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CLINICAL STUDY

CT quantification of COVID-19 pneumonia extent to predict individualized outcome

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ABSTRACT
OBJECTIVES: This study aimed to predict individual COVID-19 patient prognosis at hospital admission using artificial intelligence (AI)-based quantification of computed tomography (CT) pulmonary involvement.
BACKGROUND: Assessing patient prognosis in COVID-19 pneumonia is crucial for patient management and hospital and ICU organization.
METHODS: We retrospectively analyzed 559 patients with PCR-verified COVID-19 pneumonia referred to the hospital for a severe disease course. We correlated the CT extent of pulmonary involvement with patient outcome. We also attempted to define cut-off values of pulmonary involvement for predicting different outcomes.
RESULTS: CT-based disease extent quantification is an independent predictor of patient morbidity and mortality, with the prognosis being impacted also by age and cardiovascular comorbidities. With the use of explored cut-off values, we divided patients into three groups based on their extent of disease: (1) less than 28 % (sensitivity 65.4 %; specificity 89.1 %), (2) ranging from 28 % (31 %) to 47 % (sensitivity 87.1 %; specificity 62.7 %), and (3) above 47 % (sensitivity 87.1 %; specificity, 62.7 %), representing low risk, risk for oxygen therapy and invasive pulmonary ventilation, and risk of death, respectively.
CONCLUSION: CT quantification of pulmonary involvement using AI-based software helps predict COVID-19 patient outcomes *(Tab. 4, Fig. 4, Ref. 38)*. Text in PDF *www.elis.sk*
KEY WORDS: COVID-19, pneumonia, computed tomography, artificial intelligence, ground glass opacity

Introduction

COVID-19 pneumonia has become a global pandemic and a significant and urgent worldwide threat to healthcare systems (1). Since the beginning of the pandemic in Slovakia, 346,149 people have been infected, 255,300 patients have been cured, and 8,894 deaths have been recorded. At the peak of the pandemic, in years 2021 and 2022, the numbers were continuously and rapidly increasing (2). The high rate of patient hospitalizations has placed an enormous burden on hospitals, leading to a reduction in routine healthcare. Despite the development of antiviral therapies, the frequency of severe forms of the disease requiring intensive therapy, as along with the mortality rate, remained high (3, 4, 5). The ability to predict the course of the disease was needed to help with patient management and planning for intensive care units and COVID-19 wards. Various inflammatory biomarkers have been evaluated to predict disease outcomes and intensive therapy need in patients with COVID-19 infection (6, 7, 8, 9, 10). Chest computed tomography (CT) became widely used during the COVID-19 pandemic (11, 12). It is a non-invasive method, which enables evaluation of the extent of pneumonia, follow-up of the evolution of the disease, and recognize complications including bacterial superinfection and thrombotic or embolic events (13, 14). The role of artificial intelligence in radiology imaging is substantially growing due to its ability to quantify X-ray and CT findings rapidly and precisely.

This study aimed to explore whether CT-based artificial intelligence quantification of lung disease and other co-factors can predict outcomes in patients with COVID-19 pneumonia. Lots of machine learning tools have been developed to diagnose and prognose COVID-19 pneumonia based on X-ray and CT images. However, a large number of them were found not to be of potential clinical use due to methodological flaws and/or underlying biases

