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Article

Differential Complete Blood Count for Diagnosis of COVID-19?

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Abstract: Background: The World Health Organization (WHO) has declared COVID-19 a public health emergency of international concern. In this context, effective and affordable diagnostic procedures are essential for identifying and managing cases. Complete blood counts (CBC) are among the most common and readily available diagnostic tests. The current study aimed to evaluate the efficacy of CBC in diagnosing COVID-19 and identifying cases. **Patients and Methods:** A case-control study was conducted on 173 patients at Ain Shams University Hospitals over a period of three months. Patients were allocated into two groups according to COVID-19 PCR results: Group 1 included patients with COVID-19 positive PCR, and Group 2 included patients with COVID-19 negative PCR. **Results:** The study found that differential CBC had significant value in diagnosing COVID-19 disease. Many COVID-19 patients had lymphopenia and leucopenia compared to non-COVID-19 suspected patients. The low values of leukocytes, neutrophils, lymphocytes, and eosinophils with a CBC test were found to be valuable in the initial diagnosis of COVID-19. **Conclusion:** The definitive diagnosis of COVID-19 requires RT-PCR analysis, which is time-consuming and less accessible. Thus, the initial diagnosis and treatment of patients may be delayed. This study suggests that CBC, which is easily available and affordable, can be valuable in the early identification of COVID-19 cases, allowing for prompt treatment and management.

Keywords: Complete blood count, COVID-19, Diagnosis, Case control study, Leucopenia, Lymphopenia

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1. Introduction

The COVID-19 pandemic has affected over 200 countries worldwide, with more than 13 million cases reported. The World Health Organization (WHO) has declared COVID-19 as a pandemic disease, highlighting the urgency of effective interventions to mitigate its spread. To address this urgent need, many cities have established designated fever clinics to triage suspected COVID-19 patients from those with similar symptoms [1]. Rapid diagnosis and isolation of cases are key strategies in the containment of outbreaks and reducing the spread COVID-19 [2]. The efficient triage protocols are essential for identifying suspected cases of COVID-19 and implementing timely interventions, including isolation, further diagnostic examination, and treatment [3, 4]. The COVID-19 pandemic has prompted the rapid establishment of designated fever clinics across epidemic regions for triaging suspected patients. The hallmark symptoms of COVID-19, including fever, fatigue, sore throat, diarrhea, and respiratory symptoms such as dry cough and shortness of breath [5].

However, the symptoms of COVID-19 are not entirely specific and can overlap with those of other non-bacterial community-acquired pneumonia or common upper respiratory infections, leading to potential misdiagnosis. As a result, accurately and effectively triaging suspected COVID-19 patients from those with similar respiratory symptoms at the fever clinic becomes a critical and challenging task. Therefore, innovative strategies and effective tools need to be implemented to support the accurate identification and isolation of suspected COVID-19 patients and reduce the spread of the virus. The diagnostic tool for COVID-19 is the detection of SARS-CoV-2 nucleic acid in clinical specimens, such as nasopharyngeal and oropharyngeal (throat) swabs. However, Polymerase Chain Reaction (PCR) testing can be expensive and not always feasible for widespread community testing. Therefore, identifying simple and readily available laboratory biomarkers is essential to facilitate effective triage at fever clinics, distinguishing suspected COVID-19 patients from those with COVID-19-like symptoms. The aim of our study is to identify simple and readily available laboratory biomarkers, such as CBC (complete blood count), to facilitate effective triage at fever clinics, distinguishing suspected COVID-19 patients from those with COVID-19-like symptoms. Specifically, our study aimed to evaluate the efficacy of CBC in the diagnosis and identification of COVID-19 cases.

2. Patients and Methods

A case-control study was conducted on a total of 173 patients recruited from Ain Shams University Hospitals over a three-month period since the beginning of data collection. Patients were divided into two groups based on their COVID-19 PCR results: **Group** 1 included patients with a positive COVID-19 PCR, while **Group** 2 included patients with a negative COVID-19 PCR.

The study included patients aged 18 years or older with new onset of fever ≥ 38°C and new respiratory symptoms, such as new continuous cough with or without sputum, sore throat, sneezing, new onset of nasal discharge and congestion, new onset of hoarseness of voice, new onset of dyspnoea, new onset of loss of taste and smell, and new onset of abdominal pain and diarrhoea.

