The Impact of Charlson Comorbidity Index on mortality from SARS-CoV-2 virus infection and A novel COVID 19 mortality index: CoLACD

Short Title: COVID 19 mortality index: CoLACD

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ABSTRACT

Objective: The aim of this study is to find out the potential risk factors including Charlson Comorbidity index (CCI) score associated with death in COVID-19 cases hospitalized due to pneumonia and try to find a novel COVID-19 mortality score for daily use.

Methods: All patients diagnosed as confirmed or probable COVID-19 pneumonia whom hospitalized in our Chest Diseases Education and Research Hospital between March 11, 2020 and May 15,2020 were enrolled. The optimal cut-off values, sensitivity and specificity values and odds ratios to be used in mortality prediction of the novel scoring system created from these parameters were calculated by ROC analysis according to the area under the curve and Youden index.

Results: Over 383 patients (n:33 deceased, n:350 survivors) univariate and multivariate regression analysis showed that CCI and lymphocyte ratio were prognostic factors for COVID-19 related mortality. Using this analysis, a novel scoring model **CoLACD** (**Co**VID-19 **L**ymphocyte ratio, **A**ge, **C**CI score, **D**yspnea) was established. The cut-off value of this scoring system, which determines the mortality risk in patients, was 2.5 points with 82% sensitivity and 73% specificity (AUC = 0.802, 95% CI 0.777-0.886, p <0.001). The risk of mortality was 11.8 times higher in patients with a CoLACD mortality score higher than 2.5 points than patients with a score lower than 2.5 (OR = 11.8 95% CI 4.7-29.3 p <0.001).

Conclusion: This study showed that by using the CoLACD mortality score, clinicians may achieve a prediction of mortality in COVID-19 patients hospitalized for pneumonia.

Key words: COVID 19, mortality, Charlson Comorbidity Index, virus infection, pneumonia

What's already known about this topic?

There are few scoring systems for predicting mortality in COVID-19 infected patients which were clinically impractical.

What does this article add?

We created a novel mortality model called CoLACD with four prognostic parameters only; CoVID-19 lymphocyte ratio, age, Charlson Comorbidity index score, dyspnea.

This study showed that by using the CoLACD mortality score, clinicians may achieve a prediction of mortality in COVID-19 patients hospitalized for pneumonia.

INTRODUCTION

Beginning in December 2019 a novel corona virus spread from Wuhan, China to the whole World and being accepted as a pandemic by WHO since March 11, 2020.[1] The first case diagnosed in our country was 11th March 2020.[2] Since then there are numerous cases infected by COVID 19 and hospitalized due to disease severity. Urging early identification for severe cases is needed because thousands of people died from COVID-19 pandemic.

Epidemiologic, demographic, clinical, laboratory, and radiological characteristics are studied for determining the COVID-19 severity in various studies.[3,4] In recent studies older age, coexisting cardiovascular and cerebrovascular disease, lactate dehydrogenase and d dimer levels, level of $CD3^{+}CD8^{+}$ T-cells are studied for predictors of mortality however there is still a need for a simple scoring system for predicting mortality and determining severe disease for early intervention. Also, as this breakout now accepted as a pandemic not all hospitals have the capacity or the availability to have sophisticated laboratory equipment.

Charlson comorbidity index (CCI) score is developed in 1987 and since then used for the impact of comorbidities on mortality prediction is several studies.[5-7] Since COVID-19 pneumonia severity is affected by age and comorbidity we believe that this simple index, symptoms and basic laboratory findings may be used in order to predict mortality in COVID-19 infected hospitalized patients. Therefore, the aim of this study is to find out the potential risk factors including CCI score associated with death in COVID-19 cases hospitalized due to pneumonia and try to find a novel COVID-19 mortality score for daily use.

