Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

ORIGINAL ARTICLE

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

Jennifer G. Whisenant, PhD,[a] Javier Baena, MD,[b] Alessio Cortellini, MD,[c,*] Li-Ching Huang, PhD,[a] Giuseppe Lo Russo, MD, PhD,[d] Luca Porcu, PhD,[e] Selina K. Wong, MD,[a] Christine M. Bestvina, MD,[f] Matthew D. Hellmann, MD,[g] Elisa Roca, MD, PhD,[h] Hira Rizvi, MD,[g] Isabelle Monnet, MD,[i] Amel Boudjemaa, MD,[i] Jacobo Rogado, MD,[j] Giulia Pasello, MD, PhD,[k,l] Natasha B. Leighl, MD,[m] Oscar Arrieta, MD,[n] Avinash Aujayeb, MBBS,[o] Ullas Batra, MD,[p] Ahmed Y. Azzam, MD,[q] Mojca Unk, MD, MSc,[r] Mohammed A. Azab, MD,[s] Ardak N. Zhumagaliyeva, MD, PhD,[t] Carlos Gomez-Martin, MD,[b] Juan B. Blaquier, MD,[u] Erica Geraedts, MD,[v] Giannis Mountzios, MD, PhD,[w] Gloria Serrano-Montero, MD,[j] Niels Reinmuth, MD,[x] Linda Coate, MD,[y,z] Melina Marmarelis, MD,[aa] Carolyn J. Presley, MD, MHS,[bb] Fred R. Hirsch, MD,[cc] Pilar Garrido, MD, PhD,[dd] Hina Khan, MD,[ee] Alice Baggi, MD,[ff] Celine Mascaux, MD,[gg,hh] Balazs Halmos, MD,[ii] Giovanni L. Ceresoli, MD,[jj] Mary J. Fidler, MD,[kk] Vieri Scotti, MD,[ll] Anne-Cécile Métivier, MD,[mm] Lionel Falchero, MD,[nn] Enriqueta Felip, MD, PhD,[oo] Carlo Genova, MD, PhD,[pp,qq] Julien Mazieres, MD, PhD,[rr] Umit Tapan, MD,[ss] Julie Brahmer, MD,[tt] Emilio Bria, MD,[uu,vv] Sonam Puri, MD,[ww] Sanjay Popat, MD,[xx,yy] Karen L. Reckamp, MD,[zz] Floriana Morgillo, MD, PhD,[aaa] Ernest Nadal, MD, PhD,[bbb] Francesca Mazzoni, MD,[ccc] Francesco Agustoni, MD,[ddd] Jair Bar, MD,[eee] Federica Grosso, MD,[fff] Virginie Avrillon, MD,[ggg] Jyoti D. Patel, MD,[hhh] Fabio Gomes, MD,[iii] Ehab Ibrahim, MD,[jjj] Annalisa Trama, PhD,[kkk] Anna C. Bettini, MD,[lll] Fabrice Barlesi, MD, PhD,[mmm]

*Corresponding author.

Drs Whisenant and Baena contributed equally in this work.