Patients with an explained cause of fever, such as urosepsis, wound infection, or cellulitis, as well as those on chemotherapy or immunosuppressant agents, patients with aplastic anaemia and blood malignancies, and patients with chronic kidney disease and/or chronic liver disease were excluded from the study.

3. Study procedures

All selected patients underwent a comprehensive evaluation, which included a detailed medical history with an emphasis on the onset of symptoms and history of contact with a confirmed case. A thorough clinical examination was conducted, with a particular focus on respiratory symptoms. Laboratory investigations were performed, which included a differential CBC, CRP, AST, ALT, and serum ferritin. Additionally, nasopharyngeal and oropharyngeal swabs were collected from all patients. Patients were also subjected to High-resolution computed tomography (HRCT) imaging.

4. Ethical Considerations

Approval for this study was obtained from the Institutional Review Board (IRB) of Ain Shams Medical School prior to the commencement of the study, and all patients provided written informed consent prior to their participation. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

5. Statistical Analysis

Various descriptive analyses were performed to characterize the sample, including the calculation of frequency, percent, mean, and standard deviations. Normal distribution of the variables was assessed using the Kolmorov-Smirnov test. Mann-Whitney and Wilcoxon Rank tests were used for comparisons of continuous variables, while Pearson's Chi square test was utilized for categorical variables. Correlations between quantitative variable were estimated via Pearson's Correlation test. Furthermore, the internal consistency of COVID-19 detection using CBC and PCR was evaluated using the Cronbach Alpha test. The level of significance was set at P≤0.05.

6. Results

The present case-control study comprised 86 cases (PCR COVID-19 Positive) and 87 controls (PCR COVID-19 Negative). Table 1 displays the non-significant difference in age between the case and control groups.

Table 1. Comparison of Age between Case and Control Groups.

Age	Number	Mean ± SD	Student's t-test value	P Value (Sig)
Case Group	87	47.90±16.86	0.402	0.688 (NS)
Control Group	86	48.93±16.95		

NS: Non-Significant.

Table 2 presents the non-significant results between the case and control groups regarding gender and past medical history, with the exception of anemia, which showed a significant difference between the two groups.

Table 2. Comparison of Past Medical History between Case and Control Groups.

Variable		Case Group	Control Group	Total	X^2 Value	P Value (Sig)
Gender	Male	47 (54%)	36 (41.9%)	83 (48.0%)	2.563	0.109 (NS)
	Female	40 (46%)	50 (58.1%)	90 (52.0%)		
CND	+ve	51 (58.6%)	48 (55.8%)	99 (57.2%)	0.139	0.709 (NS)
	+ve	51 (58.6%)	48 (55.8%)	99 (57.2%)		
DM	-ve	48 (55.2%)	49 (57.0%)	97 (56.1%)	0.057	0.811 (NS)
	+ve	39 (44.8%)	37 (43.0%)	76 (43.9%)		
HTN	-ve	58 (66.7%)	51 (59.3%)	109 (63.0%)	1.006	0.316 (NS)
	+ve	29 (33.3%)	35 (40.7%)	64 (37.0%)		
IHD	-ve	82 (94.3%)	81 (94.2%)	163 (94.2%)	0.000	0.985 (NS)
	+ve	5 (5.7%)	5 (5.8%)	10 (5.8%)		
Stroke	-ve	78 (89.7%)	83 (96.5%)	161 (93.1%)	0.132	0.076 (NS)
	+ve	9 (10.3%)	3 (3.5%)	12 (6.9%)		
Heart Failure	-ve	83 (95.4%)	80 (93.0%)	163 (94.2%)	0.449	0.503 (NS)
	+ve	4 (4.6%)	6 (7.0%)	10 (5.8%)		
Anemia	-ve	87 (100%)	81 (94.2%)	168 (97.1%)	5.209	0.022 (Sig)
	+ve	0 (0%)	5 (5.8%)	5 (2.9%)		

NS: Non-Significant Sig: Significant.

Table 3 illustrates the presence of significant differences between the case and control groups with respect to fever, cough, sore throat, and diarrhea, highly significant differences with regard to vomiting, and very highly significant differences in the occurrence of dyspnea and anosmia.

Table 3. A Comparison of Current Presenting Symptoms between Case and Control Groups.

