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ORIGINAL ARTICLE

# A Definitive Prognostication System for Patients With Thoracic Malignancies Diagnosed With Coronavirus Disease 2019: An Update From the TERAVOLT Registry

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**ABSTRACT**

**Introduction:** Patients with thoracic malignancies are at increased risk for mortality from coronavirus disease 2019 (COVID-19), and a large number of intertwined prognostic variables have been identified so far.

**Methods:** Capitalizing data from the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry, a global study created with the aim of describing the impact of COVID-19 in patients with thoracic malignancies, we used a clustering approach, a fast-backward step-down selection procedure, and a tree-based model to screen and optimize a broad panel of demographics and clinical COVID-19 and cancer characteristics.

**Results:** As of April 15, 2021, a total of 1491 consecutive eligible patients from 18 countries were included in the analysis. With a mean observation period of 42 days, 361 events were reported with an all-cause case fatality rate of 24.2%. The clustering procedure screened 73 covariates in 13 clusters. A further multivariable logistic regression for the association between clusters and death was performed, resulting in five clusters significantly associated with the outcome. The fast-backward step-down selection procedure then identified the following seven major determinants of death: Eastern Cooperative Oncology Group—performance status (ECOG-PS) (OR = 2.47, 1.87–3.26), neutrophil count (OR = 2.46, 1.76–3.44), serum procalcitonin (OR = 2.37, 1.64–3.43), development of pneumonia (OR = 1.95, 1.48–2.58), C-reactive protein (OR = 1.90, 1.43–2.51), tumor stage at COVID-19 diagnosis (OR = 1.97, 1.46–2.66), and age (OR = 1.71, 1.29–2.26). The receiver operating characteristic analysis for death of the selected model confirmed its diagnostic ability (area under the receiver operating curve = 0.78, 95% confidence interval: 0.75–0.81). The nomogram was able to classify the COVID-19 mortality in an interval ranging from 8% to 90%, and the tree-based model recognized ECOG-PS, neutrophil count, and c-reactive protein as the major determinants of prognosis.

**Conclusions:** From 73 variables analyzed, seven major determinants of death have been identified. Poor ECOG-PS was found to have the strongest association with poor outcome from COVID-19. With our analysis, we provide clinicians with a definitive prognostication system to help determine the risk of mortality for patients with thoracic malignancies and COVID-19.



*Keywords:* COVID-19; Cancer; Thoracic; NSCLC; TERAVOLT; Registry

## Introduction

Coronavirus disease 2019 (COVID-19), a respiratory tract infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had an impact on health care that will be felt for decades to come. The rapid global spread of this unpredictable virus led the WHO to declare a pandemic in March 2020, with more than 219 million confirmed cases and 4.5 million deaths as of September 13, 2021.

Early on it was determined that certain populations, including the elderly and those with underlying comorbidities, were more susceptible to develop severe forms of COVID-19 and experience detrimental outcomes as compared with the general population.[1–5] The initial reports from single institutions reported conflicting data among patients with a cancer diagnosis, which led the oncology community to create registries and determine the true impact of COVID-19 on this vulnerable patient population. As the pandemic spread, the data identified prognostic factors, including patient demographics, comorbidities and concomitant medications, tumor characteristics and anticancer treatments, and clinical and laboratory findings at COVID-19 diagnosis, including COVID-19–related complication and COVID-19–specific therapies associated with mortality in patients with cancer.[6–12] Professional societies began to release guidelines for treatment and surveillance, whereas the health care environment restructured to accommodate telemedicine and remote visits to minimize patient contact with an infected health care system.[13]

The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) is an active global registry that was established in March 2020 to understand the impact of COVID-19 infection on patients with thoracic malignancies in academic and community practices globally. Given the disease characteristics and the common target organ, patients with thoracic malignancies have been found to experience higher morbidity and mortality from SARS-CoV-2 infection, with case fatality rates ranging from 22% to 41%.[6,7,14–16] In addition to reporting on outcomes associated with morbidity and mortality, TERAVOLT aims to determine the risk factors associated with poor outcomes, to provide practitioners

with real-time data on therapies that may affect survival to COVID-19, and to evaluate long-term impacts on care and the delay in care to patients with both curable and incurable thoracic malignancies.[8,9,15] The aim of this update of the TERAVOLT registry is to identify and select the variables with the greatest prognostic impact to ensure continual and timely care of our patient population.

## Materials and Methods

### *Study Procedures*

The database was designed to collect cross-sectional data, including patient and disease characteristics for both cancer and COVID-19 along with treatments received and complications and longitudinal cohort data that are related to the association between potential prognostic factors and clinical outcomes.

Institutions across the globe were invited to participate in the study. In total, 114 centers across 19 countries have activated the study, of which 92 have contributed data. Eligibility criteria were patients with thoracic cancer (NSCLC, SCLC, mesothelioma, thymic epithelial tumors, and other neuroendocrine tumors with pulmonary origin) with a COVID-19 diagnosis defined as any of the following: laboratory-confirmed (using reverse-transcriptase polymerase chain reaction/serology) infection or suspected SARS-CoV-2 infection on the basis of radiological findings consistent with COVID-19 pneumonia and clinical symptoms (i.e., body temperature $>37.5^{\circ}$C, cough, decrease of oxygen saturation of at least 5%, cough, diarrhea, otitis, dysgeusia, myalgia, arthralgia, conjunctivitis, and rhinorrhea). Asymptomatic patients found to be positive for SARS-CoV-2 were included in this analysis; these patients were tested by their centers on the basis of institutional policies or known exposure to a confirmed-positive individual. Patients of any age, sex, primary tumor, or stage of disease were eligible, including those receiving active anticancer treatment and in clinical follow-up.

