Research Square

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Detection of Serum KL-6 and SARS-CoV-2 Antibody in Patients with Coronavirus Disease 2019 and the Diagnostic Value in Severe Disease

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Abstract

Background: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a significant threat to human health, but its clinical manifestations vary greatly among individuals. Early detection and treatment are important for severely ill patients to improve their prognosis and reduce the risk of death.

Methods: In the present study, serum markers were detected and analyzed in moderately ill and severely ill patients.

Results: The results found that there were statistically significant differences in age, serum Krebs von den Lungen-6 (KL-6) and Immunoglobulin A (IgA) levels between severely ill patients and moderately ill patients ($P < 0.05$). The cut-off of using KL-6 alone for the diagnosis of severely ill patients was 298.91 U/mL, with an AUC of 0.737, a sensitivity of 100%, and a specificity of 43%. When the diagnosis was performed using KL-6 in combination with Interleukin-6 (IL-6), an indicator of infection, the AUC was 0.776, with a sensitivity and specificity of 82% and 69%, respectively. When the three above were used in combination for diagnosis, the AUC was 0.785, and the sensitivity and specificity were 100% and 59%, respectively. After rehabilitation, the serum levels of KL-6, C-reactive protein (CRP), as well as antibodies, IgA, IgM and IgG, were significantly lower than those in the early stage of hospitalization.

Conclusion: In the present study, KL-6 and IgA were found to have some diagnostic efficacy for severely ill patients with COVID-19, but larger cohort studies are still needed for further confirmation, which in turn improves the diagnostic and therapeutic efficiency of severely ill patients.

Background

Coronavirus disease 2019 (COVID-19) is a global infectious disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which poses a threat to human health [1, 2]. The clinical manifestations of patients with coronavirus disease 2019 vary greatly, from no symptoms in patients with asymptomatic infection to dry cough, fever, and nasal congestion in moderately ill patients, while severely ill patients may present with chest tightness, asthma, and dyspnea, and critically ill patients may have secondary multiple organ dysfunction and the disease can be fatal [3–6]. Most moderately ill patients can recover after symptomatic and supportive treatment, while COVID-19 in severely ill/critically ill patients can be life-threatening due to a series of rapid pathophysiological changes such as body inflammatory response and "cytokine storm" [7–9]. Current diagnostic and therapeutic regimens emphasize early evaluation, and early treatment of severely ill/critically ill patients to help improve patient prognosis and reduce the risk of death [10–13]. We previously reported serum SARS-CoV-2 specific Immunoglobulin A (IgA) is positively correlated with disease severity [14], and Krebs von den Lungen-6 (KL-6) is a good indicator for lung injury and inflammation in COVID-19 patients [15].

In the present study, we detected and analyzed the serum markers of moderately ill and severely ill patients to explore the value of each indicator in assessing the severity of patients, assisting in the

diagnosis of severely ill patients, and improving the efficiency of diagnosis and treatment.

Methods

Subjects

We retrospectively assessed 64 Coronavirus disease 2019 (COVID-19) patients at the Second People' Hospital of Fuyang City, Anhui Province, China, between January 26, 2020 and February 16, 2020. COVID-19 diagnosis was confirmed by reverse-transcript polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA from sputum or throat swab with Novel Coronavirus (2019-nCoV) Nucleic Acid Detection KIT (Shanghai BioGerm Medical Technology Co., Ltd, Shanghai, China); patients with positive results were enrolled. This study was approved by the Ethical Committee for Clinical Studies in the Second People' Hospital of Fuyang City (No. 20200229008).

Clinical data collection

The clinical data of the patients were obtained by searching for the electronic medical records, including age, gender, onset time, clinical typing, and clinical examination results. Clinical test results included Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Urea, Creatinine (CREA), Cystatin C (CYSC), Uric acid (UA), Creatine Kinase (CK), Creatine Kinase-MB (CK-MB), Lactate Dehydrogenase (LDH), Hydroxybutyrate Dehydrogenase (HBDH), Homocysteine (HCY), C-reactive protein (CRP), Interleukin-6 (IL-6), and Procalcitonin (PCT).

Laboratory tests

The serum concentrations of human Surfactant Protein D (SP-D), Chemokine C-C motif Ligand 18 (CCL-18), and active and pro-Matrix Metalloproteinase 7 (total MMP-7) were measured using ELISA (Research & Diagnostics Systems, Inc.). The serum concentrations of SARS-CoV-2 spike (RBD) specific IgA, IgM, IgG antibodies and Krebs von den Lungen-6 (KL-6) were measured using chemiluminescent methods (Kangrun Biotech.).

