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Four Unique Laboratory Characteristics Applied to Assess the Severity of COVID-19

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1. Abstract

1.1. Aims: The sudden outbreaking of COVID-19 worldwide has brought into sharp increased burden of economic and treatment. How to simply, quickly and accurately assess the severity of patients with COVID-19 in the early stage after hospital admission is essential for healthcare systems.

1.2. Methods: To support precise decision making and clinical planning in hospitals, 84 blood samples of patients with COVID-19 who confirmed in the First Affiliated Hospital of the University of Science and Technology at Anhui and 25 blood samples of patients with COVID-19 in two hospitals at Shantou were collected. Machine learning tools were introduced to explore and validate the most significant predictive laboratory indicators of assessing the severity of disease.

1.3. Results: A new model combing four significant potential <http://acmcasereports.com>

biomarkers including C-reactive protein, albumin, globulin, and sodium levels was applied to predict the severity of patients with COVID-19. Comparing to three current popular assessment systems for pneumonia, we found that the new model's accuracy of the prediction performed better by using the AUC index, NRI index and the net benefit method.

1.4. Conclusions: In conclusion, our study was demonstrated to be a simple and operable severity assessment model to quickly predict the severity of patients after hospital admission. It ensured patients with higher severity to get treatment priorities and reduce the burden of the healthcare systems

2. Introduction

Coronavirus disease (COVID-19), a coronavirus pneumonia, is a highly infectious disease and is an ongoing outbreak in the world. Symptoms of patients with COVID-19 always include fever, cough,

fatigue and respiratory complications. Increasing mortality rate is the heaviest burden of COVID-19 worldwide because of the insufficient medical conditions. Hence, identifying patients with severe/critical disease is important because of high mortality rates among hospitalized patients. The ability to evaluate disease severity is crucial because it guides therapeutic options and helps clinicians make clinical decisions [1]. Up to date, there is no suitable prediction biomarkers for clinicians to classify patients with COVID-19 who require immediate medical attention after hospital admission. The capacity to assess the severity of patients with COVID-19 has become an urgent challenge. There are three main pneumonia severity scoring systems are applied to help us to assess the severity of patents with COVID-19 in clinical trial, including the Clinical Pulmonary Infection Score (CPIS), Confusion-Urea-Respiratory Rate-Blood pressure-65 (CURB-65) and the pneumonia severity index (PSI). However, none of them specifically designed for COVID-19 has been reported. Hankunyuan et al. reported a higher proportion of older than young and middle-aged COVID-19 patients with PSI grade IV and V [2]. Wu suggested that the PSI can be used to stratify patients with COVID-19 after hospitalization [3]. Liu indicated that the increase in CURB-65 score occurred concomitantly with the aggravation of acute respiratory distress syndrome in patients with COVID-19 [4]. In a multi-center study in Zhejiang province, patients with COVID-19 were classified by PSI and CURB-65 together, treated as a supplementary classification system for clinical assessment after admission [5].

According to the “Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial version 6)” published by the National Health Commission of China, only patients with decreased arterial oxygen partial pressure or respiratory distress could be classified as having severe/critical disease [6].

In order to reduce the pressure on healthcare system and ensure patients with higher severity to get treatment priorities, we aim to explore a simple and operable severity assessment to quickly assess the severity of patients after hospital admission. To identify some robust and interpretable biomarkers to assess the severity of patients, we developed and validated a mathematical model based

on laboratory characteristics in three retrospective cohort studies from 3 hospitals in 2 provinces in China. Finally, we also compared the discriminate accuracy of these selected significant biomarkers with that of the CPIS, CURB-65 and PSI.

3. Materials & Methods

3.1. Study Design and Patients

This was a retrospective study of three cohorts with COVID-19 diagnosed the “Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial version 6)” published by the National Health Commission of China [6]. The derivation cohort comprised 84 patients admitted from January 20 to February 20, 2020 to the First Affiliated Hospital of the University of Science and Technology of China. The validation data were for 13 patients from the First Affiliated Hospital of Shantou University Medical College and 12 patients from Shantou Central Hospital admitted from January 19 to February 20, 2020. All these patients were confirmed to have SARS-CoV-2 infection by RT-PCR of samples from the respiratory tract by the Centers for Disease Control and Prevention. Patients with COVID-19 were divided into mild, common, severe and critical groups according to Chinese protocol for managing COVID-19 [6].

