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A definitive prognostication system for patients with thoracic malignancies diagnosed with COVID-19: an update from the TERAVOLT registry.

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On behalf of the TERAVOLT study group ¥

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¥ A complete list of investigators in the TERAVOLT registry that provided data for this analysis is provided in the Supplementary appendix.
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ABSTRACT

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

Methods: Capitalizing data from the 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, clinical COVID-19 and cancer characteristics.

Results: As of April 15, 2021, 1491 consecutive evaluable 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 approximately 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 then identified seven major determinants of death 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 (CRP) (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 ROC analysis for death of the selected model confirmed its diagnostic ability (AUC 0.78; 95%CI: 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 CRP as the major determinants of prognosis.

Conclusion: From 73 variables analyzed, seven major determinants of death have been identified. Poor ECOG-PS demonstrated 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, mortality, 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 healthcare that will be felt for decades to come. The rapid global spread of this unpredictable virus led the World Health Organization to declare a pandemic in March 2020, with over 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 prone to develop severe forms of COVID-19, and experience detrimental outcomes as compared to 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, clinical and laboratory findings at COVID-19 diagnosis, as well as COVID-19-related complication and COVID-19 specific therapies associated with mortality in patients with cancer[9,10,12-16]. Professional societies began to release guidelines for treatment and surveillance, while the healthcare environment restructured to accommodate telemedicine and remote visits to minimize patient contact with an infected healthcare system[6].

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 shown to experience higher morbidity and mortality from SARS-CoV-2 infection, with case fatality rates ranging from 22% to 41%[7–11]. In addition to reporting on outcomes associated with morbidity and mortality, TERAVOLT aims to determine the risk factors associated with poor outcomes, as well as provide practitioners with real-time data on therapies that may impact survival to COVID-19 and evaluate long-term impacts on care and the delay in care to patients with both curable and incurable thoracic malignancies[8,12,13]. 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.

METHODS

Study procedures

The database was designed to collect cross-sectional data, including patient and disease characteristics both for cancer and for COVID-19 along with treatments received and complications, as well as longitudinal cohort data that is 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 (non-small cell lung cancer [NSCLC], small cell lung cancer, 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 RT-PCR/serology) infection; or suspected SARS-CoV-2 infection based on radiological findings consistent with COVID-19 pneumonia and clinical symptoms (i.e., fever >37.5°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 based on institutional policies or known exposure to a confirmed-positive individual. Patients of any age, gender, tumor histology, or stage of disease were eligible, including those receiving active anti-cancer 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 de-identified 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[14] 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 COVID-19 earlier than this date was allowed. The database is divided into 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, gender, race and ethnicity, smoking status,

stage of cancer at COVID-19 diagnosis (American Joint Committee on Cancer clinical stages[15]), type of thoracic malignancy, past and current (>3 months relative to COVID-19 diagnosis) oncological treatment, 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 based on available literature data, and are updated on the basis of emerging evidence of COVID-19 and its impact on the general population and cancer patients.

Aims and clinical endpoints

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[16,17]. 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 endpoint of interest. Considering the study design, which was not developed for reporting long-term outcomes, a dichotomized endpoint 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: 1) patient demographics (gender, age, body mass index [BMI], smoking status), 2) comorbidities (chronic obstructive pulmonary disease [COPD], 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 (pre-existent oxygen therapy, ACE inhibitors, angiotensin II receptor blockers, non-steroidal anti-inflammatory 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 three months of COVID-19 diagnosis, line of therapy, prior radiotherapy, prior oncological surgery), 5) full blood count information (hemoglobin, neutrophils, lymphocytes, eosinophils, platelets and

neutrophils to lymphocytes ratio, 6) general biochemistry and metabolic profile (triglycerides, glucose, creatinine, sodium, potassium, calcium, ferritin, albumin, creatine phosphokinase [CRP], alanine aminotransferase, aspartate transaminase, gamma-glutamyl transferase, lactate dehydrogenase, interleukin 6, c-reactive protein [CRP], bilirubin, procalcitonin, fibrinogen, D-dimer, troponin I, troponin T, prothrombin time), 7) respiratory parameters (SpO2, PaO2/FiO2 Ratio, CO2), 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 ±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 (IQR) for continuous variables. All variables have been dichotomized for the analysis and summary measures for association with the outcome were assessed by univariable binary logistic models. Results were reported through odds ratios (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 components-based clustering (OPCC) approach as a system of variables reduction. The OPCC approach was used to screen and identify specific subsets of variables showing association with mortality. The VARCLUS and SCORE procedures were used according to 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 AIC 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 were used to internally validate and calibrate the prediction model; bootstrap was performed with 1000 resamples.