Statistical methods

Statistical analysis of data was performed using the SPSS 22.0 software package. Data are presented as counts and percentages for categorical data and medians and interquartile ranges (IQRs) for continuous data. χ^2-test was used for intergroup comparison of categorical data, *t*-test was used for intergroup comparison of measurement data conforming to normal distribution, and Mann–Whitney *U*-test was used for measurement data not conforming to normal distribution. The diagnostic efficacy of serum marker levels in severely ill patients was analyzed using receiver operating characteristic (ROC) curves, and the area under the ROC curve (AUC) was used to evaluate the diagnostic efficacy. The sensitivity and specificity were selected according to the optimal screening cut-off value when the Youden index was the largest. $P < 0.05$ was considered statistically significant.

Results

Patients' basic characteristics

As shown in Table 1, there were 52 moderately ill patients (26 males and 26 females) and 12 severely ill patients (9 males and 3 females) among 64 patients with confirmed diagnosis. There was no significant difference in gender across different types of COVID-19 ($\chi^2 = 2.459$, $P = 0.117$). The mean age of moderately ill patients was 42 (31, 51.75) years, and the age of severely ill patients was 53.5 (49, 66.75) years. The age was significantly different across different types of COVID-19 ($t = -3.786$, $P < 0.001$).

Table 1
Characteristics of 64 COVID-19 patients.

Age	All patients		Non-severe group		Severe group	
(y)	Male	Female	Male	Female	Male	Female
< 21	4	1	4	1	0	0
21–30	4	3	4	3	0	0
31–40	7	7	6	7	1	0
41–50	9	6	6	5	3	1
51–60	6	11	4	10	2	1
60–70	3	1	2	0	1	1
> 70	2	0	0	0	2	0
Median age	43	47	39.5	42	52	59
Total	35	29	26	26	9	3

Comparison of serum marker detection results between severely ill and moderately ill patients

The results of serum biomarkers in the early stage of hospitalization are shown in Table 2. The levels of KL-6 and IgA were significantly elevated in severely ill patients compared with moderately ill patients, and the difference was statistically significant ($P < 0.05$). In addition, the levels of serum IL-6, IgM and IgG were also higher in severely ill patients than in moderately ill patients, but the difference was not statistically significant ($P > 0.05$).

Table 2
Laboratory findings of COVID-19 patients and comparison between the non-severe and the severe groups.

	Non-severe group(n = 52)	Severe group(n = 12)	*P* value
ALT (U/L)	27 (17.25, 40.5)	26.5 (21.5, 59.25)	0.375
AST (U/L)	26 (20, 32.5)	27 (19.75, 36)	0.611
UREA (mmol/L)	3.3 (2.7, 3.88)	4.1 (3.2, 5.05)	0.251
CREA (μmol/L)	65.5 (54.25, 75.75)	68.5 (57.5, 71.75)	0.981
CysC (mg/L)	0.8 (0.71, 0.9)	0.85 (0.78, 1.02)	0.240
UA (μmol/L)	268.5 (214.25, 326.75)	234.50 (208.25, 262.50)	0.400
CK (U/L)	40.5 (34, 55.75)	38 (28.25, 62.25)	0.642
CK-MB (U/L)	11 (8, 14.75)	11 (11, 16.5)	0.402
LDH (U/L)	186 (171, 224.50)	193.50 (171, 303)	1.191
HBDH (U/L)	130.50 (120, 151.25)	139 (128.25, 210)	0.112
HCY (μmol/L)	12.4 (9.4, 16.85)	11.3 (9.35, 13.5)	0.278
CRP (mg/L)	4.2 (2.125, 14.75)	8.85 (1.3, 74.57)	0.570
IL-6 (pg/L)	5.8 (3, 17.28)	38.7 (7.2, 48.88)	0.156
PCT (ng/L)	0.03 (0.02, 0.05)	0.045 (0.0225, 0.085)	0.274
SP-D (ng/L)	4.39 (1.94, 7.11)	4.64 (1.89, 11.04)	0.709
CCL-18 (pg/L)	31.27 (21.18, 42.64)	31.41 (10.19, 49.38)	0.981
MMP-7 (ng/L)	2.84 (2.34, 3.58)	3.52 (2.37, 4.47)	0.213
KL-6 (U/mL)	317.07 (235.84, 440.51)	446.81 (350.86, 728.58)	**0.015**
IgG (COI)	16.8 (6.73, 25.94)	26.13 (18.57, 29.82)	0.093
IgM (COI)	5.37 (1.47, 17.71)	7.22 (4.12, 13.52)	0.256
IgA (COI)	4.65 (2.88, 15.68)	9.97 (6.93, 57.94)	**0.029**