3.2. Data Collection

We reviewed all clinical data, laboratory characteristics and chest CT scans (Table 1). The clinical data included demographic information, underlying comorbidities, symptoms and signs. Laboratory characteristics included routine blood tests, biomarkers for monitoring functions of multiple organs, and infection-related biomarkers. All data were collected within 24 hr after admission. According to the guideline for patients with confirmed COVID-19 from the National Health Commission in China, patients with mild clinical presentation (no pneumonia) may not initially require hospitalization. Hence, we removed data for 3 patients with mild disease from the derivation cohort because of possible bias. In addition, only 6 patients with a critical clinical presentation were confirmed after hospitalization, we merged 6 patients with critical presentation into patients with severe clinical presentation to avoid bias. Data for 81 patients with 35 variables were retained.

Table 1: Demographics, Clinical Indicators and Laboratory Characteristics in Two Cohorts

		Hefei Derivation cohort (n-84)	Shantou validation Cohort (n-25)
Group	Mild	3(3.57%)	9(36.00%)
	common	56(66.67%)	10(40.00%)
	Severity/Critical	27(32.14%)	6(24.00%)
gender	male	50(59.52%)	10(40.00%)
	female	34(40.48%)	15(60.00%)
age		47(5-91)	38(12-75)
respiratory		20(15-40)	20(18-24)
Temperature		36.85(36-39.5)	368(36.1-39.2)
SBP		121(100-175)	124(105-166)
DBP		76(60-108)	81(66-113)
HR		85(60-112)	90(55-128)
CRP C-reactive protein		17.7(0.5-150)	4.375(0.499-93.3)

ESR- erythrocyte sedimentation rate	38.5(3-145)	8(2-30)
BNP- brain natriuretic peptide	1116.89(20-5601)	60.7(18-1433)
cTnI Troponin I	0.08(0.0-3.10)	0.01(0-0.01)
ALB-albumin	43.05 (30-54)	40.86(34.12-50.8)
GLB-Globulin	28(15.6- 52.8)	31.5(24.26-39.52)
TG -triglyceride	2.64(0.59-9.51)	1.08(0.51-10.92)
ALT-Alanine aminotransferase	22.59(8-23.6)	23(7.22-126.79)
AST-Aspartate aminotransferase	27(14-182)	24.23(12-65.69)
CK-creatinine kinase	87.25(2-1062.6)	71.47(15.77-827)
CK-MB creatine kinase M B	10.95(4.4-57.6)	13(3.77-33)
Cr -creatinine	65(4-1561)	82.26(46-119.5)
BUN -Blood urea nitrogen	4.155(1.57-269)	4.13(2.48-6.57)
Cys C-Cystatin C	1.08(0.43-13.79)	0.93(90.68-10.3)
LDH Lactate dehydrogenase	243.5(130-936)	202(128-354)
Na-sodium	137(126-146)	139(35.6-43.2)
GLU-glucose	6.24(4.05-21.08)	5.26(2.23-17)
PCT-Procalcitonin	0.15(0.01-1.87)	0.05(0.02-1.39)
WBC -white blood cell	5.34(2.08-2.77)	4.9(2.2-2.6)
NE-Neutrophils	3.75(1.37-20.89)	2.485(0.89-9.9)
LY-lymphocyte	1.075(0.22-5.61)	1.4(0.7-3.2)
HCT-Hematocrit	0.411(0.257-.506)	0.431(0.32-44.8)
PLT-Platelet	163.5(72-363)	220(86-367)
PT-prothrombin time	14.5(10.7-19.9)	10.65(9.7-12.8)
APTT-Activated partial thromboplastin time	38.65(25.4-52.3)	26.2(21.1-33.3)
Fib-Fibrinogen	3.23(1.04-6.45)	3.05(1.53-6.78)
D-dimer D-Dimer	0.25(1.5-38.2)	180(60-850)
I-Bil Indirect bilirubin	8.7(2.0-29.0)	10.735(6.130.05)
D-Bil Direct bilirubin	5.5(1.5-38.2)	2.71(1.2-5.75)

