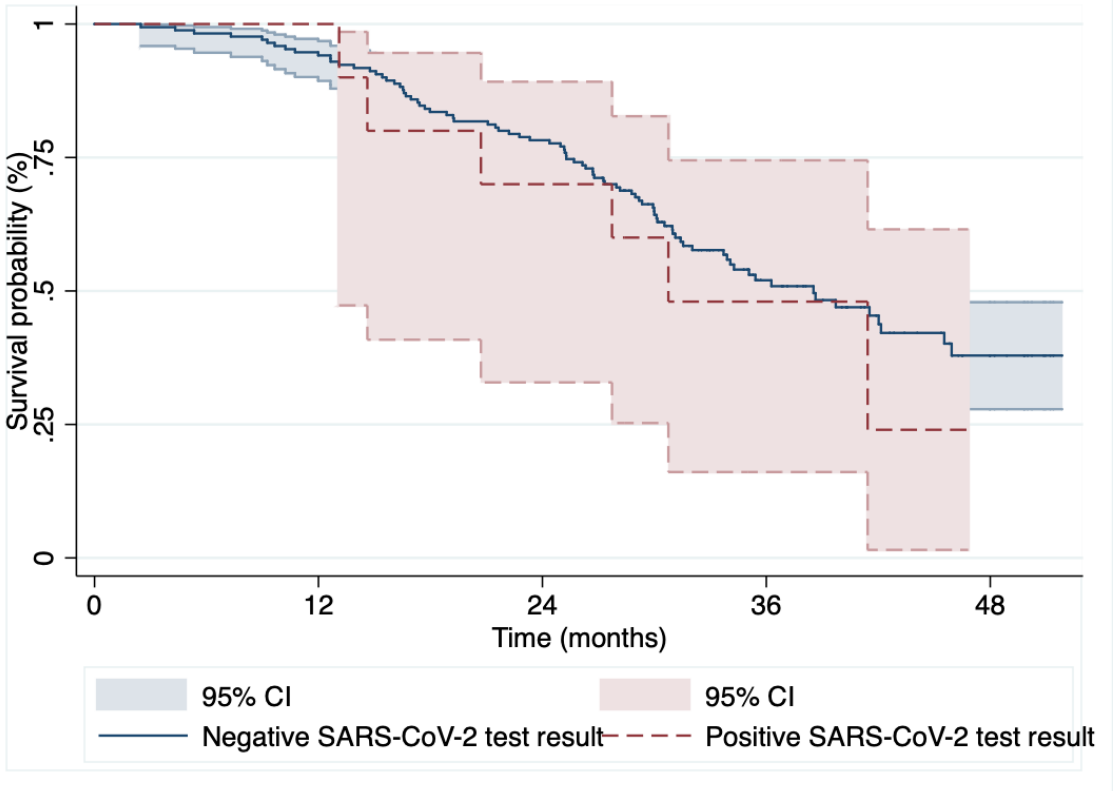

FIGURE 7. Survival curve (calculated using the Kaplan–Meier estimator) among patients with lip, oral cavity, and pharynx (C00-C14) cancer, according to SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Infected patients with lip, oral cavity, and pharynx cancer had higher risk for death but results were not statistically significant. The only significant independent variables associated with higher risk were older age and III/IV cancer stage as shown in Table 6.

TABLE 6. Adjusted hazard ratio (95% confidence interval) for death by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result) in lip, oral cavity, and pharynx (C00-C14) patients.

Parameters[a]	**HR adjusted for covariates**	95% CI
SARS-CoV-2 test result		
Negative	**1.00**	
Positive	**1.97**	0.83-4.69
Age (years)	**1.04**	1.02-1.07
Sex		
Female	**1.00**	
Male	**0.84**	0.45-1.55
Stage		
I/II	**1.00**	
III/IV	**2.98**	1.35-6.55

[a] SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result), age (continuous), sex (male vs. female), tumor stage (I/II vs. III/IV).
HR, hazard ratio; 95% CI, 95% confidence interval.

Patients with digestive organs sited cancers and positive SARS-CoV-2 infection had higher SP after 12 months, but after equal SP at 24 months from diagnosis, results were higher for non-infected patients at 36 months from cancer diagnosis just as demonstrated by Table 4 and Figure 8.

