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Disease Severity and CT Score as Predictors of COVID-19 Outcomes: A Single-Center Study

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ABSTRACT

Objectives: *to find a must common anchor point(s) in daily clinical work with COVID-19 patients, which could suggests to us the possible outcome.*

Materials and Methods: *The study population consisted of 956 patients diagnosed and hospitalized with COVID-19 between March 2020 and March 2023 at Zadar General Hospital, Croatia. Data collection was both, prospective and retrospective. All the patients were grouped according to the National Institutes of Health (NIH) guidelines disease severity criteria. Computed tomography (CT) was performed mostly in the severe and critically ill patients and in a number of moderately ill patients with signs of disease progression. The CT score was calculated based on the extent of lobar involvement. The two primary objectives of our investigation of disease outcome were death and oxygen-dependence/independence in survivors at discharge from hospital.*

Results: *The mortality rate was 31.8% (304/956); oxygen-dependence were recorded in 109 (11.4%) of patients at discharge from hospital. Our results showed that there was a statistically significant correlation between the variables of age and comorbidities and death outcome. The results of the binary regression analysis of disease severity in predicting the disease outcomes, death/survival, and oxygen-dependence at discharge showed that the severity of clinical condition was a statistically significant predictor of both disease outcomes.*

The one-way analysis of variance (ANOVA) to predict the influence of the CT score values on the disease outcomes showed that there was no statistical significant difference in CT score values between the deceased patients and those who survived. However, the ANOVA analysis of variance to predict the influence of the CT score values on oxygen-dependence or independence at discharge showed a statistical significant difference ($F(1,643) = 32.37$, $p < 0.05$) in the CT scores between the patients who were oxygen-dependent ($M = 9.75$, $Sd = 9.65$) and those who were oxygen-independent ($M = 4.96$, $Sd = 7.68$) at discharge.

Conclusion: *Our results showed that the categorization of patients according to their disease severity and CT score could be good anchor points in daily clinical works with COVID-19 patients, which could suggests to us the possible outcome to have been expected in moderate, and particularly in severe/critical patients at their admission to hospital.*

Keywords
COVID-19, Disease severity, CT score, Mortality, Oxygen-dependence.

Introduction
During the COVID-19 (coronavirus disease 2019) pandemic, caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which lasted from January 2020 to May 2023, a countless number of clinical and epidemiological investigations were published. These studies included more than 50 prognostic systems to predict disease outcome; the most frequently used predictor variables were age, chronic comorbidities (COPD, diabetes, hypertension, obesity, cancer), male gender, some radiologic and laboratory parameters [1,2].

However, calculating too much of various clinical and laboratory variables showed to be impractical in daily hospital life, particularly during the epidemic. Our three years of experience with COVID-19 patients showed that disease severity and CT score at the time of their hospitalization could be of significant reliability in the prediction of the disease outcome but also it could be decisive in further clinical judgment.

Materials and Methods
The study population consisted of 956 patients diagnosed and hospitalized with COVID-19 between March 2020 and March 2023 at Zadar General Hospital, Croatia. Data collection was both, prospective and retrospective; diagnostic and clinical parameters were completed in all of the patients.

Eligible patients were adult patients aged over the age of 18. They were real-time reverse transcription polymerase chain reaction (RT-PCR) positive for SARS-CoV-2, had radiologically confirmed pneumonia and a need for supplemental oxygen. All the patients were grouped according to the National Institutes of Health (NIH) guidelines disease severity criteria [3]. Exclusion criteria included pregnant or lactating women, hepatic cirrhosis or raised aminotransferases level greater than five times the upper limit of normal, and patients with severe renal impairment (estimated glomerular filtration rate < 30mL/min/1.72m^2) or patients on dialysis. The initial evaluation included chest wx-ray, electrocardiogram (ECG), complete blood count (CBC) with differential and metabolic profile, including liver and renal functional tests, C-reactive protein (CRP), D-dimer, ferritin, interleukin-6 (IL-6) and procalcitonin. Computed tomography (CT) was performed mostly in the severe and critically ill patients and in a number of moderately ill patients with signs of disease progression. The CT score was calculated based on the extent of lobar involvement [4].

