# LDH-to-leukocyte ratio predicts COVID-19 diagnosis and CRP-to-lymphocyte ratio predicts prognosis of patients with COVID-19

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# Abstract

Routine blood parameters are altered in patients with COVID-19 with differences depending on the severity of the disease. Therefore, they may predict diagnosis as well as prognosis of patients with COVID-19 and may be helpful when resources are limited.

All patients admitted to our hospital were analyzed for routine blood parameters and SARS-CoV-2 screening results on admission. Primary endpoint was the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis of routine blood parameters with PCR as gold standard.

A total of 115 patients were included in the study. Median age was 79 years and male/female ratio was 49%/51%. 77 (67%) patients had PCR confirmed COVID-19. The lactate dehydrogenase (LDH) to leukocyte (WBC) ratio was the best diagnostic predictor (AUC 0.82), markedly better than the single parameters LDH (AUC 0.72) and WBC (AUC 0.75). Optimum cut-off of LDH/WBC ratio was 24.7 nU (sensitivity 87%, specificity 76%). The best single parameter for predicting a severe course of COVID-19 patients were CRP (AUC 0.83) and absolute lymphocyte count (ALC, AUC 0.77). Their ratio CRP/ALC surpassed both with an AUC of 0.88. Optimum cut-off was 77 n*mg (sensitivity 83%, specificity 80%).

Our study showed, that on admission the LDH/WBC ratio is a diagnostic predictor of COVID-19 in symptomatic patients. In patients with COVID-19 the CRP/ALC ratio predicts severe course and probability of survival. Both are simple and good tools and may be helpful during pandemic when resources are limited.


# 1. Introduction

Since December 2019, an emerging infectious disease (COVID-19), caused by the novel coronavirus SARS-CoV-2, has emerged in Wuhan, China [1], [2]. The majority of cases have mild or asymptomatic course [3]. Symptoms of the COVID-19 infection are highly nonspecific, including respiratory symptoms, fever, cough, dyspnea, and viral pneumonia [4]. Thus diagnosis of COVID-19 relies on tests specific to SARS-CoV-2 such as real-time polymerase chain reaction (PCR), which represents the gold standard for routine and confirmatory diagnosis of COVID-19. The capacitiy of PCR methods, however, is limited by their requirement of high-level facilities and instruments. Therefore, PCR results are not usually available when they are urgently needed.

Under the pressure of the COVID-19 pandemic triage programs have been developed for intensive-care treatment under resource scarcity in rich countries [5]. For low-income settings adoption of triage strategies with a more simple and reasonable approach has been proposed [6]. In the triage setting the significance of an exact diagnosis is decreasing and the impact of the expected prognosis increasing.

In March 2020, some patients were admitted with suspicion of COVID-19 to our general hospital in Bavaria, Germany. At that time the delay in PCR test results was significant at that time and the new and faster test we used temporarily, failed to reliably detect SARS-CoV-2 in respiratory samples [7]. A recent

study showed that a few hematologic parameters were clearly altered in COVID-19 patients with differences between ICU and non ICU patients [8]. Altered hematological parameters may be caused by SARS-CoV-2, i.e. by the disease itself or by the severity of the disease, caused by mechanisms such as cytokine storm [9]. Therefore, we analyzed routine blood parameters for their potential to predict COVID-19 diagnosis as well as to predict prognosis in patients with confirmed COVID-19 during the admission procedure in the emergency department.

## 2. Materials And Methods

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee of the Ludwig-Maximilians-University, Munich, Germany approved this study (approval number 20-432).

During the SARS-CoV-2 pandemic patients admitted to our hospital were screened for SARS-CoV-2 with PCR assay from throat swabs and routine blood parameters were determined. Evaluation of blood parameter results for predicting diagnosis as well as prognosis was performed using receiver operating characteristic (ROC) and survival analysis.

### 2.1. Inclusion and exclusion criteria

Records of all patients admitted to our general hospital from April 1 to April 30, 2020 were analyzed for routine blood parameter and SARS-CoV-2 screening results on admission. Inclusion criteria were documented results of a SARS-CoV-2 PCR assay and a minimum of routine blood parameters, including a complete blood count with differential as well as the lactate dehydrogenase (LDH) and the C-reactive protein (CRP). Patients were excluded only if data was incomplete.