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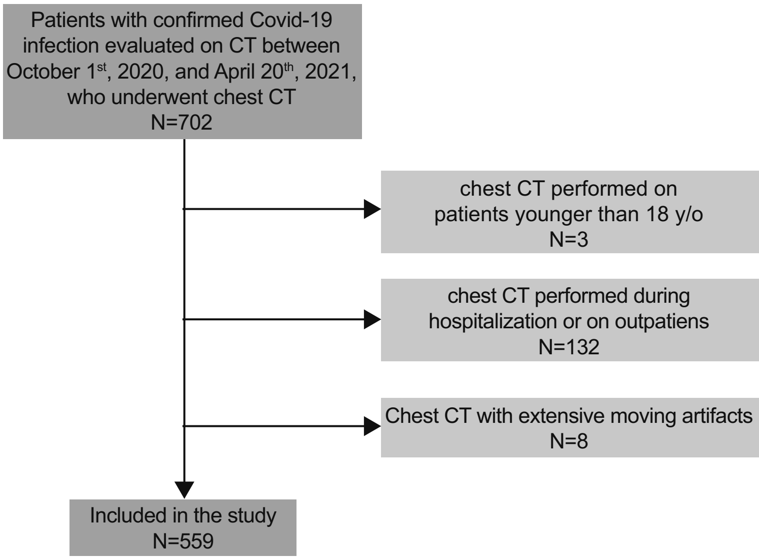

Figure 1. Flowchart of included patients shows the process of applying inclusion and exclusion criteria.

(15). For this reason, we decided to use the tools that were readily available in daily practice and were tested on large datasets of lung CT images in the US, Canada, and Europe (16).

We investigated whether the assessment of the extent of disease via chest CT could contribute to the accuracy of predicting patients' morbidity, the need for oxygen therapy, invasive pulmonary ventilation, and mortality in our studied cohort. Alongside other factors, we established correlations between the extent of pneumonia on chest CT, cardiovascular and pulmonary comorbidities, patients' age, height, weight, and BMI. Our aim was not only to demonstrate that AI-based CT quantification of the extent of pneumonia can predict patient outcomes, but also to quantify the hazard rates for the likelihood of requiring oxygen therapy and invasive pulmonary ventilation, as well as patient death.

Several published studies demonstrated the feasibility of using CT findings as well as AI-based CT evaluation to predict COVID-19 pneumonia patients' outcome in various ways (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27). However, to the best of our knowledge, the hazard rates based on AI-driven CT percentages of the extent of COVID-19 pneumonia on such a large dataset of patients have not been defined yet. By establishing this definition, we can predict the course of disease for each patient more precisely. This information can influence the choice of further therapeutic strategy and may impact the decision to implement alternative treatment or modify the management strategy. Finally, the availability of information about the hazard rate for invasive pulmonary ventilation can improve the optimization of patient flow within the hospital.

Table 1. Baseline characteristics of the enrolled patients (continuous variables).

	Range	Mean	SD
Age (years)	21–91	60.47	13.93
Height (cm)	140–200	171.54	9.36
Weight (kg)	45–160	88.36	18.8
BMI[a]	16.53–56.69	30.04	6.03
Extent of disease (CT quantification) %	0–87	29.29	24.42
Length of hospital stay (days)	2–161	10.95	10.72

[a] Body mass index

Table 2. Baseline characteristics of the enrolled patients (categorical variables).

	Available patients' records	Number of affected patients	%
Sex (female/male)	559	253/306	54.7/45.3
Pulmonary comorbidities	515	94	16.8
Cardiovascular comorbidities	521	312	55.8
Diabetes mellitus	515	112	20%
Oxygen therapy	513	318	56.9
Invasive pulmonary ventilation	513	31	5.5
Death	514	77	13.8

Materials and methods

Patient selection and study design

In this study, we retrospectively evaluated all patients admitted to hospital during the Delta wave of the COVID-19 pandemic from October 1, 2020, to April 20, 2021, in two institutions in Slovakia, namely in the Faculty Hospital in Nitra, Slovakia, and University Hospital – St. Michal Hospital in Bratislava, Slovakia. The study was approved by corresponding ethics committees. All the included patients were adults, had COVID-19 infection confirmed by a positive antigen test or polymerase chain reaction throat swab test, and had undergone a CT scan of the chest on admission. We excluded poor-quality CT scans caused by extensive movement/respiratory artifacts (Fig. 1). This study included 559 patients (aged 21–91 years, mean age 60.47 years), of whom 253 were females (aged 24–91 years, mean age 62.48 years) and 306 were males (aged 21–89 years, mean age 58.7 years).