All the patients received supportive care according to the care standard (supplemental oxygen, low molecular weight heparin and dexamethasone except in a few cases); the only antiviral drug used was remdesivir in a certain number of patients [5]. Research was approved by the Ethics Committee of Zadar General Hospital (under number 02-3673/21-9/21). All the patients gave verbal consent for the treatment since they were unable to give their written informed consent due to isolation precautions and the Ethics Committee waived the requirement. All investigations were conducted according to the principles expressed in the Declaration of Helsinki.

The two primary objectives of our investigation of disease outcome were death and oxygen-dependence/independence in survivors at discharge from hospital.

Statistical analysis
To answer the question of whether the sociodemographic variables of the patients predicted the outcome of the disease, a binary regression analysis was performed. Age (shown as a mean value with standard deviation because of statistical method used), sex (0- women, 1- male) and the presence of comorbidities (0– no comorbidities, 1- comorbidities) were used as predictors, and the criterion variable was the disease outcome (0- death, 1- survival). The set model was statistically significant (χ^2=20.41, df=3; $p < 0.05$) and the Nagelkerke R2 value was 0.207.

To examine the contribution of clinical disease severity in predicting the disease outcomes, two separate binary regression analyses were performed for two different variables. In the first, the criterion variable was the disease outcome in terms of patient survival or death (0-death; 1-survival; N=956). In the second, in survivors (N=637), the criterion variable was patient dependence or independence on oxygen at the time of discharge (0-oxygen-independent; 1- oxygen dependent). In both of the analyses, the severity of clinical symptoms was included as a predictor (1- moderate, 2- severe, 3- critical); two patients, hospitalized with mild symptoms were excluded from the analysis.

Also, a one-way analysis of variance (ANOVA) was performed to correlate the disease outcome and patient oxygen dependence at discharge and CT score values. Here we must point out that in this analysis the CT score was taken as the mean value with standard deviation, so the complete extent of the results was obtained.

Results
Characteristics of the study population are shown in Table 1; two patients categorized as "mild" disease were excluded from the statistical analysis.

Table 1: Characteristics of the study population.

Age with regard to gender	M ± SD	Range		Frequncy	%
Men Women	68,6 ± 13,89 71,4 ± 14,26	20-93 22-100	-2,93; p<.05		
Sex	Men			643	67.7
	Women			313	32.7
Severity of disease	Mild			2	0.2
	Moderate			280	29.3
	Severe			451	47.2
	Critical			223	23.3
Number of comorbidities	0 (no comorbidity)			155	16.2
	1 and more			801	83.8
Disease outcome	Discharge			652	68.2
	Death			304	31.8

CT score	Moderate	42	
	Severe	42	
	Critical	30	
Oxygen dependence at discharge	Yes	109	11.4
	No	543	56.8

*SD- standard deviation.

Table 2 Shows the results of the binary regression analysis of the disease outcome (death/discharge) related to variables of age, sex and comorbidities.

Table 2: Prediction of disease outcome (death/survival) depending on variables of age, sex and comorbidities.

Variable	B	Standard error	p-value	95% confidence interval	
				Lower	Upper
Sex	-.292	.160	>.05	.546	1.023
Age	-.060	.007	<.01	.929	.954
Comorbidities	-.571	.192	<.01	.388	.824

Sex: 1-women; 2-men; Comorbidities (hypertensio, diabetes, oncological and imunological disease): 0-no, 1-yes; Disease outcome: 0-death, 1-survive.