### 2.2. Endpoints

Primary endpoint was the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis of routine blood parameters predicting diagnosis with the SARS-CoV-2 PCR assay as gold standard. Secondary endpoints were the survival probability and the ROC analysis for prediction of severe course defined as death or the need for mechanical ventilation in COVID-19 patients.

### 2.3. Statistics

According to the retrospective nature of this study sample size calculation was not performed. Results are given in numbers and percent or median and interquartile range (IQR). The exact 95% confidence interval of rates was calculated by the Clopper and Pearson method. Survival analysis was carried out using the Kaplan-Meier method and the Log-Rank test to compare two groups of patients. Blood

parameter results were compared using a Mann-Whitney U test for independent variables. All statistical tests were performed using SPSS.

## 3. Results And Discussion

From April 1 to April 30, 2020 173 patients were admitted to our hospital. In 115 cases results of SARS-CoV-2 PCR screening and minimum blood parameters including a complete blood count with differential as well as LDH and CRP on admission were documented. Patient characteristics were listed in table 1.

## Table 1

Patient characteristics (n=115). Data are median (IQR) or number (%)

| | |
|---|---|
| Age, years | 78.8 (64.2 – 84.0) |
| Male/female | 56/59 (48.7%/51.3%) |
| Duration of hospital stay, days | 4 (2 – 8) |
| Survivors/non-survivors | 92/23 (80%/20%) |
| Department | |
| Internal Medicine | 109 (94.8%) |
| Surgery | 2 (1.7%) |
| Otorhinolarynology, Head and Neck Surgery | 4 (3.5%) |
| Chest CT scan | 96 (83.5%) |
| Clinical Diagnosis | |
| COVID-19, PCR confirmed | 77 (67.0%) |
| Suspected COVID-19, PCR negative | 6 (5.2%) |
| Circulatory | 8 (7.0%) |
| Respiratory | 6 (5.2%) |
| Genitourinary | 3 (2.6%) |
| Poisoning | 2 (1.7%) |
| Digestive | 2 (1.7%) |
| Infectious | 2 (1.7%) |
| Bleeding (ENT) | 2 (1.7%) |
| Other | 7 (6.1%) |

ENT = Ear, Nose, Throat

Laboratory values for all patients included as well as those for PCR confirmed COVID-19 and non COVID-19 patients were listed in table 2.

## Table 2

Routine laboratory values on admission for all patients included, for PRC confirmed COVID-19 and PCR negative (non COVID-19) patients.

| Blood parameter | Total (n = 115) | COVID-19 (n = 77) | Non COVID-19 (n = 38) | p value |
|---|---|---|---|---|
| White blood cell count, /nL | 7.2 (5.2 – 9.9) | 6.3 (4.6 – 8.3) | 9.1 (7.1 – 13.3) | ≤ 0.001 |
| Lymphocyte count, /nL | 0.99 (0.67 – 1.45) | 0.94 (0.67 – 1.28) | 1.03 (0.70 – 1.64) | 0.393 |
| Platelet count, /nL | 209 (156 – 263) | 184 (142 – 246) | 238 (184 – 264) | 0.013 |
| LDH, U/L | 264 (189 – 353) | 290 (216 – 372) | 191 (168 – 256) | ≤ 0.001 |
| CRP, mg/dL | 5.39 (1.32 – 11.40) | 5.53 (2.03 – 11.50) | 4.01 (0.49 – 10.18) | 0.160 |
| High-sensitivity cardiac troponin I, pg/mL | 20.0 (9.2 – 40.3) | 16.8 (8.8 – 31.6) | 25.8 (17.5 – 58.4) | 0.016 |
| D-dimer, mg/L | 1.20 (0.60 – 2.57) | 1.07 (0.59 – 2.41) | 1.77 (0.71 – 2.65) | 0.252 |

Data are median (IQR). P values were calculated by Mann-Whitney U test. LDH = Lactate dehydrogenase, CRP = C-reactive protein

Screening SARS-CoV-2 PCR assay was positive in 77 (67.0%) and clinical COVID-19 diagnosis was made in 83 (72.2%) out of all 115 patients included. In PCR negative patients COVID-19 diagnosis was suspected based on typical findings of chest CT (n = 6). Assuming a correct clinical diagnosis, sensitivity of PCR from throat swabs was 92.8% (77/83, 95% CI 84.9% – 97.3%).