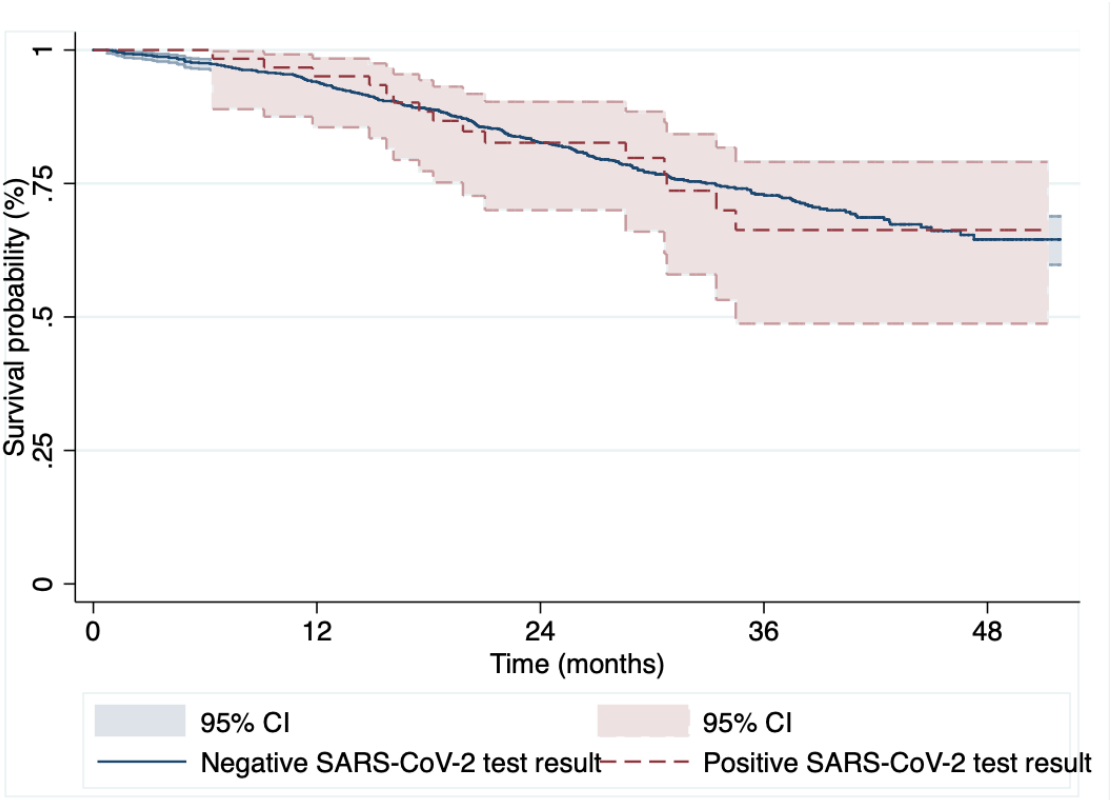

FIGURE 8. Survival curve (calculated using the Kaplan–Meier estimator) among patients with digestive organs (C15-C26) cancer, according to SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

For digestive organs cancer patients, the risk of death was significantly associated with older ages and more advanced disease stages. Results are represented in Table 7.

TABLE 7. Adjusted hazard ratio (95% confidence interval) for death by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result) in digestive organs (C15-C26) patients.

Parameters[a]	**HR adjusted for covariates**	95% CI
SARS-CoV-2 test result		
Negative	**1.00**	
Positive	**0.78**	0.46-1.32
Age (years)	**1.02**	1.01-1.03
Sex		
Female	**1.00**	
Male	**1.19**	0.93-1.52
Stage		
I/II	**1.00**	
III/IV	**5.54**	3.97-7.75

[a] SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result), age (continuous), sex (male vs. female), tumor stage (I/II vs. III/IV).
HR, hazard ratio; 95% CI, 95% confidence interval.

The survival curve of patients with colorectal sited cancers and with negative or positive SARS-CoV-2 test result and using the Kaplan-Meier estimator is presented in Figure 9. The SP in non-infected patients is lower than in infected patients after 12 and 24 months of diagnosis as observed in Table 4.

