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Lymphopenia: A predictive marker of disease severity in COVID-19 infection

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ABSTRACT

Background. *With the latest COVID-19 deaths reported to WHO now exceeding 3.3 million, COVID-19 has developed into a milestone of our medical generation, causing disruption in communities and hospital services. With complications raging from respiratory failure to inflammatory complication and even thrombotic events, we wanted to establish if lymphopenia is a predictive marker of disease severity in patients infected with SARS-CoV-2.*

Material and methods. *152 patients were included from 4 different departments of Colentina Clinical Hospital in this retrospective observational study beginning with July 2020 to March 2021. All of these patients were confirmed with COVID-19 by real-time reverse transcriptase polymerase chain reaction test for nasal and pharyngeal swab samples. As including criteria we have set the patients hospitalized confirmed with COVID-19, with at least 10 days of hospitalization. The data in demographic, basic clinical and laboratory characteristics and particular evolution was obtained from electronical medical records from each department involved in the study, by maintaining personal data confidentially. We set up criteria for lymphopenia as absolute lymphocyte count below 1.5 x 1000/μl, based on the laboratory reference values. The study group was divided into several groups: male and female, ICU (Intensive Care Unit) and non-ICU, deceased and released, lymphopenia at day 1 (day of admission to hospital) , lymphopenia at day 10 (10 days after hospital admission).*

Results. *The age of the patients ranged from 17 to 92, with the median age of 57.62. Enrolled were 73 (47.4%) female patients and 79 (52.6%) male patients, with an ICU admission rate of 35.71% (55 patients), and a mortality rate of 21.43% (33 patients). Patients who have a severe form of COVID-19 and are admitted to the ICU for mechanical ventilation did not recover and died ($p < 0.001$). Male patients may have higher risk of requiring admission in ICU (p value = 0.357) and higher risk of death (p value = 0.241). Even in our small group of 152 patients, the elderly patients suffered a more severe form of the disease, which was reflected on the number of admission days ($p = 0.07$). In our specific population, based on the statistics, if we take the number of lymphocytes on the day of admission as the dependent factor, we can safely say that there is a statistically significant correlation between lymphopenia at day 1 and the ICU admission ($p < 0.001$) or death ($p = 0.014$). The number of lymphocytes following 10 days of admission is another prognostic marker as we can see from the results of statistic tests: there is a statistically significant correlation between lymphopenia at day 10 and the ICU admission ($p < 0.001$) or death ($p < 0.001$).*

Age is another predictive factor regarding the number of lymphocytes following 10 days of admission ($r = -0.078$ and $p = 0.356$).

Conclusion. *Lymphopenia is an easy-to-determine, efficient and reliable biomarker to establish the disease evolution in patients with COVID-19.*

Keywords: lymphopenia, COVID-19, predictive marker

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INTRODUCTION

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019 (1). The virus that causes COVID-19 is referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); it was previously known as 2019-nCoV. This virus is affecting people worldwide, causing disruption in communities and hospital services. It belongs to the family of Coronaviridae with a genomic similarity of 80% to SARS-CoV (2). The main objective of our study was to assess hematological and biochemistry parameters (mainly lymphocyte count) and identify if lymphopenia is a predictive marker of disease severity and death in COVID-19 infection.

The most notably described complications of COVID-19 are:

- respiratory failure – the major complication in patients with severe disease is acute respiratory distress syndrome (ARDS) and can manifest shortly after the onset of dyspnea. In the study described above, ARDS developed after 8 days after onset of symptoms in 20%, and mechanical ventilation was implemented in 12.3% (3,4,5).
- cardiac and cardiovascular complications – may include arrhythmias, myocardial injury, heart failure and possibly shock (3).
- thromboembolic events – venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE), can be common in severely ill patients with COVID-19, as specially in patients in the intensive care unit (ICU), with a range from 10 to 40% (6). In another study, arterial thrombotic events, including acute stroke (even in patients below 50 years, without risk factors) and limb ischemia, have also been reported (7).
- inflammatory complications – In some cases, patients with severe COVID-19 have laboratory evidence of an extreme inflammatory response, with persistent fevers, elevated markers (D-dimer, CRP and ferritin), and elevated proinflammatory cytokines. These abnormalities have been associated with critical and possibly fatal illness (8,9).
- laboratory abnormalities - a particular set of laboratoryfeatures have been associated with worse outcome LDH, D-dimer, CRP, troponin, CPK, ferritin and absolute lymphocyte count (10,11).