In patients with COVID-19 LDH levels were significantly higher ($p \leq 0.001$) and white blood cell (WBC) counts were significantly lower ($p \leq 0.001$) compared with non COVID-19 patients. Therefore, we further investigated the ratio of both (LDH/WBC, unit: nU) as a predictor of PCR confirmed COVID-19 diagnosis. Boxplots of the distribution of the LDH/WBC ratio depending on SARS-CoV-2 PCR are shown in figure 1.

ROC curves of WBC count (lower levels predict COVID-19), as well as LDH and LDH/WBC ratio (higher levels predict COVID-19) as predictors of PCR confirmed COVID-19 are shown in figure 2.

ROC analysis of single blood parameters predicting PCR confirmed COVID-19 diagnosis on admission showed AUC values of at least 0.7 for LDH and WBC count only (table 3, column 2). The AUC of the LDH/WBC ratio as a diagnostic predictor was highest with 0.82 (0,73 – 0,91). The optimum cut-off of the LDH/WBC ratio was 24.7 nU (sensitivity 87%, specificity 76%, accuracy 83%, PPV 87%, NPV 74%). Severe course defined as death (n = 15), the need for mechanical ventilation (n = 3) or both (n = 5) was observed in 23 (30%) patients out of 77 with PCR confirmed COVID-19. The best two single parameter for predicting severe course were CRP (higher levels predict severe course, AUC 0.83) and absolute lymphocyte count (ALC, lower levels predict severe course, AUC 0.77) (table 3, column 3). The AUC of their ratio CRP/ALC was 0.88 with an optimum cut-off of 77 n*mg (sensitivity 83%, specificity 80%, accuracy 81%, PPV 63%, NPV 91%).

# Table 3

Area under the curve (95% CI) of the ROC analysis for predicting PCR confirmed COVID-19 (diagnosis) in all patients included and for predicting severe course (prognosis) in patients with PCR confirmed COVID-19

| Blood parameter | AUC – Diagnosis (n = 115) | AUC – Prognosis (n = 77) |
|---|---|---|
| White blood cell count | 0.75 (0.67 – 0.83) | 0.54 (0.39 – 0.68) |
| Lymphocyte count, absolute | 0.55 (0.45 – 0.65) | 0.77 (0.67 – 0.88) |
| Platelet count | 0.64 (0.56 – 0.73) | 0.51 (0.38 – 0.64) |
| LDH | 0.72 (0.63 – 0.81) | 0.62 (0.50 – 0.75) |
| CRP | 0.58 (0.48 – 0.68) | 0.83 (0.75 – 0.91) |
| High-sensitivity cardiac troponin I | 0.65 (0.55 – 0.74) | 0.75 (0.65 – 0.85) |
| D-dimer | 0.57 (0.47 – 0.68) | 0.62 (0.48 – 0.75) |
| LDH/WBC ratio | 0.82 (0.74 – 0.90) | 0.52 (0.39 – 0.65) |
| CRP/ALC ratio | 0.58 (0.47 – 0.68)) | 0.88 (0.81 – 0.95) |
| LDH/ALC ratio | 0.64 (0.55 – 0.74) | 0.75 (0.64 – 0.86) |

LDH = Lactate dehydrogenase, CRP = C-reactive protein, LDH/WBC ratio = lactate dehydrogenase / white blood cell count ratio, ALC = absolute lymphocyte count

Survival analysis in PCR confirmed COVID-19 patients is shown in figures 3a) – 3c). Groups are defined by CRP (cut-off 7.0 mg/dL), absolute lymphocyte count (cut-off 0.8 /nL), and CRP/ALC ratio (cut-off 70 n*mg). Median survival of groups defined by these cut-offs for CRP, ALC, and CRP/ALC ratio were 11.6 days versus not yet reached ($p \leq 0.001$), 11.1 versus 33.0 days ($p = 0.003$), and 11.1 versus 33.0 days ($p \leq 0.001$), respectively.