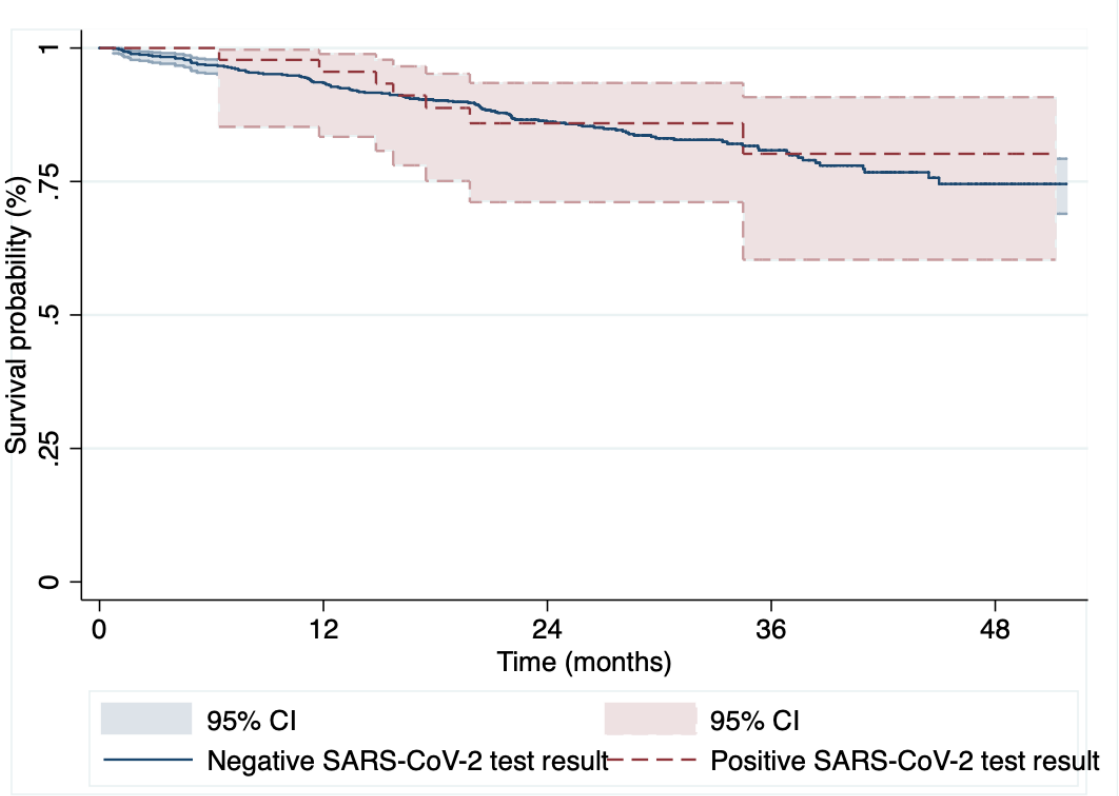

FIGURE 9. Survival curve (calculated using the Kaplan–Meier estimator) among patients with colorectal (C18-C21) cancer, according to SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

The HR for death in patients with colorectal cancer by SARS-CoV-2 test result adjusted for age, sex, and cancer stage are presented in Table 8. Patients with colorectal cancer had significant higher risk for death in older ages and advanced disease stages.

TABLE 8. Adjusted hazard ratio (95% confidence interval) for death by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result) in colorectal (C18-C21) patients.

Parameters[a]	HR adjusted for covariates	95% CI
SARS-CoV-2 test result		
Negative	**1.00**	
Positive	**0.75**	0.35-1.61
Age (years)	**1.02**	1.01-1.04
Sex		
Female	**1.00**	
Male	**1.10**	0.77-1.57
Stage		
I/II	**1.00**	
III/IV	**5.90**	3.38-10.31

[a] SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result), age (continuous), sex (male vs. female), tumor stage (I/II vs. III/IV).
HR, hazard ratio; 95% CI, 95% confidence interval.

Figure 10 represents the survival curve of patients with respiratory and intrathoracic organs cancer and Table 4 describes lower SP in infected patients at selected timepoints although the results were not statistically significant.