The evaluated variables, namely age, sex, body mass index (BMI), presence of cardiovascular and pulmonary comorbidities, need for oxygen therapy or invasive pulmonary ventilation, length of hospitalization, and mortality during hospitalization, were collected from the patients' medical records (Tabs 1 and 2).

CT data acquisition

While performing the CT scans, we took strict precautions to minimize the hazardous exposure of patients and health care professionals to SARS-CoV-2 (28,29) and also followed the recommendations of the Slovak Radiology Society (30). Chest CT scans were performed on a 2 × 128-slice dual-source, dual-energy

CT scanner (Siemens SOMATOM Definition Flash, Erlangen, Germany) used in the University Hospital – St. Michal Hospital in Bratislava, Slovakia, or on a 128-slice CT scanner (Siemens SOMATOM Edge, Erlangen, Germany) used in the Faculty Hospital in Nitra, Slovakia. The patients underwent non-enhanced chest CT (covering the area from lung apices to the diaphragm) while in a supine position. To reduce respiratory artifacts, we performed all CT examinations with the breath held at the end of the inspiration phase. We adhered to the dedicated COVID-19 CT protocol as per the published recommendations (31,32,17), making specific adjustments to our equipment as follows. For the Siemens SOMATOM Definition Flash, we utilized a tube voltage of 80–120 kV, modulated tube current, auto mAs CareDose 4D (Siemens, Erlangen, Germany), a pitch of 1.2, and rotation time of 0.5 s. The lung images were reconstructed with a slice thickness of 1.0 mm using the I70 very sharp kernel algorithm while the mediastinal structures were evaluated with a soft-tissue kernel of the I31f medium-sharp algorithm. In the case of Siemens SOMATOM Edge, we employed a tube voltage of 120 kV, modulated tube current, auto mAs CareDose 4D (Siemens, Erlangen, Germany), a pitch of 1.2, and rotation time of 0.5 s. The lung images were reconstructed at a slice thickness of 1.0 mm using the Br59 kernel algorithm, while the mediastinal structures were evaluated with a softer kernel of the Bf37 algorithm. We used mediastinal window levels with the width set at 350/50 Hounsfield units (HU), and lung window levels with the width set at 1200/−600 HU, for all the patients.

Software analysis

We evaluated the lung involvement of COVID-19 pneumonia using Syngo.via CT Pneumonia Analysis software (Siemens Healthineers, Erlangen, Germany). It enables the operator to analyze scans for research purposes effectively. The CT Pneumonia Analysis prototype performs automated lung opacity analysis on axial CT data with slice thicknesses up to 5 mm. In general, the image quality of the lesion detection and quantification algorithms depends on characteristics of the original CT dataset, such as spatial resolution, noise, and artifacts. For good spatial resolution, it is recommended to use thin axial reconstructions (with a slice thickness below 1.5 mm). For our analysis, we employed non-contrasted chest CT scans with a slice thickness of 1mm. The AI algorithm automatically detected and quantified abnormal tomographic patterns commonly present in lung infections, such as ground-glass opacities (GGOs) and consolidations. Based on the 3D segmentations of the lesions, lungs, and lobes, the algorithm quantified the overall extent of abnormalities and the presence of high-opacity abnormalities both globally and in individual lobes. The CT pneumonia analysis recognizes affected lung parenchyma when the algorithm detects high-attenuation abnormalities in the given part of the lung. A pixel lens tool is provided for interactive inspection of HU values. Furthermore, the software calculates the following:

- The opacity score for a given region. This score is calculated for each lobe. For the left/right lung, the opacity score is the sum of values of respective lobes, and for the total opacity score, all lobe values are summed up.
- Lung volume (ml), and the volume of opacities as an absolute value of lung parenchyma affected by infection (ml).
- Percentage of opacity within a given lung region (%), and global percentage of opacity calculated for all the lung parenchyma (%) (33).
- In our study, the disease extent was quantified as the global percentage of opacity (Fig. 2). The Syngo.via CT Pneumonia software prototype was applied to each included patient's CT study.