The results showed that there was a statistically significant correlation between the variables of age and comorbidities and death outcome. Both variables could explain 17% of the variance in the criteria; the variance of the outcome of death age could explain 16% of the variance, in the direction that the older the age, the more likely the outcome to be fatal. Comorbidities have less impact on mortality, 5% of the variance in the criteria.

The results of the binary regression analysis of the disease outcome at discharge (oxygen-dependence or independence at discharge) related to variables of age, sex and comorbidities (data are not presented) showed that there was no statistical correlation (χ^2 =1.16, df=3; p>0.05) between oxygen-dependence or independence in patients and those variables.

The results of the binary regression analysis of disease severity in predicting the disease outcomes are shown in Table 3.

Table 3: Prediction of disease outcome (A) survival/death and (B) oxygen dependence/independence at discharge depending on disease severity*.

	β estimate	Standard error	p-value	95% Confidence Interval	
				Lower	Upper
Disease outcome A (N=956)	-2.02	.14	<.01	.10	.18
Disease outcome B (N=637)	2.23	.230	<.01	5.91	14.56

*Predictor — Clinical severity of disease: 1-moderate, 2-severe, 3-critical.

The results of the binary regression analysis of disease severity in predicting the disease outcomes, death/survival, and oxygen dependence/independence at discharge (Table 3) showed that the severity of clinical condition was a statistically significant predictor of both disease outcomes. In explaining the variance in the outcome of death or survival (χ^2 =302.56, df=1; p< 0.01), the severity of the disease could explain 38% of the variance in the criteria, in the direction that the more severe the clinical condition, the more likely the outcome to be fatal. A more severe clinical condition was also significantly associated with a higher likelihood that an individual was oxygen dependent at discharge (χ^2 =138.06, df=1; p <0.01), with clinical severity as a predictor explaining 33% of the variance in the criteria.

The ANOVA test to predict the influence of the CT score values on the disease outcomes and oxygen-dependence in survival patients at discharge are shown in Figures 1 and 2.

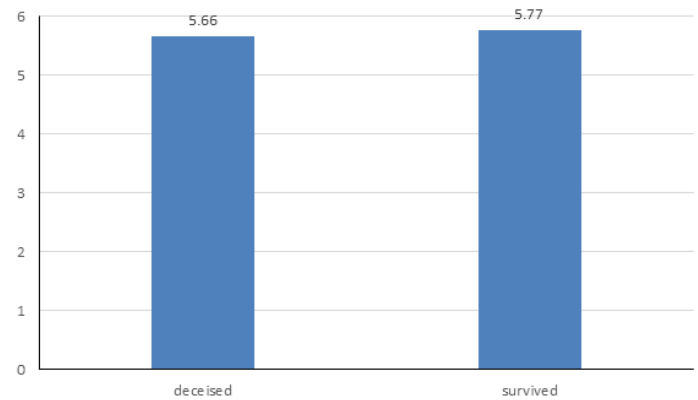

Figure 1: Prediction of disease outcome (death/survival) depending on the CT score values.

The one-way analysis of variance (ANOVA) to predict the influence of the CT score values on the disease outcomes death or survival (Figure 1) showed that there was no statistical significant difference ($F_{(1,952)}$ = 0.27, p> 0.05) in CT score values between the deceased patients (M= 5.66, Sd=9.5) and those who survived (M=5.77, Sd= 8.2).

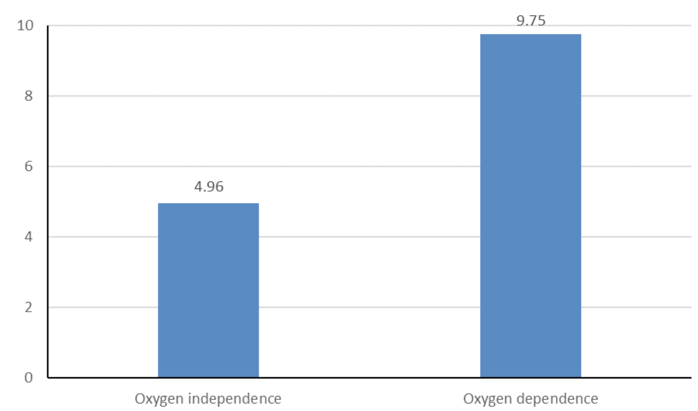

Figure 2: Prediction of disease outcome (oxygen dependence/ independence) depending on the CT score values.