## 3.1. Discussion

With this analysis we searched for a simple and fast decision-making tool for the acute setting of an emergency department and aimed at synergistic effects when combining two single parameters. Analysis of the discriminating power of routine blood parameters was performed by means of ROC analysis [10]. The higher the AUC the better the discriminating power, with AUC values of 0.8 – 0.9 considered good or excellent while the AUC value of the random baseline is 0.5 [11], [12].

Potential risk factors in COVID-19, which could help to identify patients with poor prognosis at an early stage have been reported recently [13]–[15]. Among these risk factors were routine blood parameters, such as D-dimer, LDH and the absolute lymphocyte count. Other blood parameters, such as procalcitonin or interleukin-6, may not be available in time in smaller hospitals with limited resources or in acute and ambulatory care settings. Furthermore, some of the factors only gained significance in the course of the disease having limited discriminating power initially.

The first and crucial step however, remains the correct diagnosis as soon as possible. Confirmatory diagnosis by means of SARS-Cov-2 PCR is usually not available in time due to limitations as a results of the requirements for high-level facilities and instruments. The potential of routine blood tests as a diagnostic tool has been published recently [16], [17]. Ferrari et al. evaluated single parameters and reported the identification of 70% of either COVID-19 positive or negative patients by empirical thresholds of aspartate aminotransferase (AST) and LDH [16]. LDH was missing in notable 76 of 207 (36.7%) patients. Cut-off levels of >210 U/L and >35 U/L for LDH and AST, respectively, for COVID-19 positivity as well as of <25 U/L for AST for COVID-19 negativity were empirically adopted. This partial combination of

two single parameters with different thresholds predicting COVID-19 positivity and negativity resulted in 87 of 207 (42.0%) patients remaining unclassified.

A very complex strategy including machine learning was evaluated by Brinati et al. [17]. Different models comprising 14 single parameters were compared with SARS-CoV-2 PCR. The best performing model achieved the following results: AUC 84%, sensitivity 92%, specificity 65%, PPV 83%, accuracy 82%. The sensitivity of this model is impressive, but the need for 14 items and a web-based tool may limit its practicability.

Some research focused on PCR confirmed COVID-19 patients only and evaluated prognostic factors [18]–[20]. Yang et al. analyzed parameters of a complete blood count with differential and the CRP but no other serum parameters. In their study the neutrophile to lymphocyte ratio (NLR) was the best independent factor for poor clinical outcome in COVID-19 with an AUC of 0.84. The optimum cut-off was 3.3 (sensitivity 64%, specificity 88%) [18]. Survival analysis was performed for groups defined by the optimum NLR cut-off determined by ROC analysis and demonstrated significant differences with a mean survival of 6.3 versus 13.5 days ($p < 0.001$). Median survival was not reported but can be roughly estimated from the Kaplan-Meier plots provided at a little over 8 days versus just less than 13 days with a difference of about 4.5 days. This suggests a very poor prognosis of the patients analyzed even in the low risk group defined by the optimum NLR cut-off. Another study demonstrated the NLR as independent risk factor for critical illness in COVID-19. AUC of ROC analysis was 0.85 in the derivation cohort [19]. Optimum cut-off was 3.13 (sensitivity 87.5%, specificity 71.7%, PPV 31.8%, NPV 97.4%).

In our study the ratio of the best two single parameter LDH and WBC was superior in predicting COVID-19 diagnosis with an optimum cut-off of about 25 nU (AUC 82%, sensitivity 87%, specificity 74%, PPV 87%, NPV 74%). In predicting severe course of COVID-19 the ratio of the best two single parameter CRP and ALC was superior. Optimum cut-off was 77 n*mg (AUC 0.88, sensitivity 83%, specificity 80%, PPV 63%, NPV 91%). The AUC value of the CRP/ALC ratio in our study (0.88) was higher than the AUCs of prognostic parameters such as the procalcitonin (0.80) or the $FiO_2$ in patients with $O_2$-supply (0.76) in a cohort of 99 patients with COVID-19 in Switzerland [15].

