3-2-2021

Analysis of absolute lymphocyte count in patients with COVID-19

Zachary Illg
Henry Ford Health, ZIllg1@hfhs.org

Gregory Muller
Henry Ford Health, gmuller2@hfhs.org

Matthew Mueller
Henry Ford Health

Justin Nippert
Henry Ford Health

Brian Allen
Henry Ford Health, ballen3@hfhs.org

Recommended Citation

Illg Z, Muller G, Mueller M, Nippert J, and Allen B. Analysis of absolute lymphocyte count in patients with COVID-19. Am J Emerg Med 2021; 46:16-19.

American Journal of Emergency Medicine 46 (2021) 16–19

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Analysis of absolute lymphocyte count in patients with COVID-19

Zachary Illg, DO *, Gregory Muller, DO, Matthew Mueller, DO, MPH [1], Justin Nippert, DO, Brian Allen, MD

Department of Emergency Medicine, Henry Ford Wyandotte Hospital, Wyandotte, MI, USA

ARTICLE INFO

Article history:
Received 2 February 2021
Received in revised form 15 February 2021
Accepted 21 February 2021
Available online xxxx

Keywords:
COVID-19
Coronavirus
Absolute lymphocyte count
Lymphopenia

ABSTRACT

Introduction: Symptoms of COVID-19 vary in severity and presentation. When admitting patients to the hospital, it is desirable to isolate patients with COVID-19 from those without the disease. However, reliably identifying patients with COVID-19 in the emergency department before hospital admission is often limited by the speed and availability of testing. Previous studies determined a low lymphocyte count is commonly found in patients with COVID-19. We sought to explore the sensitivity of absolute lymphocyte count in patients presenting to the emergency department requiring subsequent hospitalization who were found to have COVID-19.
Methods: A retrospective chart review was performed on 312 patients with laboratory-confirmed COVID-19 who were admitted to the hospital from the emergency department. The absolute lymphocyte count for these patients was used to calculate sensitivities at various cut-off values. The relationships between absolute lymphocyte count and variables, including age, sex, need for intubation, and mortality, were also explored.
Results: Cut-off values for absolute lymphocyte count ranged from 1.1 K/uL to 2.0 K/uL, with sensitivities of 72% and 94%, respectively. Additionally, lower mean absolute lymphocyte counts were identified in males, patients who required intubation, and patients who died.
Conclusion: Knowing the sensitivity of absolute lymphocyte count in patients with COVID-19 may help identify patients who are unlikely to have the disease. Additionally, absolute lymphocyte count can be used as a marker of disease severity in patients with COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus that causes coronavirus disease (COVID-19) [1]. Symptoms of COVID-19 vary in severity and presentation, and many patients with COVID-19 may be asymptomatic or have only mild symptoms [2]. When admitting patients to the hospital, it is desirable to isolate patients with COVID-19 from those without the disease. However, reliably identifying patients with COVID-19 in the emergency department (ED) before hospital admission is often limited by the speed and availability of SARS-CoV-2 testing.

Current research suggests that lymphopenia, defined as a low lymphocyte count, is commonly present in patients with COVID-19 [3,4]. There is also evidence that the degree of lymphopenia correlates with illness severity in patients with COVID-19 [5-7]. The converse may also be true; those without lymphopenia may be unlikely to have COVID-19, but currently, there is a paucity of data to support this.

Turn-around-time for absolute lymphocyte count (ALC) is much quicker than SARS-CoV-2 testing, with results obtained while the patient is in the ED. We explore the relationship between lymphopenia and COVID-19 in patients who present to the ED and require hospitalization.

2. Methods

2.1. Design

A retrospective chart review was performed to assess the relationship between ALC and infection from SARS-CoV-2 in patients with laboratory-confirmed COVID-19 who were admitted to the hospital from the ED. We hypothesized that in patients presenting to the ED requiring subsequent hospitalization, ALC cut-off values could be used to help physicians identify patients who are unlikely to have COVID-19. ALC and secondary variables, including age, sex, need for intubation (either in the ED or during hospitalization), and mortality, were of interest

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease; ED, emergency department; ALC, absolute lymphocyte count; RT-PCR, reverse transcription-polymerase chain reaction; CBC, complete blood count; WBC, white blood count; CDC, Centers for Disease Control and Prevention; AGPs, aerosol-generating procedures.

* Corresponding author at: Henry Ford Wyandotte Hospital, Department of Emergency Medicine, 2333 Biddle Avenue, Wyandotte, MI 48192, USA.
E-mail address: zillg1@hfhs.org (Z. Illg).
[1] Present address: Department of Anesthesiology, Division of Critical Care, University of California, San Diego, San Diego, CA, USA.

https://doi.org/10.1016/j.ajem.2021.02.054
0735-6757/

to the authors. The need for intubation and death were used to qualify disease severity.