Although these laboratory features are associated with severe disease in patients with COVID-19, they have not been clearly demonstrated to have prognostic value (12,13,14).

Starting from the findings in literature about coronaviruses, we tried to evaluated the importance of lymphopenia as a predictive marker of disease severity in COVID-19 patients.

The mechanism of lymphocyte damage is not fully elucidated in patients infected with SARS CoV 2 (15-18). There are several hypotheses: The virus infects lymphocytes, causing lymphocytes to express the coronavirus receptor ACE2 and thus become targets of the virus (15). The virus affects lymphatic organs causing damage to the thymus or spleen and lead to lymphopenia. Inflammatory cytokines such as TNFα, IL-6 and other inflammatory cytokines could induce lymphocyte apoptosis and decreased lymphocyte count (16). The metabolic disorders, such as hyperlactic acidemia, might suppress the proliferation of lymphocytes causing lymphopenia (17). Thorough research will identify the mechanisms of lymphopenia in COVID-19 (18).

The SARS CoV2 infection has different forms of manifestation with varying degrees of severity. There have been proposed, in the literature, models for evaluating the prognosis of the disease, such as TLM (Time-Ly% model). In a study published by Li Tang in 2020, a Time-LYM% model was validated as an independent criterion of COVID - 19 classification (18): percentage of lymphocytes (LYM%) remained higher than 20% in moderate type of patients with COVID-19, 10-12 days after symptom onset, while in severe forms, LYM % remains below 20%.

Lymphocyte evaluation can be a useful tool in COVID - 19 classification and indicator of sever evolution (18).

MATERIAL AND METHODS

This retrospective observational study included 152 COVID-19 patients hospitalized from different Departments of Colentina Clinical Hospital Bucharest (Hematology, Intensive Care Unit 1, Pneumology) in July 2020 – March 2021.

The age of the patients ranged from 17 to 92, with the median age of 57.62 (Table 1).

TABLE 1. *Mean age*

	Mean	Std. Deviation	N
Age	**57.62**	16.043	152
#admission days	20.67	12.252	151

In the study, there were also included 11 patients with lymphoproliferation.

To set up the inclusion criteria we analized the literature, and we evaluated the model proposed by Tan et

al., which proves that percentage of lymphocytes (LYM%) remained higher than 20% in moderate type of patients with COVID-19, 10-12 days after symptom onset, while in severe forms, LYM % remains below 20% (18).

We set up criteria for lymphopenia as absolute lymphocyte count below 1.5 x 1000/µl, based on the laboratory reference values. We performed the test at the GRAL Laboratory, Bucharest, Romania.

Starting from the findings we tried to evaluated lymphopenia as a predictive marker of disease severity in COVID-19 infection. As including criteria we have set patients hospitalized confirmed with COVID-19, with at least 10 days of hospitalization. The approval of the Hospital Ethical Committee was obtained prior to starting this study.

All of the 152 patients enrolled in the study were confirmed with COVID-19 by real-time reverse transcriptase polymerase chain reaction (PCR) test for nasal an pharyngeal swab samples. The data in demographic, basic clinical and laboratory characteristics and particular evolution saw obtained from the hard copy and electronical medical records from each department involved in the study, by maintaining personal data confidentially.

The study group was divided into several groups: male and female, ICU and non-ICU, deceased and released, lymphopenic or non-lymphopenic at admission (day 1) and Day 10 of hospitalization (day 10).

Statistical analysis

We performed Eta-square tests and Chi-square to assess the differences between different groups; Pearson correlation, One-sample t-test, and ANOVA were used to to assess clinical parameters (days of admission, laboratory values [e.g. lymphocytes at the moment of admission and 10 days after], age and sex) in patients with COVID-19. In all of these tests we obtained p value that was considered statistically significant for $p < 0.05$. All statistical analysis were performed by using SPSS Statistics software version 26.0.