Investigators from participating institutions entered data into a REDCap (research electronic data capture) database, with each institution assigned a unique center number and used their own deidentified patient number. This numbering scheme allowed for the opportunity to query investigators for additional clarification regarding the data entered and ask for additional clinical data that emerged as our understanding of COVID-19 expanded during the pandemic. REDCap is a secure web platform[10] for building and managing online databases and surveys; it provides easy data handling (with audit trails for reporting, monitoring, and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Clinical data were extracted from medical records of consecutive patients starting March 23, 2020, and will be collected until the end of the pandemic; retrospective data collection from patients diagnosed with having COVID-19 earlier than this date was allowed. The database is divided into the following four main categories: demographics, comorbidities, oncological history, and course of COVID-19, including diagnosis, clinical, radiological, and laboratory outcomes and COVID-19–specific therapy. Basic demographics included age, sex, race and ethnicity, smoking status, stage of cancer at COVID-19 diagnosis (American Joint Committee on Cancer clinical stages[11]), type of thoracic malignancy, past and current ($>$3 mo relative to COVID-19 diagnosis) oncological treatments, comorbidities, concomitant medications, and need for hospital admission. Oncological outcomes were also collected to evaluate the effect of this pandemic on treatment delays. Initial database fields were chosen on the basis of available literature data and are updated on the basis of emerging evidence of COVID-19 and its impact on the general population and patients with cancer.

### *Aims and Clinical End Points*

In this study, we presented a comprehensive analysis with a definitive prognostic stratification of the TERAVOLT study population, which has been updated and further implemented with new data.[12,17] Our aim was to provide a more comprehensive prognostic model for patients with thoracic malignancies and COVID-19, encompassing and optimizing the broad variety of available information.

Acknowledging the competing influence of the underlying thoracic malignancy in determining mortality within the medium-longer term, we attempted at a possible distinction of acute, likely COVID-19–related deaths from later, likely cancer-related deaths as already done elsewhere.[18,19] In doing that, we elected mortality within the observation period (from COVID-19 diagnosis to death/last follow-up) as clinical end point of interest. Considering the study design, which was not developed for reporting long-term outcomes, a dichotomized end point allowed us to discriminate early deaths (e.g., death during hospitalization) as opposed to alive/discharged patients who were considered censored with respect to COVID-19–related mortality.

All the considered variables were screened at the time of COVID-19 diagnosis and included the following: (1) patient demographics (sex, age, body mass index, smoking status); (2) comorbidities (chronic obstructive pulmonary disease, asthma, and other forms of lung fibrosis, diabetes, history of immunodeficiency, cardiovascular diseases, chronic renal disease, autoimmune

diseases, hypertension, chronic hepatitis, history of hepatitis B/C, history of tuberculosis, and other comorbidities); (3) baseline medications at COVID-19 diagnosis (preexistent oxygen therapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nonsteroidal antiinflammatory drugs, corticosteroids, immune suppressants, acetylsalicylic acid, anticoagulation therapy); (4) oncological features (histology, Eastern Cooperative Oncology Group—performance status [ECOG-PS], tumor stage at COVID-19 diagnosis, receipt of chemotherapy within 3 mo of COVID-19 diagnosis, line of therapy, previous radiotherapy, previous oncological surgery); (5) full blood cell count information (hemoglobin, neutrophils, lymphocytes, eosinophils, platelets, and neutrophil-to-lymphocyte ratio; (6) general biochemistry and metabolic profile (triglycerides, glucose, creatinine, sodium, potassium, calcium, ferritin, albumin, creatine phosphokinase, alanine aminotransferase, aspartate transaminase, gamma-glutamyl transferase, lactate dehydrogenase, interleukin 6, C-reactive protein (CRP), bilirubin, procalcitonin (PCT), fibrinogen, D-dimer, troponin I, troponin T, prothrombin time); (7) respiratory parameters (peripheral capillary oxygen saturation, partial pressure of oxygen/fraction of inspired oxygen ratio, carbon dioxide); and (8) radiological findings at COVID-19 diagnosis (bilateral involvement, consolidations, interstitial abnormalities, vascular thickening, COVID-19 pneumonia, pleural effusion, image changes, ground-glass images). All covariates are also summarized as additional appendix.

### *Statistical Analysis*

Given the descriptive nature of the project, which focused on estimation rather than hypothesis testing, no formal power calculation was performed. At the beginning of the study, we estimated that 150 participating institutions each entering at least five consecutive patients, a sample size of 750 patients, would have produced confidence intervals (CIs) of plus or minus 2% for estimates of proportions. Descriptive statistics of patient demographics and clinical characteristics were reported as frequencies (proportions) for categorical variables and median with interquartile range for continuous variables. All variables have been dichotomized for the analysis, and summary measures for association with the outcome were evaluated by univariable binary logistic models. Results were reported through ORs with 95% CIs. Patients with missing values were excluded from univariable but included in multivariable analyses as reference terms.