The study received approval by the authors' Institutional Review Board before data collection or analysis. The authors performed all data abstraction, and an initial meeting was held between authors to ensure consistent and accurate data collection methods and documentation. Additional meetings were held as-needed to resolve any questions regarding data collection.

2.2. Setting

This study took place at Henry Ford Wyandotte Hospital (HFWH), a 360-bed community-based teaching hospital located in the Detroit Metropolitan area whose ED receives approximately 60,000 visits a year.

2.3. Sample

The sample population consisted of adult patients who presented to the HFWH ED between March 20, 2020, and May 5, 2020, required hospital admission and had a positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) result. A positive SARS-CoV-2 RT-PCR result was found either in the ED or during hospitalization. Inclusion criteria included patients aged ≥18 years, hospital admission, COVID-19 as confirmed by SARS-CoV-2 RT-PCR, and a complete blood count (CBC) with ALC obtained in the ED or during hospitalization. Exclusion criteria included patients aged <18 years, discharged from the ED, negative SARS-CoV-2 RT-PCR testing, and no ALC obtained during ED encounter or hospitalization duration. A total of 312 patients were eligible for inclusion in our study based on inclusion criteria. One patient was excluded from data analysis due to a pre-existing diagnosis of chronic lymphocytic leukemia with an ALC of 72.16 K/uL. As such, 311 patients were included for data analysis.

2.4. Data Collection & Measurement

Blood samples for laboratory evaluation were collected at the patient's bedside by ED nurses or physicians while in the ED. Only data from the first blood draw that included ALC was included in our analysis. All patients in our study had a CBC with ALC drawn in the ED; thus, no blood samples acquired upon hospitalization were used in our analysis. CBC samples were assessed by the HFWH laboratory on a UniCel DxH 800 Coulter Cellular Analysis System. The white blood cell (WBC) count was derived using the Coulter Principle. The ALC was then derived from the sample's calculated lymphocyte percentage and WBC count and was expressed in microliters (uL).

Sample testing for SARS-CoV-2 was similarly acquired by an ED nurse or physician during a patient's ED encounter using a nasal or nasopharyngeal swab. Samples obtained from March 15, 2020, through March 26, 2020, were analyzed using the Centers for Disease Control and Prevention (CDC) RT-PCR assay on a Roche LC480 thermocycler at Henry Ford Hospital in Detroit, Michigan. From March 27, 2020, through the end of the study period, the RT-PCR assay was analyzed on a NeumoDx, Diasorin Simplexa, or Cephelid GenXpert automated RT-PCR platform. The results from all samples were expressed as either positive or negative. A positive result was defined by the expression of one of two genetic targets on the SARS-CoV-2 genome in quantity greater than the predetermined fluorescence threshold.

2.5. Data analysis

The primary outcome of interest was the ALC of patients who required hospitalization during our study period, as we hypothesized that ALC could be used to help physicians identify patients who are unlikely to have COVID-19. The secondary outcome of interest was the relationship, if any, between ALC and disease severity in patients who required hospitalization. ALC was compared for all variables using Kruskal-Wallis tests with mean, standard deviation, median, and interquartile range presented. Pearson's correlation coefficient was computed to assess the association between age and ALC. The need for intubation and death were used to qualify disease severity. Sensitivity and the corresponding 95% confidence intervals were determined at different cut-off values.

In addition to assessing ALC as a continuous measure, patients were divided into groups based on the normal range for ALC (1.10–4.00 K/uL). There were two patients with an ALC above the normal range; therefore, patients in the normal range and above normal range were grouped. All variables were compared between the normal/above normal ALC values and the below normal ALC values using *t*-tests for age and chi-square tests for categorical covariates. For categorical variables, the number and percentages were presented. For quantitative variables, the mean and standard deviation were presented. The testing level for

Table 2
ALC sensitivity at cutoff values

ALC cutoff	Sensitivity	95% lower confidence limit	95% upper confidence limit
1.1 (K/uL)	72%	67%	77%
1.25 (K/uL)	78%	73%	82%
1.5 (K/uL)	85%	81%	89%
2.0 (K/uL)	94%	91%	96%