Analysis of the diagnostic efficacy of serum markers in severely ill patients

ROC curves were used to analyze the diagnostic efficacy of using various parameters for diagnosing severely ill patients with COVID-19, and the single test of KL-6 had the best efficacy in diagnosing severely ill patients, followed by IL-6 and IgA (Fig. 1). The cut-off of using KL-6 alone for the diagnosis was 298.91 U/mL, with an AUC of 0.737, a sensitivity of 100%, and a specificity of 43%. When the two tests were used

in combination for diagnosis, KL-6 combined with IL-6 showed the best diagnostic efficacy, with an AUC of 0.776 and a sensitivity and specificity of 82% and 69%, respectively. The AUC of the combined diagnosis of the three tests of KL-6, IL-6 and IgA was 0.785, with a sensitivity and specificity of 100% and 59%, respectively.

Results of serum marker tests in patients at different stages

The patients had changes in the levels of multiple serum biomarkers at 3-month follow-up compared with early hospitalization, as shown in Table 3. Among them, CRP, an inflammatory indicator, and KL-6, an indicator of pulmonary fibrosis, were significantly reduced, suggesting that the patients' condition had improved. Notably, the levels of all three antibodies, IgA, IgM, and IgG, were significantly reduced, and the differences were statistically significant ($P < 0.001$).

Table 3
Laboratory findings of COVID-19 patients and comparison between in hospitalization and at follow-up.

	In hospitalization(n = 40)	At follow-up(n = 40)	*P* value
ALT (U/L)	29 (20, 42)	21 (15.5, 36.5)	0.208
AST (U/L)	27 (18, 33.25)	20 (17.75, 26)	**0.001**
UREA (mmol/L)	3.55 (2.925, 4.35)	4.2 (3.625, 5.05)	**< 0.001**
CREA (μmol/L)	69.5 (57, 76.75)	67.5 (52.75, 75.75)	0.603
CysC (mg/L)	0.875 (0.755, 0.99)	0.83 (0.7125, 0.945)	0.107
UA (μmol/L)	270 (234.25, 328.75)	292 (255, 369.75)	0.252
CK (U/L)	38.5 (29.75, 46.25)	65.5 (47.75, 83.5)	**< 0.001**
CK-MB (U/L)	11 (7.75, 14.75)	8.5 (4.5, 12)	0.334
LDH (U/L)	184 (166.25, 206.25)	212 (183, 232.75)	0.089
HBDH (U/L)	129 (120, 146.25)	150 (132.75, 162)	**0.016**
HCY(μmol/L)	12.5 (9.9, 15.975)	16.3 (11.875, 18.95)	**0.001**
CRP (mg/L)	8.7 (2.65, 33.125)	2.25 (1.45, 3.675)	**0.004**
SP-D (ng/L)	3.81 (1.943, 7.411)	5.14 (2.896, 7.497)	**0.006**
CCL-18 (pg/L)	32.46 (15.09, 41.10)	19.79 (12.24, 34.25)	0.135
MMP-7 (ng/L)	3.16 (2.39, 4.24)	3.77 (3.09, 4.64)	**0.002**
KL-6 (U/mL)	351.01 (253.95, 471.83)	79.85 (44.12, 138.90)	**< 0.001**
IgG (COI)	22.75 (13.78, 26.54)	2.97 (1.03, 7.63)	**< 0.001**
IgM (COI)	6.8 (3.06, 13.77)	0.17 (0.09, 0.65)	**< 0.001**
IgA (COI)	7.73 (3.89, 26.73)	0.72 (0.18, 1.99)	**< 0.001**

Discussion

The clinical features of COVID-19 patients are diverse, with some patients having mild symptoms and some progressing into severe cases, which can be life-threatening. Early identification of severely ill patients will be beneficial to improve patient's prognosis and reduce mortality. In the present study, we investigated potential biomarkers in severely ill patients by analyzing the results of serological index indicators in patients at the early stage of hospitalization.