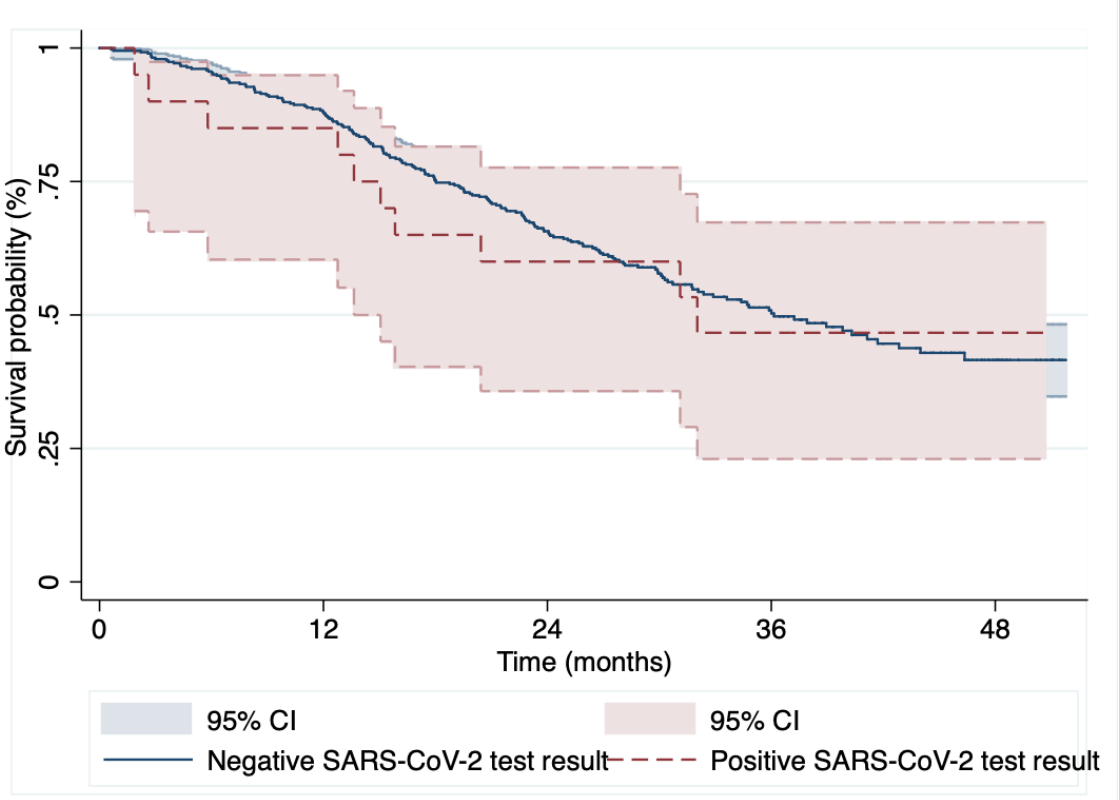

FIGURE 10. Survival curve (calculated using the Kaplan–Meier estimator) among patients with respiratory and intrathoracic organs (C30-C34) cancer, according to SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Table 9 presents HR for death in patients with respiratory and intrathoracic organs cancer by SARS-CoV-2 positive test result. Both older age and later stages are independent risk factors for death in these patients.

TABLE 9. Adjusted hazard ratio (95% confidence interval) for death by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result) in in respiratory and intrathoracic organs (C30-C39) patients.

Parameters[a]	**HR adjusted for covariates**	95% CI
SARS-CoV-2 test result		
Negative	**1.00**	
Positive	**1.11**	0.59-2.11
Age (years)	**1.02**	1.01-1.04
Sex		
Female	**1.00**	
Male	**0.91**	0.66-1.26
Stage		
I/II	**1.00**	
III/IV	**5.24**	3.29-8.35

[a] SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result), age (continuous), sex (male vs. female), tumor stage (I/II vs. III/IV).
HR, hazard ratio; 95% CI, 95% confidence interval.

Patients with lung cancer and COVID-19 infection had lower SP 12, 24 and 36 months after the cancer diagnosis as described in Table 4 and represented in Figure 11, although none of these results achieved statistical significance.