RESULTS

We studied and compared the number of lymphocytes at admission (Day 1) and Day 10, the number of hospitalization days, the admission on ICU and death. The study's purpose was to determine if there is a correlation between the age, gender, count of lymphocytes at day 1 and day 10 and the number of hospitalization days, admission on ICU and death.

First of all, we needed to divide our patients into several groups: Male and female, ICU and non ICU, deceased and discharged (Figures 1, 2 and 3).

Enrolled in our study there were 73 (47.4%) female patients and 79 (52.6%) male patients, with an ICU admission rate of 35.71% (55 patients), and a mortality rate of 21.43% (33 patients).

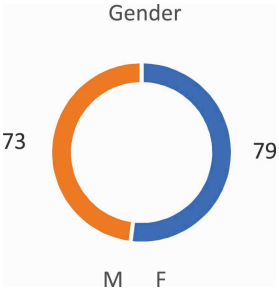

FIGURE 1. *Graphic representation of gender*

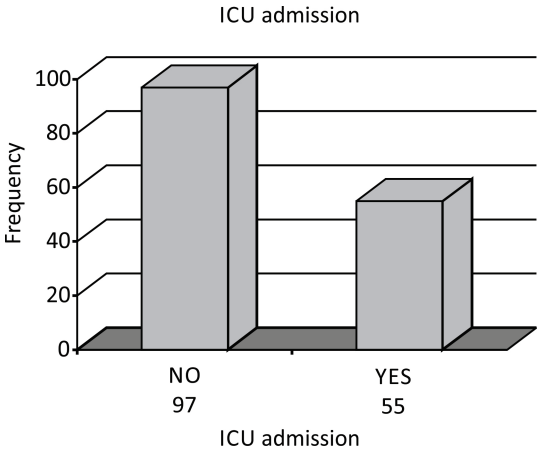

FIGURE 2. *Graphic representation of number of ICU admissions*

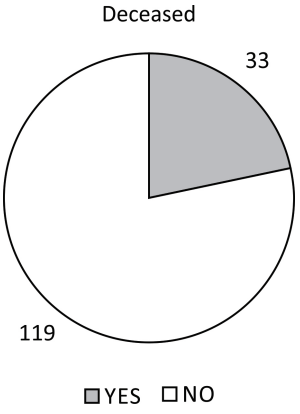

FIGURE 3. *Graphic representation of number of deceased patients*

We wanted to know if there was any significant correlation between ICU admission and death, and thus, performed a Chi-square test, with the result being as followed: chi-square of 67.447 with a continuity correction of 64.127 and $p < 0.001$. From this test, we can firmly stipulate that a significant number of patients who have a severe form of COVID-19 and are admitted to the ICU for mechanical ventilation do not recover and died (Table 2).

TABLE 2. *Chi-square test between ICU admission and mortality*

	Value	df		Asymptotic Significance (2sided)	Exact Sig. (2sided)	Exact Sig. (1sided)
Pearson Chi-Square	67.447[a]		1	.000		
Continuity Correction[b]	64.127		1	.000		
Likelihood Ratio	73.153		1	.000		
Fisher's Exact Test					**.000**	**.000**
Linear-by-Linear Association	67.003		1	.000		
N of Valid Cases	152					

We have performed a Chi-square test to determine if, in our studied population, there was an increased risk of death based on the patients gender, and discovered the following: chi-square of 1.54 with a continuity correction of 1.090 and p value = 0.148 (one sided correlation) and p value = 0.241 (two sided correlation). Another Chi-square test was used to determine if there was an increased risk of ICU admittance based on the patients gender: chi-square = 0.287, p value = 0.357 (Tables 3 and 4). According to our results, we can say that male patients may have higher risk of requiring admission in ICU (p value = 0.357) and higher risk of death (p value = 0.241).