Disclosure: Dr. Whisenant reports receiving support for this research from IASLC/Lung Ambition Alliance and personal royalties/licenses from Anasys Instruments. Dr. Baena reports receiving personal fees from AstraZeneca, Bristol-Myers Squibb, and Roche and nonfinancial support from Angelini. Dr. Cortellini reports receiving speaker fees/grant consultancies from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Eisai, and Novartis. Dr. Lo Russo reports receiving personal fees from AstraZeneca, Italfarmaco, Lilly, Novartis, Pfizer, and Roche; support for attending meetings/travel from Bristol-Myers Squibb, Italfarmaco, Merck Sharp & Dohme, and Roche; and participation as a DSMB or advisory board member for AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Sanofi. Dr. Porcu reports receiving personal fees from Ipsen and Italfarmaco. Dr. Bestvina declares receiving personal consulting fees from AstraZeneca, Bristol-Myers Squibb, CVS, Genentech, Jazz, Johnson & Johnson, Novartis, Pfizer, Regeneron/Sanofi, Seattle Genetics, and Takeda; speakers bureau for Merck; and institutional contracted research from AstraZeneca and Bristol-Myers Squibb. Dr. Monnet declares receiving travel support from Pfizer, Takeda, and Behringer Ingelheim. Dr. Rogado reports receiving personal fees from Roche, AstraZeneca, Merck, Ferrer, Persan Farma, and Fresenius Kabi; travel expenses from Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, and AstraZeneca; and advisor consultancies from Fresenius Kabi. Dr. Arrieta reports receiving institutional grants and contracts from AstraZeneca, Merck, and Roche and personal payments from AstraZeneca, Boehringer Ingelheim, Lilly, Pfizer, and Roche. Dr. Unk reports receiving personal consulting fees and participation in a data safety monitoring board or advisory board from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda. Dr. Zhumagaliyeva reports receiving support for the work of this manuscript from the Center for Nuclear Medicine and Oncology of Semey, Semy, Kazakhstan. Dr. Blaquier reports receiving payment for an educational event and travel support from Amgen. Dr. Mountzios reports receiving grants or contracts from AstraZeneca, Bristol-Myers Squibb, Amgen, Gilead Pharmaceuticals, GlaxoSmithKline, Immunomedics, Merck, Merck Sharp & Dohme, Novartis, Roche, and Sanofi; consulting fees from Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda; and support for meetings/travel from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Roche, Sanofi, and Takeda. Dr. Marmarelis reports receiving consulting/honoraria from Boehringer Ingelheim, Novocure, AstraZeneca, Janssen, Takeda, Blueprint Pharmaceuticals, Bristol-Myers Squibb, and Ikena; research support from Eli Lilly, Trizell, Merck, and AstraZeneca; stock from Gilead, Merck, Portola Pharmaceuticals, Bluebird Biosciences, Novartis, Janssen, and Pfizer; and medical writing support for Novartis. Dr. Hirsch reports receiving personal consulting fees from Bristol-Myers Squibb, AstraZeneca/Daiichi, Sanofi/Regeneron, Novartis, Merck, Amgen, and OncoCyte. Dr. Garrido declared having

Anne-Marie Dingemans, MD, PhD,[nnn] Heather Wakelee, MD,[ooo] Solange Peters, MD, PhD,[ppp] Leora Horn, MD,[a] Marina Chiara Garassino, MD,[f] Valter Torri, MD,[e] On behalf of the TERAVOLT study group[¥]

[a]Vanderbilt University Medical Center, Nashville, Tennessee
[b]Hospital Universitario 12 de Octubre, Madrid, Spain
[c]Department of Surgery and Cancer, Imperial College London, London, United Kingdom
[d]Thoracic Oncology Unit, Medical Oncology Department, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale dei Tumori, Milan, Italy
[e]Oncology Department, Istituto di Ricerche Farmacologiche Mario Negri Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Milan, Italy
[f]Department of Medicine, University of Chicago Comprehensive Cancer Center, University of Chicago, Chicago, Illinois
[g]Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York
[h]Thoracic Oncology—Lung Unit, Ospedale Pederzoli, Peschiera d/G, Verona, Italy
[i]Service de Pneumologie, Centre Hospitalier Intercommunal de Créteil, Créteil, France
[j]Seccion de Oncologia Medica, Hospital Universitario Infanta Leonor, Madrid, Spain
[k]Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy
[l]Medical Oncology 2, Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy
[m]Division of Medical Oncology/Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
[n]Thoracic Oncology Unit, Instituto Nacional de Cancerología (INCan), México City, México
[o]Respiratory Department, Northumbria Healthcare NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom
[p]Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Center, New Delhi, India
[q]Faculty of Medicine, October 6 University, Giza, Egypt
[r]Department of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[s]KasrAlAiny School of Medicine, Cairo University, El Cairo, Egypt
[t]Semey Medical University, Center for Nuclear Medicine and Oncology of Semey, Semey, Kazakhstan