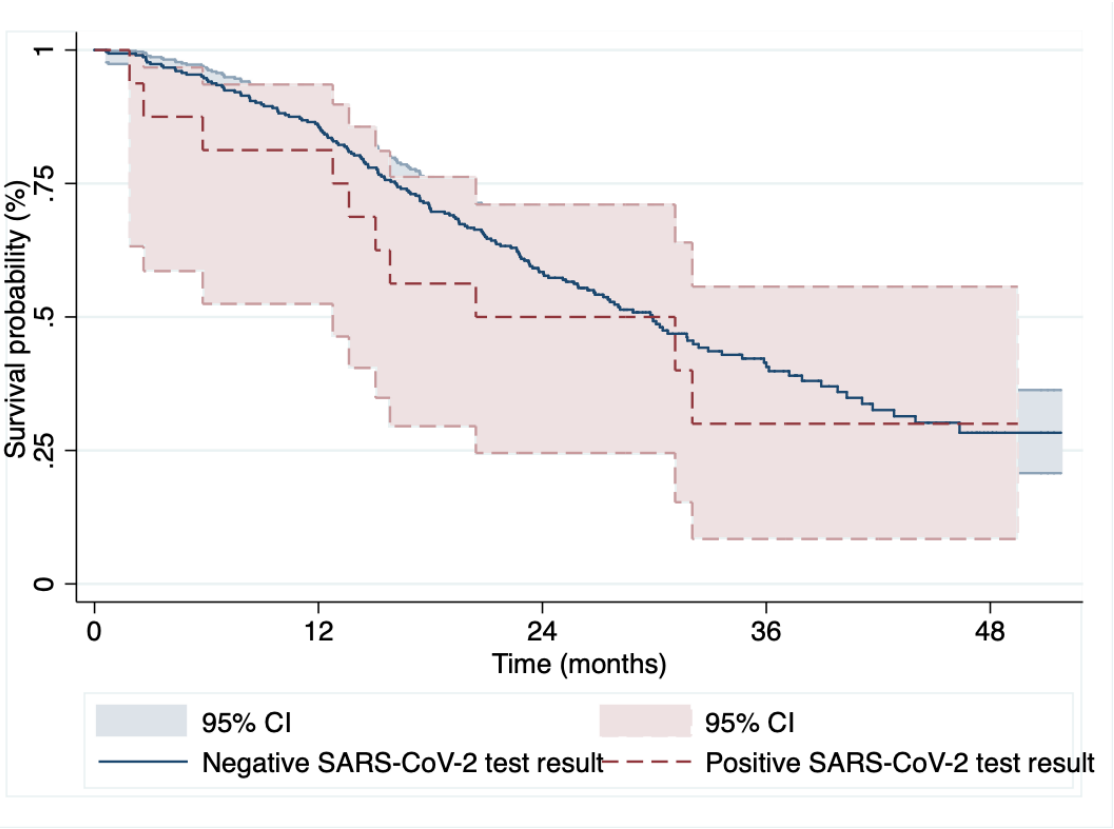

FIGURE 11. Survival curve (calculated using the Kaplan–Meier estimator) among patients with lung (C34) cancer, according to SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Only advanced disease increases the risk of death in lung patients significantly, as described in Table 10.

TABLE 10. Adjusted hazard ratio (95% confidence interval) for death by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result) in in lung cancer (C34) patients.

Parameters[a]	**HR adjusted for covariates**	95% CI
SARS-CoV-2 test result		
Negative	**1.00**	
Positive	**1.19**	0.63-2.27
Age (years)	**1.02**	1.00-1.03
Sex		
Female	**1.00**	
Male	**1.11**	0.79-1.54
Stage		
I/II	**1.00**	
III/IV	**4.32**	2.64-7.07

[a] SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result), age (continuous), sex (male vs. female), tumor stage (I/II vs. III/IV).
HR, hazard ratio; 95% CI, 95% confidence interval.

Impact of COVID-19 in cancer patients' first treatments by cancer subtypes

The time in days from diagnosis until first treatment is described in Table 11 and represented in Figure 12. Overall, when comparing this time gap before the COVID-19 pandemic with times during the COVID-19 pandemic, we observe a decrease in days (95.62 vs. 69.87 days). Almost all cancer subtypes had similar results, mainly hematological cancers, and lymphomas. Those whose time gap increased were lip, oral cavity, and pharynx (78.07 vs. 81.00 days), respiratory and intrathoracic organs (72.81 vs. 75.84 days), and lung cancer patients (74.43 vs. 75.74 days).

