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Case Series

Lymphopenia in Covid-19: A single center retrospective study of 589 cases

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ABSTRACT

Background: Lymphopenia is one of features that helps identify patients with severe Covid-19. This retrospectively study analyzed the association of lymphopenia with the severity of COVID-19 infection, determinate the predictive factors of lymphopenia and the significance of mortality in patient with lymphopenia.
Methods: This retrospective study included patients diagnosed with Covid-19 and admitted to intensive care unit of our university hospital center From Mars 1st 2020, to December 31st' 2020.
Results: In this study, 589 patients were included, a group had lymphopenia with 357 cases (60.06%) and the non-lymphopenia group with 232 cases (39.4%). The median age of our patients having lymphopenia was 65 years (56–76). Hypertension and diabetes were noted in the majority of patients with lymphopenia than in the non-lymphopenia group. Lymphopenia was strongly correlated to the inflammatory biomarkers of COVID-19 and were significant. A significant correlation was found between lymphopenia group and CT scan. Lymphopenia was observed as an indicator of prolonged duration of hospitalization but was not significant.
Conclusion: Analytical data from this retrospective study shows the importance in the association between lymphopenia and the severity of COVID-19 infection, hence the need for dynamic monitoring of the number of lymphocytes on admission and during hospitalization of these patients.

1. Introduction

COVID-19 is a new disease that appeared in December 2019 in Wuhan, Hubei province China, Millions of people have been infected and died from this Infection [1]. Patients with COVID-19 have developed several types of clinical manifestations, acute respiratory failure is the most common syndrome which requires oxygen supplementation and which have sometimes progressed to multiorgan failure or even death [2]. Different markers have been used for early identification and predicting patients with severe Covid-19 disease [3], the lymphopenia is the prominent abnormality parameters occurring in the majority of critical and severe Covid-19 patients [4]. A study in Hong Kong reported that lymphopenia was observed in 98% of patients with Sars-CoV-2 infection [5]. A significant decrease of lymphocyte count is noted in the severe group of patients with Covid-19 than non-severe group [6]. The mechanisms of this phenomenon have not yet been elucidated [7]. In the literature, there are studies that explain the different mechanisms leading to the decrease in lymphocytes counts during viral infection with COVID-19, angiotensin converting enzyme (ACE2) is a main receptor for Sars-Cov-2 as well as Sars-CoV-2, this enzyme used by the virus to enter the host and caused damage in lymphoid organ [8]. However, ACE2 has been observed in different organs such as the heart, liver, brain, kidneys, intestine, bladder, thyroid and testes, in addition to respiratory tract cells [9,10].

Predictors indicating the severity of COVID-19 disease with lymphopenia have been shown in studies being the clinical manifestations of

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COVID-19, including fever, dyspnea, cough, and asthenia which may develop organ failure, patients with comorbidity indicating a high mortality rate, inflammatory tests (lymphopenia, Lactate dehydrogenase, Interleukin 6, ferritin, fibrinogen and CRP) and the degree of damage on the chest CT scan [7,11].

The present study retrospectively analyzed the frequency and the association of lymphopenia with the severity of COVID-19 infection, determinate the predictive factors of lymphopenia and the significance of mortality in patient with lymphopenia.

2. Patients and methods

In this single-center retrospective study, we analyzed all patients with clinical, biological and/or radiological manifestations of COVID-19 admitted to our Intensive Care Unit (ICU) at the Mohammed VI University Hospital Center of Oujda, Morocco, from Mars 1st 2020, to December 31st, 2020. The inclusion and exclusion criteria were presented in this figure (Fig. 1). The collect information was made retrospectively on data from patient's medical records and a questionnaire.

Continuous variables were categorized, as it is easier to interpret and also for the simplicity of reporting results. For common laboratory values, we used the cutoff points which were widely recognized and adopted in clinical practice. Leukopenia was defined as white blood cell count $<4.0 \times 10^9$/L and thrombocytopenia as platelet count$<100 \times 10^9$/L.

The sample were also divided into two groups depending on the presence of lymphopenia (Lymphocyte count $<1.0 \times 10^9$/L) and clinical, laboratory, treatment and outcome data were gathered and compared between patients with and without lymphopenia.