METHODS

Study Population

This study was approved by both the Scientific Committee of our hospital and Ministry of Health COVID-19 Scientific Research Evaluation Committee date/number 21.05.2020/4329. For this retrospective, non-interventional, a single-center case cohort study, we enrolled all patients diagnosed as confirmed or probable COVID-19 pneumonia whom hospitalized in our Chest Diseases Education and Research Hospital between March 11, 2020 and May 15,2020. The probable and definite diagnosis of COVID-19 pneumonia and all treatment strategies were based on the Guidelines by the Scientific Committee of Ministry of Health (8). All patients hospitalized for COVID-19 pneumonia underwent nasopharyngeal swab test for SARS-CoV-2 virus using real-time reverse-transcriptase- polymerase-chain-reaction (RT-PCR). Positive result on RT-PCR assay of nasal and pharyngeal swab specimens

were accepted as laboratory-confirmed patient. Severity of the disease is based on the Guidelines by the Scientific Committee of Ministry of Health.[8]

Data collection

The information for all participants including demographic data, comorbidities, clinical characteristics, laboratory parameters and outcomes, were collected prospectively. Charlson comorbidity score is calculated from the collected data and information needed is gained from hospitals e-database settings. Mortality data is obtained from hospitals e-information and operating system. Two researchers reviewed and double checked the e-data collection forms. Missing data are mentioned by numbers in the tables.

Statistical Analysis

Analyses were performed with SPSS software v 25.5 (IBM, NY, USA). To determine whether continuous data are normally distributed, Shapiro-Wilk and Kolmogorov-Smirnov normality tests were used. Mann-Whitney U test was used to compare parameters that were not normally distributed, and Chi-square and Fisher's exact test were used for comparison of categorical data. Results were given as median (min-max), number and percentage (%). P value <0.05 was considered statistically significant. The predictive values of the parameters for mortality were calculated with univariate and multivariate logistic regression analyzes. The optimal cut-off values, sensitivity and specificity values and odds ratios to be used in mortality prediction of the scoring system created from these parameters were calculated by ROC analysis according to the area under the curve and Youden index. The results were presented with 95% confidence intervals.

RESULTS

Clinical data

Between March 11, 2020 and May 15, 2020 there were 485 patients admitted to our Chest Diseases Education and Training Hospital in Izmir with a confirmed or suspected diagnosis of COVID-19 infection. After excluding outpatient patients and absence of pneumonia there remained 383 patients whom hospitalized for COVID-19 pneumonia in a between March 11, 2020 and May 15, 2020 (*Figure 1*). There was a male predominance in the cohort (57.2%). The median hospitalization time was 6 (1-34) days in the cohort. Demographic data of the whole cohort, the characteristics of the deceased and survivors are showed in *Table 1*. The median CCI score was 1 (0-11) in the cohort, the median score of the deceased groups was significantly higher compared to survivors [5 (0-11) - to 1 (0-10)], ($p<0.001$) (*Table 1*). If we look at the distribution of the age groups between deceased and

survivors, there were older patients in the deceased group (p=0.05). When we compared the 16 different symptoms on admission, only dyspnea was significantly different between two groups (p<0.001) (*Table 1*). Of the three physical examination findings on admission none of them were different between groups (*Table 1*).

Laboratory findings

54.5% of the patients were RT-PCR confirmed COVID-19 pneumonia, being PCR confirmed was not different between the deceased and the survivor groups (*Table 2*). Number of leucocytes, number of lymphocytes and lymphocytes % were statistically significantly different between groups (*Table 2*). Other laboratory findings which are different between groups are mentioned in *Table 2*. Of the whole cohort 68.9% of the patients had an abnormal finding on their Chest X-Ray, however 95.6% had a High-Resolution Computerized Tomography (HRCT) finding.

Predictors of mortality

When the predictive power of risk factors determined for mortality was evaluated with univariate analysis, it was found that patients with dyspnea had a 7.3 times higher mortality risk (OR = 7.3 95% CI 3.1-17.3). Likewise, mortality risk of patients over 65 years of age was higher than other age groups (*Table 3*). The cut-off value of lymphocyte%, which determines the mortality risk, was 17.65% with 88% sensitivity and 63% specificity (AUC=0.802, 95% CI 0.726-0.878, p<0.001), while the cut-off value of the CCI score for mortality was determined as 2.5 with 78% sensitivity and 74% specificity (AUC 0.853, 95% CI 0.787-0.920, p<0.001). Patients with lymphocyte% value below 17.65 had a 9.7 times higher mortality risk compared to patients with lymphocyte% above this percentage (OR=9.7; 95%CI 3.7-25.8; P<0.001). And the mortality risk of patients with a CCI score above 2.5 was 10.7 times higher than those with a CCI score of less than this value (OR=10.7; 95%CI 4.5-25.6; P<0.001) (*Table 3*).