TABLE 3. *Chi-square test between gender and mortality*

	Value	df		Asymptotic Significance (2sided)	Exact Sig. (2sided)	Exact Sig. (1sided)
Pearson Chi-Square	1.540[a]		1	.215		
Continuity Correction[b]	1.090		1	.296		
Likelihood Ratio	1.542		1	.214		
Fisher's Exact Test					**.241**	**.148**
Linear-by-Linear Association	1.530		1	.216		
N of Valid Cases	152					

TABLE 4. *Chi-square test between gender and ICU admission*

	Value	df		Asymptotic Significance (2sided)	Exact Sig. (2sided)	Exact Sig. (1sided)
Pearson Chi-Square	.287[a]		1	.592		
Continuity Correction[b]	.135		1	.714		
Likelihood Ratio	.287		1	.592		
Fisher's Exact Test					**.616**	**.357**
Linear-by-Linear Association	.285		1	.593		
N of Valid Cases	152					

We wanted to see is there was a correlation between age and number of admission days; based upon these, using Pearson correlation we can assess the following: r value = 0.148, p = 0.07. Even in our small group of 152 patients (Figure 4), the elderly patients suffered a more severe form of the disease, which was reflected on the number of admission days (Table 5).

TABLE 5. *Pearson correlation between age and number of admission days*

		Age	No of days of admission
Age	Pearson Correlation	1	.148
	Sig. (2-tailed)		**.070**
	N	152	151
No of days of admission	Pearson Correlation	.148	1
	Sig. (2-tailed)	.070	
	N	151	151

To identify the risk of death based on the number of admission days, we had to divide our population into two groups: patients admitted into the ICU and deceased patients. To assess the statistical significance previously said parameters, we have conducted several tests, including Eta-square test and One-sample t Test, with the following results: looking at the One-Sample t Test we can firmly say that the number of admission days directly influences death rates among our studied population (t=23.335, p < 0.001 for the "deceased" parameter; t = 20.730, p < 0.001 for the" number of days of admission" parameter). To confirm, we used the Eta test (p = 0.469 for the "deceased dependent" parameter, p = 0.026 for the "number of days of admission dependent" parameter). Another Eta descriptive test was used to assess ICU admitted patients (p = 0.492 for the "ICU dependent" parameter, p = 0.218 for the "Number of days of admission" parameter). (Tables 6, 7 and 8).

We looked at whether lymphopenia is a predictive marker for disease severity in COVID-19 infection, by conducted several statistical test, including Eta and Pearson correlation. The criteria set up for lymphopenia was absolute lymphocyte count below 1,5 x 1000/µl, according to GRAL Laboratory reference values. We

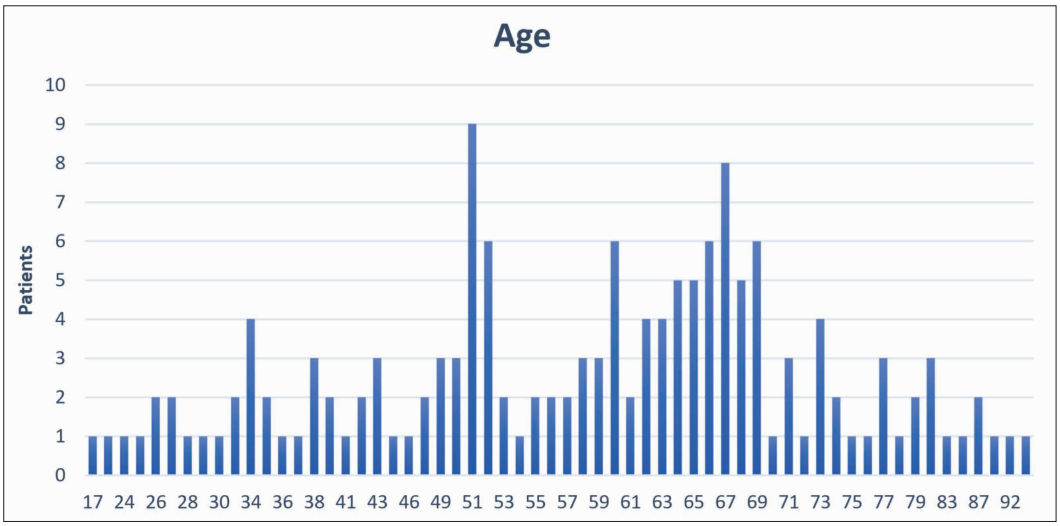

FIGURE 4. *Graphic representation of age distribution*

TABLE 6. *One-Sample t Test between number of admission days and number of deceased patients*