advisory roles or receiving speakers fees from AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Lilly, Merck Sharp & Dohme, Medscape, Novartis, Pfizer, Roche, Takeda, and TouchIme; support for travel/meetings from AstraZeneca, Bristol-Myers Squibb, and Roche. Dr. Khan reports receiving study funding from the Bristol-Myers Squibb Foundation for Diversity in Clinical Trials and participated to advisory boards for Sanofi Genzyme. Dr. Mascaux reports receiving personal consulting fees from Amgen, AstraZeneca, Bristol-Myers Squibb, Kephren, Merck Sharp & Dohme, Pfizer, Roche, Sanofi, and Takeda; receiving support for travel from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, and Roche; and having European Patent Application EP19305434.3. Dr. Ceresoli declared having consulting/advisory role for Novocure and speaker's bureau from Novocure, Zai Laboratory, Merck Sharp & Dohme Oncology, AstraZeneca, and Bristol-Myers Squibb/Medarex. Dr. Fidler reports receiving consulting fees from Silverback, G1 Therapeutics AstraZeneca, Rakuten, Beigene, and Daiichi; speakers bureau from Beigene and Jazz; and research support from Biodesix, Pfizer/EMD Serono, AstraZeneca, Jounce, CytomX Therapeutics, Merck, Novartis, Rakuten, and Alkermes. Dr. Métivier reports receiving personal payment for expert testimony from Merck Sharp & Dohme, Novartis, and Takeda. Dr. Felip reports receiving research funding to the institution from Grant for Oncology Innovation, Merck Healthcare KGAa, and Fundacion Merck Salud; personal consulting fees from Amgen, AstraZeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, F. Hoffmann-LaRoche, GlaxoSmithKline, Janssen, Medical Trends, Merck Sharp & Dohme, Merck Serono, Peptomyc, Pfizer, Puma Biotechnology, Regeneron, Sanofi, and Takeda; serving in data safety and monitoring for Syneos Health; serving in the speakers bureau and participating in manuscript writing or educational events for Amgen, AstraZeneca, Bristol-Myers Squibb, Lilly, F. Hoffmann-La Roche, Janssen, Medscape, Merck Sharp & Dohme, Merck Serono, Peervoice, Pfizer, Springer, and Touch Medical; and serving as member of the board for Grifols. Dr. Genova reports receiving personal honoraria for presentations from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Roche, and Takeda. Dr. Julien Mazieres reports receiving personal fees from Merck, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Daiichi, and Pfizer and grants from Roche, AstraZeneca, Pierre Fabre. Dr. Bria reports receiving speakers' and travels' fees from Merck Sharp & Dohme, AstraZeneca, Pfizer, Eli Lilly, Bristol-Myers Squibb, Novartis, and Roche and institutional research grants from AstraZeneca and Roche. Dr. Puri reports receiving advising/consulting fees from AstraZeneca and G1 Therapeutics. Dr. Tapan declares receiving advisory fees from Sanofi and educational grant from Pfizer. Dr. Reckamp reports receiving personal consulting fees from Amgen, Calithera, AstraZeneca, Blueprint, Boehringer Ingelheim, Daiichi Sankyo, EMD Serono, Genentech, GlaxoSmithKline, Janssen, Lilly, Merck KGA, Mirati, Takeda, and Tesaro; nonfinancial support from Seattle Genetics; and research support to institution from Calithera, Blueprint, Daiichi Sankyo, Genentech, Elevation Oncology, and Janssen. Dr. Nadal reports receiving research support from Bristol-Myers Squibb, Merck Serono, Pfizer, and Roche; personal consulting fees or honoraria from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Serono, Pfizer, Lilly, Amgen, Boehringer Ingelheim, AstraZeneca, Takeda, Sanofi, and Bayer; and participation in data safety monitoring board for Apollomics. Dr. Mazzoni reports receiving personal fees for participation in an advisory board from Lilly, Roche, and Takeda. Dr. Grosso reports receiving personal fees for advisory role, speaker engagements, and travel and accommodation expenses from Merck Sharp & Dohme, Novocure, Bristol Meyer Squibb, Boehringer Ingelheim, Pharmamar, and Novartis. Dr. Grosso reports receiving personal fees and travel support from Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Novocure, and Pharmamar; speakers bureau for Novocure; and honoraria for educational events from Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, and Novartis. Dr. Gomes reports receiving personal payments for educational events from AstraZeneca, Merck, and Roche. Dr. Dingemans reports receiving research support from Amgen; consulting fees from Roche, Boehringer Ingelheim, AstraZeneca, Pharmamar, Bayer, Sanofi, and Amgen; payment for lectures or presentations from Eli Lily, AstraZeneca, Chiesi, Pfizer, Takeda, and Jansen; and participation in data safety monitoring board for Roche and Takeda. Dr. Wakelee reports receiving research funding to the institution from ACEA Biosciences, Arrys Therapeutics, AstraZeneca/Medimmune, Bristol-Myers Squibb, Clovis Oncology, Genentech/Roche, Merck, Novartis, Seattle Genetics, Xcovery, Eli Lilly, Pfizer, and Helsinn; compensated advisory board from AstraZeneca, Xcovery, Jannsen, Daiichi Sankyo, Blueprint, Mirati, and Helsinn; and uncompensated advisory board for Merck, Takeda, Genentech/Roche, and Cellworks. Dr. Peters reports serving as consultant/advisory board member for AbbVie, Amgen, AstraZeneca, Bayer, Beigene, Biocartis, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, ecancer, Eli Lilly, Elsevier, Foundation Medicine, Illumina, Imedex, IQVIA, Incyte, Janssen, Medscape, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, OncologyEducation, Pharma Mar, Phosplatin Therapeutics, PER, Pfizer, PRIME, Regeneron, RMEI, Roche/Genentech, RTP, Sanofi, Seattle Genetics, and Takeda; receiving speaker fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, ecancer, Eli Lilly, Illumina, Imedex, Medscape, Merck Sharp and Dohme, Novartis, PER, Pfizer, Prime, Roche/Genentech, RTP, Sanofi, and Takeda; and receiving grants/research supports from (sub) investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, AstraZeneca, Biodesix, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, GlaxoSmithKline, Illumina, Lilly, Merck Sharp and Dohme, Merck Serono, Mirati, Novartis, Pfizer, Phosplatin Therapeutics, and Roche/Genentech (all to institution). Dr. Chiara Garassino reports receiving grants and research support to the