Statistical analysis

IBM SPSS Statistics for Windows version 28.0 (IBM Corporation, Armonk, NY, USA, released 2021) and GraphPad Prism version 8.4 (GraphPad Software, San Diego, CA, USA) were used for the statistical analysis.

The included patient data were tabulated. The basic descriptive statistics were summarized using the mean and standard deviation for continuous variables and frequency (percentage) for categorical variables. We used the Shapiro–Wilk test to check the normal distribution of analyzed data.

An independent-sample unpaired *t*-test was used to analyze the differences between two patient groups with respect to categorical variables, while the Pearson correlation test was applied for continuous variables. The Pearson correlation test was also used to define the influence of the extent of CT pulmonary involvement on the severity of the disease course, which was defined as the length of hospitalization. All the deceased patients

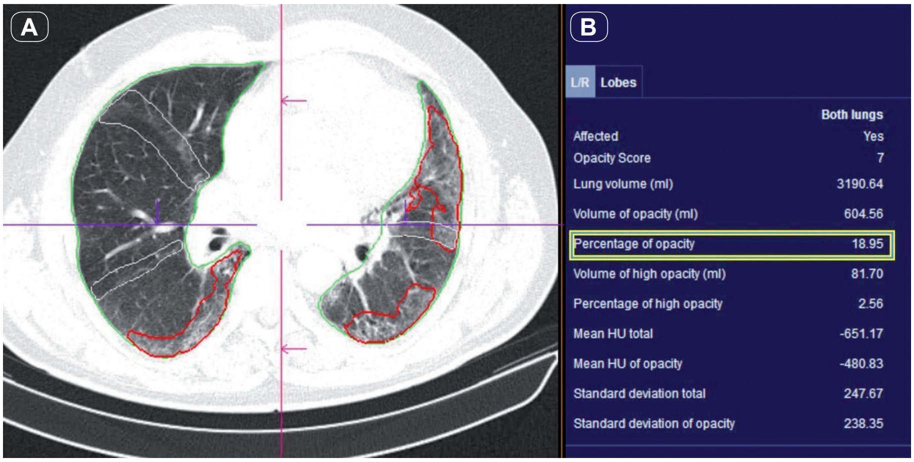

Figure 2. Software evaluation: the pulmonary involvement extent of a patient with COVID-19 pneumonia.

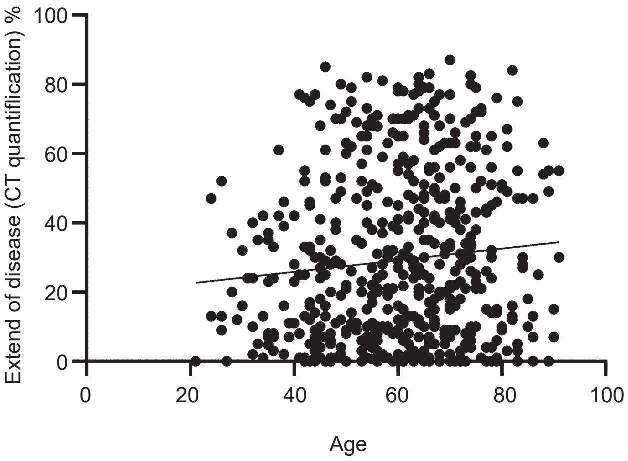

Figure 3. Analysis of the correlation of AI-evaluated CT extent of pulmonary disease and patient age.

were excluded from this analysis. The receiver operating characteristic (ROC) curve was used to determine the specificity and sensitivity of the extent of CT pulmonary involvement to predict the need for oxygen therapy or invasive pulmonary ventilation and the risk of death of the patients in our study. Finally, we selected the cut-off values for the need of oxygen therapy and invasive pulmonary ventilation, as well as for patients' morbidity, using the Youden index.