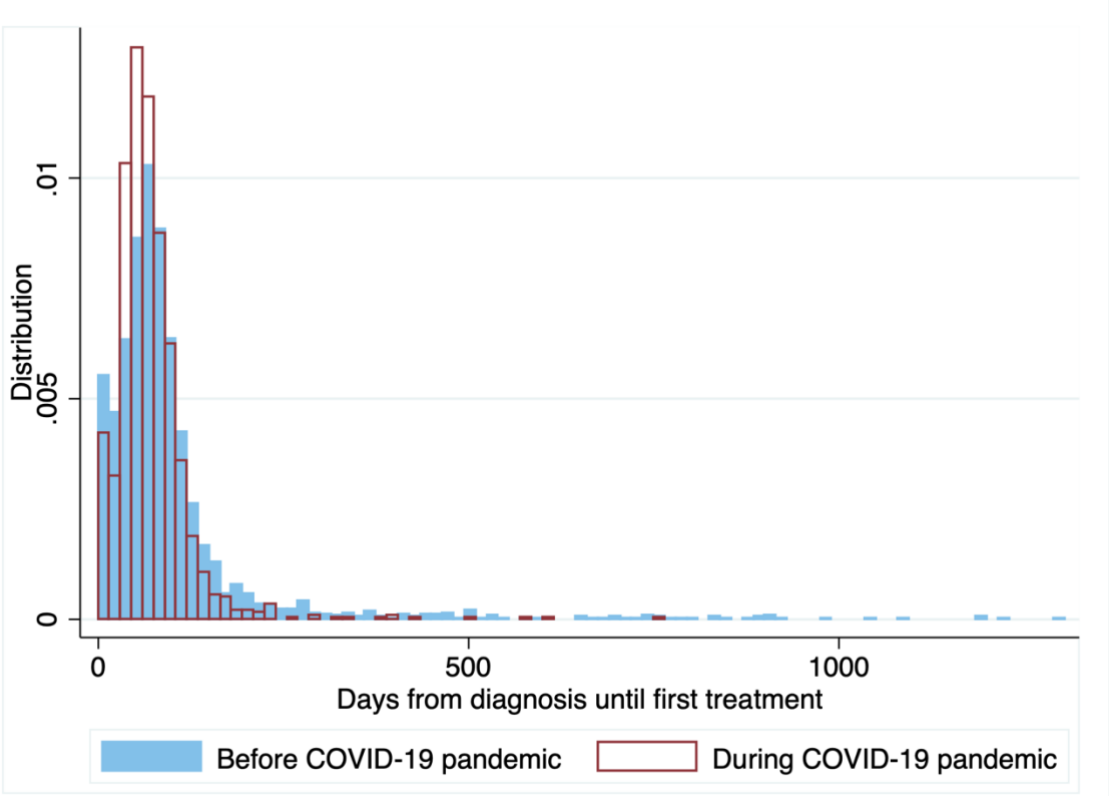

FIGURE 12. Patients' time from diagnosis until first treatment in days represented in a histogram by period (before COVID-19 pandemic vs. during COVID-19 pandemic)

TABLE 11. Time until first treatment in live and death patients by SARS-CoV-2 test result (negative SARS-CoV-2 test result vs. positive SARS-CoV-2 test result).

Time until first treatment (n=3,869) [a]	**Year of diagnosis**							
	Before COVID-19 pandemic				**During COVID-19 pandemic**			
	n	**Mean**	(SD)	min-max	**n**	**Mean**	(SD)	min-max
Overall	**2,308**	**95.62**	(120.37)	0-1300	**1,561**	**69.87**	(51.49)	0-764
Lip, oral cavity, and pharynx (C00-C14)	**174**	**78.07**	(51.13)	0-471	**4**	**81.00**	(26.97)	56-112
Digestive organs (C15-C26)	**764**	**79.54**	(53.34)	0-715	**366**	**61.96**	(36.68)	0-389
Colorectal (C18-C21) [b]	**398**	**73.39**	(44.80)	0-458	**348**	**60.79**	(32.99)	0-389
Respiratory and intrathoracic organs (C30-C39)	**294**	**72.81**	(56.95)	0-410	**101**	**75.84**	(51.39)	0-294
Lung (C34) [b]	**216**	**74.43**	(62.69)	0-410	**97**	**75.74**	(51.58)	0-294
Bone, articular cartilage, and soft tissue (C40-C41, C45-C49)	**40**	**87.83**	(83.07)	0-455	**68**	**72.66**	(52.01)	0-339
Skin (C43-C44)	**0**	**NA**	NA	NA	**0**	**NA**	NA	NA
Breast (C50)	**427**	**79.74**	(57.10)	0-759	**817**	**67.97**	(30.41)	0-239
Genitourinary organs (C51-C68)	**326**	**165.57**	(203.92)	0-1300	**82**	**129.65**	(141.73)	0-764
Female genital organs (C51-C58) [b]	**67**	**64.70**	(83.20)	0-492	**15**	**55.07**	(28.71)	0-98
Male genital organs (C60-C63) [b]	**207**	**222.26**	(226.32)	0-1300	**52**	**177.38**	(149.49)	0-764
Central nervous system (C69-C72)	**3**	**0**	0	0	**0**	**NA**	NA	NA
Endocrine glands (C73-C75)	**32**	**106.59**	(72.91)	0-275	**74**	**74.26**	(64.93)	0-403
Malignant neoplasm without specification of site (C80)	**9**	**85.11**	(25.68)	46-119	**1**	**68**	NA	68
Hematological (C81-C86, C88, C90-C96, D46-D47, D71, D73-D74)	**196**	**132.92**	(246.88)	0-1224	**44**	**36.86**	(52.66)	0-266
Lymphoma (C91-C95) [a]	**131**	**144.34**	(249.50)	0-1224	**11**	**70.64**	(73.91)	9-266

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; SD, standard deviation; NA, not applicable.