	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference Lower	Upper
Deceased	23.335	151	**.000**	.783	.72	.85
No of days of admission	20.730	150	**.000**	20.669	18.70	22.64

TABLE 7. *Eta test between number of admission days and deceased patients*

Nominal by Interval	Eta	Deceased Dependent	**.469**
		No of days of admission Dependent	**.026**

TABLE 8. *Eta test between number of admission days and ICU admission*

Nominal by Interval	Eta	ICU Dependent	**.492**
		No of days of admission Dependent	**.218**

analyzed the presence of lymphopenia at day 1 (at hospital admission) and day 10 and we correlated with duration of hospitalization, ICU admission or death (Tables 9, 10, 11, 12, 13 and 14).

TABLE 9. *Lymphopenia at D1 and number of days of admission*

Directional Measures			
			Value
Nominal by Interval	Eta	lymphopenia int Dependent	.509
		No of days of admission Dependent	.131

TABEL 10. *Lymphopenia at D10 and number of days of admission*

Directional Measures			
			Value
Nominal by Interval	Eta	lymphopenia d10 Dependent	.498
		No of days of admission Dependent	.291

TABEL 11A,B. *Lymphopenia at D1 and ICU admission*

A. Lymphopenia int * ICU Crosstabulation				
Count				
		ICU		Total
		yes	no	
lymphopenia int	yes	46	52	98
	no	9	45	54
Total		55	97	152

B. Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	13.817[a]	1	.000		
Continuity Correction[b]	12.537	1	.000		
Likelihood Ratio	14.809	1	.000		
Fisher's Exact Test				**.000**	**.000**
Linear-by-Linear Association	13.726	1	.000		
N of Valid Cases	152				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 19.54.					
b. Computed only for a 2x2 table					

TABEL 12A,B. *Lymphopenia at D1 and death*

A. Lymphopenia int * Deceased Crosstabulation				
Count				
		Deceased		Total
		yes	no	
lymphopenia int	yes	27	71	98
	no	6	48	54
Total		33	119	152

B. Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.536[a]	1	.019		
Continuity Correction[b]	4.611	1	.032		
Likelihood Ratio	6.007	1	.014		
Fisher's Exact Test				**.023**	**.014**
Linear-by-Linear Association	5.500	1	.019		
N of Valid Cases	152				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 11.72.					
b. Computed only for a 2x2 table					

TABEL 13A,B. *Lymphopenia at D10 and ICU admission*

lymphopenia d10 * ICU Crosstabulation				
Count				
		ICU		Total
		da	nu	
lymphopenia d10	yes	43	27	70
	no	11	59	70
Total		54	86	140

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	30.870[a]	1	.000		
Continuity Correction[b]	28.971	1	.000		
Likelihood Ratio	32.465	1	.000		
Fisher's Exact Test				**.000**	**.000**
Linear-by-Linear Association	30.649	1	.000		
N of Valid Cases	140				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 27.00.					
b. Computed only for a 2x2 table					

TABEL 14A,B. *Lymphopenia at D10 and death*

lymphopenia d10 * Deceased Crosstabulation				
Count				
		Deceased		Total
		da	nu	
lymphopenia d10	yes	26	44	70
	no	6	64	70
Total		32	108	140

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	16.204[a]	1	.000		
Continuity Correction[b]	14.624	1	.000		
Likelihood Ratio	17.202	1	.000		
Fisher's Exact Test				**.000**	**.000**
Linear-by-Linear Association	16.088	1	.000		
N of Valid Cases	140				
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 16.00.					
b. Computed only for a 2x2 table					

In our specific population, based on the statistics given by the test above, if we take the number of lymphocytes on the day of admission as the dependent factor, we can safely say that there is a statistically significant correlation between lymphopenia at day 1 and the ICU admission ($p < 0.001$) or death ($p = 0.014$).