The results of the present study showed that serum KL-6 and IgA levels were significantly elevated in severely ill patients compared with moderately ill patients. KL-6 is a high-molecular-weight mucin expressed by type II alveolar epithelial cells (AECII). When AECII is injured, more KL-6 is secreted through its proliferation and differentiation and leaks through the basement membrane into the blood circulation, thereby increasing KL-6 levels in serum [16, 17]. KL-6 is one of the important markers of pulmonary fibrosis, and KL-6 is elevated in the serum of patients with interstitial pneumonia, and the degree of elevation has a correlation with the occurrence and severity of interstitial lung disease [18–19]. d'Alessandro et al. also confirmed that the serum KL-6 could diagnose severe COVID-19, with a cut-off of 406.5 U/ml, an AUC of 0.824, and a sensitivity and specificity of 83% and 89%, respectively [20]. In the report of Awano et al., serum KL-6 value of 371 U/ml was used as the optimal cut-off to evaluate disease severity with a sensitivity of 85.7% and specificity of 96.6% [21]. In the present study, the cut-off of using KL-6 alone for the diagnosis of severely ill patients was 298.91 U/mL, with an AUC of 0.737, a sensitivity of 100%, and a specificity of 43%. Although the sensitivity was good, the specificity was low, and the cut-off was also different from the findings of d'Alessandro et al [20]. The diagnostic efficacy of KL-6 for severe disease in patients with COVID-19 remains to be confirmed by larger cohort studies.

IL-6 is a commonly used rapid detection indicator of infectious diseases and one of the important inflammatory factors triggering cytokine storm in patients with COVID-19 [22, 23]. After SARS-CoV-2 virus infection, pathogenic T cells are rapidly activated and factors such as Granulocyte-macrophage Colony Stimulating Factor (GM-CSF) and IL-6 are abundantly produced, thus forming an inflammatory storm and leading to severe immune damage in lungs and other organs [24]. IL-6 levels progressively increase in severely ill patients with COVID-19 and have been demonstrated to be an early warning indicator of progression into severe disease [25]. In the present study, the serum IL-6 levels were elevated in severely ill patients compared with moderately ill patients, but the difference was not statistically significant (Table 2). However, the results of ROC curve analysis still showed that IL-6 had some efficacy in diagnosing severely ill patients: The AUC was 0.720, and the sensitivity and specificity were 64% and 80%, respectively. IL-6 had better diagnostic efficacy combined with KL-6, with an AUC of 0.776 and sensitivity and specificity of 82% and 69%, respectively. The present study also found that IgA was significantly elevated in severely ill patients with COVID-19 and could be used as one of the potential markers for the diagnosis of progression into critical disease, and the results were consistent with the results of the study conducted by Ma et al. [14].

At the three-month follow-up, a number of serum marker levels changed in patients with coronavirus disease 2019, suggesting that the patients' condition had recovered. In addition to a significant decrease in the level of the inflammatory factor CRP, KL-6, an indicator of pulmonary fibrosis, was also significantly reduced. In addition, all three antibodies specific to SARS-CoV-2, IgA, IgM, and IgG, were very significantly down-regulated, consistent with the results reported in previous studies [14, 26]. It is worth investigating whether recovered patients will have the same risk of infection as that of previously uninfected people when encountering the SARS-CoV-2 virus again [26].

In summary, close monitoring and tracking of serum KL-6, IL-6 and IgA, three potential risk indicators of severe disease, and early intervention will likely avoid the progression into severe disease of COVID-19 and improve patient prognosis, which has important clinical significance. However, disease progression is an ongoing process, and the present study is limited by no continuous monitoring in patients due to condition restrictions. In addition, although the present study suggested that KL-6, IL-6 and IgA had potential value in the diagnosis of progression into severe coronavirus disease 2019, the limitations of this study, which include the limited number of cases and the retrospective nature of study, indicate that this value needs to be confirmed by a larger cohort study.

Conclusions

KL-6 and IgA were found to have some diagnostic efficacy for severely ill patients with COVID-19 in this study, but larger cohort studies are still needed for further confirmation, which in turn improves the diagnostic and therapeutic efficiency of severely ill patients.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RT-PCR: Reverse-transcript polymerase chain reaction; KL-6: Krebs von den Lungen-6; IgA: Immunoglobulin A; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CREA: Creatinine; CYSC: Cystatin C; UA: Uric acid; CK: Creatine Kinase; CK-MB: Creatine Kinase-MB; LDH: Lactate Dehydrogenase; HBDH: Hydroxybutyrate Dehydrogenase; HCY: Homocysteine; CRP: C-reactive protein; IL-6: Interleukin-6; PCT: Procalcitonin; SP-D: Surfactant Protein D; CCL-18: Chemokine C-C motif Ligand 18; MMP-7: Matrix Metalloproteinase 7; IQRs: medians and interquartile ranges; AUC: the area under the ROC curve; ROC curve: receiver operating characteristic curve; AECII: type II alveolar epithelial cells; GM-CSF: Granulocyte-macrophage colony stimulating factor.