3.3. Statistical Analysis

For the derivation cohort, some laboratory characteristics had missing data. After deleting 2 variables with high missing rate (>25%), we imputed the remaining data by using multiple imputation [7, 8]. We also handled the collinearity and filtering with mis-measured outliers by considering the results of variance inflation factor and correlation analysis together [9,10]. A model including 35 candidate predictors was fitted by using cforest implementation with the Random Forest (RF) classification model [11]. During this analysis, the importance of various conditioning factors can be measured quantitatively, and we found several negative importance variables. We kept running a loop function to remove negative values. The importance of severity of COVID-19-related variables was weighted by using the weight of evidence (woe) method to improve the predictive accuracy [12]. Finally, four significant selected biomarkers were selected by using a generalized linear model (glm) with the stepwise Bayesian information criterion method. The prediction model was depicted by the nomogram. Internal validation was conducted 100 times by splitting 80% of data into a training set with ntrain = 62 samples and 20% into a test set with ntest = 15 samples. Then we counted the total times each predictive variable was present in each model. Moreover, external validation involved using data for 25 patients with COVID-19 from 2 hospitals in Shantou. We used 3 common ways to quantify the discrimination accuracy of these 4 models with the validation cohort. The area under the Receiver Operating Characteristic (ROC) Curve (AUC) was used to describe the diagnostic ability of a binary classifier system [13]. The Net Reclassification Index (NRI) was used to evaluate the improvement in risk prediction by

adding a marker to a set of baseline predictors [14,15]. Decision Curve Analysis (DCA) was used to evaluate and compare prediction models that incorporate clinical consequence [16]. In this study, we used DCA to graphically describe the clinical usefulness of each classifier based on a potential threshold for misclassification (x axis) and the net benefit of using the model to risk-stratify patients (y axis) relative to assuming that no patient will be misclassified.

Statistical analyses were performed with R v3.6.3 and p<0.05 was considered statistically significant.

4. Results

Table 1 describes participant characteristics. The derivation cohort and validation cohort showed few major differences existed. The derivation cohort was based on 84 patients with COVID-19 from Hefei. After filtering collinearity and outliers, 77 patients with COVID-19 were retained. The full model was approximated by a small model including the 14 most predictive variables by using RF. Only 13 predictive variables were retained after deleting variables with strength of evidence less than “very strong”. Figure 1 shows the weight of evidence of importance of variables related to severity of COVID-19. Four significant biomarkers were selected, including: CRP (P = 0.001), ALB (P = 0.014), GLB (P = 0.013) and sodium (P = 0.006) (Table 2). The nomogram was depicted in Figure 2 and the final prediction model was described in formula 1: $\text{Logit}(p)=76.579+0.064*CRP-0.259*ALB+0.287*GLB-0.567*sodium. \dots\dots(1)$

In internal validation, the random-splitting was repeated 100 times and results are described in Table 3. CRP and sodium level ap-

peared 100 times, ALB level 72 times and GLB level 85 times and so were selected to build the model in the training dataset. Table 2 also describes the results of other severity-measurement models. Both them demonstrated that four selected laboratory characteristics can be regarded as potential biomarkers for identifying the severity of patients with COVID-19.

The AUC for the CPIS score was highest (AUC_{CPIS} = 0.988) and that for four biomarkers was lower, 0.881 (Figure 2). However, the ability to discriminate patients with severe/critical and common disease was better by using four biomarkers than the CPIS, mainly because the CPIS overestimates the variance when the AUC is close to 1 and it is not realistic in clinical trials [17]. DCA demonstrated that the prediction model built by four biomarkers improved the accuracy of classification against the threshold probabilities of three popular classifiers. Table 4 suggested that the new prediction model was the best in the 4 systems because the values of three NRIs were > 0. The new prediction model was always superior to other 3 models across a wide range of threshold probabilities (Figure 3). For example, the highest difference between the new prediction model and CPIS was at a threshold probability around 0.41. At that threshold, the net benefit for the new prediction model was about 0.29 and 0.1 for CPIS. At that threshold, using the new prediction model over the CPIS to classify patients and make clinical decisions, the probability of more profitable treatment was 28% (95% CI 0.29-0.1).