Interestingly, the lymphocyte-to-C-reactive protein ratio (i.e. ALC/CRP ratio, the reciprocal of CRP/ALC ratio) has been described as marker of inflammation and outcome in patients with different gastrointestinal cancers [21], [22] and as marker for intestinal ischemia in strangulated abdominal wall hernias [23] recently, but not in COVID-19 or other infectious diseases.

It is worthy to note, that only some factors were diagnostic as well as prognostic. The LDH was an acceptable diagnostic factor in the ROC analysis as well as a good predictor of survival in the Kaplan-Meier analysis (data not shown). On the other hand the lymphocytes, well known as prognostic factor in COVID-19 showed nearly identical distributions in patients with and without COVID-19 whereas the good diagnostic predictor LDH/WBC ratio failed to predict severe course.

The spectrum of symptoms caused by SARS-CoV-2 infections ranges from frequent asymptomatic course to ARDS and multiple-organ failure caused by cytokine storm [9]. All patients enrolled in this study were admitted to our hospital, no asymptomatic patients were included. Most COVID-19 patients had pulmonary involvement as shown by chest CT. LDH is an intracellular enzyme and its release a marker of necrosis. Therefore, the LDH/WBC ratio will depend on a certain minimum of severity of disease and pulmonary involvement to become diagnostic. It will fail to reliable discriminate SARS-CoV-2 positivity from negativity among asymptomatic individuals without pulmonary involvement and therefore will not be a substitute for PCR testing in the screening setting. The same applies for chest CT, an excellent tool in the early diagnostic evaluation of symptomatic patients [24], [25].

## 4. Conclusion

Our study showed, that on admission the LDH/WBC ratio is a diagnostic predictor of COVID-19 in symptomatic patients. In patients with COVID-19 the CRP/ALC ratio predicts severe course and probability of survival. Both ratios are simple and good tools and may be helpful during pandemic when resources are limited.

## Declarations

# Data Availability

The data used to support the findings of this study are available from the first author and corresponding author upon request.

# Conflicts of Interest

The authors declare that they have no conflicts of interest.