Considering the high number of variables and the likelihood of overlap, we used an orthoblique principal component–based clustering (OPCC) approach as a system of variable reduction. The OPCC approach was used to screen and identify specific subsets of variables revealing association with mortality. The VARCLUS and SCORE procedures were used according to the SAS code provided by Black and Watanabe.[20] A further backward stepwise selection was performed to define clusters with strongest association with the outcome.

Binary logistic regression was also used to develop and internally validate the definitive predictive multivariable model for mortality, by introducing each binary predictor in a fully fitted model. A fast-backward step-down selection with total residual Akaike information criteria as the stopping rule was used to identify the variables that explain the bulk of mortality. The variable selection and the prognostic nomogram were performed and drawn up using the fastbw and the nomogram functions of the "rms" package in R.[21] The validate function of the "rms" package in R was used to internally validate and calibrate the prediction model; bootstrap was performed with 1000 resamples.

A receiver operating characteristic curve with the estimation of the area under the receiver operating curve was then used to evaluate the diagnostic ability of the built prediction model. The classification and regression tree (CART) methodology developed by Breiman et al.[22] was used for the recursive partitioning analysis encompassing the variables selected by the previous model, to define a tree with a hierarchical classification of variables. The "rpart" package in R was used to apply the CART methodology.[23] For the purpose of the CART analysis, patients with missing values were included as reference terms.

In view of the registry design, which was not developed to evaluate long-term outcomes, patients reported as alive/discharged were considered right censored. Nevertheless, because the point estimate for follow-up was not available for right-censored patients and considering the study aim of reporting COVID-19–related mortality, the restricted mean survival time was used to estimate the mean follow-up. All analyses were done using the SAS software version 9.4 (Copyright 2016 by SAS Institute Inc., Cary, NC). Predictive multivariable regression model was developed and internally validated using the R software version 4.1.0 (May 18, 2021)—R Core Team (2021).[24]

## Results

### *Patient Characteristics*

From March 2020 to April 2021, a total of 1591 consecutive patients were entered into the database and evaluated for inclusion in the present analysis. Overall, 100 were excluded on the basis of eligibility criteria (Fig. 1) and 1491 eligible patients from 89 institutions

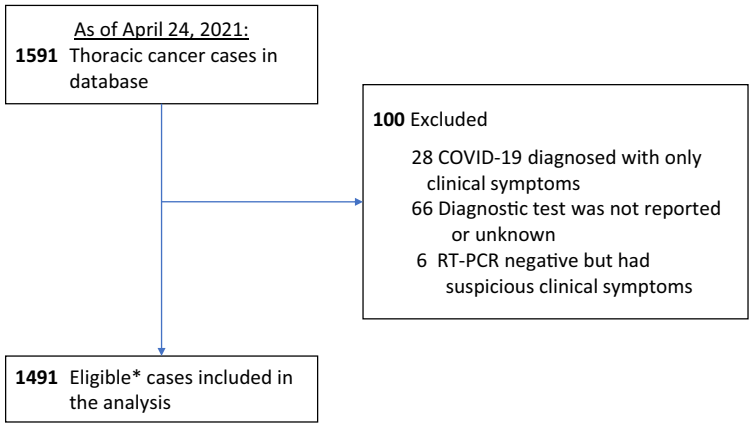


**Figure 1.** Consort flow diagram for the included population. COVID-19, coronavirus disease 2019; RT-PCR, reverse-transcriptase polymerase chain reaction.

across 18 countries were included in the analysis (Supplementary Table 1).

Laboratory-confirmed SARS-CoV-2 infection (reverse-transcriptase polymerase chain reaction/serology/antigen) was reported for 1432 patients (96%), and 59 (6%) were diagnosed on the basis of highly suspicious radiological/clinical findings. A summary of all demographic and clinical characteristics is included in Table 1, and a full detailed list of all cancer- and COVID-19–related features according to the outcome is available in Supplementary Table 2. Most of the patients were male (57.3%), white (72.2%), and former/current smokers (77.8%); median age was 67 years with 57.3% aged more than or equal to 65 years. As expected, most patients had at least one comorbidity (82.3%), including hypertension (48%), chronic obstructive pulmonary disease (24.5%), diabetes (19.3%), ischemic heart disease (13.1%), and were receiving concomitant non–cancer-related medications at COVID-19 diagnosis (73.4%). Of note, 13% of the patients were on corticosteroids before COVID-19 diagnosis. Median body mass index was 25 (range: 11–87). The most represented type of tumor was NSCLC (79.7%), followed by SCLC (12.4%); other thoracic malignancies represented 7.9% of the cohort. Most patients had stage IV disease at COVID-19 diagnosis (67.8%), with an ECOG-PS of 0 to 1 (71.9%) and had received antineoplastic treatments within 3 months of COVID-19 diagnosis (64.5%), most often chemotherapy alone (38.8%). COVID-19–oriented therapy included anticoagulation (37.2%), antibiotics (48.7%), antivirals (18.9%), antifungals (2.6%), corticosteroids (33.4%), interleukin (IL)-6 inhibitors (3.1%), and antimalarials (16.4%). The mean observation period was 42 days (range: 1–60); 361 events were reported, resulting in an all-cause case fatality rate of 24.2%.