Variable		Case Group	Control Group	Total	X^2 Value	P Value (Sig)
Fever	-ve	15 (17.2%)	29 (33.7%)	44 (25.4%)	6.193	0.013 (Sig)
	+ve	72 (82.8%)	57 (66.3%)	129 (74.6%)		
Cough	-ve	21 (24.1%)	34 (39.5%)	55 (31.8%)	4.728	0.03 (Sig)
	+ve	66 (75.9%)	52 (60.5%)	118 (68.2%)		
Dyspnea	-ve	30 (34.5%)	58 (67.4%)	88 (50.9%)	18.798	0.000 (VHS)
	+ve	57 (65.5%)	28 (32.6%)	85 (49.1%)		
Diarrhea	-ve	72 (82.8%)	57 (66.3%)	129 (74.6%)	6.193	0.013 (Sig)
	+ve	15 (17.2%)	29 (33.7%)	44 (25.4%)		
Anosmia	-ve	66 (75.9%)	86 (100%)	152 (87.9%)	23.627	0.000 (VHS)
	+ve	21 (24.1%)	0 (0%)	21 (12.1%)		
Sore Throat	-ve	66 (75.9%)	76 (88.4%)	142 (82.1%)	4.602	0.032 (Sig)
	+ve	21 (24.1%)	10 (11.6%)	31 (17.9%)		
Vomiting	-ve	86 (98.9%)	77 (89.5%)	163 (94.2%)	6.891	0.009 (HS)
	+ve	1 (1.1%)	9 (10.5%)	10 (5.8%)		

Sig: Significant VHS: Very highly Significant. HS: Highly Significant.

Tables 4 and 5 present the qualitative and quantitative results of the laboratory investigations comparing the case group and control group. The analysis shows non-significant differences in eosinocytopenia and neutropenia, highly significant differences in monocytosis, and very highly significant differences in lymphopenia and leucopenia. The comparison also reveals non-significant differences in High CRP, and a very highly significant difference in serum ferritin between the case and control groups. Additionally, there were very highly significant differences observed in High ALT and AST levels between the two groups.

Table 4. Comparison of laboratory investigations between case and control groups.

Variable		Case Group	Control Group	Total	X^2 Value	P Value (Sig)
Leucopenia	Positive	21 (24.1%)	4 (4.7%)	25 (14.5%)	13.284	0.000 (VHS)
	Negative	66 (75.9%)	82 (95.3%)	148 (85.5%)		
Neutropenia	Positive	12 (13.8%)	5 (5.8%)	17 (9.8%)	3.107	0.078 (NS)
	Negative	75 (86.2%)	81 (94.2%)	156 (90.2%)		
Lymphopenia	Positive	53 (60.9%)	21 (24.4%)	74 (42.8%)	23.540	0.000 (VHS)
	Negative	34 (39.1%)	65 (75.6%)	99 (57.2%)		
Eosinocytopenia	Positive	35 (40.2%)	25 (29.1%)	60 (34.7%)	2.378	0.123 (NS)
	Negative	52 (59.8%)	61 (70.9%)	113 (65.3%)		
Monocytosis	Positive	2 (2.3%)	14 (16.3%)	16 (9.2%)	10.071	0.002 (HS)
	Negative	85 (97.7%)	72 (83.7%)	157 (90.8%)		
High CRP	Positive	64 (73.6%)	58 (67.4%)	122 (70.5%)	0.780	0.377 (NS)
	Negative	23 (26.4%)	28 (32.6%)	51 (29.5%)		
Serum Ferritin	Positive	44 (50.6%)	11 (12.8%)	55 (31.8%)	28.473	0.001 (VHS)
	Negative	43 (49.4%)	75 (87.2%)	118 (68.2%)		

High ALT	Positive	25 (28.7%)	7 (8.1%)	32 (18.5%)	12.169	0.000 (VHS)
	Negative	62 (71.3%)	79 (91.9%)	141 (81.5%)		
High AST	Positive	20 (23.0%)	5 (5.8%)	25 (14.5%)	10.319	0.001 (VHS)
	Negative	67 (77.0%)	81 (94.2%)	148 (85.5%)		

VHS: Very highly Significant NS: Non-Significant HS: Highly Significant.

Table 5. Comparison of laboratory investigations between case and control groups.