Declarations

Ethics approval and consent to participate

All procedures in this study were performed according to the ethical standards and approved by the Ethical Committee for Clinical Studies in the Second People' Hospital of Fuyang City (No. 20200229008).

Consent for publication

All authors read and approved the publication of this manuscript.

Availability of data and materials

All data supporting the conclusions of this article are included in this manuscript.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

HW performed the laboratory tests and prepared the draft manuscript. LC collected the clinical data. YZ, LL and MX conducted statistical analyses. BS designed the KL-6 test method. YG, TJ and ML designed and supported the study.

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Figures

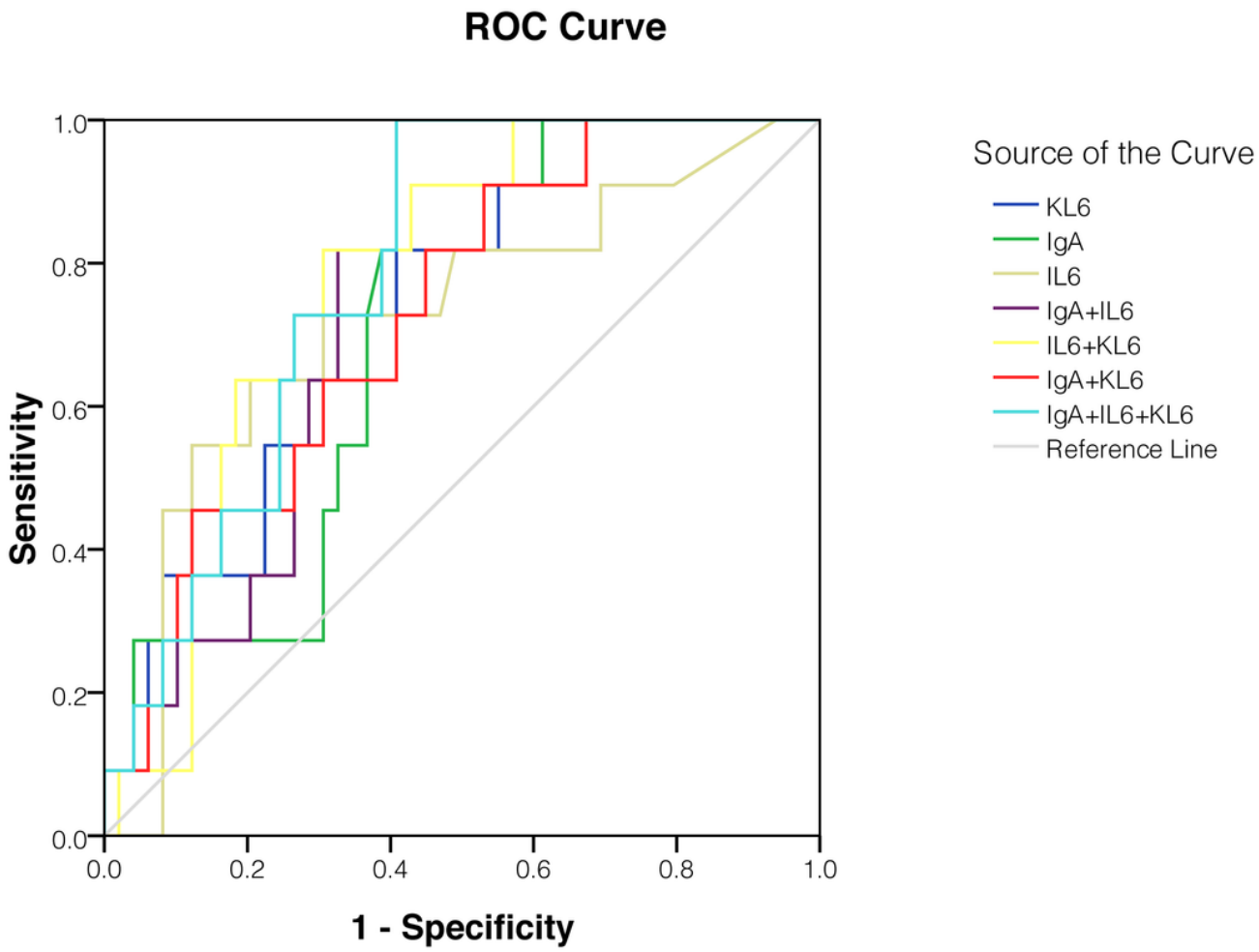

Figure 1

ROC curve used to evaluate the diagnostic efficacy in severe disease of COVID 19.