## Cluster Analysis

Overall, 73 variables were included in the analysis. Supplementary Table 3 summarizes the univariable binary logistic regression analysis with relevant cutoffs for each covariate. A significant association with the outcome was reported for three variables among demographics, five variables among comorbidities, three variables among concomitant medications, three variables among oncological features, six variables among the full blood cell count information, 17 variables among the general biochemistry and metabolic profile, two variables among the respiratory function parameters, and seven variables among the radiological findings. The OPCC procedure grouped the 73 covariates into 13 clusters, as reported in the clustering dendrogram in Supplementary Figure 1. Clusters 1, 2, 3, 4, 5, 6, 7, 9, 10, and 13 revealed a significant correlation between mortality and the linear combination of all variables within each cluster (Supplementary Table 4). The further multivariable backward stepwise selection (entry level $p = 0.0038$) individuated clusters 3, 4, 5, 9, and 13 as significantly associated with the outcome.

## Development of the Prognostic Nomogram and CART Methodology

With the aim of defining key determinants of mortality, we included each of 73 variables in a full fitted

**Table 1.** Demographics and Clinical Characteristics

| Patients' Characteristics | All Patients (N = 1491) |
|---|---|
| Age, y (median) | 67.0 (60.0-74.0) |
| >65 | 855/1491 (57.3%) |
| ≤65 | 636/1491 (42.7%) |
| Total | 1491 |
| Sex | |
| Female | 634/1489 (42.6%) |
| Male | 853/1489 (57.3%) |
| Other | 2/1489 (0.1%) |
| Total | 1489 |
| Smoking status | |
| Current | 264/1429 (18.5%) |
| Former | 848/1429 (59.3%) |
| Never | 317/1429 (22.2%) |
| Total | 1429 |
| Race | |
| White | 1058/1465 (72.2%) |
| Black or African American | 123/1465 (8.4%) |
| Other | 284/1465 (19.4%) |
| Total | 1465 |
| Region | |
| Europe | 875 (58.8%) |
| North America | 504 (33.9%) |
| North Africa | 31 (2.1%) |
| Central America | 27 (1.8%) |
| South Asia | 20 (1.3%) |
| Middle East | 15 (1.0%) |
| Central Asia | 10 (0.7%) |
| South America | 9 (0.6%) |
| Total | 1491 |
| Cancer stage at COVID-19 diagnosis | |
| I | 115/1443 (8.0%) |
| II | 79/1443 (5.5%) |
| III | 270/1443 (18.7%) |
| IV | 979/1443 (67.8%) |
| Total | 1443 |
| Cancer diagnosis | |
| SCLC | 184/1489 (12.4%) |
| NSCLC, squamous | 277/1489 (18.6%) |
| NSCLC, nonsquamous | 841/1489 (56.5%) |
| NSCLC, NOS | 69/1489 (4.6%) |
| Malignant pleural mesothelioma | 58/1489 (3.9%) |
| Thymic carcinoma | 8/1489 (0.5%) |
| Thymoma | 23/1489 (1.5%) |
| Carcinoid/neuroendocrine | 29/1489 (1.9%) |
| Total | 1489 |
| ECOG—performance status | |
| 0 | 332/1315 (25.2%) |
| 1 | 612/1315 (46.5%) |
| 2 | 253/1315 (19.2%) |
| 3 | 95/1315 (7.2%) |
| 4 | 23/1315 (1.7%) |
| Total | 1315 |
| Currently undergoing anticancer treatment | |
| Yes | 954/1480 (64.5%) |
| No | 526/1480 (35.5%) |
| Total | 1480 |
| Lines of therapy | |
| 0 | 312/1379 (22.6%) |
| 1 | 638/1379 (46.3%) |
| 2 | 242/1379 (17.5%) |
| 3 | 116/1379 (8.4%) |
| ≥4 | 71/1379 (5.1%) |
| Total | 1379 |

COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

model using a fast-backward step-down selection, with total residual Akaike information criteria as the stopping rule. The resulting multivariable model is reported in Table 2 and consisted of seven major determinants of the outcome, including age (OR = 1.71, 95% CI: 1.29–2.25), ECOG-PS (OR = 2.47, 95% CI: 1.86–3.26), stage at COVID-19 diagnosis (OR = 1.96, 95% CI: 1.45–2.65), neutrophils (OR = 2.46, 95% CI: 1.76–3.44), PCT (OR = 2.37, 95% CI: 1.63–3.43), CRP (OR = 1.89, 95% CI: 1.89–3.43), and pneumonia (OR = 1.95, 95% CI: 1.48–2.57). The receiver operating characteristic curve analysis for the computed multivariable model confirmed its good performance in estimating the outcome, with an area under the receiver operating curve of 0.78 (95% CI: 0.75–0.80) (Supplementary Fig. 2). On the basis of the estimated regression coefficients from the obtained final multivariable prognostic model, we developed a prognostic nomogram (Fig. 2) to assign patients with thoracic malignancies and COVID-19 a death probability.

The Sankey diagram provided in Figure 3 offers a visual expression of the CART analysis with the hierarchical classification of variables. The first node was split on the basis of ECOG-PS. Among patients with an ECOG-PS of 0 to 1, the second split was defined by serum CRP, whereas among patients with an ECOG-PS greater than or equal to 2, by neutrophil count. Third-generation splits were defined by tumor stage at COVID-19 diagnosis among patients with neutrophil count greater than the upper limit of normal (ULN), by serum PCT among patients with CRP greater than the ULN, and by radiological finding of pneumonia among patients with neutrophil count less than or equal to the ULN and with CRP less than or equal to the ULN.