A receiver operating characteristic (ROC) curve with the estimation of the area under the receiver operating curve (AUC) 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, in order to define a tree with a hierarchical classification of variables. The 'rpart' package in R was used to apply 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. However, since 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 the SAS software version 9.4 [Copyright © 2016 by SAS Institute Inc., Cary, NC, USA]. Predictive multivariable regression model were developed and internally validated using the R software version 4.1.0 (2021-05-18) -- R Core Team (2021)[24].

RESULTS

Patient characteristics

From March 2020 to April 2021, 1591 consecutive patients were entered into the database and evaluated for inclusion in the present analysis. Overall, 100 were excluded based on eligibility criteria (**Figure 1**) and 1491 eligible patients from 89 institutions across 19 countries were included in the analysis (**Supplementary Table 1**).

Laboratory confirmed SARS-CoV-2 infection (RT-PCR/serology/antigen) was reported for 1432 patients (96%), while 59 (6%) were diagnosed based on highly suspicious radiological/clinical findings. A summary of all demographic and clinical characteristics is included in **Table 1,** while a full detailed list of all cancer and COVID-19 related features according to the outcome is available in **Supplementary Table 2.** The majority of patients were male (57.3%), white (72.2%), and former/current smokers (77.8%); median age was 67 with 57.3% aged ≥ 65 years. As expected, most patients had at least one comorbidity (82.3%), including hypertension (48%), COPD (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 patients were on corticosteroids prior to COVID-19 diagnosis. Median BMI was 25 (range: 11-87). The most represented type of tumor was NSCLC (79.7%), followed by small cell lung cancer (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 0-1 (71.9%) and had

received antineoplastic treatments within three 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%), 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 (CFR) 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 cut-offs 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 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 showed 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 model using a fast backward step-down selection, with total residual AIC 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), procalcitonin (OR 2.37, 95%CI: 1.63-3.43), CRP (OR 1.89, 95%CI: 1.89-3.43), pneumonia (OR 1.95, 95%CI: 1.48-2.57). The ROC curve analysis for the computed multivariable model confirmed its good performance in estimating the outcome, with an AUC of 0.78 (95%CI: 0.75-0.80) (**Supplementary Figure 2**). On the basis of the estimated regression coefficients from the obtained final multivariable prognostic model, we developed a prognostic nomogram (**Figure 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 0-1, the second split was defined by serum CRP, while among patients with an ECOG-PS ≥2, by neutrophil count. Third generation splits were defined by tumor stage at COVID-19 diagnosis among patients with neutrophil count >ULN (upper limit of normal), by serum PCT among patients with CRP > ULN, and by radiological finding of pneumonia among patients with neutrophil count ≤ULN and with CRP ≤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 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.[26,27]

The final analysis included 1491 patients and reported an all-cause case fatality rate of 24.2%, which is similar to other published data[28,29]. 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, procalcitonin, c-reactive protein, and development of pneumonia. In addition, the OPCC procedure clearly demonstrated how among the wide range of factors commonly 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 prior to prescribing care.

To that purpose, we developed both the inference tree and the prognostic nomogram. The CART methodology firmly established an ECOG-PS ≥ 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 procalcitonin in patients with a good PS. The importance of ECOG-PS is pointed out in different cohort studies such as CCC19 and ACHOCC-19[30,31]. These additional few characteristics should be included in

the diagnostic algorithm of patients with thoracic neoplasia. Our data demonstrated 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[32]. It has been described that a systemic pro-inflammatory response driven by excess cytokines affects the lymphopoiesis alongside an aberrant compensatory granulopoiesis[33]. Although some publications support the effectiveness of PCT in patients with cancer[34–36], its considerable cost means 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[34], 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[37]. In fact, a high PCT is usually sustained by a rise in interleukin (IL)-6, IL-1β, and Tumor Necrosis Factor-α, while viral infections tend to prevent PCT production through the interferon-γ mediated signaling[38]. However, 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[39].