The ANOVA analysis of variance to predict the influence of the CT score values on oxygen-dependence or independence at discharge (Figure 2) showed a statistical significant difference ($F_{(1,643)}$ =32.37, p<0.05) in the CT scores between the patients who were oxygen-dependent (M=9.75, Sd=9.65) ant those who were oxygen-independent (M=4.96, Sd=7.68) at discharge.

Discussion

At the beginning of May 2023, the head of the UN World Health Organization (WHO) declared the end of COVID-19 as a public health emergency, stressing that it does not mean the disease is no longer a global threat, what could be confirmed by growing number of cases in our region toward the end of 2023.

In our study of 956 patients with COVID-19, 304 (31.8%) died; 652 patients survived (68.2%); 109(11.4%) of them were discharged as oxygen-dependent and 543 (56.8%) as oxygen-independent. In assessment of COVID-19 outcomes one critical systematic review suggested that age, CT scoring, lactate dehydrogenase, sex, C reactive protein, comorbidities and lymphocyte count were the main predictors [2]. Among countless clinical and epidemiological studies of the most applicable prediction model for COVID-19 outcome, however, none of them were recommended for the routine use because of their high risk of bias.

The intention of our investigation was not to create a prediction model for prognosis but to find a most common anchor point(s) in daily clinical work with COVID-19 patients, which could suggests to us the possible outcome to have been expected in some categories of patients at their admission to hospital. The most common denominators of progression and mortality risk in many studies of COVID-19 were age, male sex and comorbidities [1,6]. Older age by its decreased cellular and humoral immunity could lead to impaired response to viral infections [7,8]. Also, an epidemiologic study, which compared the age-related susceptibility to SARS-CoV-2 infection between individuals older than 60 and younger ones, confirmed the greater biological susceptibility to infection among older people [9]. Another study which compared younger patients and those above 59 years, showed that the older patients were several times more likely to die after having developed symptoms [10]. Besides, in a meta-analysis from 37 studies, it was shown that older age significantly increased the risk of mortality, and the pooled odds ratio (OR) and hazard ratio (HR) were 2.61 (95% CI 1.75-3.47) ND 1.31 (95% CI 1.11-1.51) respectively [1].

Many studies showed that male sex was much more predisposed to a more severe COVID-19 and fatal outcome of the disease than the female sex [1,6,11]. Underlying biological mechanism for sex differences were generally explained by differences in immune response [11-13].

Many studies showed that the presence of comorbidities (hypertension, diabetes, chronic cardiovascular and pulmonary diseases, etc.) were associated with a more severe disease and high rate of fatal outcome in COVID-19 patients [1,14-17]. It is suggested that individuals with comorbidities and clinical features associated with severity should be monitored closely, and preventive efforts should especially target these high-risk populations [17,18].

The results of our binary regression analysis confirmed the association of age and comorbidities (but not sex) with the risk of fatal outcome. Moreover, this analysis showed that there was no association between the variables of age, sex and comorbidities and oxygen dependence/independence in patients at discharge from hospital.

The severity of clinical condition, however, has shown to be a statistically significant predictor of both disease outcomes. In explaining the variance in the outcome of death or survival, the severity of the disease could explain 38% of the variance in the criteria, and in the direction that the more severe the clinical condition the more likely the outcome to be fatal. A more severe clinical condition was also significantly associated with a higher likelihood that an individual was oxygen dependent at discharge, with clinical severity as a predictor explaining 33% of the variance in the criteria.