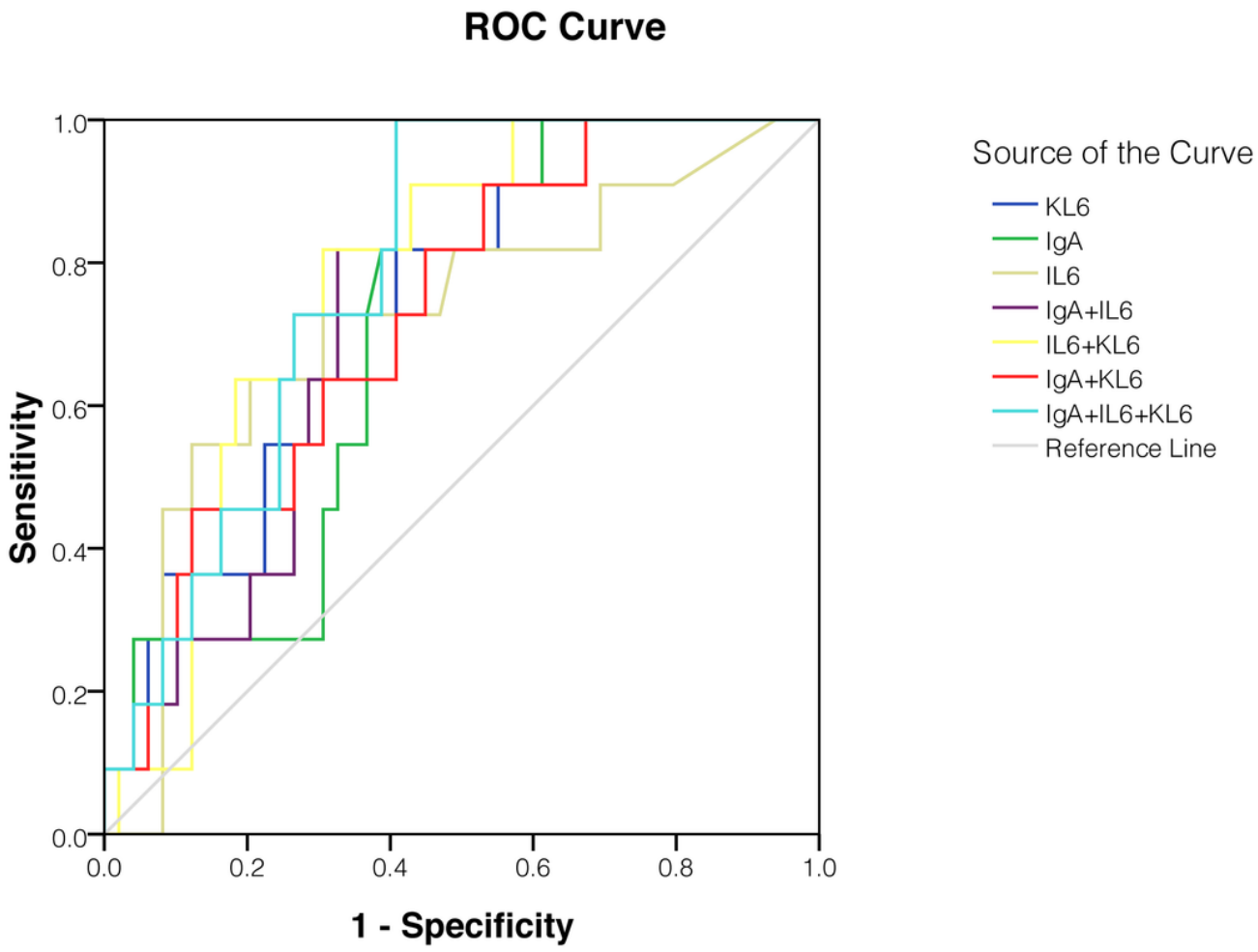

Figure 1

ROC curve used to evaluate the diagnostic efficacy in severe disease of COVID 19.