We acknowledge that a weakness in the current study is the timeframe 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[40–44]. In addition, both testing and hospital capacity have been enhanced[45–47] and initial specific safety and efficacy data of anti-SARS-CoV-2 vaccines in patients with cancer are emerging.[48,49] From this perspective, with the inclusion of more recently diagnosed patients, our own data demonstrated a decline in mortality from 33% to 24%[8]. This finding was expected and mirrors a general time-dependent improvement of clinical outcomes as reported elsewhere[19,50]. 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. Additionally, the data cut-off of April 2021 allows us to assume that a very small minority of patients would have received at least one dose of SARS-CoV-2 vaccine prior to 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. However, the mean follow-up of 42 days allows as to assume that the median observation period exceeds 60 days. In addition, we purposely focused this

analysis on a dichotomized endpoint to depict early and COVID-19 related mortality. We must also acknowledge as a study limitation the lack of some variables that are routinely assessed in oncological care of thoracic cancer patients, including genomic features (e.g., epidermal growth factor receptor 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 upon our previous findings, which established chemotherapy as the only systemic therapy affecting the outcome[8], and small cell lung cancer as the tumor type with the highest mortality[51].

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 impact 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[52–55]. Against this evolving scenario, a more tailored, comprehensive, and properly powered prognostication system like the one presented in this study will be a useful tool for clinicians as they develop oncology treatment plans for their patients.

Ethics approval and consent to participate

Local Institutional Review Board (IRB) 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 IRB. 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: pseudonymisation 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.

Authors' Contributions

All authors contributed to the publication according to the ICMJE guidelines for the authorship. 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 has 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.

The first, last and corresponding authors had full access to the data and final responsibility to submit for publication.

The CREDIT statement for authors' contributions is provided as supplementary material.

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Availability of Data and Material

The datasets generated during and/or analysed during the current study are not publicly available due 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.

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FIGURES' LEGEND

Figure 1: Consort Flow diagram for the included population.

Figure 2: Prognostic nomogram including major determinants of mortality: occurrence of pneumonia (yes vs no), age (≤ 65 vs > 65 years old), neutrophil count (> vs ≤ upper limit of normal - ULN), procalcitonin (> vs ≤ ULN), c-reactive protein (> vs ≤ ULN), ECOG-PS (≥ 2 vs 0-1), disease stage at COVID-19 (Stage IV vs Stage 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 ♦ shows the absence of it. The sum of the different determinants stablishes the risk of death.

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 vs ≥ 2: 371 patients). Among patients with an ECOG-PS 0-1, the second split was defined by serum CRP (normal: 741 patients vs high: 379 patients), while among patients with an ECOG-PS ≥2, by neutrophil count (normal: 269 patients vs high: 102 patients). Third generation splits were defined by tumor stage at COVID-19 diagnosis among patients with neutrophil count >ULN (upper limit of normal) (Stage I-III: 26 patients, with a CFR of 38.5%; vs STAGE IV 76 patients, with a CFR of 64.5%) , by serum PCT among patients with CRP > ULN (PTC normal: 302 patients, with a CFR of 25.7% vs PTC high: 77 patients, with a CFR of 50.5%) and by radiological finding of pneumonia among patients with CRP ≤ ULN and with neutrophil count ≤ ULN (pneumonia present: 224, with a CFR of 25.7% and 50.5%, respectively vs 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/). CRP: c-reactive protein; PTC: procalcitonin; CFR: case fatality rate. Patients with missing values were included as reference terms.