Table 3. Correlation of the AI-analyzed CT extent of the pulmonary involvement with patient morbidity, mortality, and other co-factors.

	Disease extent (CT quantification) Mean (%)	SD	p * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$
Gender			NS[a] (0.051)
Male	31.15	24.16	
Female	27.06	24.60	
Pulmonary comorbidities			NS[a] (0.611)
Yes	27.32	23.56	
No	28.75	24.45	
Cardiovascular comorbidities			** (0.01)
Yes	30.66	24.46	
No	25.03	23.72	
Diabetes mellitus			NS[a] (0.136)
Yes	31.59	23.76	
No	27.68	24.34	
Oxygen therapy			*** (<0.001)
Yes	38.59	24.23	
No	12.32	12.90	
Invasive pulmonary ventilation			*** (<0.001)
Yes	53.77	21.84	
No	26.90	23.51	
Death			*** (<0.001)
Yes	46.51	26.87	
No	25.41	22.38	

[a] not significant

Results

The results of the AI evaluation of the CT extent of pulmonary disease in relation to the survival and morbidity of the patients were significant. The AI-analyzed CT extent of pulmonary disease correlated with the need for oxygen therapy (38.59 ± 24.23 % vs 12.32 ± 12.90 %) and invasive pulmonary ventilation (53.77 ± 21.84 % vs 26.90 ± 23.51 %), as well as with patient death (46.51 ± 26.87 % vs 25.41 ± 22.38 %). The extent of pulmonary disease was also significantly higher in the patients with cardiovascular comorbidities (30.66 ± 24.46 % vs 25.03 ± 23.72 %) while no relationship with the presence of pulmonary comorbidities or diabetes mellitus in the included patients was revealed.

The AI-evaluated CT extent of pulmonary disease positively correlated with the patients' age ($p = 0.025$) (Fig. 3) and length of hospital stay in the surviving patients ($p < 0.001$) (Fig. 4) but was not related to their height ($p = 0.80$), weight ($p = 0.15$), or BMI ($p = 0.10$) (Tab. 3).

With the use of explored cut-off values of the CT extent of the disease, we could divide our patients into three groups. The first group included patients with a CT extent of disease up to 28 %. These patients yielded low risk for all three investigated entities, namely oxygen therapy, invasive pulmonary ventilation, and death. The patients in the second group with a disease extent ranging from 28% to 47 % showed a 6-fold or higher increase in risk for the need of oxygen therapy compared to patients with a disease extent lower than 28 % (sensitivity 65.4 %; specificity 89.1 %). Within this group, there was a subgroup of patients with the disease extent ranging from 31% to 47 % who had a 2.33-fold or higher increase in the risk for the need of invasive pulmonary ventilation. Finally, there was a third group with patients whose disease extent on admission was above 47 %. These patients had a 3-fold or higher increase in the risk of death (sensitivity 87.1 %; specificity 62.7 %) (Tab. 4).

Discussion

Chest CT plays an essential role for the management of lung diseases. The radiologist's role is indeed indispensable in the evaluation of lung CT scans. This comprises the following main steps:

- Identification of the type of COVID-19 pneumonia lung involvement
- Assessment of possible bacterial superinfection, and
- Determination of other COVID-19-dependent or independent findings in detail.

Radiologists can evaluate and interpret the extent of COVID-19 pneumonia lung involvement qualitatively with a high degree of precision.

Different types of chest CT severity scoring systems for evaluation of CT findings in COVID-19 pneumonia have been proposed and are in daily use by radiologists worldwide. The

Table 4. Cut-off values and hazard rates to predict oxygenation, invasive pulmonary ventilation and death.