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# Figures

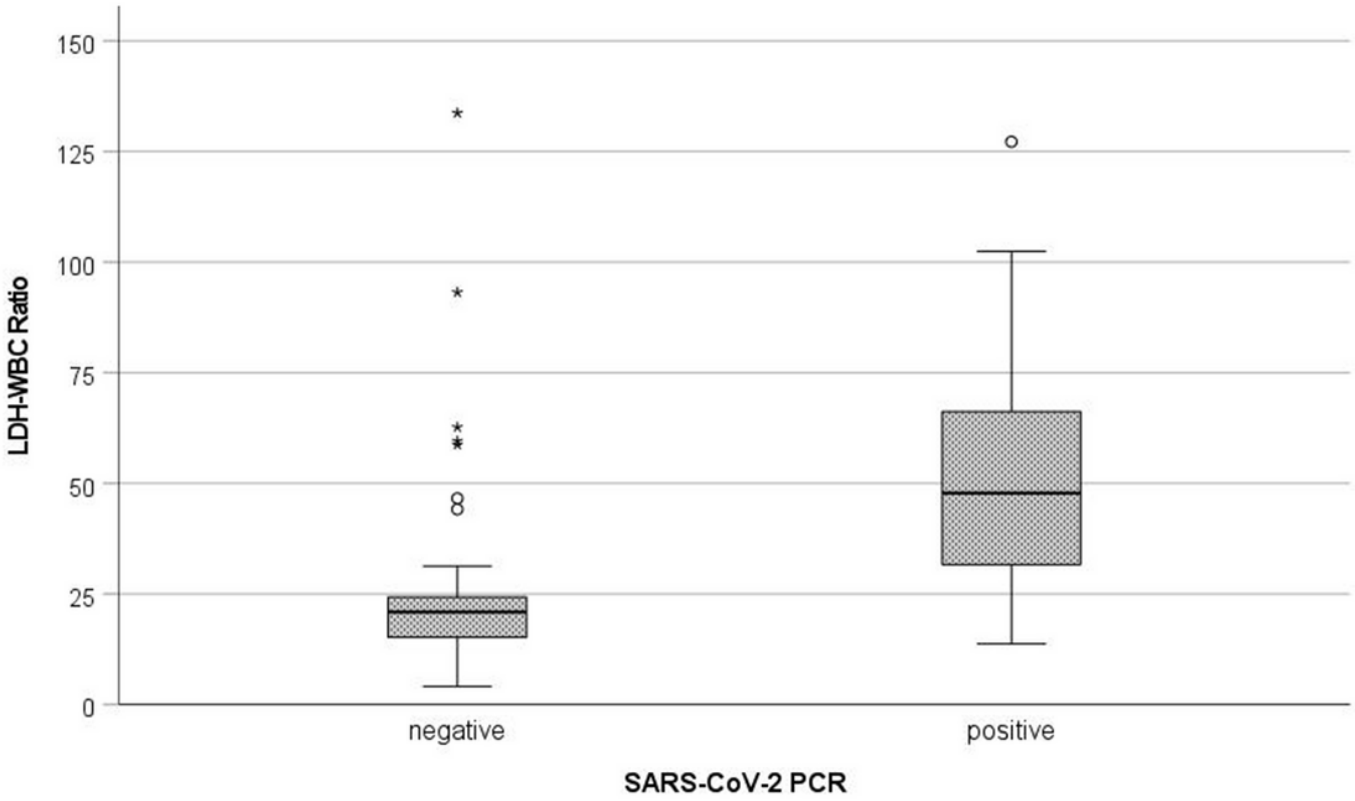
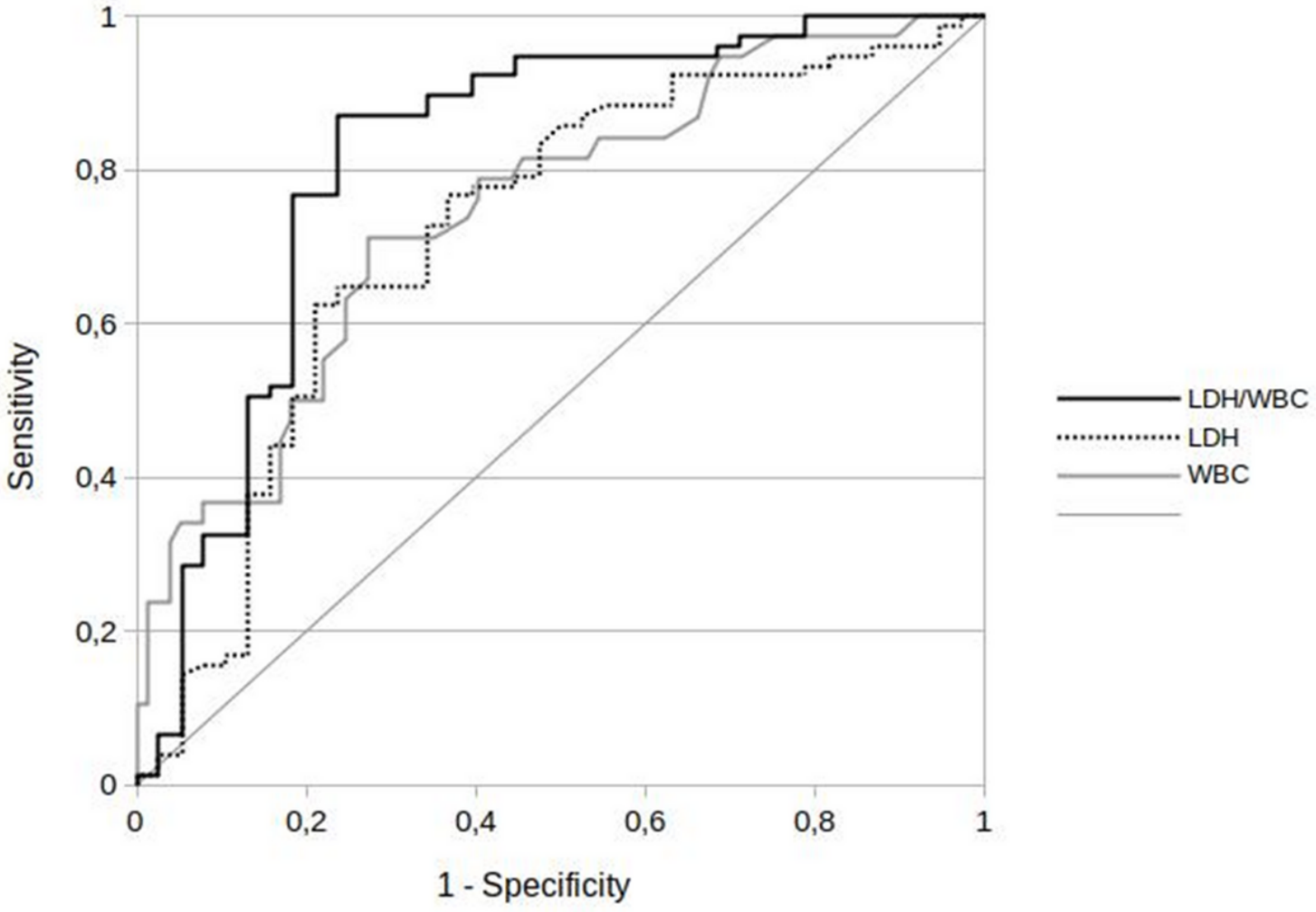