All patients in our cohort underwent CT scan at their admission and lung damages from COVID-19 were classified into two grades: general or non-severe (10–50% of scanner impairment) and severe (50–100%).

Statistical analysis was performed using the SPSS software version 21.0. Qualitative variables were expressed as counts and percentage and quantitative variables as mean±standard deviation (SD) or as median (interquartile range (IQR)). then a univariate analysis was performed to compare between two groups of patients with lymphopenia and other without lymphopenia. The comparison of values was performed by the 2-tailled Student *t*-test or the Mann-Whitney *U* test, as appropriate for quantitative variables and by CHI-2 test or Fisher exact test for qualitative variables. Kaplan-Meier survival curves and log-rank tests were used to describe the effect of the lymphopenia on in-hospital mortality.

This study does not require a formal ethical committee approval. Access to patient data was authorized by the Mohammed VI university hospital and approved by the head of the department, taking into account the retrospective design of this study. The requirement of patient consent has been lifted. Data anonymity was respected in accordance with national and international guidelines. Our study was registered in Research Registry under the number: 7098.

This case series has been reported in line with the PROCESS Guideline [12].

3. Results

The total number of patients included in the present study were 589 cases hospitalized in intensive care unit for management of acute respiratory failure due to COVID-19 pneumonia. Among them, 357 patients (60.6%) had lymphopenia on his admission to the ICU (group with lymphopenia) while 232 patients (39.4%) had normal lymphocyte counts (group without lymphopenia). The median age of patients having lymphopenia on admission was 65 years ((IQR: 56–76) vs 62 years (IQR: 47–70) in non-lymphopenia group), which mean significantly older than patients without lymphopenia ($P < 0{,}0001$). No significance difference was observed in the median of BMI in lymphopenia group than non-lymphopenia group (the median of 26 kg/m^2 ((IQR: 24–28) vs 26 kg/m^2 (IQR: 23–28) respectively with $P = 0.2$). Men were predominant in group with lymphopenia (74.2% vs 55.6% in non-lymphopenia group) and was considering significant ($P < 0{,}0001$) compared to women with 25.8% in lymphopenia group. The results of epidemiological characteristics of our patients in the two groups are shown in Table 1.

In our study, the medical history of patients with lymphopenia was as follow: 36.1% of patients in group with lymphopenia had a high blood pressure compared to 26.7% of patients in group without lymphopenia; diabetes was noted in 36.4% of cases with lymphopenia compared to 25.0% of patients without lymphopenia; cardiovascular disease with 14.3% in lymphopenia group versus 12.1% in non-lymphopenia group and chronic renal failure was found in 24 cases with lymphopenia or a percentage of 6.7% compared to 4.7% in non-lymphopenia group. However, the difference was significant only for hypertension and diabetes with a P value at 0.017; $P = 0.004$ respectively. The frequencies of the most clinical symptoms of COVID-19 infection were significantly higher in the group with lymphopenia (Fever $P = 0.004$; cough $P = 0.028$, dyspnea $P < 0.0001$ and asthenia $P = 0.001$).

The analyzed laboratory parameters shown that the most biomarkers of patients infected with Sars-Cov-2 were significant and strongly correlated to lymphopenia. Leukopenia and thrombocytopenia weren't associated significantly with lymphopenia ($P = 0.13$; $P = 0.07$ respectively). However, the median of white blood cell counts was a little high