	Cut-off value of pulmonary involvement (in %)	Sensitivity %	Specificity %	Hazard rates
Oxygen therapy	28	65.4	89.1	6
Invasive pulmonary ventilation	30.5	87.1	62.7	2.33
Death	46.5	60	80.2	3.03

best-known CT severity scores are the chest CT severity score (CT-SS), chest CT score, total severity score (TSS), modified total severity score (m-TSS), and three-level chest CT severity score. CT-SS is an adaptation of a method previously used to describe ground-glass opacities, interstitial opacities, and air trapping correlated with clinical and laboratory parameters in patients recovered from SARS. The chest CT score is calculated for each of the five lobes based on the extent of parenchymal involvement. The total severity score primarily quantifies the inflammatory abnormalities in each of the five lobes of both lungs, including the presence of GGOs, consolidation, or mixed GGOs. The modified total severity score incorporates the characterization of abnormalities into the previously described total severity score (TSS), using the same scoring range of 0 to 4 points. In the three-level chest severity score, the extent and nature of pulmonary involvement are assessed at three levels: above the carina (upper level), from the carina down to the superior margin of the inferior pulmonary vein (middle level), and below the inferior pulmonary vein (lower level). The severity scoring proved to have significant implications for establishing a precise diagnosis, management, and follow-up of COVID-19 cases (34). However, the precision of measurements is limited by doctors' experience and is extremely time-consuming and skill-dependent, which can be generally applied to any CT scoring system. (35). AI-driven lung involvement quantification is therefore a valuable, easy-to-use, and far less time-consuming method to evaluate the extent of disease (36). Its results are defined as a percentage of lung involvement, which is easy to interpret.

In this study, we provided evidence that the AI-analyzed CT extent of COVID-19 pneumonia can independently predict patient morbidity and mortality, serving as a valuable tool for guiding further patient management. Our study also highlights the impact of other co-factors, such as cardiovascular comorbidities and patient age, on the extent of the disease. On the other hand, we did not establish a correlation of patients' height, weight, BMI, and pulmonary comorbidities with patient morbidity or mortality. Similar findings have been validated and published worldwide (17, 18, 19, 20). Some authors showed the value of AI-based evaluation of chest CT findings in the diagnosis and monitoring of the disease (37). Other published studies used combinations of biomarkers or clinical factors and AI-based chest CT findings to predict the outcome of patients with COVID-19 pneumonia. Gresser et al. tried to predict the possibility of the need for extracorporeal membrane oxygen therapy in ICU patients with COVID-19 pneumonia. They revealed that AI-based quantitative assessment of lung volume involvement on admission CT, particularly if combined with the sequential organ failure assessment score, is a non-invasive and easily accessible tool to support risk stratification of extracorporeal membrane oxygen therapy requirements in patients with severe COVID-19 upon ICU admission. It can assist in early patient assessment and resource management (21). In their study, Weikert et al. demonstrated excellent patient management using a combination of demographic parameters, CT metrics, and laboratory findings to predict outcomes for patients with COVID-19 pneumonia (38). In several published studies, authors developed various scoring systems for AI evaluation of findings, differing in their approaches to the assessment of patient outcomes, (22, 23, 24). Wang et al. proved that AI-based findings derived from CT imaging and clinical data have a potential to predict the risk of future deterioration toward critical illness among patients with COVID-19 (25). Only a limited number of published studies provided the threshold values of findings to describe the hazards of morbidity and mortality. Chabi et al. evaluated the possibility of AI-based quantification of the pulmonary extent of disease to predict clinical deterioration or death. They