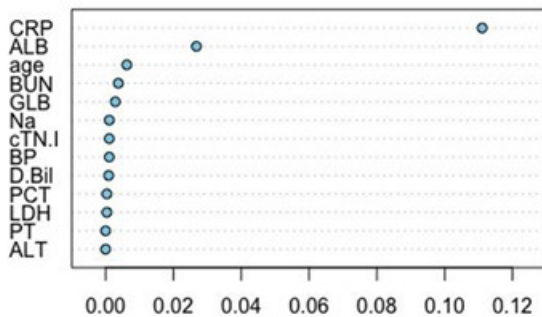


Figure 1: Weight of evidence of importance of variables related to severity of COVID-19. CRP, C-reactive protein; ALB, albumin; GLB, globulin; BUN, blood urea nitrogen; PCT, procalcitonin; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate transaminase; BP, blood pressure; Na, sodium; cTN.I, cardiac troponin I; D.Bil,direct bilirubin; PT,prothrombin time.

Table 2: Results of generalized linear model

		Estimate	P.value
new-model	intercept	76.573	0.005
	CRP	0.064	0.001
	ALB	-0.259	0.014
	GLB	0.282	0.013
	sodium	-0.567	0.006
CPIS	intercept	-5.212	1.63E-05
	CPIS	1.836	3.61E-05
CURB.65	intercept	-1.027	2.77E-04
	CURB.65	1.455	1.70E-02
PSI	in tercept	-4.578	8.78E-06
	PSI	0.078	5.09E-05

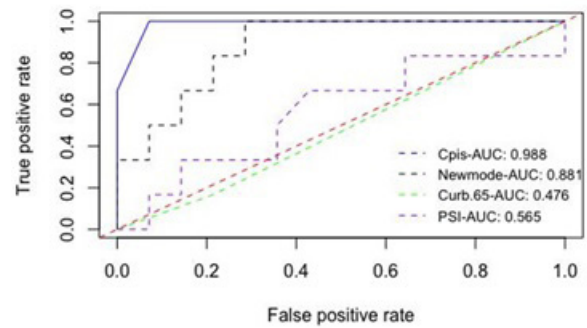


Figure 2: Area under the receiver operating characteristic curve (AUC) for measurement scores. CPIS, Clinical Pulmonary Infection Score; CURB-65, Confusion-Urea-Respiratory Rate-Blood pressure-65; PSI, pneumonia severity index.

Table 3: Occurrences for significant variables by 100 repeats

	CRP	ALB	GLB	sodium
Times	94	72	85	94

Table 4: Rustles of NRI index

	CPIS	CURB.65	PSI
new-model	0.533	0.513	0.659

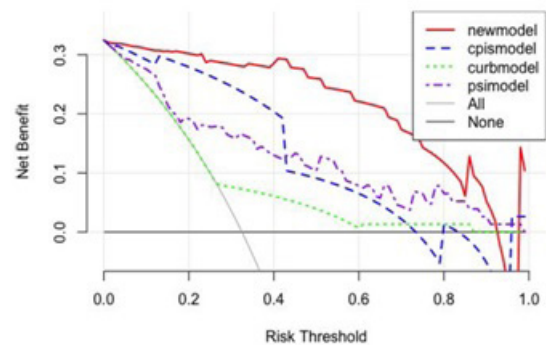


Figure 3: Threshold probabilities of models.