A Novel Scoring Model

To create a simple score and facilitate clinical use, a novel scoring model was established **CoLACD** (**Co**VID-19 **L**ymphocyte ratio, **A**ge, **C**CI score, **D**yspnea) mortality score which scores from 0 to 5 points (*Table 4*). The cut-off value of this scoring system, which determines the mortality risk in patients, was 2.5 points with 82% sensitivity and 73% specificity (AUC= 0.802, 95% CI 0.777-0.886, p<0.001) (*Figure 2*). The risk of mortality was 11.8 times higher in patients with a CoLACD mortality score higher than 2.5 points than patients with a score lower than 2.5 (OR=11.8; 95% CI 4.7-29.3; p<0.001).

When the predictive power of risk factors included in the CoLACD scoring system for mortality risk was evaluated by multivariate logistic regression analysis, CCI score and Lymphocyte% value was found to be important risk factors for mortality. (OR=1.5; 95% CI 1.2-1.8; p<0.001 and OR=0.9; 95% CI 0.8-1.0; p=0.002, respectively) (*Table 5*)

DISCUSSION

During the Covid 19 pandemic, with using a simple scoring system during the first admission, for the prediction of patients who will have a severe course, can be life-saving. Therefore, with this study a novel scoring model CoLACD, is developed for prediction of mortality at admission. This study showed that the risk of mortality was 11.8 times higher in patients with a CoLACD mortality score higher than 2.5 points than patients with a score lower than 2.5 points.

In several studies it has been shown that comorbidities play an important role in COVID-19 infected patients. Charlson comorbidity index which is a component of our novel score is valid and a reliable tool for predicting mortality.[5] However, its impact on COVID pneumonia is not studied properly. With this study we showed that having a high comorbidity score increases the like hood of mortality 10.7 times. A cut off value of 2.5 (which means>3points) is an independent risk factor for mortality prediction. Our second component age is the basic factor of severity, which has become a consensus in the recent publications in COVID-19 and also in Severe acute respiratory syndrome (SARS) infection.[9,10] In one of the first studies determining the characteristics of COVID-19 infection Guan et al showed that Lymphopenia was observed in 82.1% of patients.[11] In several studies it has been found that the lymphocyte percentage descend with the disease, which indicates the direct result of viral infection.[12-14] And last component of this novel scoring model is the absence of a respiratory symptom dyspnea; in a metanalysis by Hu et al showed that the incidence of dyspnea was 21.4 % (95CI 15.3-27.5 %) in COVID-19 infected patients.[15] In a review by Pesola et al investigating 10 studies, suggested that dyspnea was an independent predictor of mortality with point estimates by odds ratio, rate ratio or hazard ratios ranging from 1.3 up to 2.9-fold greater than baseline.[16] Therefore, a symptom predictor of mortality can be used a component of a mortality scoring system.

Factors associated with poor prognosis have been shown in several studies, including age, comorbidities, lymphocytes, laboratory parameters like; serum ferritin, cardiac troponin, lactate dehydrogenase-dimer, IL6, level of $CD3^{+}CD8^{+}$ T-cells.[4,17-19] But surely a single

parameter won't be enough for predicting severe patients. Therefore, there are new scores developed for COVID severity (CALL) and also some well-known scores which were nowadays adapted to COVID-19 (MuLBSTA, qSOFA, CURB-65 and NEWS2).[20-23]

Ji et al developed a novel scoring model for obtaining the severe COVID-19 patients called CALL score.[21] It was developed for progressive risk estimation using 4 parameters; comorbidity, age, lymphocyte number and LDH. Using a cutoff value of 6 points, the positive and negative predictive values were 50.7% (38.9% - 62.4%) and 98.5% (94.7% - 99.8%), respectively in this model.[21] In the CALL model comorbidity was not specified properly and there was only with/without option however in this novel CoLACD model a verified comorbidity index CCI score is used.