[u]Thoracic Oncology Section, Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina
[v]Groene Hart Ziekenhuis, Gouda, The Netherlands
[w]Fourth Department of Medical Oncology and Clinical Trials Unit, Henry Dunant Hospital Center, Athens, Greece
[x]Asklepios Kliniken GmbH, Asklepios Fachkliniken Muenchen, Gauting, Germany
[y]Cancer Trials Ireland, Dublin, Ireland
[z]Mid-Western Cancer Centre, University Hospital Limerick, Limerick, Ireland
[aa]Division of Hematology and Oncology, Department of Internal Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[bb]The Ohio State University Comprehensive Cancer Center, Columbus, Ohio
[cc]Center for Thoracic Oncology, Tisch Cancer Institute and Icahn School of Medicine Mount Sinai, New York, New York
[dd]IRYCIS, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain
[ee]The Warren Alpert Medical School of Brown University, Providence, Rhode Island
[ff]Medical Oncology Unit, Department of Medical-Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia at ASST-Spedali Civili, Brescia, Italy
[gg]Service De Pneumologie, Hôpitaux Universitaires De Strasbourg, Strasbourg, France
[hh]Université De Strasbourg, Inserm UMR_S 1113, IRFAC, Laboratory Streinth (Stress REsponse and INnovative THerapy against Cancer), ITI InnoVec, Strasbourg, France
[ii]Division of Oncology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York
[jj]Department of Medical Oncology, Cliniche Humanitas Gavazzeni, Bergamo, Italy
[kk]Department of Hematology, Oncology, and Cell Therapy, Rush University Medical Center, Chicago, Illinois
[ll]Department of Oncology, Radiation Therapy Unit, Careggi University Hospital, Florence, Italy
[mm]Department of Pneumology, Hôpital Foch, Suresnes, France
[nn]Service de Pneumologie et Cancérologie Thoracique, L'Hôpital Nord-Ouest, Villefranche S/S, France
[oo]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
[pp]UO Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[qq]Dipartimento di Medicina Interna e Specialità Mediche (DIMI), Università degli Studi di Genova, Genoa, Italy
[rr]Toulouse University Hospital, Institut Universitaire du Cancer, Université Paul Sabatier, Toulouse, France
[ss]Section of Hematology and Medical Oncology, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts
[tt]Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland
[uu]Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[vv]Medical Oncology, Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy
[ww]Division of Medical Oncology, The Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah
[xx]Lung Unit, Royal Marsden National Health Service Foundation Trust, London, United Kingdom
[yy]The Institute of Cancer Research, London, United Kingdom
[zz]Division of Medical Oncology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California
[aaa]Department of Precision Medicine, Medical Oncology and Haematology, Università degli studi della Campania L. Vanvitelli, Naples, Italy
[bbb]Thoracic Oncology Unit, Department of Medical Oncology, Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain
[ccc]Medical Oncology, Careggi University Hospital, Florence, Italy
[ddd]Medical Oncology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy
[eee]Institute of Oncology, Sheba Medical Center, Tel HaShomer, Ramat Gan, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[fff]Mesothelioma and Rare Cancer Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
[ggg]Department of Medical Oncology, Centre Léon Bérard, Lyon, France
[hhh]Division of Hematology and Oncology, Northwestern University, Chicago, Illinois
[iii]Medical Oncology Department, The Christie NHS Foundation Trust, Manchester, United Kingdom
[jjj]The Clatterbridge Cancer Center NHS Foundation Trust, Birkenhead, United Kingdom
[kkk]Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy
[lll]Medical Oncology Department, ASST Papa Giovanni XXIII, Bergamo, Italy
[mmm]Gustave Roussy Institute, Villejuif, Aix Marseille University, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France
[nnn]Erasmus University Medical Center, Rotterdam, University Maastricht, Maastricht, The Netherlands
[ooo]Stanford Cancer Institute, Stanford University, Stanford, California