5. Discussion

There were two notable jobs in our study. Firstly, four high-risk factors were found. They had been demonstrated to precisely and quickly quantify the severity of patients with COVID-19. Secondly, these four significant predicted biomarkers can be easily obtained in any hospital. A simple and easily operable model was very useful because it can help clinicians to quickly identify the severity of patients after hospital admission when the medical resources were limited. Our study developed and externally validated a new severity measurement specifically designed to assess patients with COVID-19. It had better discriminative ability than other measures in 3 cohorts. It classified patients with COVID-19 into a common group and severe/critical disease group with higher accuracy than 3 existing popular classifiers for pneumonia. The NRI and DCA analysis also demonstrated that it was the best classifier. The discriminative ability of it was also externally validated. Four biomarkers were thought as potential risk factors of COVID-19 in our study. Firstly, we found that CRP level were positively correlated with the severity of COVID-19. It was consistent with some previous studies. CRP can activate the complement system to enhance

the regulation of lymphocytes and promote the phagocytosis of macrophages to eliminate the invading pathogens [18, 19]. Some studies of COVID-19 showed that CRP level was significantly increased specifically in patients with severe disease [20, 21]. The reason might be some inflammatory factors such as interleukin 6, interleukin 1, tumor necrosis α could promote the synthesis of CRP by hepatocytes [18]. Ko et al. found that $CRP \geq 2\text{mg/dl}$ was one of the predictive factors for pneumonia development of Middle East respiratory syndrome (MERS), while $CRP \geq 4\text{mg/dl}$, low albumin level, male, hypertension, thrombocytopenia, lymphopenia were regarded as the predictive factors for respiratory failure [22]. A recent retrospective study also showed that CRP levels of patients with COVID-19 were also significantly higher in the death group on admission [23]. Liu et al. reported that IL-6 and CRP could be used as independent factors to predict the severity of COVID-19, and those patients were more likely to have severe complications while their CRP level larger 41.8mg/L [24]. Wang also suggested that CRP level can be regarded as an important biomarker in the early stage of COVID-19 because CRP could reflect lung lesions and disease severity [25]. Albumin was the second potential biomarker found in our study. It could be detected in the blood and was a protein made in the liver. Albumin could prevent leakage of the fluids from the blood into other organs [26]. Increasing number of studies showed that low albumin levels were associated with poorer outcomes of patients with COVID-19 [27]. Albumin concentration was suggested as an independent risk factor for mortality in patients with pneumonia and also found associated with COVID-19 [28,29]. A systematic reviewed and meta-analysis showed that hypoalbuminemia status increased risk of severe COVID-19 [30]. Our study also described that lower sodium was a risk factor for severe COVID-19 infection. Sodium was considered a predictor in several scoring systems for assessing pneumonia, including the PSI and Acute Physiology and Chronic Health Evaluation II. Hyponatremia was the most common electrolyte disorder in clinical practice and severe hyponatremia was associated with increased mortality [31]. Berni et al. found that sodium was inversely correlated with IL-6 in COVID-19 patients, directly correlated with PaO_2/FiO_2 ratio [32]. Stephan J.L Bakker gave a hypothesis about that low sodium balance may augment cellular damage at a certain virus load and increase the risk of developing severe and fatal COVID-19 infection by their experimental and epidemiological data [33]. Finally, globulin was suggested to be positively relative with the severity of COVID-19. Yafei Zhang demonstrated that the globulin level in severe COVID-19 patients is significantly increased while comparing to the mild patients because the promoted immunoglobulin synthesis [27].

In addition, the CPIS, a diagnostic algorithm, is mainly applied for ventilator-associated pneumonia and community-acquired pneumonia. Most studies indicated that CPIS had inaccurate sensitivity and specificity [34-37]. The CPIS was suggested to have

high inter-observer variability and is not available for multiple centers study [37, 38]. The CURB-65 score consists of 5 separate elements: confusion, uremia, respiratory rate, blood pressure, and age ≥ 65 . The CURB-65 is relatively simple to use. The PSI involves 20 clinical variables defining 5 classes of increasing risk of mortality. It has been extensively validated. However, the inappropriate weights of age or inappropriate threshold values for both the PSI and CURB-65 result in a potential underestimation of severe pneumonia, especially in young people [39, 40]. A major limitation of the current study is the insufficient sample size. As more raw data will be collected in the future, we would have the ability to optimize our new model. Another limitation of our study was that we had to combine patients with critical presentation to severe presentation because there were only 6 patients with a critical clinical presentation in our study.

6. Conclusion

In conclusion, this study has identified four indicators for evaluating the severity of COVID-19 after hospital admission. The simple and operable new prediction model using these four indicators can achieve convenient detection, early intervention and increase the survival rate in patients with COVID-19.

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