Zang et al developed a scoring model for predicting severity for COVID-19 patients using age, WBC, neutrophil, GFR and myoglobin. This score was not mortality specific but predictor for severity. The scoring system was applied to calculate the predictive value and found that the percentage of ICU admission (20%, 6/30) and ventilation (16.7%, 5/30) in patients with high risk was much higher than those (2%, 1/50; 2%, 1/50) in patients with low risk ($p = 0.009$; $p = 0.026$).[22]

Myrstad et al in their study with 66 participants aimed to find the ability of the NEWS2 score and other clinical risk scores at emergency department admission to predict severe disease and in-hospital mortality in covid-19 patients.[23] They found that A NEWS2 score ≥ 6 at admission predicted severe disease with 80.0% sensitivity and 84.3% specificity (Area Under the Curve (AUC) 0.822, 95% CI 0.690–0.953) and also found that NEWS2 was superior to qSOFA score ≥ 2 (AUC 0.624, 95% CI 0.446–0.810, $p < 0.05$) and other clinical risk scores for this purpose.[23]

These scores either have multiple parameters or need sophisticated laboratory findings. Some of them need calculation and hard to remember the components of the scores. Therefore, in the current pandemic situation and knowing the importance of early identification of severe patients a simple score may help the clinician. In the first health settings without need of an even pulse oximeter by just asking comorbidities, asking the symptom; dyspnea, a simple hemogram parameter may be helpful for directing the treatment and determining the course of the disease.

However, this study has some limitations. First of all, this is a single center study but we have consecutively included all COVID-19 patients hospitalized for COVID-19 pneumonia from the start of the pandemic. Also, the hospital that this study takes place on is the only specific pulmonary diseases education and training hospital in the Aegean region.

Because of this study's retrospective design CoLACD score should be validated prospectively. Also, a single time clinical evaluation at admission may not reflect the course of the disease. And lastly as this study was non-intervention some laboratory parameters like LDH, D-Dimer, serum ferritin was absent in some patients. However, all components of CoLACD score were complete in the files and the hospital database system. Therefore, we tried to build a mortality score on basic laboratory parameters which is in routine use in first line health settings.

This study showed that a novel model including 4 parameters: CCI score, Lymphocyte ratio, age and dyspnea achieved a prediction of mortality in COVID-19 patients hospitalized for pneumonia. If validated with prospective studies, CoLACD score can be used for effective utilization of medical resources in the COVID-19 pandemic for decreasing mortality.

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interest

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Table 1. Comparison of demographic and clinical. findings of COVID-19 patients who died and survived

Demographic and clinical data	**Total n=383**	**Deceased n=33**	**Survivors n=350**	**p value**
Age groups n (%)				
15-49 years	171 (44.6%)	6 (18.2%)	165 (47.1%)	**0.005**
50-64 years	129 (33.7%)	15 (45.5%)	114 (32.6%)	
≥65 years	83 (21.7%)	12 (36.4%)	71 (20.3%)	
Gender n (%)				
Male	219 (57.2%)	24 (%72.7)	195 (%55.7)	0.059
Female	164 (42.8%)	9 (%27.3)	155 (%44.3)	
Charlson Comorbidity Index score median (min-max)	1 (0.0-11.0)	5.0 (0.0-11.0)	1.00 (0.0-10.0)	**<0.001**
Smoking history	n=295	n=24	n=271	
Non-smoker	171 (58.0%)	7 (%29.2)	164 (%60.5)	**<0.001**
Ex-smoker	73 (24.7%)	15 (%62.5)	58 (%21.4)	
Active-smoker	51 (13.3%)	2 (%8.3)	49 (%18.1)	
Symptoms on admission				
Fever n (%)	145 (37.9%)	9 (%27.3)	136 (%38.9)	0.190
Conjunctival concession n (%)	1 (0.3%)	0 (%0.0)	1 (%0.3)	1.000
Nasal concession n (%)	9 (2.3%)	0 (%0.0)	9 (%2.6)	0.617
Headache n (%)	31 (8.1%)	2 (%6.9)	29 (%9.2)	0.759
Cough n (%)	242 (63.2%)	19 (%57.6)	223 (%63.7)	0.485
Sore throat n (%)	72 (18.6%)	2 (%6.1)	70 (%20.0)	0.050