Various studies offered various laboratory parameters as significant predictors of disease outcome, but neither one of them, nor some other combinations, were accepted as critical parameter(s) for disease outcome [1,2,6,19]. Our results (data are not presented) confirmed that certain laboratory parameters could be helpful in a daily clinician's practice to improve treatment, but neither of them or in combination, cannot be taken into consideration for the prediction of the disease outcome due to its high risk of bias.

In order to examine the influence of CT score values on the disease outcomes and oxygen-dependence in survival patients at discharge, we performed the one-way analysis of variance. The results showed that there was no statistically significant difference in the CT score values between the deceased patients and those who survived.

However, at the same time, the results showed that the CT score value had a statistically significant influence on the oxygen-dependence or independence in discharged patients and this could be of great help for clinicians to reduce the risk of disease worsening in such patients.

The usefulness of CT finding on admission was reported in a small cohort of patients in which CT scores were much higher in the deceased compared to the survival patients (30 (IQR 7–13) vs 12 (IQR 11–43), 0.021), P = 0.021); moreover, in the scores in the mortality group markedly increased in a short time suggesting a progressive course of pneumonia [20]. Others also confirmed that the CT severity score (combined with age and history of at least one underlying disease) had a high sensitivity and specificity in predicting adverse outcomes [21,22]. In one earlier prospective study, we showed that the high CT grade of lung damage is the only independent prognostic factor of clinical outcome in patients treated with tocilizumab, regardless of administration time or criteria of tocilizumab use [23].

Some studies suggested that CT scoring method is acceptable method to predict mortality although an optimal cutoff value of a CT score was different (with various sensitivity and specificity levels) in different studies [20,24-26]. Moreover, in one of this study (148 patients with mortality rate of 37%) the area under the curve of CT score for discriminating of recovered patients from deceased individuals and the optimal CT score threshold were measured [25]. Moreover, a very recent small retrospective study showed that a higher CT score could predict the likelihood of death or ECMO management even in patients with moderte COVID-19 pneumonia [27].

Our study did not confirmed the predictive value of CT score in mortality of CIVOD-19 patients but clearly showed its' association with oxygen dependence/independence in survival patients at discharge from hospital, what could be the clue in their further judgment and treatment. Altogether, there is no doubt that much more prospective studies are needed for more precisely placement of CT score model(s) among the key factors of COVID-19 outcome.

During the COVID-19 pandemic, an infinite number of patient factors that may correlate with the disease outcome were described. Increased mortality was mostly associated with older age, pre-existing comorbidities, severe CT lung damage, hypoxemia, various laboratory alterations and some organ dysfunction; moreover, some prognostic models used a combination of some markers in an effort to increase its sensitivity and specificity [20]. It is obvious that the mentioned parameters have shown to be of certain values depending primarily on the study population and methodology applied. However, it is also clear that none of them alone, or combined, have enough sensitivity and specificity to be taken as a key prognostic parameter(s), although they are very useful in a routine clinician's work.

In the routine assessment of the disease outcome, our choice to take the NIH disease severity categories (moderate, severe, critical) at patient admission to hospital showed to be an acceptable predictors of both our primary outcomes, for the fatal outcome and oxygen dependence in patients discharged from hospital; in addition, high CT scores showed a significant correlation with the oxygen-dependence /independence in discharged patients (what was not the case with the common used variables of age, sex and comorbidities).

An oxygen saturation measurement by pulse oximetry on room air at sea level in the mentioned disease severity categorization may be an important limitation of our study because of its possibility of an inaccurate measurement of hypoxemia, dependence of skin thickness or temperature or of some other body factors (3). In addition, there are other disease severity classifications using some other systems for disease severity assessment [28,29], as well as some other CT score models [22,24,25,30].

In summary, whatever categorization of patients according to their disease severity criteria and CT model are used, it's using at admission of patients could be a simple and practical way to reduce not only the case fatality rate but also to improve the outcome in a significant number of COVID-19 patients.

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