

Original article

Can Hemogram Parameters Predict a Positive PCR Result in COVID-19?

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Abstract

Objective: Quick diagnosis of COVID-19 has been an important factor to manage the ongoing pandemic at hospitals and other health facilities. We aimed to investigate the effects of PCR test on hemogram parameters in COVID-19 patients. **Materials and Methods:** We collected hemogram data of 120 nasopharyngeal and oropharyngeal combo swab PCR positive and 119 PCR negative patients admitted to our hospital's COVID-19 clinics with COVID-19 symptoms between 1 April 2020 and 24 June 2020. **Results:** Age, MPV and NLR were found to be higher; hemoglobin, neutrophil, lymphocytes, basophil, platelet, PCT, WBC levels were lower in PCR positive cases. The highest sensitivity, 75 % is found on WBC count with cut off 7.15. **Conclusion:** Lower leukocyte count than 7.15, lower neutrophil count than 4.91, greater NLR than 2.95, lower platelet than 221.5 may give an idea about the diagnosis of SARS-CoV-2 infection.

Keywords: PCR; COVID-19; infectious disease; pandemics; hemogram

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Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified in early 2020 and has caused more than 145 million confirmed cases and more than 3,000,000 deaths all over the world during the COVID-19 pandemic outbreak(1). "Confirmed case" is defined by WHO (World Health Organization) as "a person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms" (2). It seems like to affect plenty of people from all over the world for some more time according to modelling studies for the pandemic outbreak(3). WHO suggests real time reverse transcription polymerase chain reaction quantification RT-PCR (qRT-PCR) test to identify SARS-CoV-2 (4). RT-PCR is the gold standard test to determine SARS-CoV-2 infection presently (5). Time consuming manual process, expensive kits and biosafety environment necessities and false negative

results are disadvantages of RT-PCR tests during pandemic outbreak. Time is very important to detect cases, contacts and to stop the transmission of the virus earlier.

Covid19 starts a cascade of events related to inflammation and thrombosis. Quantifying some blood cell subtype proportions like white blood cell (WBC) count, neutrophil (N) count, lymphocyte (L) count, the neutrophil-lymphocyte ratio (NLR), the mean platelet volume (MPV), the platelet-lymphocyte ratio level (PLR) and red blood cell distribution width (RDW) may give idea about the diagnosis and prognosis of the infection. NLR, PLR and MPV are progressively being utilized as biomarkers of chronic inflammation recently(6). NLR is being used as a pointer of systemic inflammation in preeclampsia, coronary artery disease and ulcerative colitis(7)(8). PLR may give an idea about the status of thrombosis and inflammation(9).

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Viral antigen tests have also been tried to detect SARS-CoV-2 antigens during the pandemic outbreak. Immunochromatographic assay and biosensor based tests have been developed. The sensitivity of immunochromatographic assays vary from 16 % to 85 % (10).

Antibody testing against SARS-CoV-2 has also been used for the diagnosis of recent and past COVID-19 infection. Specific Ig M antibody against SARS-CoV-2 can be produced within the first 5-7 days of the infection and could be used to demonstrate recent infection, while it takes 10-15 days to develop Ig G antibody which may persist perceptible for months (11). Ig A can be established in mucosal secretions within the first 6-8 days, but the importance of it remains unclear (12). Antibody tests are usually not enough to diagnose as a single test.

Hemogram test is cheap and very widely used all over the world and displays the numbers of many different cell types related to the human immune system. Hematological complications caused by COVID-19 also increases the importance of hemogram. Here in this article, we aimed to investigate the effects of PCR test on hemogram parameters in COVID-19 patients.

Materials and Methods

Data collection

Patients' nasopharyngeal and oropharyngeal combo swab samples for SARS-CoV-2 detection were collected after admission and physical examination in Emergency Room. Patients with critical, serious, fair general situation and radiologic examination were hospitalized, blood samples for hemogram and biochemistry tests were collected routinely. Hemogram data of PCR positive and negative patients were collected from Laboratory Information Management System of our hospital.

We collected hemogram data of 120 nasopharyngeal and oropharyngeal combo swab PCR positive and 119 PCR negative patients admitted to our hospital's COVID-19 clinics with COVID-19 symptoms between 1 April 2020 and 24 June 2020. PCR and hemogram tests were performed on the same day or the next day of the former.