Fatigue n (%)	141 (36.8%)	12 (%36.4)	129 (%36.9)	0.955
Sputum n (%)	41 (10.7%)	7 (%21.2)	34 (%9.7)	0.069
Hemoptysis v	4 (1.0%)	1 (%3.0)	3 (%0.9)	0.304
Dyspnea n (%)	144 (37.6%)	26 (%78.8)	118 (%33.7)	**<0.001**
Nausea and vomiting n (%)	31 (8.1%)	5 (%15.2)	26 (%7.4)	0.169
Diarrhea n (%)	28 (7.3%)	1 (%3.0)	27 (%7.7)	0.493
Myalgia n (%)	77 (20.1%)	4 (%12.1)	73 (%20.9)	0.231
Chills n (%)	27 (7.0%)	1 (%3.0)	26 (%7.4)	0.494
Anosmia n (%)	13 (3.4%)	0 (%0.0)	13 (%3.7)	0.396
Anorexia n (%)	50 (13.1%)	6 (%18.2)	44 (%12.6)	0.360
Physical Examination Findings				
Redness in the throat n (%)	21 (6.3%)	0 (%0.0)	21 (%6.8)	0.239
Swelling of the tonsils n (%)	3 (0.9%)	0 (%0.0)	3 (%1.0)	1.000
Enlarged lymph node n (%)	2 (0.5%)	1 (%3.7)	1 (%0.3)	0.155

Table 2. Comparison of laboratory and radiological findings of COVID-19 patients who died and survived

	Total n=383	**Deceased n=33**	**Survivors n=350**	**p value**
Laboratory findings				
RT-PCR + n (%)	210 (54.5%)	22 (%66.7)	188 (%53.7)	0.153
Leukocyte median (min-max)	6500 (2600-31900)	10800 (4100-31900)	6250 (2600-30900)	**<0.001**
Neutrophil median (min-max)	4400 (400-30300)	6900 (2800-28000)	4350 (400-30300)	**<0.001**
Neutrophil % median (min-max)	70.0 (26.3-98.1)	75.8 (26.3-96.2)	70.0 (34.5-98.1)	**<0.001**
Lymphocyte median (min-max)	1200 (100-9600)	1000 (200-9600)	1200 (100-5500)	0.088
Lymphocyte % median (min-max)	20.1 (1.2-55.8)	10.7 (1.7-30.5)	20.6 (1.2-55.8)	**<0.001**
Monocyte median (min-max)	500 (0-9000)	600 (100-8600)	500 (0-9000)	0.053
Monocyte % 382 median (min-max)	7.9 (0.5-24.8)	6.4 (0.5-16.1)	8.0 (0.7-24.8)	0.081
Platelet median (min-max)	231000 (45000-840000)	300000 (65000-645000)	228000 (45000-840000)	**0.007**
Hemoglobin median (min-max)	13.2 (7.8-17.7)	12.1 (7.8-15.7)	13.3 (8.0-17.7)	**<0.001**
CRP 380 median (min-max)	4.5 (0.1-377.5)	18.1 (1.2-340.5)	3.9 (0.1-377.5)	**<0.001**
Glucose 375 median (min-max)	110 (53-531)	127 (53-315)	108 (58-531)	**0.021**
BUN 340 median (min-max)	26.9 (9.2-131.0)	37.3 (15.5-131.0)	26.5 (9.2-123.0)	**<0.001**
Creatinin 382 median (min-max)	0.8 (0.4-3.2)	1.0 (0.5-3.0)	0.8 (0.4-3.2)	0.093
AST 380 median (min-max)	20.0 (7.0-134.0)	29.0 (10.0-132.0)	20 (6.0-134.0)	0.058
ALT 380 median (min-max)	21.5 (4.0-255.0)	22.0 (4.0-78.0)	21.0 (5.0-255.0)	0.486
Total bilirubin 307 median (min-max)	0.39 (0.08-4.73)	0.38 (0.09-1.17)	0.37 (0.06-4.73)	0.857
Total protein 246 median (min-max)	6.6 (4.3-72.4)	6.2 (4.2-8.9)	6.7 (4.5-8.0)	**<0.001**
Albumin 250 median (min-max)	4.0 (1.9-5.2)	3.1 (1.9-3.9)	4.0 (2.1-5.2)	**<0.001**