## Discussion

During the first year of the pandemic, the registry-based response allowed health care systems to promptly adapt to the escalating threat posed by SARS-CoV-2 and progressively develop guidelines and recommendations to balance patient shielding and oncological continuity of care with a reliance on telemedicine.[25] Moreover, in this context, TERAVOLT has been the

**Table 2.** Final Multivariable Logistic Model for the Association With Death. Fast-Backward Step-Down Variable Selection With Total Residual AIC as Stopping Rule

| Variables | OR (95% CI); *p* Value |
|---|---|
| Age (>65 vs. ≤65 y) | 1.71 (1.29-2.25); 0.0001 |
| ECOG-PS (≥2 vs. 0-1) | 2.47 (1.86-3.26); <0.0001 |
| Stage at COVID-19 diagnosis (VI vs. <IV) | 1.96 (1.45-2.65); <0.0001 |
| Neutrophils (> vs. ≤ULN) | 2.46 (1.76-3.44); <0.0001 |
| Procalcitonin (> vs. ≤ULN) | 2.37 (1.63-3.43); <0.0001 |
| CRP (> vs. ≤ULN) | 1.89 (1.43-3.43); <0.0001 |
| Pneumonia (yes vs. no) | 1.95 (1.48-2.57); <0.0001 |

AIC, Akaike information criteria; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group—performance status; ULN, upper limit of normal.

landmark tumor-specific registry devoted to the understanding of the impact of COVID-19 on patients with thoracic malignancies to provide practitioners and patients with outcomes data describing the impact of infection on mortality to allow for an informed decision on care. Although mortality data suggest that patients with thoracic malignancies experience worse COVID-19 outcomes overall, the identified baseline prognostic factors among demographics, comorbidities, tumor, and COVID-19 characteristics seem to be similar across different malignancies.[7,26]

The final analysis included 1491 patients and reported an all-cause case fatality rate of 24.2%, which is similar to other published data.[27,28] Capitalizing on the extended sample size and the granularity of clinical information collected from 73 variables, we have identified seven major determinants of mortality, including age, ECOG-PS, tumor stage, neutrophil count, PCT, CRP, and development of pneumonia. In addition, the OPCC procedure clearly revealed how among the wide range of factors typically considered in clinical practice, there are often several associations and their unrestricted inclusion in prognostic models generate a high level of collinearity and redundancy. These findings might be highly informative in the clinic, allowing providers an impartial patient assessment before prescribing care.

To that purpose, we developed both the inference tree and the prognostic nomogram. The CART methodology firmly established an ECOG-PS greater than or equal to 2 as the strongest determinant of mortality, suggesting clinicians should take it into consideration first when assessing patients, followed by neutrophil count and tumor stage in patients with a poor PS, and by serum CRP and PCT in patients with a good PS. The importance of ECOG-PS is pointed out in different cohort studies, such as CCC19 and ACHOCC-19.[29,30] These additional few characteristics should be included in the diagnostic algorithm of patients with thoracic neoplasia.