PCR tests were performed with RT-PCR test kits provided by the Turkish Health Ministry (Biospeedy COVID-19 RT-qPCR version 1 and 2). Swab samples including viral transport medium were studied with RT-qPCR method according to the manufacturer

instructions (Bioeksan, Istanbul, Turkey). The Test kit detects the RdRp (RNA dependent RNA polymerase) single gene fragment of SARS-CoV-2 specifically. World Health Organisation (WHO) published a document which declares that single discriminatory target in RT-PCR tests is accepted adequate in areas where COVID-19 virus is widely spread on 19th March 2020 at the beginning of the pandemic outbreak (13). Internal control is provided by the human RNase P gene in the test kit. The LightCycler 480 System (Roche Diagnostics GmbH, Mannheim, Germany) is used to perform gene amplification reactions and signal detections. Specimens indicating positive signal in internal control and RdRp region were regarded as positive while specimens indicating a positive signal in internal control and negative result in RdRp region were regarded as negative. If the cycle threshold (Ct) values detected below 40 with appropriate curves, the test is regarded as positive, if the Ct value was 0, the test was regarded as negative. PCR tests were concluded in approximately 16 hours after the test was ordered. Hemogram tests were performed on Mindray Hematology Analyzer (Shenzhen, P. R. China) and concluded on the same day. 120 PCR positive and 119 PCR negative patients with hemogram data were randomly chosen and parameters in the hemogram test were compared with biostatistical methods. 11 parameters of the hemogram test were collected to analyze. These parameters are;

White Blood Cell, neutrophil, lymphocytes, neutrophil/ lymphocytes ratio (NLR), basophil, platelet count, Hemoglobin, Red Cell Distribution Width (RDW), Mean Corpuscular Hemoglobin (MCH), Mean Platelet Volume (MPV), plateletcrit (PCT).

Statistical methods:

We compared numerical data from two independent groups by using Mann-Whitney U test. We used chi-square test for categorical variables. We used ROC analysis and logistic regression for each parameter to predict the existence of the disease as a dependent outcome. We used the Python programming language (14) and IBM SPSS for Mac OS, Version 22 (15) to prepare and analyse the data.

Results

Age, MPV and NLR were found to be significantly higher; hemoglobin, neutrophil, lymphocytes, basophil, platelet, PCT, WBC levels were lower in PCR positive cases than those of PCR negative cases.

There were no statistical differences between two groups concerning RDW and MCH values. Gender did not have any statistically significant effect on being tested positive.

Cut off points, specificity and sensitivity of Hemogram parameters are shown in Table 1. The highest sensitivity, 75 % is found on WBC count with cut off 7.15. According to these results, a patient with WBC count lower than 7.15 is PCR positive with probability 0.75, and a patient with WBC count more than 7.15 is PCR negative with probability 0.61. The second highest sensitivity, 67 % is found on neutrophil count with cut off 4.91. So a patient with neutrophil count less than 4.91 is PCR positive with probability 0.67, and a patient with neutrophil count more than 4.91 is PCR negative with probability 0.62. Best predicting parameters are WBC, neutrophil, lymphocyte, basophil and PLT counts.

Table 1. Cut off points, specificity and sensitivity of Hemogram parameters

Parameters	Cut off	Sensitivity %	Specificity %	p Value
RDW	13.55	54.2	54.8	0.357
MPV	9.85	42.5	69.6	0.026*
NLR	2.95	60	57.4	0.045*
Hemoglobin	14.45	36.5	80	0.018*
Neutrophil	4.915	67	62.5	0.001**
Lymphocyte	1.85	64.3	78.3	0.001**
Basophil	0.025	65.2	70	0.001**
PLT	221.5	63.5	67.5	0.001**
PCT	0.255	37.4	82.5	0.002**
WBC	7.15	75.7	61.7	0.001**
MCH	28.85	66.1	43.3	0.489

* p<0.05, statistically significant, ** p<0.005, statistically very significant

Logistic Regression

A logistic regression was executed to understand the impacts of age, basophil, RDW, and MCH on the likelihood that the participants have COVID-19 (Table 2). The logistic regression model was statistically significant by Hosmer-Lemeshow test, $\chi^2(8)=20.01$, p<0.01. Collinearity was observed among neutrophil, lymphocyte, and WBC, but their contribution to the logistic regression was not significant. The model explained 38.2% (Nagelkerke R²) of the variance in COVID -19 and correctly classified 73.7% of cases (Table 3). Increasing age was associated with a slight increase in the likelihood of having COVID -19, but increasing MCH or RDW

was associated with a decrease in the likelihood of having COVID -19.