Table 1
Comparing absolute lymphocyte count

Variable	Level	Absolute lymphocyte count (K/uL)			
		N	Mean (SD)	Median (IQR)	Kruskal-Wallis *P*-value
Sex	Female	164	1.06 (0.71)	0.80 (0.6, 1.3)	0.041
	Male	147	0.90 (0.62)	0.80 (0.5, 1.1)	
Intubated	No	228	1.01 (0.66)	0.80 (0.6, 1.2)	0.048
	Yes	83	0.91 (0.72)	0.80 (0.4, 1.1)	
Died	No	226	1.01 (0.66)	0.80 (0.6, 1.2)	0.047
	Yes	85	0.91 (0.72)	0.76 (0.5, 1.02)	
Severity	Death with Intubation	51	0.96 (0.83)	0.76 (0.4, 1.1)	0.093
	Death without Intubation	34	0.85 (0.51)	0.75 (0.5, 1.0)	
	Intubation without death	32	0.83 (0.50)	0.80 (0.5, 1.1)	
	Neither death or intubation	194	1.04 (0.67)	0.80 (0.6, 1.3)	
Age group	<50	47	1.08 (0.63)	1.00 (0.7, 1.3)	0.145
	50–59	49	0.92 (0.50)	0.80 (0.5, 1.2)	
	60–69	70	0.89 (0.67)	0.70 (0.5, 1.0)	
	70–79	59	0.90 (0.53)	0.80 (0.5, 1.3)	
	80+	86	1.11 (0.84)	0.80 (0.6, 1.2)	

Table 3
Comparing grouped absolute lympocyte count

Covariate	Statistics	Level	Below normal ALC $N = 210$	Normal/above normal ALC $N = 101$	P-value[a]
Sex	N (Col %)	Female	105 (50)	59 (58.42)	0.164
	N (Col %)	Male	105 (50)	42 (41.58)	
Age	N		210	101	0.131
	Mean (SD)		68.08 (15.86)	64.99 (18.71)	
Intubated	N (Col %)	No	150 (71.43)	78 (77.23)	0.279
	N (Col %)	Yes	60 (28.57)	23 (22.77)	
Died	N (Col %)	No	146 (69.52)	80 (79.21)	0.073
	N (Col %)	Yes	64 (30.48)	21 (20.79)	
Severity	N (Col %)	Death with Intubation	38 (18.1)	13 (12.87)	0.315
	N (Col %)	Death without Intubation	26 (12.38)	8 (7.92)	
	N (Col %)	Intubation without Death	22 (10.48)	10 (9.9)	
	N (Col %)	Neither Death or Intubation	124 (59.05)	70 (69.31)	

[a] The p-value is calculated by t-test for age and chi-square test for categorical covariates.

all comparisons was 0.05. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 311 patients with COVID-19, as confirmed by SARS-CoV-2 RT-PCR, were included in the data analysis. Patient ages ranged from 18 to 97 years, with the mean age being 67.1 years (SD = 16.9). Breakdown of the variables analyzed were as follows: 147 (47.3%) patients were male, 83 (26.7%) patients were intubated, 85 (27.3%) patients died, 51 (16.4%) patients died while intubated, 34 (10.9%) patients died without intubation, 32 (10.3%) patients required intubation and survived, and 194 (62.4%) patients survived without intubation.

Additionally, 2 (0.6%) patients had ALC values above the normal range, 99 (31.8%) patients had ALC values within the normal range, and 210 (67.5%) patients had ALC values below the normal range. The normal range used for ALC was 1.10–4.00 K/uL, as this was the range used by the HFWH laboratory for reporting normal versus abnormal results. The mean ALC of patients in our study was 0.99 K/uL (SD = 0.67), while the median ALC was 0.80 K/uL (IQR = 0.6,1.2).

ALC values were compared among the various subgroups analyzed (Table 1). Male patients had a lower ALC than female patients, with means of 0.90 K/uL and 1.06 K/uL, respectively ($p = 0.041$). Patients who required intubation had a lower ALC (0.91 K/uL) than those who did not (1.01 K/uL) ($p = 0.048$). Patients who died had a lower ALC (0.91 K/uL) than those who survived (1.01 K/uL) ($p = 0.047$). The correlation between age and ALC was not statistically significant ($p = 0.850$). There were no significant differences in ALC based on the combination of intubations and death ($p = 0.093$) and age groups ($p = 0.145$).

The sensitivity of ALC in our patient population was assessed using different cut-off values, as outlined in Table 2. Cut-off values ranged from 1.1 K/uL to 2.0 K/uL, with sensitivities of 72% and 94%, respectively.

Lastly, no significant differences were appreciated between the below normal ALC group and the normal/above normal ALC group for any of the variables in Table 3, including sex, age, need for intubation, or death.

4. Discussion

Availability and turn-around-time for SARS-CoV-2 PCR testing remain the rate-limiting step in diagnosing COVID-19 in many hospitals and health systems. Our study identified ALC cut-off values with corresponding sensitivities that may be used as a surrogate marker to help identify patients who are unlikely to have COVID-19 upon hospital admission and allow for rapid cohorting of patients.