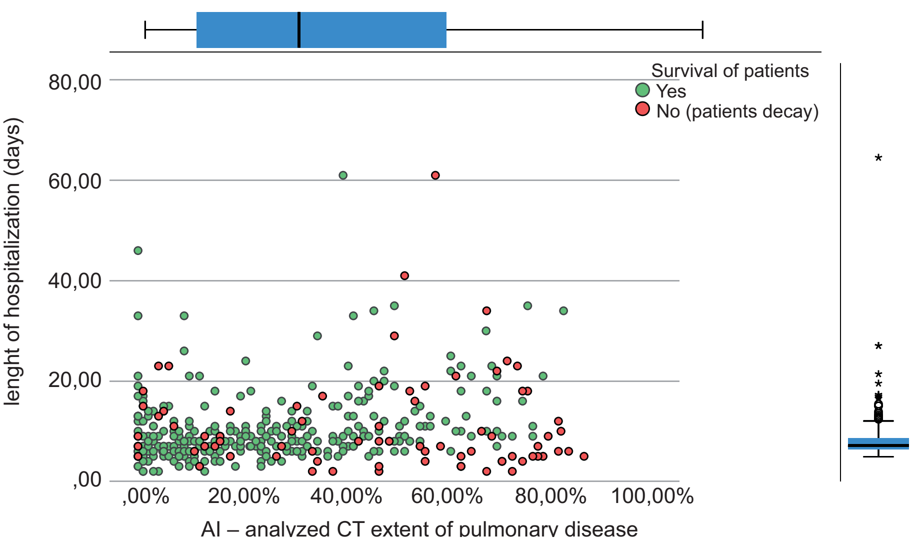

Figure 4. Analysis between the AI-evaluated CT extent of pulmonary involvement and the severity of the disease course defined as the length of hospital stay.

found that the threshold value of 33 % or more of lung volume occupied by lung opacities provided an 81 % sensitivity, and that 2 % or less of lung volume occupied by consolidation provided an 87 % specificity for predicting the clinical deterioration or death. Their study reported results similar to ours, but only in regard to the entities of deterioration or death of patients, while we explored the threshold values of lung involvement on CT scans in a more detailed manner. Furthermore, their study was performed on a smaller cohort of patients (26). Another study evaluated the threshold values based on the airspace opacities scoring method. It proved that the probability of each outcome was a result of a logistic function of the opacity scoring (25% risk of intensive care unit admission with a score of 13/25, 25 % risk of intubation with 17/25, and 25 % mortality with 20/25). The length of hospitalization, intensive care unit stay, and need for intubation were associated with larger airspace opacity scores (p = 0.032, 0.039 and 0.036, respectively). Scoring systems are a different method to assess AI results, which we consider to be less precise compared to the percentage of the volume of affected lungs. Also, the patient population in the above study was smaller and less homogenous compared to ours (27). In our study, we defined the hazard rates using statistical methods, namely, regression analysis and the Youden index. Since these results may be influential for further patient and hospital management, this method can be established as a baseline method for novel AI-based prediction approaches.

The major strength of our study lies in the large-sized and homogeneous cohort of patients Although our study was conducted across two centers, we employed CT scanners of the same manufacturer, highly similar CT protocols, and identical AI software for all the patients included in the study. The patient therapy adhered to the same national recommendation. At the time of the evaluation, all included patients resided in the same region of Slovakia. Moreover, a majority of the included patients were Caucasians of Slovak origin, a factor that may hold relevance. To the best of our knowledge, there are no similar studies published or conducted specifically on patients from Slovakia.

The known underlying biases were specifically addressed in the analyzed tool. Our approach shows solid evidence of making reliable predictions with established statistical learning methods, which warrants a wider adoption into clinical practice. Furthermore, utilizing traditional learning algorithms may serve as a baseline for model comparisons employing novel AI-based prediction approaches (15).

In our study, we provided evidence that AI-driven CT quantification of the percentage of the extent of lung involvement is an independent predictor of patient morbidity and mortality.

We showed that other co-factors, such as cardiovascular comorbidities and patient age, have impact on morbidity and mortality of the patients with COVID-19 pneumonia. In particular, we defined the cut-off values for the AI-calculated percentage of the lung involvement and provided hazard rates for the need of oxygen therapy, invasive pulmonary ventilation, as well as for death. We consider the definition of these cut-off values the main outcome of our study as it can have a substantial impact on the prediction of patient outcomes and hospital management.

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