Na 379 median (min-max)	138 (117-146)	137 (131-147)	139 (117-167)	**0.004**
K 379 median (min-max)	4.3 (1.1-6.0)	4.3 (2.6-5.5)	4.3 (1.1-6.0)	0.400
LDH 278 median (min-max)	217 (97-2246)	422 (119-2246)	218 (97-969)	**<0.001**
Ferritin 261 median (min-max)	206.7 (8.5-2465.5)	726.1 (102.0-2465.5)	190.8 (8.5-1787.2)	**<0.001**
D-dimer 308 median (min-max)	670.0 (114-10000)	1868.5 (397-10000)	662 (114-10000)	**<0.001**
Troponin-T 287 median (min-max)	4.5 (0.0 3089.0)	19.4 (0.0-3089.0)	3.9 (0.0-269.0)	**<0.001**
Radiological findings				
Findings on the x-ray n(%)	264 (68.9%)	31 (%93.9)	233 (%66.6)	**0.001**
X-ray 264 n(%)				
Bilateral	170 (64.4%)	20 (%64.5)	150 (%64.4)	0.988
Unilateral	94 (35.6%)	11 (%35.5)	83 (%35.6)	
HRCT findings 367 n(%)	351 (95.6%)	31 (%96.9)	320 (%96.9)	0.720

CRP: C reactive protein. BUN:Blood urea nitrogen.AST:Aspartate aminotranferase. ALT:Alanine aminotransferase. LDH: lactate dehydrogenase. HRCT: High Resolution Computorised Tomograhhy of the lungs

Table 3. Univariate analysis of mortality risk factors: dyspnea, age groups, lymphocyte % and CCI score in patients with COVID-19

	OR	95% CI	P value
Dyspnea			
With & Without	7.3	3.1-17.3	**<0.001**
Age groups			
≥65 years vs <65 years	2.3	1.1-4.5	**<0.001**
≥65 years vs 50-65 years	1.3	0.6-2.9	**<0.001**
≥50 years vs <50 years	4.0	1.6-9.9	**<0.001**
50-65 years vs <50 years	3.6	1.4-9.6	**<0.001**
Lymphocyte % <17.65% vs >17.65	9.7	3.7-25.8	**<0.001**
CCI score >2.5 vs <2.5	10.7	4.5-25.6	**<0.001**

CCI: Charlson Comorbidity Index score

Table 4. The calculation of CoLACD score

	points
Lymphocytes %	
≥17.6	0
<17.6	1
Age	
<50	0
50-65	1
≥65	2
CCI score	
≥3	1
<3	0
Dyspnea	
With	1
Without	0

CCI: Charlson Comorbidity Index score

Table 5. Multivariate logistic regression analysis of mortality risk factors for patients with COVID-19

	OR	95%CI	P value
Age groups			
50-64 vs <50 years	1.3	0.4-4.4	0.652
≥65 vs <50 years	0.7	0.2-2.7	0.634
CCI score	1.5	1.2-1.8	**<0.001**
Dyspnea	2.5	0.9-6.7	0.079
Lymphocytes %	0.9	0.8-1.0	**0.002**

CCI: Charlson Comorbidity Index score

Figure 1. Flowchart of the study

Figure 2. ROC curve of CoLACD mortality score. AUC=0.831; 95%CI 0.777-0.886; p<0.001