Table 1: Demographics and clinical characteristics

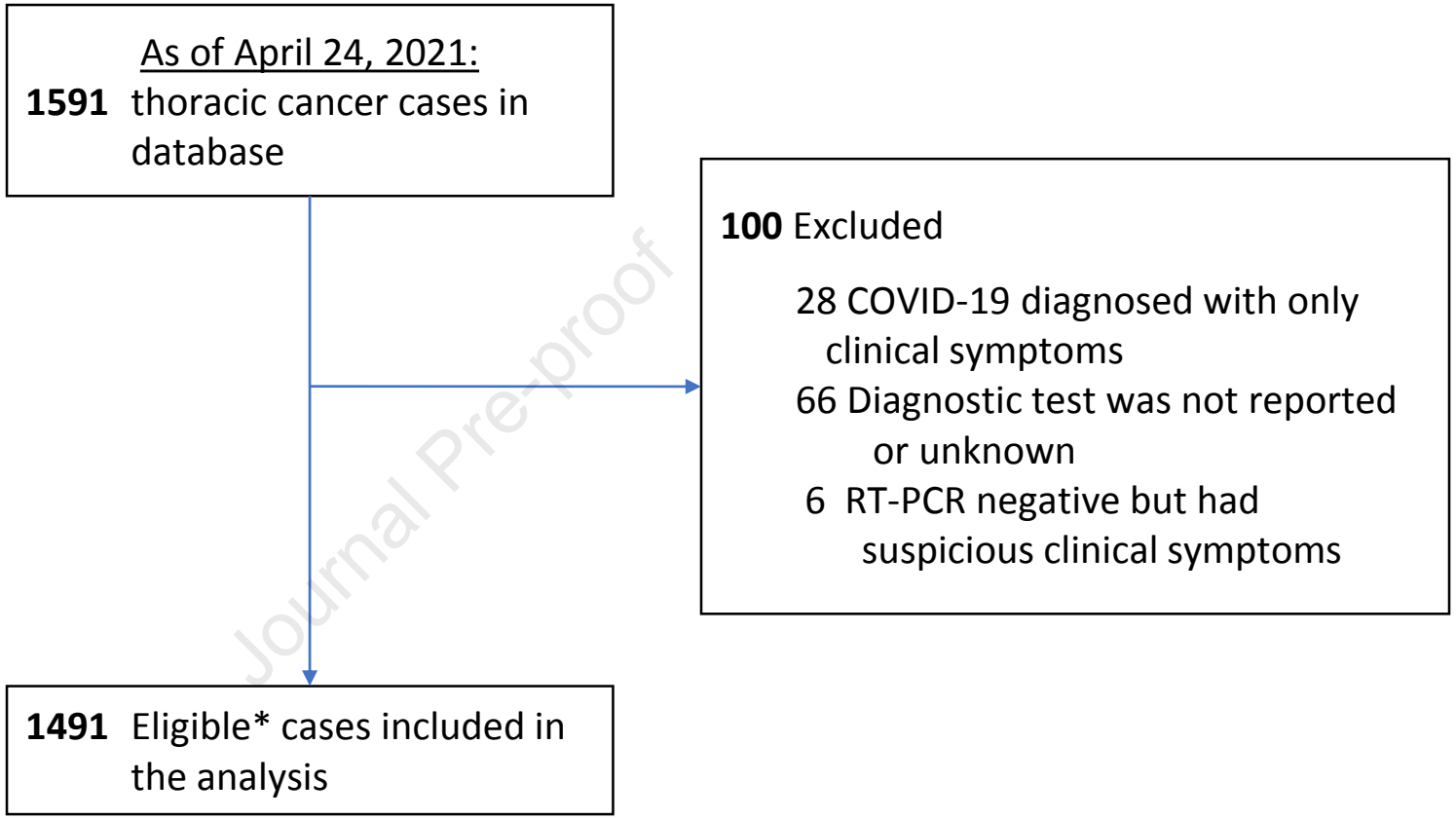
	All patients (n=1491)
Age, years (median)	67.0 (60.0-74.0)
> 65	855/1491(57.3%)
≤ 65	636/1491 (42.7%)
Total	1491
Sex	
Female	634/1489 (42.6%)
Male	853/1489 (57.3%)
Other	2/1489 (0.1%)
Total	1489
Smoking Status	
Current	264/1429 (18.5%)
Former	848/1429 (59.3%)
Never	317/1429 (22.2%)
Total	1429
Race	
White	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	
Small Cell Lung Cancer	184/1489 (12.4%)
NSCLC, squamous	277/1489 (18.6%)
NSCLC, non-squamous	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 anti-cancer 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

Table 2: Final multivariable logistic model for the association with death. Fast backward step-down variable selection with total residual AIC as stopping rule.