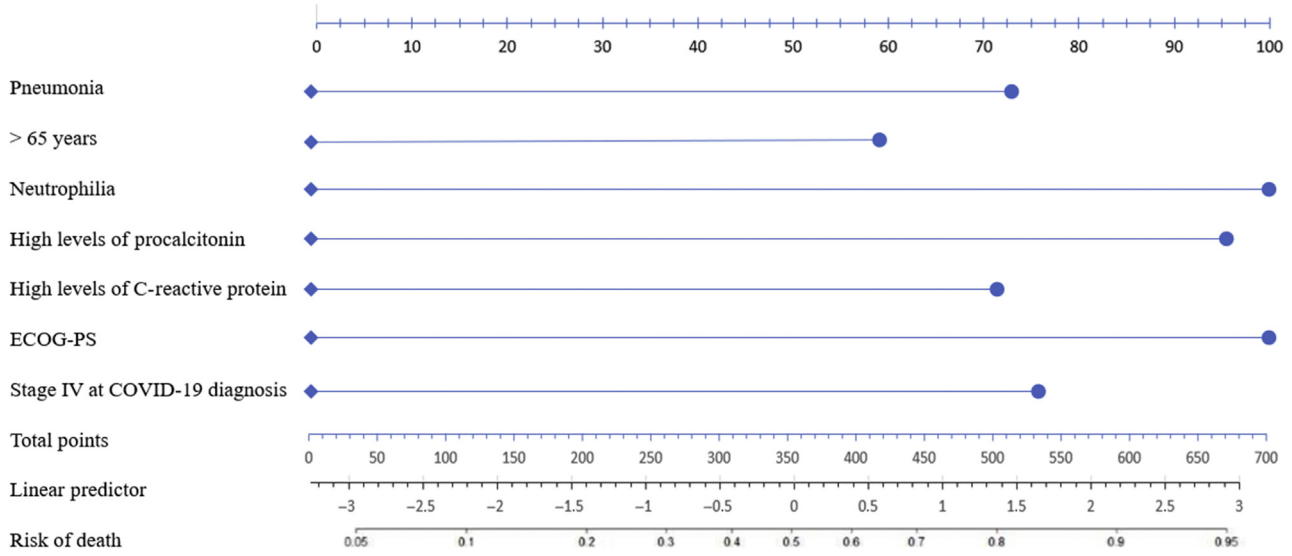


**Figure 2.** Prognostic nomogram including the following major determinants of mortality: occurrence of pneumonia (yes versus no), age (≤65 versus >65 y old), neutrophil count (> versus ≤ ULN), procalcitonin (> versus ≤ ULN), C-reactive protein (> versus ≤ ULN), ECOG-PS (≥2 versus 0-1), and disease stage at COVID-19 (stage IV versus stages I-III). The nomogram is able to classify the COVID-19 mortality risk in an interval ranging from 8% to 90%. In the nomogram, the determinants of mortality are represented with two symbols. On one hand, ○ represents the presence of this predictor. On the other hand, the symbol ◆ reveals the absence of it. The sum of the different determinants establishes the risk of death. COVID-19, coronavirus disease 2019; ECOG-PS, Eastern Cooperative Oncology Group—performance status; ULN, upper limit of normal.

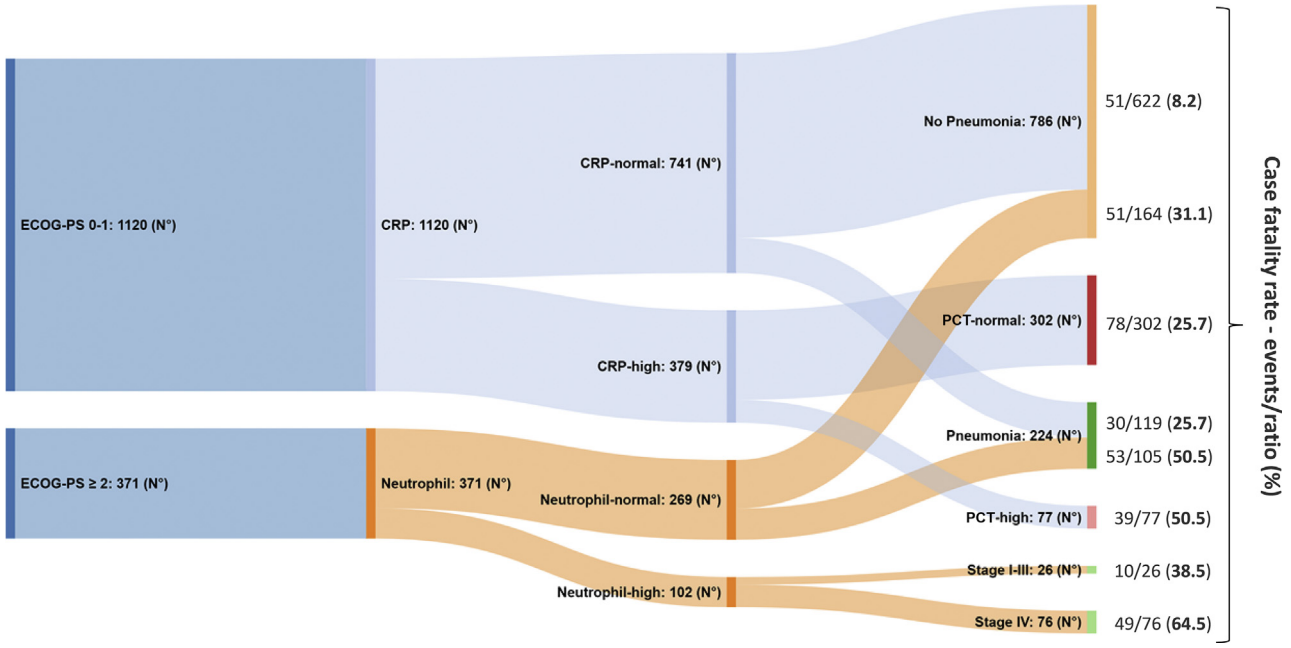


**Figure 3.** Sankey diagram offering a visual expression of the CART analysis with the hierarchical classification of variables. The first node was split on the basis of ECOG-PS (0-1: 1120 patients versus ≥2: 371 patients). Among the patients with an ECOG-PS of 0 to 1, the second split was defined by serum CRP (normal: 741 patients versus high: 379 patients), whereas among the patients with an ECOG-PS of greater than or equal to 2, by neutrophil count (normal: 269 patients versus high: 102 patients). Third-generation splits were defined by tumor stage at COVID-19 diagnosis among the patients with neutrophil count > ULN (stages I-III: 26 patients with a CFR of 38.5% versus stage IV: 76 patients with a CFR of 64.5%), by serum PCT among patients with CRP > ULN (PCT normal: 302 patients with a CFR of 25.7% versus PCT high: 77 patients with a CFR of 50.5%), and by radiological finding of pneumonia among patients with CRP less than or equal to ULN and with neutrophil count less than or equal to ULN (pneumonia present: 224 with a CFR of 25.7% and 50.5%, respectively, versus pneumonia absent: 786 patients with a CFR of 8.2% and 31.1%, respectively). Diagram created using SankeyMATIC web tool (available at: https://sankeymatic.com/). Patients with missing values were included as reference terms. CART, classification and regression tree; CFR, case fatality rate; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group—performance status; PCT, procalcitonin; ULN, upper limit of normal.

Our data revealed that special consideration to neutrophilia and serum PCT should be considered.