[a] 106 patients didn't had any first treatment related to the first primary tumor in study although they did a SARS-CoV-2 test while treating other tumor and 2 patients were excluded due to missing data.

[b] Some specific cancer subtypes are specified, making sum of counts and proportions sum more than the total number of patients.

Discussion

In our study we compared patients with cancer and positive or negative SARS-CoV-2 test result and we found that younger patients with more advanced cancer stages (III/IV) or cancer diagnosed between 2020 and 2021 had more frequently a positive test result. There were no statistically significant differences all for other characteristics between these two groups such as sex, BMI, alcohol and tobacco consumption, comorbidities, and number of tumors. Positive SARS-CoV-2 test result cancer patients didn't have a significant higher risk for death even when comparing different cancer subtypes, and the CFR was higher for all cancer subtypes except for colorectal, bone, articular cartilage, and soft tissue, all hematological cancers and lymphoma. The median time of follow-up was 95.62 and 69.87 months for non-infected and infected patients, respectively. Survival curves according to cancer subtype and by test result revealed overlapping 95% CI, thus, these results had no statistical significance. After the multivariable analysis, in the overall sample the only independent risk factors for death were those already known in clinical practice such as male sex, older age and advanced cancer stage. The median number of days from diagnosis until the first treatment was lower during the COVID-19 pandemic for overall patients and all cancer subtypes, except for cancers in the lip, oral cavity, and pharynx, respiratory and intrathoracic organs, and lung cancer.

This cohort was younger (60.51) when compared with other cancer cohorts [53, 67, 75-82], patients had less comorbidities (44.5% with Charlson comorbidity index=0) [80, 81] and were more likely to be overweight/obese (44.6%) [81]. Sex distribution (55.2% females) and smoking status prevalence (31.5% ever smoked) were similar to other published studies and, in the same way, arterial hypertension was the most prevalent comorbidity (36.6% of all patients) [53, 75, 76, 78, 80-82].

In the literature, the most prevalent cancer subtypes described in COVID-19 infected patients were breast, colorectal, prostate, lung, and hematological and in this study, breast, colorectal, lung cancer and lymphoma were the most frequently diagnosed types of cancer [75-78, 80-82]. Stage IV cancers had similar prevalence with those found in literature [75, 78, 80, 81], although differences were found when comparing with non-infected patients (60.7% vs. 45.9%; p-value<0.001). These results corroborate previous findings found in a study conducted at IPO-Porto which analyzed cancer diagnosis in 2019 and 2020 (before and during COVID-19 pandemic). Additionally, an increase in stage IV diagnosis was also found [62, 63]. The proportion of patients that have done surgery as first treatment was higher in negative patients than in positive SARS-CoV-2 patients, and possible explanations could be that infected patients had more advanced cancer stages and different types of cancer in relation to non-infected patients. These two factors could also influence the higher proportion of infected patients detected in more recent years of diagnosis.

The global CFR of infected patients was similar with other reports (21.5%) [53, 75-82, 115]. The CFR of specific subtypes was also comparable, except for digestive organs (29% to 67% in literature vs. 24.5%), hematological (29% to 58% in literature vs. 12.5%), lymphoma (31% to 50% in literature vs. 8.3%), female genital organs (12% to 38% in literature vs. 50.0%), skin (12% to 35% in literature vs. 50.0%) lip, oral cavity, and pharynx (13% to 24% in literature vs. 60.0%) [53, 55, 75-82, 115, 116].

Contrastingly to another published study (HR: 1.33; 95% CI: 1.09-1.56) [56], the risk of death in the overall sample was not statistically significant when comparing patients by serological result (HR: 1.07; 95% CI: 0.79-1.44). In the multivariable analysis, the result of SARS-CoV-2 was not an independent risk factor for death. For each of the 5 subtypes of cancer that were analyzed, older age and advanced stage showed a significant worse probability of survival, except for lung cancer. In a published meta-analysis, cancer patients with COVID-19 had higher risk of death according to sex (male) age (older age) diagnosis of COPD, respiratory system disease and cerebrovascular disease [34]. Comparatively to this report, patients in our cohort were younger, had less comorbidities, mostly had no clinical history of COPD or cerebrovascular disease and most of them were females, thus, having a more favorable prognosis and less risk of death. Additionally, at IPO-Porto, patients were asked to notify the hospital's secretariat if they had any symptoms that suggested a COVID-19 infection and SARS-CoV-2 screening was mandatory before treatments or invasive procedures. Therefore, we can deduce that infected patients were probably asymptomatic when tested. This study setting and the prognostic factors may have contributed to the fact that no statistically significant results were found for risk of death.