Variable	**OR (95%CI); p-value**
Age (> 65 vs ≤ 65 years)	1.71 (1.29-2.25); 0.0001
ECOG-PS (≥ 2 vs 0-1)	2.47 (1.86-3.26); 0.0000
Stage at COVID-19 diagnosis (VI vs < IV)	1.96 (1.45-2.65); 0.0000
Neutrophils (> vs ≤ ULN)	2.46 (1.76-3.44); 0.0000
Procalcitonin (> vs ≤ ULN)	2.37 (1.63-3.43); 0.0000
CRP (> vs ≤ ULN)	1.89 (1.43-3.43); 0.0000
Pneumonia (yes vs no)	1.95 (1.48-2.57); 0.0000

Figure 1: Consort Flow



*Eligible refers to those cases with a laboratory confirmed (RT-PCR, serology, antigen) diagnosis of COVID-19 OR suspicious radiological symptoms with clinical symptoms.

Figure 2: Nomogram

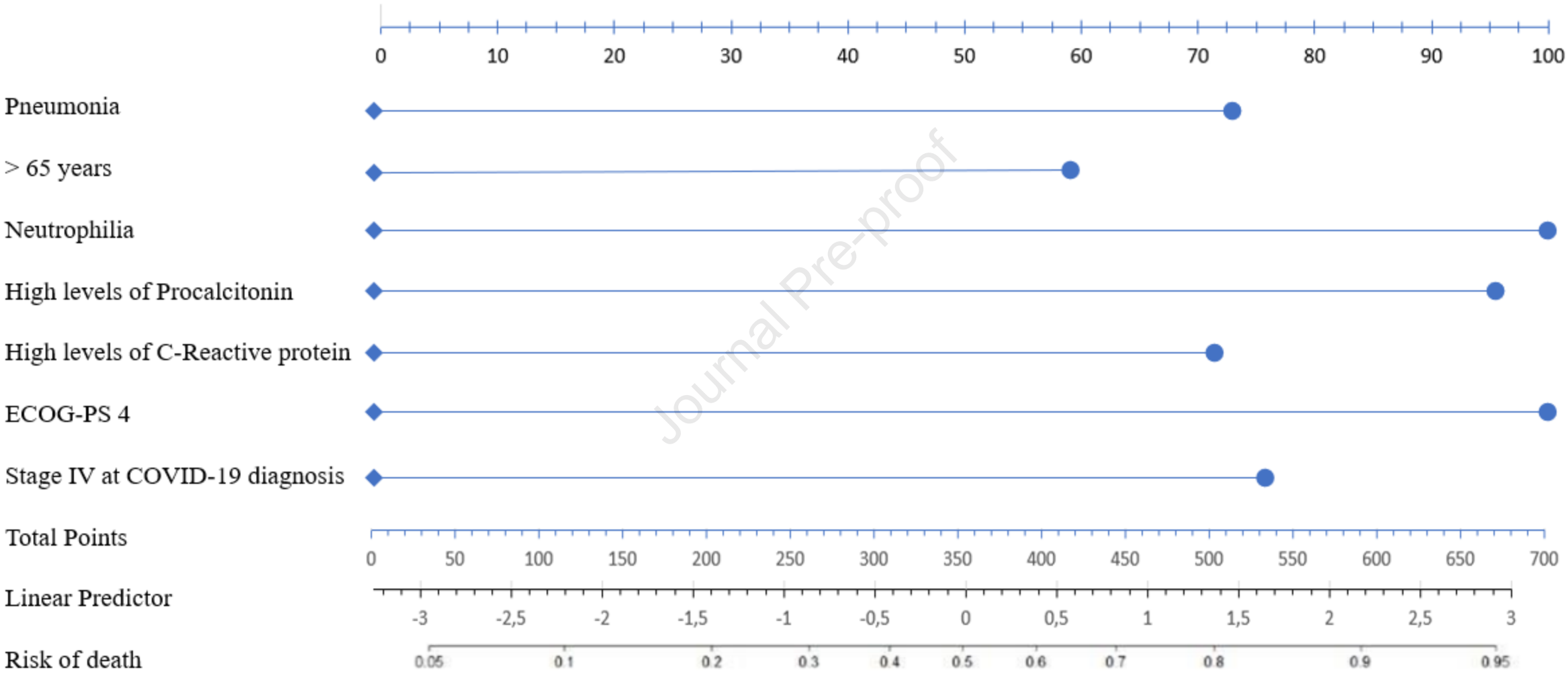
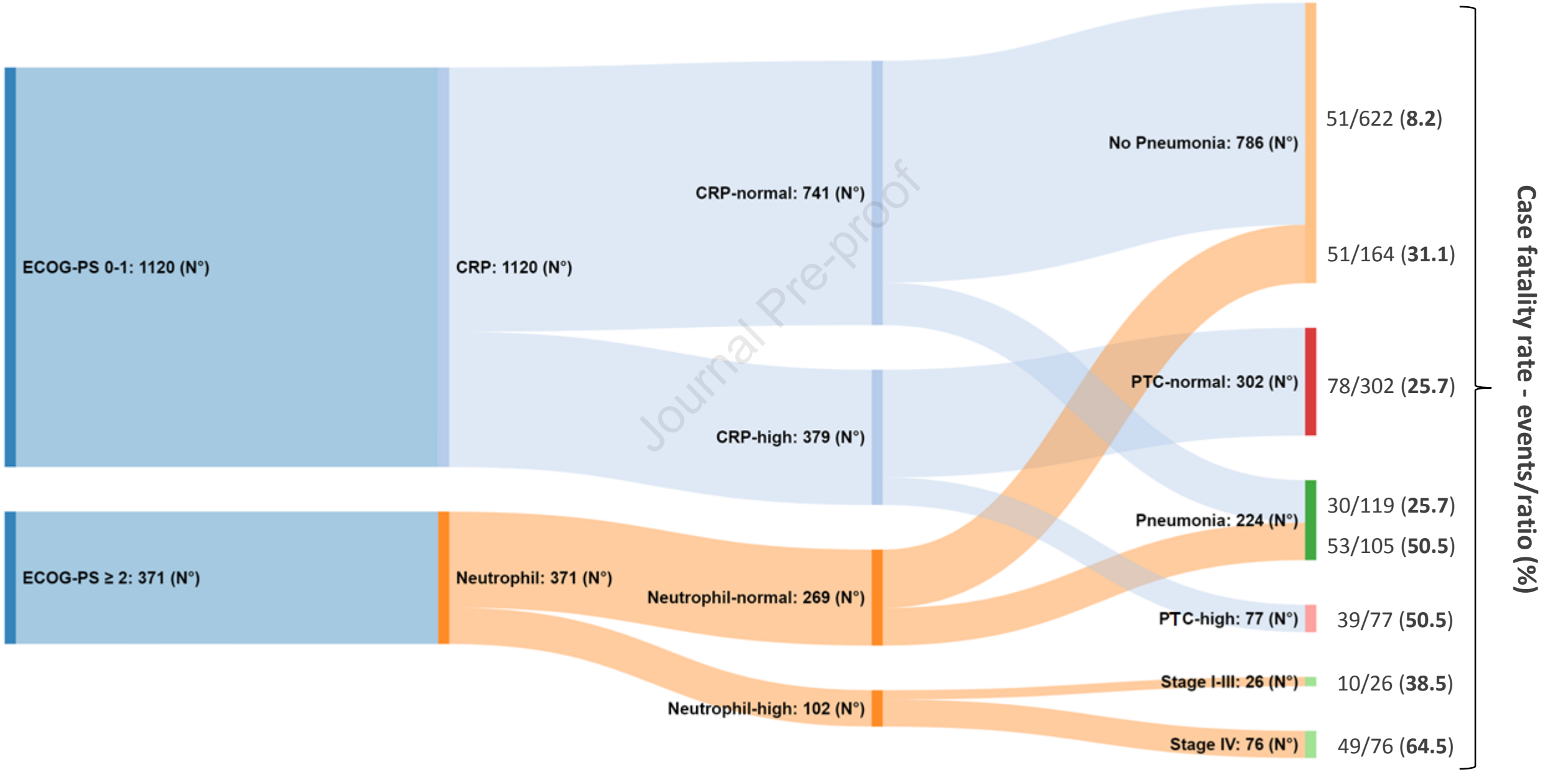


Figure 3: Sankey diagram



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