The number of lymphocytes following 10 days of admission is another prognostic marker as we can see from the results of the test above: there is a statistically significant correlation between lymphopenia at day 10 and the ICU admission ($p<0.001$) or death ($p < 0.001$).

Age is another predictive factor regarding the number of lymphocytes following 10 days of admission ($r = -0.078$ and $p = 0.356$) (Table 15).

TABLE 15. *Pearson correlation between age and number of lymphocytes at day 10*

		Age	Day 10 Lymphocytes
Age	Pearson Correlation	1	-.078
	Sig. (2-tailed)		**.356**
	N	152	141
Day 10 Lymphocytes	Pearson Correlation	**-.078**	1
	Sig. (2-tailed)	.356	
	N	141	141

DISCUSSIONS

Enrolled in our study there were 152 patients: 73 (47.4%) female patients and 79 (52.6%) male patients, with an ICU admission rate of 35.71% (55 patients), and a mortality rate of 21.43% (33 patients).

Because the ICU admission rate and mortality rate were relatively close to each other, we looked at whether there was a correlation between ICU admission and death and we can firmly stipulate that a significant number of patients who have a severe form of COVID-19 and are admitted to the ICU for mechanical ventilation died ($p < 0.001$).

We wanted to know if there was an increased risk of death based on the patients gender. According to our results, we can say that male patients may have higher risk of requiring admission in ICU (p value = 0.357) and higher risk of death (p value = 0.241). In many studies we have found that there is no statistical difference between male and female patients and the likelihood of death, but in a meta-analysis of 3,111,714 globally reported cases, Peckham et al. demonstrated that, whilst there is no difference in the proportion of males and females with confirmed COVID-19, male patients have almost three times the odds of requiring intensive treatment unit admission (OR = 2.84; 95% CI = 2.06, 3.92) and higher odds of death (OR = 1.39; 95% CI = 1.31, 1.47) compared to females (19). The results of our statistical analysis correlates with Peckham et al. study.

We wanted to see is there was a correlation between age and number of admission days. Even in our small group of 152 patients, the elderly patients suffered a more severe form of the disease, which was reflected on the number of admission days ($p = 0.07$). From the literature, we found that COVID-19 is often more severe in people older than 60 years. In analysis of 419 patients from five hospitals in Shanghai, Hubei, and Jiangsu Provinces, Dai et al. demonstrated that comorbidity, albumin (ALB) level, C-reactive protein (CRP) level, and age ≥ 60 years were identified as the most influential risk factors for the severity of COVID-19 in these patients (20). The results of our statistical analysis correlates with Dai et al. study.

We tried to identify the risk of death based on the number of admission days. Based on these tests we can extrapolate the following conclusion: The longer the patient is admitted, the worse the prognosis ($p < 0.001$).

Focusing on the main objective of our study we found that, if we take the number of lymphocytes on the day of admission as the dependent factor, we can safely say that there is a statistically significant correlation between lymphopenia at day 1 and the ICU admission ($p < 0.001$) or death ($p = 0.014$).

The number of lymphocytes following 10 days of admission is another prognostic marker: in our specific population, there is a statistically significant correlation between lymphopenia at day 10 and the ICU admission ($p < 0.001$) or death ($p < 0.001$).

Among the articles studied we found a strong correlation between the percentage of lymphocytes and the progression of the disease, which was also noted in the study carried out on our department. In most patients, lymphocytes decreased by 5% in the first 2 weeks after onset of the disease, whice is which is in line with our data (11,18).

Age is another predictive factor regarding the number of lymphocytes following 10 days of admission ($r = -0.078$ and $p = 0.356$).

CONCLUSIONS

Lymphopenia is an easy-to-determine, efficient and reliable biomarker to establish the disease evolution in patients with COVID-19.

In our study, we found a correlation between lymphopenia and the ICU admission or death, that is clinically useful in determining the prognosis of patients with COVID-19. More study would be necessary to better understand the role of the lymphocyte in a patient infected with SARS-CoV-2.

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