Current CDC recommendations advise, if possible, avoiding aerosol-generating procedures (AGPs) in patients with COVID-19 as these procedures may increase the risk of viral transmission [8]. AGPs commonly performed in the ED include non-invasive positive pressure ventilation, endotracheal intubation, airway suctioning, high-flow oxygen delivery, and nebulized medication administration. Knowing the sensitivity of ALC in patients with COVID-19 may help physicians identify patients who are unlikely to have the disease, allowing patients who benefit from AGPs to receive timely treatment in the ED without exposing nurses, physicians, and respiratory therapists to infectious pathogens. Furthermore, expeditious cohorting of patients unlikely to have COVID-19 allows for the early removal of isolation precautions, reducing hospital costs and resource utilization through diminished personal protective equipment use.

Our data also demonstrates the degree of lymphopenia correlates with COVID-19 severity, specifically, the need for intubation and death. As such, ALC may serve as a prognostic indicator in patients with COVID-19, allowing physicians to pursue more aggressive treatment regimens in patients at risk for severe disease.

4.1. Limitations

All patients requiring admission to HFWH during the study dates underwent SARS-CoV-2 RT-PCR testing, regardless of symptoms or reason for hospital admission. Cases of a positive SARS-CoV-2 RT-PCR result after resolution of COVID-19 have been reported [9]. As such, patients included in our study might have had a positive SARS-CoV-2 RT-PCR without active COVID-19 and required admission for an alternate reason (i.e., acute surgical issue), resulting in the inclusion of patients without active COVID-19 in our study.

Our study only included patients who required hospital admission. It did not include patients who were discharged from the ED with confirmed or suspected COVID-19. As such, further studies should be conducted to determine if the ALC cut-off values found in our study extend to this population.

There are a multitude of variables and disease processes that lead to lymphopenia. These include bacterial and fungal sepsis, corticosteroid use, chemotherapy and radiation therapy, and trauma [10]. Patients in our study may have had factors independent of COVID-19 that contributed to a decreased ALC.

Our study was designed to assess the sensitivity of ALC in patients with COVID-19. As such, only patients with COVID-19 were included in our study. Additional studies are needed to determine the specificity and positive and negative predictive values of ALC as it relates to COVID-19.

5. Conclusion

Knowing the sensitivity of ALC in patients with COVID-19 may help identify patients who are unlikely to have the disease upon hospital admission, allowing for rapid cohorting of patients and safe utilization of

AGPs in place of SARS-CoV-2 RT-PCR testing. Additionally, ALC can be used as a marker of disease severity in patients with COVID-19.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Zachary Illg: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Gregory Muller**: Methodology, Investigation, Writing - original draft. **Matthew Mueller**: Methodology, Writing - original draft, Writing - review & editing. **Justin Nippert**: Investigation, Writing - original draft, Writing - review & editing. **Brian Allen**: Conceptualization, Methodology, Investigation, Writing - original draft.

Declaration of Competing Interest

None.

Acknowledgements

None.

References

[1] Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization; 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it Accessed December 30, 2020.
[2] Nishiura H, Kobayashi T, Miyama T, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis. 2020;94:154–5. https://doi.org/10.1016/j.ijid.2020.03.020.
[3] Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020;95(7):834–47. https://doi.org/10.1002/ajh.25829.
[4] Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. https://doi.org/10.1056/NEJMoa2002032.
[5] Zhao Q, Meng M, Kumar R, et al. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a systemic review and meta-analysis. Int J Infect Dis. 2020;96:131–5. https://doi.org/10.1016/j.ijid.2020.04.086.
[6] Henry B, Cheruiyot I, Vikse J, et al. Lymphopenia and neutrophilia at admission predicts severity and mortality in patients with COVID-19: a meta-analysis. Acta Biomed. 2020;91(3):e2020008. https://doi.org/10.23750/abm.v91i3.10217.
[7] Huang G, Kovalic AJ, Graber CJ. Prognostic value of leukocytosis and lymphopenia for coronavirus disease severity. Emerg Infect Dis. 2020;26(8):1839–41. https://doi.org/10.3201/eid2608.201160.
[8] Infection control: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Ctr Dis Control Prev; 2021. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html Accessed December 30, 2020.
[9] Lan L, Xu D, Ye G, et al. Positive RT-PCR test results in patients recovered from COVID-19. JAMA. 2020;323(15):1502. https://doi.org/10.1001/jama.2020.2783.
[10] Castelino DJ, McNair P, Kay TW. Lymphocytopenia in a hospital population - what does it signify? Aust NZ J Med. 1997;27(2):170–4. https://doi.org/10.1111/j.1445-5994.1997.tb00934.x.