Neutrophilia is already an established marker of worse COVID-19 in the general population, and it is closely linked to lymphopenia as a proxy of immunopathology of severe COVID-19.[31] It has been described that a systemic proinflammatory response driven by excess cytokines affects the lymphopoiesis alongside an aberrant compensatory granulopoiesis.[32] Although some publications support the effectiveness of PCT in patients with cancer,[33–35] its considerable cost means that it is not available as a routine test in all centers. Several evidence links a rise in PCT to a worse outcome from COVID-19,[33] but its mechanistic role in driving severe disease remains partially unexplained and mainly relies on the identification of bacterial co-infection in COVID-19, thus explaining its negative prognostic role.[36] In fact, a high PCT is usually sustained by a rise in IL-6, IL-1$\beta$, and tumor necrosis factor-$\alpha$, whereas viral infections tend to prevent PCT production through the interferon-$\gamma$–mediated signaling.[37] Nevertheless, the prevalence of bacterial co-infections in COVID-19 also suggests that a deranged cytokine activity may independently enhance PCT secretion in severe COVID-19.[38]

We acknowledge that a weakness in the current study is the time frame by which data were collected and from various countries where access to care and mortality fluctuated during the course of the pandemic. From the time the database originated to the cutoff date, our understanding of the disease has increased leading to early hospitalizations, and empirical treatments have fallen into disuse while effective therapy was approved.[39–43] In addition, both testing and hospital capacity have been enhanced[44–46] and initial specific safety and efficacy data of anti–SARS-CoV-2 vaccines in patients with cancer are emerging.[47,48] From this perspective, with the inclusion of more recently diagnosed patients, our own data revealed a decline in mortality from 33% to 24%.[15] This finding was expected and mirrors a general time-dependent improvement of clinical outcomes as reported elsewhere.[19,49] On that note, we must recognize that we did not include the effect of SARS-CoV-2 vaccinations in the development of our algorithm given that our database was initiated in

March 2020. Furthermore, the data cutoff of April 2021 allows us to assume that a very few patients would have received at least one dose of SARS-CoV-2 vaccine before infection and that the effect of immunization campaigns did not affect the presented results.

One of the major study limitations, stemming from the registry design, is the relatively short observation period for each patient. The database was initially designed to capture the acute effects from COVID-19 infection. Nevertheless, the mean follow-up of 42 days allows us to assume that the median observation period exceeds 60 days. In addition, we purposely focused this analysis on a dichotomized end point to depict early and COVID-19–related mortality. We must also acknowledge as a study limitation the lack of some variables that are routinely evaluated in oncological care of patients with thoracic cancer, including genomic features (e.g., EGFR status), other systemic anticancer therapies (e.g., immune checkpoint inhibitors), and historical oncological data other than stage of tumor at COVID-19 diagnosis. Nevertheless, variable selection was based on our previous findings, which established chemotherapy as the only systemic therapy affecting the outcome[8] and SCLC as the tumor type with the highest mortality.[14]

The ongoing efforts including immunization campaigns and enhanced capacity will likely allow a progressive return to normal on a global scale. Despite that, SARS-CoV-2 will still affect the continuity of care of patients with cancer, given to the evolutionary nature of pandemics, vaccine hesitancy or access to it in low-income countries, and emerging new viral strains which may trigger immune-escape mechanisms.[50–53] Against this evolving scenario, a more tailored, comprehensive, and properly powered prognostication system such as the one presented in this study will be a useful tool for clinicians as they develop oncology treatment plans for their patients.

## CRediT Authorship Contribution Statement

**Marina Chiara Garassino, Valter Torri, Jennifer G. Whisenant:** Conceptualization.

**Javier Baena, Alessio Cortellini, Valter Torri, Luca Porcu:** Methodology.

**Valter Torri:** Software.

**Javier Baena, Alessio Cortellini:** Validation.

**Valter Torri, Luca Porcu:** Formal analysis.

**Alessio Cortellini, Valter Torri, Javier Baena:** Investigation.

**Jennifer G. Whisenant, Valter Torri, Marina Chiara Garassino, Leora Horn:** Resources.

**Jennifer G. Whisenant, Javier Baena, Alessio Cortellini, Li-Ching Huang, Giuseppe Lo Russo, Luca Porcu, Selina K Wong, Christine M. Bestvina, Matthew Hellman, Isabelle Monnet, Jacobo Rogado Revuelta, Giulia Pasello, Natasha B. Leighl, Alice Baggi, Amel Boudjemaa, Hira Rizvi, Carlos Gomez-Martin, Juan B Blaquier, Oscar Arrieta, Avinash Aujayeb, Ullas Batra, Ahmed Y. Azzam, Jair Bar, Mojca Unk, Mohammed Atef Azab, Ardak Nazilovna Zhumagaliyeva, Gonzalo Recondo, Erica Geraedts, Giannis Mountzios, Niels Reinmuth, Linda Coate, Melina Marmarelis, Carolyn J. Presley, Fred Hirsch, Pilar Garrido, Hina Khan, Celine Mascaux, Balazs Halmos, Giovanni L Ceresoli, May J Fidler, Vieri Scotti, Anne-Cécile Métivier, Lionel Falchero, Enriqueta Felip, Carlo Genova, Julien Mazieres, Elisa Roca, Umit Tapan, Julie Brahmer, Ullas Batra, Emilio Bria, Sonam Puri, Sanjay Popat, Karen L Reckamp, Floriana Morgillo, Ernst Nadal, Francesca Mazzoni, Francesco Agustoni, Jair Bar, Federica Grosso, Virginie Avrillon, Jyoti D Patel, Fabio Gomes, Ehab Ibrahim, Annalisa Trama, Fabrice Barlesi, Anne-Marie Dingemans, Heather Wakelee, Solange Peters, Leora Horn, Marina Chiara Garassino, Valter Torri:** Data curation.