institution from Eli Lilly, Merck Sharp & Dohme, Pfizer (MISP), AstraZeneca, Merck Sharp & Dohme International GmbH, Bristol-Myers Squibb, Boehringer Ingelheim Italia S.p.A., Celgene, Eli Lilly, Ignyta, Incyte, MedImmune, Novartis, Pfizer, Roche, Takeda, Tiziana, Foundation Medicine, GlaxoSmithKline, Spectrum Pharmaceuticals; personal consulting fees from AstraZeneca, Merck Sharp & Dohme International GmbH, Bristol-Myers Squibb, Boehringer Ingelheim Italia S.p.A., Celgene, Eli Lilly, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda, Seattle Genetics, Mirati, Daiichi Sankyo, Regeneron, and Merck; speaker fees from AstraZeneca, Merck Sharp and Dohme, and Takeda; and travel and accommodation expenses from Roche. All the declared conflict of interests are outside the submitted work. The authors declare no conflict of interest.

Address for correspondence: Alessio Cortellini, MD, Department of Surgery and Cancer, Imperial College London, Hammersmith Campus, Du Cane Road, W12 0HS London, United Kingdom. E-mail: a.cortellini@imperial.ac.uk

[¥]A complete list of investigators in the TERAVOLT registry that provided data for this analysis is provided in the Supplementary Appendix. With endorsement of the European Society of Medical Oncology, International Association for the Study of Lung Cancer, European Respiratory Society, and the European Thoracic Oncology Platform.

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2021.12.015

[ppp]Lausanne University Hospital, Lausanne University, Lausanne, Switzerland

Received 30 October 2021; revised 16 December 2021; accepted 31 December 2021
Available online - 1 February 2022

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

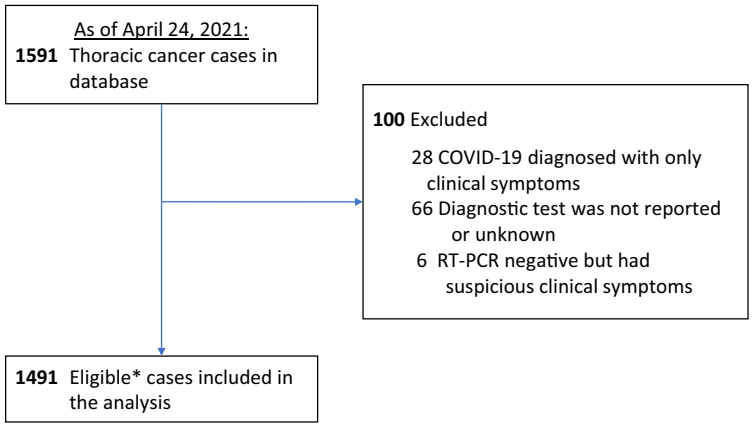

Figure 1. Consort flow diagram for the included population. COVID-19, coronavirus disease 2019; RT-PCR, reverse-transcriptase polymerase chain reaction.

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.