Table 2: Logistic regression analysis results

	β	SE β	Wald χ^2	df	p	OR Exp(β)
Constant	12.028	4.281	7.894	1	0.005*	NA
BAS#	-29.803	13.106	5.171	1	0.023*	0
RDW	-0.38	0.118	10.452	1	0.001**	0.684
MCH	-0.223	0.077	8.399	1	0.004**	0.8
Age	0.018	0.009	4.389	1	0.036*	1.018

* p<0.05, statistically significant, ** p<0.005, statistically very significant

Table 3. The observed and predicted frequencies by logistic regression with the cutoff 0.50

Observed	Predicted		% Correct
	Negative	Positive	
PCR Negative	79	35	69.3
PCR Positive	26	92	78.0
Overall % correct			73.7

Discussion and Conclusion

Fast and accurate confirmation of COVID-19 cases with or without symptoms has a very crucial importance to stop the current spread of infection. The basic reproduction number (R₀) of SARS-coV-2 varies from 2 to 4 at different studies which means that a carrier or a patient may spread the virus two to four persons on average(16). This highly contagious disease increases the importance of fast and accurate confirmation of cases to isolate them and to stop the spread. The clinicians may need additional parameters to predict a PCR positivity in Covid19 suspected cases.

We evaluated the diagnostic value of hemogram parameters which is one of the cheapest and most common tests available in almost every hospital all over the world. The gold standard RT-PCR tests require expensive equipment and biosafety conditions which may not be available widely at especially undeveloped countries(17). However hemogram itself is widely available and may give an idea to isolate patients. Isolation is a key point to stop the spread. WHO pays attention to exposure during 2 days before and 14 days after the onset of symptoms of a probable or confirmed case to determine the term contact(2). Therefore, we suggest that careful review

of hemogram parameters can provide useful clues until accurate molecular test results are available.

Hemogram parameters are valuable biomarkers in infectious diseases as an indicator of immune system activation. We found some interesting findings from our analysis of hemogram data which may give idea to clinicians and make them gain time before PCR test results. Especially white blood cell (Leukocyte) count with cut off 7.15, neutrophil count with cut off 4.91, lymphocyte count with cut off 1.85, basophil count with cut off 0.025 and platelet count with cut off 221.5 would give an idea about PCR positivity if results are lower than cut off values.

First of all, in our study, we found age was greater among positive patients. Natale et al., found older people to be more infected in Spain and Italy while in China and Korea middle or younger age groups seemed to be more infected (18). This result may be obtained due to difference in average age of populations and more widely testing executed in China and Korea than other countries. At the time of study, in our country, only symptomatic patients were being tested with PCR at early stages of pandemic outbreak. This situation would explain our finding which reveals symptomatic patients who required to be tested were at higher ages. Also elderly people are at more risk due to being vulnerable to mental health issues and chronic diseases, therefore we need to pay more attention to them during the pandemic outbreak (19).

We secondly found that NLR were greater in PCR positive patients. NLR has been promising to foresee the prognosis of COVID-19 in a few months after pandemic outbreak started. Ai-Ping Yang et al. studied the diagnostic and predictive role of age, NLR, Platelet to Lymphocyte Ratio (PLR) in COVID-19 patients and they found NLR as the best predictive parameter at the disease. They concluded that elevated age and NLR can be regarded as distinct biomarkers for poor prognosis (20). Neutrophil (NEU) is a major element of immune system, which destroys the infected cell and release the virus from the cells. Therefore, virus in outer part of the cell may be destroyed, cell-specific and humoral immunities may be stimulated (21). Then again, lymphocyte is the main factor of human immune response in viral infections (22), whereas CD4+ T lymphocytes decreases and CD8+ suppressor T lymphocyte increases in systematic inflammation (23). As a result NLR increases in a virus activated inflammation. In our study, NLR value with cut off 2.95 demonstrates PCR positivity with 60 % sensitivity, 54% specificity (Table 1).

WBC count lower than 7.15 has the biggest under the curve area according to ROC curves of our hemogram parameters (Fig 1). Gita Vita Soraya et al. studied a meta-analysis about the effect of important laboratory tests in COVID-19 diagnosis and prognosis and they have found significantly lower leukocyte, neutrophil and platelet counts in COVID-19 patients with pneumonia compared to non-COVID-19 patients with pneumonia in seven studies (24). They have also found that significantly lower lymphocyte and thrombocyte counts and significantly higher leukocyte, neutrophil, D-dimer, and CRP in severe COVID-19 patients compared to non-severe COVID-19 patients in twenty-six studies. In our study, we analysed these parameters at the beginning of the disease to indicate the diagnosis. In that mentioned meta-analysis, their findings about lower parameters are compatible with our findings, but higher leukocyte and neutrophil are found in severe COVID-19 patients which may have coinfections or comorbidities after being hospitalised. These findings also indicate the importance of hemogram sampling at the beginning and in different stages of the disease. They also concluded that thrombocyte count plays a key role in both diagnosis and prognosis, low leukocyte and neutrophil counts point out COVID-19 infection, but contrastingly higher counts reveal continuous COVID-19, and although lymphocyte, D-dimer and CRP levels did not have diagnostic measure, all may be increased in severe COVID-19 (24). This conclusion supports our findings about low leukocyte, neutrophil counts which we have found best predictor parameters of hemogram in diagnosis.