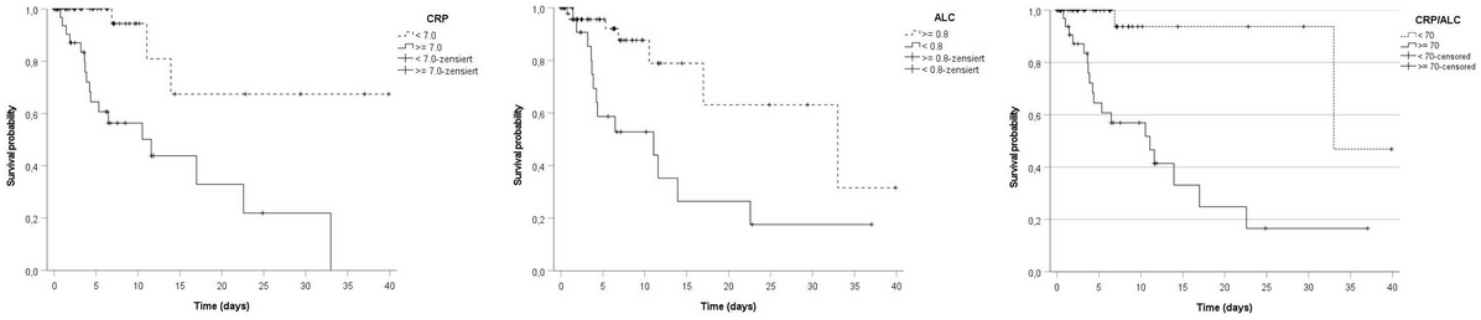

**Figure 1**

Boxplot of the lactate dehydrogenase (LDH) – white blood cell (WBC) count ratio (n = 115) in patients with (n = 77) and without (n = 38) PCR confirmed COVID-19. One outlier (293, PCR positive) not shown. P ≤ 0.001 (Mann-Whitney U test).




## Figure 2

Receiver operating characteristic curves of white blood cell count (WBC, lower levels predict COVID-19), as well as lactate dehydrogenase (LDH) and LDH/WBC ratio (higher levels predict COVID-19) as predictors of PCR confirmed COVID-19 (n = 115).




## Figure 3

Kaplan-Meier survival plots of PCR confirmed COVID-19 patients (n = 77). Groups are defined by CRP (cut-off 7.0 mg/dL, ($p \leq 0.001$), figure 3a), absolute lymphocyte count (ALC, cut-off 0.8 /nL, p = 0.003, figure

3b), and by CRP/ALC ratio (cut-off 70 n*mg, ($p \leq 0.001$), figure 3c).