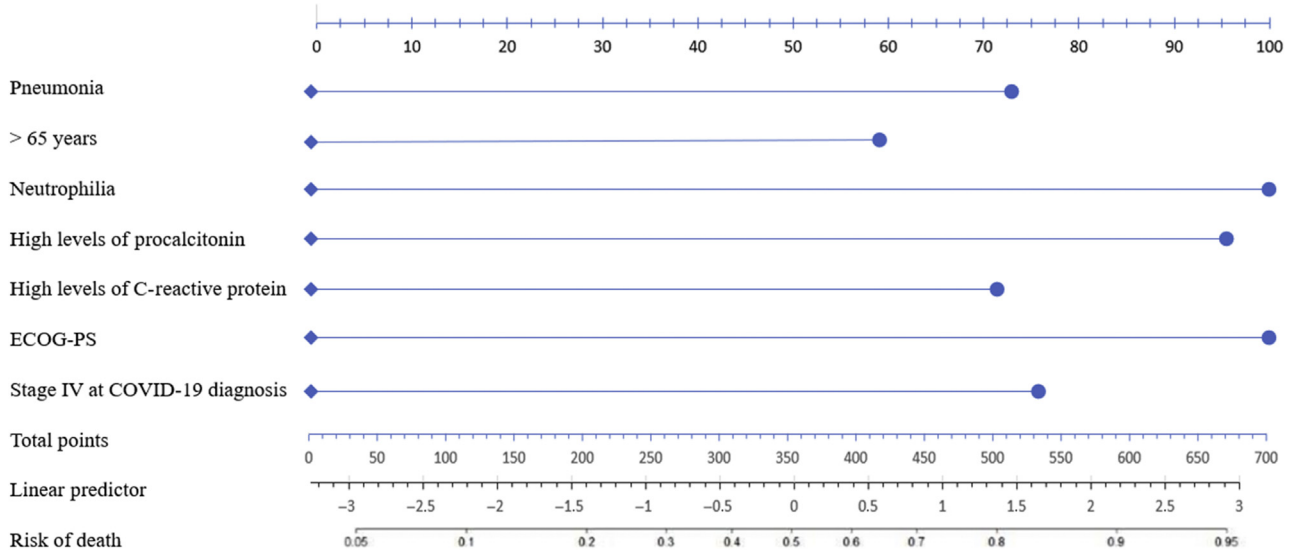

Figure 2. Prognostic nomogram including the following major determinants of mortality: occurrence of pneumonia (yes versus no), age (≤65 versus >65 y old), neutrophil count (> versus ≤ ULN), procalcitonin (> versus ≤ ULN), C-reactive protein (> versus ≤ ULN), ECOG-PS (≥2 versus 0-1), and disease stage 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.