CBC Findings	Group	Number	Mean ± SD	Student's t-test	P Value (Sig)
TLC	Case	87	7.88±4.45	2.486	0.014 (Sig)
	Control	86	9.49±4.03		
Neutrophils	Case	87	6.14±4.28	1.189	0.236 (NS)
	Control	86	6.87±3.74		
Lymphocytes	Case	87	1.19±0.78	4.490	0.000 (VHS)
	Control	86	1.77±0.91		
Eosinophils	Case	87	0.06±0.10	3.179	0.002 (HS)
	Control	86	0.13±0.19		
Monocytes	Case	87	0.37±0.27	5.062	0.000 (VHS)
	Control	86	0.62±0.36		
CRP	Case	87	66.26±57.86	-6.465	0.000 (VHS)
	Control	86	21.79±27.56		
S. Ferritin	Case	87	390.6±308.8	-3.936	0.000 (VHS)
	Control	86	232.3±211.9		
ALT	Case	87	44.36±44.88	-3.482	0.001 (VHS)
	Control	86	26.77±14.26		
AST	Case	87	46.26±60.98	-2.782	0.006 (HS)
	Control	86	26.56±25.30		

Sig: Significant VHS: Very highly NS: Non-Significant HS: Highly Significant.

Table 6 summarizes the HRCT findings of the case group and control group, with very highly statistical significant difference between them.

Table 6. Comparison between case group and control group regarding the HRCT findings.

HRCT	Case Group	Control Group	Total	X^2 Value	P Value (Sig)
Bilateral GGOs	55 (63.2%)	9 (10.5%)	64 (37.0%)	52.344	0.000 (VHS)
GGOs	2 (2.3%)	2 (2.3%)	4 (2.3%)		
Normal	30 (34.5%)	75 (87.2%)	105 (60.7%)		
Total	87 (100%)	86 (100%)	173 (100%)		

VHS: Very highly Significant.

Table 7 summarizes the sensitivities, specificities and predictive values of CBC for COVID-19, with the highest sensitivity related to lymphopenia and the highest specificity related to neutropenia.

Table 7. Diagnostic accuracy of CBC for COVID-19: sensitivity, specificity, positive predictive value, and negative predictive value.

Variable	Case Positive	Case Negative	Control Positive	Control Negative	Sensitivity	Specificity	PVP	PVN
Leucopenia	21 (24.1%)	66 (75.9%)	4 (4.7%)	82 (95.3%)	24.1%	95.3%	84%	55%
Neutropenia	12 (13.8%)	75 (86.2%)	5 (5.8%)	81 (94.2%)	13%	94%	70.5%,	49.7%
Lymphopenia	53 (60.9%)	34 (39.1%)	21 (24.4%)	65 (75.6%)	60.9%	75.6%	71.6%	65.6%
Eosinocytopenia	35 (40.2%)	52 (59.8%)	25 (29.1%)	61 (70.9%)	40.2%	70.9%,	58.3%,	53.9%
Monocytosis	2 (2.3%)	85 (97.7%)	14 (16.3%)	72 (83.7%)	2.3%	83.7%,	12.5%	45.8%

7. Discussion

As the COVID-19 pandemic continues to pose a significant public health challenge, early and accurate diagnosis of the disease remains crucial. However, the limitations of real-time PCR testing, such as high sample volume, staff shortages, and limited lab capacities, can lead to delays in receiving results. In response, this study aimed to identify simple and accessible laboratory parameters that can aid in the early diagnosis of COVID-19, specifically through a CBC test.

The study analyzed medical records of 173 individuals suspected of COVID-19, with 87 testing positive for the virus by PCR and serving as cases, while the remaining 86 tested negative and were considered controls. Each group underwent PCR testing using both nasopharyngeal and oropharyngeal swabs, HRCT, CBC with differential counts, CRP, ALT, AST, and serum ferritin level.

The median age of the COVID-19 positive group was 47.90 years old, with a higher prevalence among males compared to females. Through this study, potential biomarkers were identified that can aid in effective triage and early diagnosis of COVID-19, thereby improving patient outcomes and mitigating the spread of the disease.

Gender-based differences in susceptibility to COVID-19 have been reported in several studies [4, 6, 7]. One possible explanation for the reduced susceptibility of females to viral infections is the protective effect of X chromosomes and sex hormones, which are known to play a crucial role in innate and adaptive immunity [8].

Additionally, our study suggests that males may have been more exposed to the virus due to factors such as staying outside during curfews. In terms of comorbidities, hypertension and diabetes mellitus were found to be the most common medical conditions in COVID-19 positive cases, consistent with findings from previous studies [9, 10]. Regarding symptoms, our study found that fever, cough, and dyspnea were the most commonly reported complaints, followed by sore throat, anosmia, diarrhea, and vomiting. This is consistent with the findings of previous studies, which also reported fever and cough as the most commonly observed symptoms [1, 11, 12, 13].