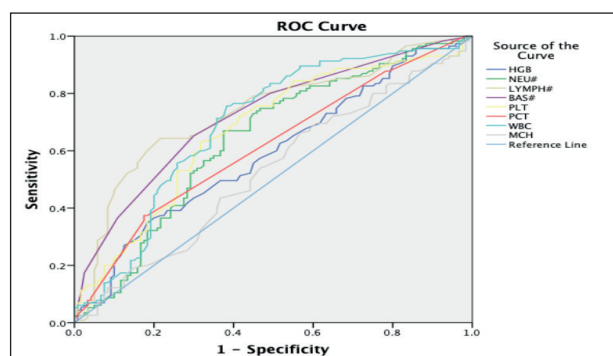


Fig 1: ROC Curves of Hemogram parameter

We also found lower platelet counts at PCR positive patients with cut off 221.5 which has 63.5 % sensitivity and 67.5 % specificity. Lippi et al. found thrombocytopenia is related to severe COVID-19

(25). This study also supports the diagnostic value of thrombocyte counts in COVID-19 infections, regardless of severity. Steady thrombocytopenia is discovered in the two COVID-19 reported cases originally suspected of dengue infection in a report from Singapore (26). The reason of thrombocytopenia is not accurately known but could be depended on many factors that inhibit thrombocyte synthesis, activation, or consumption in both beginning and severe part of the COVID-19 infection (27). SARS-CoV which is the member of the same coronavirus family with SARS-CoV-2 invade and infect progenitor cells in bone marrow, therefore thrombocyte production from megakaryocytes is inhibited and thrombocytopenia develops (28). SARS-CoV-2 may have same mechanism resulting with thrombocytopenia which should be researched profoundly.

Logistic regression analysis indicates that a model with basophil, RDW, MCH, and age explains 38.2% of the variance in COVID-19 test result and correctly predicts nearly 3 quarters of the test positive cases. These results implicate that careful analysis of routine test results provide valuable insights in evaluating COVID-19 suspected patients.

There are several limitations in our study. First, data is obtained from one center in one city, multicentral studies from different parts of world may give better idea about the virus and the reaction of human immune system to the virus. Secondly, PCR test kit used in our study targets one gene region of the virus which may also cause some a bit more percentage false negative results than PCR kits targets two gene region. WHO accepted “one gene region target” in regions where COVID-19 virus is extensively dedected and many test kits were able to detect one gene region in our country at the beginning of the pandemic outbreak. Almost all of test kits detect at least two gene region nowadays in our country. Thirdly, we did not have a chance to check computer tomography results of patients, especially PCR negative patients. We also know that PCR negative patients with computer tomography findings exist. If such patients are excluded from PCR negative control list, parameters of hemogram may have higher sensitivity and specificity. In spite of these limitations, our findings are compatible with current researches in the literature (24)(25)(26).

Pandemic outbreak is still going on all over the world, keeping causing severe acute respiratory syndrome

which leads some patients to be intubated and die. Detailed and urgent studies have been establishing to understand the disease. It is also a requirement to raise the awareness of public about the severity of the COVID-19 pandemic outbreak globally (29). Hemogram is a cheap, widely available test all over the world whereas PCR test kits are expensive and needs too much consumption material. According to hemogram results in our study, lower leukocyte count than 7.15, lower neutrophil count than 4.91, greater NLR than 2.95, lower platelet than 221.5 may give idea about the diagnosis of SARS-CoV-2 infection, and may make the clinician gain time to isolate the patient and stop the spread and start the treatment earlier. More detailed researches could be established especially with COVID-19 suspected PCR negative patients who have computer tomography findings.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethical clearance:

The study protocol was affirmed by the local institutional ethical committee of Istanbul Medeniyet University Goztepe Education and Research Hospital (New name of the hospital: Goztepe Prof. Dr. Suleyman Yalcin City Hospital) (document number: 2020/0670).

Authors's contribution:

Data gathering and idea owner of this study: AS, MA;

Study design: AS, MA, EK;

Data gathering: AS, EK, HG;

Writing and submitting manuscript: AS, MA, EK, HG, TO, ZH;

Editing and approval of final draft: AS, MA, EK, HG, TO, ZH

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