**Alessio Cortellini, Javier Baena, Marina Chiara Garassino:** Writing - original draft.

**Jennifer G. Whisenant, Javier Baena, Alessio Cortellini, Li-Ching Huang, Giuseppe Lo Russo, Luca Porcu, Selina K Wong, Christine M. Bestvina, Matthew Hellman, Isabelle Monnet, Jacobo Rogado Revuelta, Giulia Pasello, Natasha B. Leighl, Alice Baggi, Amel Boudjemaa, Hira Rizvi, Carlos Gomez-Martin, Juan B Blaquier, Oscar Arrieta, Avinash Aujayeb, Ullas Batra, Ahmed Y. Azzam, Jair Bar, Mojca Unk, Mohammed Atef Azab, Ardak Nazilovna Zhumagaliyeva, Gonzalo Recondo, Erica Geraedts, Giannis Mountzios, Niels Reinmuth, Linda Coate, Melina Marmarelis, Carolyn J. Presley, Fred Hirsch, Pilar Garrido, Hina Khan, Celine Mascaux, Balazs Halmos, Giovanni L Ceresoli, May J Fidler, Vieri Scotti, Anne-Cécile Métivier, Lionel Falchero, Enriqueta Felip, Carlo Genova, Julien Mazieres, Elisa Roca, Umit Tapan, Julie Brahmer, Ullas Batra, Emilio Bria, Sonam Puri, Sanjay Popat, Karen L Reckamp, Floriana Morgillo, Ernst Nadal, Francesca Mazzoni, Francesco Agustoni, Jair Bar, Federica Grosso, Virginie Avrillon, Jyoti D Patel, Fabio Gomes, Ehab Ibrahim, Annalisa Trama, Fabrice Barlesi, Anne-Marie Dingemans, Heather Wakelee, Solange Peters, Leora Horn, Marina Chiara Garassino, Valter Torri:** Writing - review & editing.

**Jennifer G. Whisenant, Valter Torri, Marina Chiara Garassino, Leora Horn:** Visualization.

**Marina Chiara Garassino, Leora Horn, Jennifer G. Whisenant:** Supervision.

**Jennifer G. Whisenant, Li-Ching Huang**: Project administration.

**Jennifer G. Whisenant, Marina Chiara Garassino, Leora Horn:** Funding acquisition.

**Jennifer G. Whisenant, Javier Baena, Alessio Cortellini, Li-Ching Huang, Giuseppe Lo Russo, Luca Porcu, Selina K. Wong, Christine M. Bestvina, Matthew D. Hellmann, Elisa Roca, Hira Rizvi, Isabelle Monnet, XX,[i] Amel Boudjemaa, Jacobo Rogado, Giulia Pasello, Natasha B. Leighl, Oscar Arrieta, Avinash Aujayeb, Ullas Batra, Ahmed Y. Azzam, Mojca Unk, Mohammed A. Azab, Ardak N, Zhumagaliyeva, Carlos Gomez-Martin, Juan B. Blaquier, Erica Geraedts, Giannis Mountzios, Gloria Serrano-Montero, Niels Reinmuth, Linda Coate, Melina Marmarelis, Carolyn J. Presley, Fred R. Hirsch, Pilar Garrido, Hina Khan, Alice Baggi, Celine Mascaux, Balazs Halmos, Giovanni L. Ceresoli, Mary J. Fidler, Vieri Scotti, Anne-Cécile Métivier, Lionel Falchero, Enriqueta Felip, Carlo Genova, Julien Mazieres, Umit Tapan, Julie Brahmer, Emilio Bria, Sonam Puri, Sanjay Popat, Karen L. Reckamp, Floriana Morgillo, Ernest Nadal, Francesca Mazzoni, Francesco Agustoni, Jair Bar, Federica Grosso, Virginie Avrillon, Jyoti D. Patel, Fabio Gomes, Ehab Ibrahim, Annalisa Trama, Anna C. Bettini, Fabrice Barlesi, Anne-Marie Dingemans, Heather Wakelee, Solange Peters, Leora Horn, Marina Chiara Garassino, Valter Torri:** All authors read and approved the submitted version of the manuscript (and any substantially modified version that involves the author's contribution to the study). Each author have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

## Acknowledgments

This study was awarded a grant from the Lung Ambition that supported database development and maintenance.

## Ethics Approval and Consent to Participate

Local Institutional Review Board approval was required for each center before receiving instructions on how to access the database and enter data. Written informed consent was obtained if required by the Institutional Review Board. All study procedures were in accordance with the precepts of Good Clinical Practice and the Declaration of Helsinki. According to the regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, the following requirements regarding personal data were guaranteed: pseudonymization and encryption, confidentiality, integrity, availability, resilience of treatment systems and services, and the ability to restore the availability and access of data in the event of a physical or technical accident.

## Availability of Data and Material

The data sets generated during and analyzed during the current study are not publicly available owing to privacy and ethical restrictions but are available from the corresponding author and the study steering committee on reasonable request, under a relevant data-sharing agreement with the coordinating center.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.12.015.

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