In 2020, the COVID-19 pandemic represented a challenge for societies, healthcare systems and individuals. Cancer diagnosis, treatments and follow-up appointments were frequently delayed, affecting patients' clinical outcome [62, 64-67]. In relation to time from diagnosis until first treatment in our cohort, it can be concluded that during COVID-19 pandemic, all cancer subtypes analyzed had shorter time gaps, except for lip, oral cavity, and pharynx, respiratory and intrathoracic organs, and lung cancer. Considering the two years before the pandemic (2018 and 2019), and the years during the COVID-19 pandemic (2020 and 2021), the overall time from diagnosis until first treatment was shorter (mean: 95.62 vs. 69.87 days). These results are in accordance with previous studies conducted at IPO-Porto comparing the first 3 months of the pandemic with the same period in the previous year (mean: 84 vs. 80 days, respectively) [63]. These findings can be explained as a result of less cancer diagnosis in Northern Portugal and at IPO-Porto during the COVID-19 pandemic as demonstrated by Morais, et al. (2021) where less 41.7% diagnosis occurred and less 57.1% received any treatment [62].

Strengths and limitations

As a strength of our study, it must be noticed that all patients with cancer diagnosed between 2018-2021, with a coded and validated cancer registry and that had a SARS-CoV-2 test were included in the study population. Therefore, comparability was possible between cancer patients with a positive and negative SARS-CoV-2 test result instead of comparing with an historical cohort of non-infected cancer patients or with the general population [53, 55, 62, 63, 67, 75-82, 115].

Regarding characteristics associated with variables and procedures to collect them, the fact that the laboratory results are automated and integrated with RIC with no manual intervention, eliminates the risk of missing data in respect to SARS-CoV-2 test results. This feature supports the strength of this study's data.

For this analysis, detailed patient data were obtained and analyzed. More than a descriptive analysis, this study quantifies objectively differences in CFR, survival and in the impact of COVID-19 in access to care (from diagnosis to first treatment) by cancer subtype. Complementarily with other reports, this study allows us to understand some of the impact of the COVID-19 pandemic on cancer patients.

While many strengths can be highlighted, some limitations were also found. One of the limitations of this study is related to the sample as it does not represent the totality of patients that did a RT-PCR test for COVID-19 diagnosis at IPO-Porto during 2020 and 2021, considering that only cases with a completely coded cancer registry were included. From hospital admission until the end of the coding process, there is a time lag that is considered normal, but this fact together with the current delay justifies the small number of cancer cases diagnosed in 2021 in this sample. However, this fact is not dependent of whether or not the patient performs the covid test and of its respective test result.

Although it was not possible to access information confirming vaccination status, patients diagnosed with cancer were not part of the first phase of the vaccination plan in Portugal. In fact, these patients were vaccinated on phase two that started on April 2021. Once the end of the follow-up period dates of 30th of April 2022, we cannot assume that the CFR was not influenced by the beneficial effect of vaccines.

At last, it was not possible to access information regarding other SARS-CoV-2 tests conducted outside of IPO-Porto. Therefore, only patients diagnosed with COVID-19 at IPO-Porto were considered part of the group with positive SARS-CoV-2 test result. Ultimately, some patients may have developed COVID-19 and were not integrated in the appropriate group of this cohort.

Conclusions

This study provides new evidence on CFR on each cancer subtype and on risk of death for selected cancer sites. With these results, it is possible to conclude that patients with cancer and a positive SARS-CoV-2 test result did not have higher risk of death by any cause comparatively to patients with cancer and negative SARS-CoV-2 test result, regardless of the cancer subtype. Nevertheless, the CFR is higher for patients with cancer sited in the lip, oral cavity, and pharynx, digestive organs, respiratory and intrathoracic organs, lung, skin, breast, genitourinary organs, female genital organs, and male genital organs. Moreover, time from diagnosis until the first treatment was lower during the pandemic than before the pandemic.

For future research on patients with cancer and COVID-19, all patients' data must be integrated, namely, SARS-CoV-2 test results outside of IPO-Porto, and preferably other clinical outcomes such as hospital and ICU admission, medical procedures, laboratory and imaging reports and other appropriate variables to enrich scientific knowledge more deeply.

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