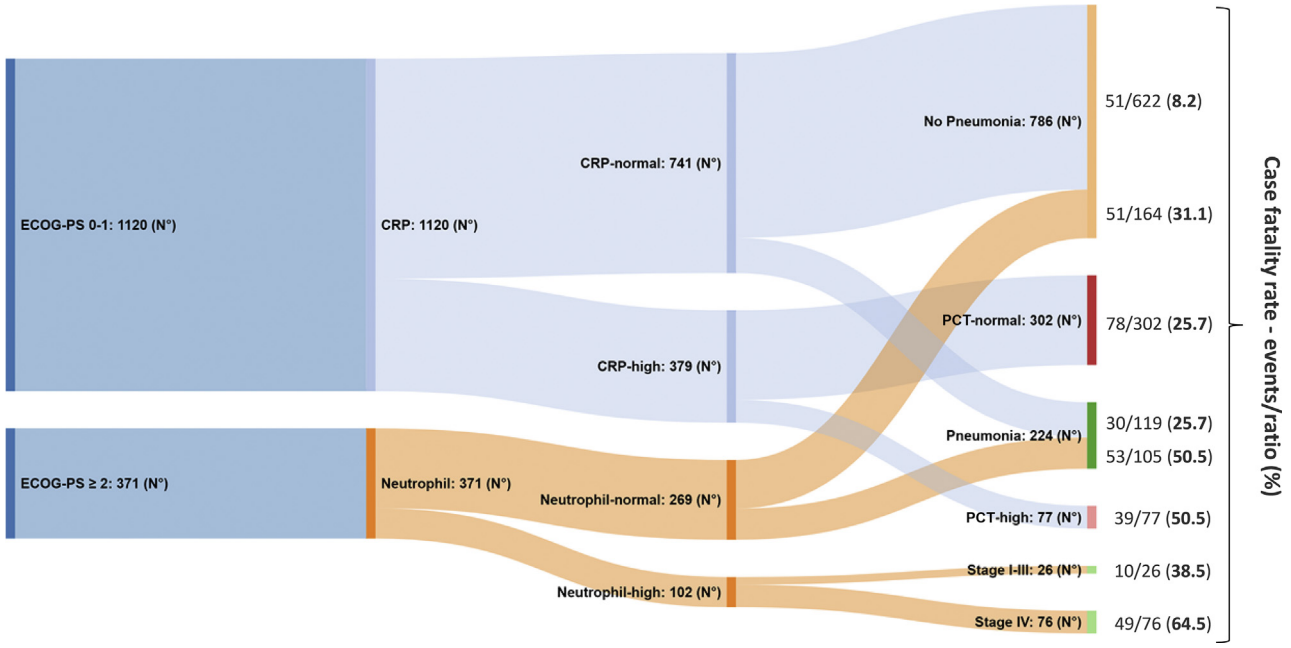

Figure 3. Sankey diagram offering a visual expression of the CART analysis with the hierarchical classification of variables. The first node was split on the basis of ECOG-PS (0-1: 1120 patients versus ≥2: 371 patients). Among the patients with an ECOG-PS of 0 to 1, the second split was defined by serum 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-1β, and tumor necrosis factor-α, whereas viral infections tend to prevent PCT production through the interferon-γ–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.

References

1. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21:335–337.
2. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069. https://doi.org/10.1001/jama.2020.1585.
3. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol*. 2020;21:e181.
4. Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. *Lancet Oncol*. 2020;21:e180.
5. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. 2020;31:894–901.
6. Lee LY, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020;395:1919–1926.
7. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. *Lancet Oncol*. 2020;21:1309–1316.
8. Whisenant JG, Trama A, Torri V, et al. TERAVOLT: thoracic cancers international COVID-19 collaboration. *Cancer Cell*. 2020;37:742–745.
9. Trama A, Proto C, Whisenant JG, et al. Supporting clinical decision-making during the SARS-CoV-2 pandemic through a global research commitment: the TERAVOLT experience. *Cancer Cell*. 2020;38:602–604.
10. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a

metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
11. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67:93–99.
12. Luo J, Rizvi H, Egger JV, Preeshagul IR, Wolchok JD, Hellmann MD. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. *Cancer Discov*. 2020;10:1121–1128.
13. Lee AJX, Purshouse K. COVID-19 and cancer registries: learning from the first peak of the SARS-CoV-2 pandemic. *Br J Cancer*. 2021;124:1777–1784.
14. Cortellini A, Dingemans AC, Arrieta O, et al. Thoracic cancers international COVID-19 collaboration (TERAVOLT): small-cell lung cancer and other rare thoracic malignancies. *Clin Cancer Res*. 2020;26(suppl 18). S12-03.
15. Garassino MC, Whisenant JG, Huang LC, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol*. 2020;21:914–922.
16. Pinato DJ, Zambelli A, Aguilar-Company J, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. *Cancer Discov*. 2020;10:1465–1474.
17. Luo J, Rizvi H, Preeshagul IR, et al. COVID-19 in patients with lung cancer. *Ann Oncol*. 2020;31:1386–1396.
18. Pinato DJ, Scotti L, Gennari A, et al. Determinants of enhanced vulnerability to coronavirus disease 2019 in UK patients with cancer: a European study. *Eur J Cancer*. 2021;150:190–202.
19. OnCovid Study Group, Pinato DJ, Patel M, et al. Time-dependent covid-19 mortality in patients with cancer: an updated analysis of the oncovid registry. *JAMA Oncol*. 2022;8:114–122.
20. Black MH, Watanabe RM. A principal components-based clustering method to identify variants associated with complex traits. *Hum Hered*. 2011;71:50–58.
21. Frank E. Harrell Jr. rms: Regression Modeling Strategies. R Package Version 6.2-0. https://CRAN.R-project.org/package=rms. Accessed July 10, 2021
22. Friedman JH, Olshen RA, Stone CJ. Classification and regression trees, by Leo Breiman, Jerome H. Friedman, Richard A. Olshen, and Charles J. Stone. Brooks/Cole Publishing, Monterey, 1984,358 pages, $27.95. https://onlinelibrary.wiley.com/doi/abs/10.1002/cyto.990080516. Accessed September 18, 2021
23. Therneau T, Atkinson B. Rpart: Recursive Partitioning and Regression Trees. R package version 4.1-15. https://CRAN.R-project.org/package=rpar. Accessed July 10, 2021
24. R: a language and environment for statistical computing. R package. https://www.gbif.org/tool/81287/r-a-language-and-environment-for-statistical-computing. Accessed September 18, 2021.
25. Elkaddoum R, Haddad FG, Eid R, Kourie HR. Telemedicine for cancer patients during COVID-19 pandemic: between threats and opportunities. *Future Oncol*. 2020;16:1225–1227.
26. Passaro A, Bestvina C, Velez Velez M, Garassino MC, Garon E, Peters S. Severity of COVID-19 in patients with lung cancer: evidence and challenges. *J Immunother Cancer*. 2021;9:e002266.
27. Provencio M, Mazarico Gallego JM, Calles A, et al. Lung cancer patients with COVID-19 in Spain: GRAVID study. *Lung Cancer*. 2021;157:109–115.
28. Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. *Lancet Oncol*. 2020;21:893-903.
29. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395:1907–1918.
30. Ospina AV, Bruges R, Mantilla W, et al. Impact of COVID-19 infection on patients with cancer: experience in a Latin American country: the ACHOCC-19 study. *Oncologist*. 2021;26:e1761–e1773.
31. Henry B, Cheruiyot I, Vikse J, et al. Lymphopenia and neutrophilia at admission predicts severity and mortality in patients with COVID-19: a meta-analysis. *Acta Biomed*. 2020;91:e2020008.
32. Fathi N, Rezaei N. Lymphopenia in COVID-19: therapeutic opportunities. *Cell Biol Int*. 2020;44:1792–1797.
33. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2017;10:CD007498.
34. Harrison M, Collins CD. Is procalcitonin-guided antimicrobial use cost-effective in adult patients with suspected bacterial infection and sepsis? *Infect Control Hosp Epidemiol*. 2015;36:265–272.
35. Ahmed S, Jafri L, Hoodbhoy Z, Siddiqui I. Prognostic value of serum procalcitonin in COVID-19 patients: a systematic review. *Indian J Crit Care Med*. 2021;25:77-84.
36. Han J, Gatheral T, Williams C. Procalcitonin for patient stratification and identification of bacterial co-infection in COVID-19. *Clin Med (Lond)*. 2020;20:e47.
37. Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. *BMC Med*. 2011;9:107.
38. Bell LCK, Meydan C, Kim J, et al. Transcriptional response modules characterize IL-1β and IL-6 activity in COVID-19. *iScience*. 2021;24:101896.
39. RECOVERY Collaborative Group, Horby P, Mafham M, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;383:2030–2040.
40. Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol*. 2020;2:e603-e612.
41. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324:1307–1316.

42. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382:1787–1799.
43. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med*. 2020;383:1813–1826.
44. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet*. 2020;395:1973–1987.
45. Hasell J, Mathieu E, Beltekian D, et al. A cross-country database of COVID-19 testing. *Sci Data*. 2020;7:345.
46. McCabe R, Schmit N, Christen P, et al. Adapting hospital capacity to meet changing demands during the COVID-19 pandemic. *BMC Med*. 2020;18:329.
47. Pimpinelli F, Marchesi F, Piaggio G, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. *J Hematol Oncol*. 2021;14:81.
48. Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol*. 2021;22:765–778.
49. Grivas P, Khaki AR, Wise-Draper TM, et al. Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. *Ann Oncol*. 2021;32:787–800.
50. Villarreal-Garza C, Vaca-Cartagena BF, Becerril-Gaitan A, et al. Attitudes and factors associated with COVID-19 vaccine hesitancy among patients with breast cancer. *JAMA Oncol*. 2021;7:1242–1244.
51. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol*. 2021;19:409–424.
52. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science*. 2020;368:860–868.
53. Barrière J, Gal J, Hoch B, et al. Acceptance of SARS-CoV-2 vaccination among French patients with cancer: a cross-sectional survey. *Ann Oncol*. 2021;32:673–674.