Our study found that leucopenia, neutropenia, and lymphopenia are potential indicators of COVID-19 disease. Specifically, we observed that 24.1% of COVID-19 patients had leucopenia, with a sensitivity of 24.1% and specificity of 95.3%. Similarly, 13.8% of patients had neutropenia, with a sensitivity of 13% and specificity of 94%, consistent with a previous study reporting low neutrophil counts in COVID-19-positive patients [12]. In contrast, Qin et al. reported that patients with severe cases tend to exhibit higher overall leukocyte counts and a greater percentage of neutrophils [14].

Similarly, Mo et al. in Wuhan, China found that COVID-19 patients had higher neutrophil counts than those who tested negative for the virus [15]. However, it is worth noting that this may be attributed to secondary bacterial infections or the use of steroids during treatment [16]. The most common hematological abnormality observed in our study was lymphopenia, with 60.9% of COVID-19 patients exhibiting this condition, and a sensitivity of 60.9% and specificity of 75.6%. Our results are consistent with previous studies, which have reported varying degrees of lymphopenia in COVID-19-positive

patients [1, 7, 11, 13, 17, 18]. The observed lymphopenia may be due to the massive recruitment of T cells and monocytes to inflamed tissues, the use of steroids, or high levels of apoptosis [19]. These findings suggest that CBC differential counts can serve as useful tools in the diagnosis of COVID-19 disease, especially when used in combination with other diagnostic methods.

A postmortem analysis of a COVID-19 patient showed substantial interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes in the lungs and heart [20], which supports the concept of lymphocyte depletion from peripheral blood. In our study, we found that eosinocytopenia, or a low eosinophil count, had a sensitivity of 40.2% and specificity of 70.9% in diagnosing COVID-19 disease. Our results revealed that 35 (40.2%) of COVID-19 patients had eosinocytopenia, compared to 25 (29.1%) of the control group. This is similar to the findings of a study conducted by Kamel et al. [10], which showed a significant decrease in eosinophil count in COVID-19 positive patients compared to COVID-19 negative patients, indicating a potential role for eosinophils as an early sign of COVID-19 infection.

Another study conducted by Li et al. showed that eosinopenia appeared in 74.7% of patients with COVID-19. Our study also found that only 2 (2.3%) patients in the case group had monocytosis, or a high monocyte count, compared to 14 (16.3%) patients in the control group. Monocytosis had a sensitivity of 2.3% and specificity of 83.7% in diagnosing COVID-19 disease. Interestingly, monocytosis was the only marker in our study that was more prevalent in the control group than the case group, suggesting that monocytosis may be protective against COVID-19 infection.

In our study, we found that high levels of CRP, ALT and AST were present in the COVID-19 positive group compared to the negative group, which is consistent with the findings of previous studies [13, 21]. Furthermore, our study revealed that high serum ferritin levels were found in 44 (50.6%) COVID-19 positive patients compared to only 11 (12.8%) patients in the control group, which is similar to the findings reported by Li et al. [22].

Finally, our study also evaluated High-resolution computed tomography (HRCT) images of 87 patients, of whom 57 (65%) had abnormal chest CT findings, including bilateral pneumonia in 55 cases (63.2%) and unilateral pneumonia in 2 (2.3%) cases. This is consistent with the findings of a study conducted by Wu et al., which showed that 55 (68.75%) of 80 patients had abnormal chest CT images, consisting of 36 cases (45.00%) of bilateral pneumonia and 19 cases (23.75%) of unilateral pneumonia [23].

In conclusion, the definitive diagnosis of COVID-19 is currently made by RT-PCR analysis. This test is time-consuming and less accessible, which can lead to delays in diagnosis and treatment. However, our study suggests that a CBC test, which is readily available and widely used in clinical practice, can be a valuable tool for the initial diagnosis of COVID-19. Specifically, low values of leukocytes, neutrophils, lymphocytes, and eosinophils were found to be indicative of COVID-19, and could therefore serve as an important screening tool for healthcare providers. This approach could help to expedite the diagnosis and treatment of COVID-19 patients, ultimately improving outcomes and reducing the burden on healthcare systems worldwide.

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