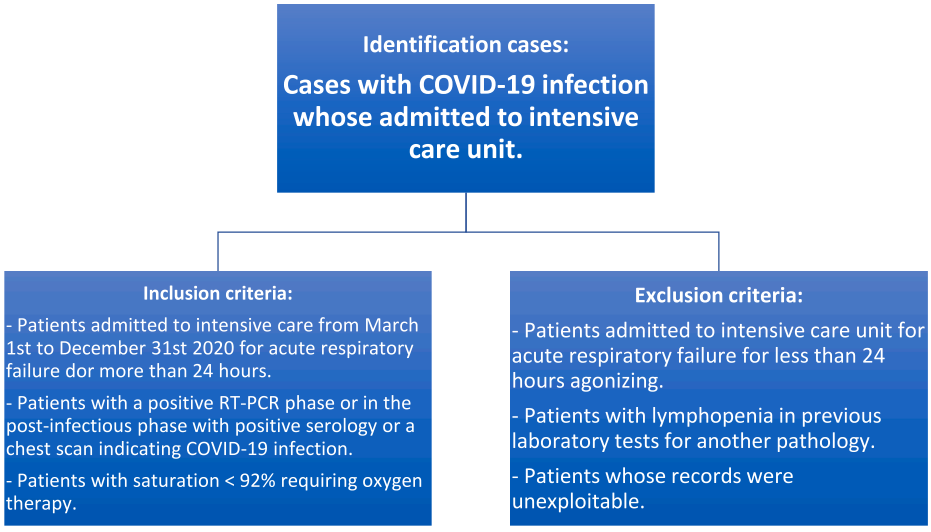

Fig. 1. Flowchart of patient's selection.

Table 1
Epidemiological, clinical and laboratory characteristics of our case series according to the presence or no of lymphopenia.

Patients parameters	Patients with lymphopenia (N = 357) (group A)	Patients with no lymphopenia (N = 232) (group B)	P value
Gender			
Male N (%)	265 (74.2)	129 (55.6)	<0.0001
Age, years, median (IQR)	65 (56–76)	62 (47–70)	<0.0001
BMI (Kg/m²), median (IQR)	26 [24–28]	26 [23–28]	0.2
Comorbidity N (%)			
Hypertension	129 (36.1)	62 (26.7)	0.017
Diabetes	130 (36.4)	58 (25.0)	0.004
Cardiovascular disease	51 (14.3)	28 (12.1)	0.44
Chronic renal failure	24 (6.7)	11 (4.7)	0.32
Symptoms N (%)			
Fever	288 (80.7)	163 (70.3)	0.004
Dyspnea	289 (81.0)	134 (57.8)	<0.0001
Cough	278 (77.9)	162 (69.8)	0.028
Asthenia	255 (71.4)	136 (58.6)	0.001
Laboratory tests median (IQR)			
White blood cell (x10⁹/L)	11.10 (7.78–14.87)	9.66 (6.71–15.12)	0.1
Platelets (x10⁹/L)	232.0 (168.5–304.0)	246.0 (180.0–335.0)	0.12
LDH (U/L)	583.0 (397.5–825.5)	435.0 (253.0–827.5)	<0.0001
CRP (mg/L)	190.27 (98.5–256.75)	146.0 (27.36–235.0)	<0.0001
Ferritin µg/L	1015.0 (546.0–2000.0)	744.5 (202.5–1681.5)	<0.0001
Fibrinogen g/L	6.8 (5.2–7.9)	6.45 (4.3–7.9)	0.023
Imaging data (CT) N (%)			
General (10–50%)	88 (25.7)	73 (37.6)	0.004
Severe (50–100%)	255 (74.3)	121 (62.4)	
Treatment N (%)			
Dexamethasone	72 (20.2)	52 (22.4)	0.51
Tocilizumab	56 (15.7)	25 (10.8)	0.09
PLEX	3 (0.8)	1 (0.4)	0.48
Respiratory support N (%)			
High concentration masks	291 (81.5)	180 (77.6)	0.24
High-flow nasal cannula	196 (54.9)	112 (48.3)	0.11
Non-invasive ventilation	101 (28.3)	37 (15.9)	0.001
Invasive ventilation	141 (39.6)	52 (22.4)	<0.0001
Duration of hospitalization median (IQR)	6 (3.0–12.0)	6 (3.0–10.0)	0.13
Prognosis			0.001
Improved and discharged N (%)	221 (61.9)	175 (75.4)	
Death N (%)	136 (38.1)	57 (24.6)	

with 11100/mm^3 (IQR 7782.0–14870.0) in patients with lymphopenia vs the median of 9660/mm^3 (IQR 6710.0–15120.0) in non-lymphopenia group (P = 0.1). There is a small difference in platelets between both groups and the counts were normal with a median of 232000/mm^3 ((IQR 168500–304000) vs 246000/mm^3 (IQR 180000–335000); P = 0.12). The median of lactate dehydrogenase (LDH) was elevated in lymphopenia group patients with 587 U/L ((IQR 426.25–827.75) vs 463 U/L (IQR 293.25–823.50) in patients with no lymphopenia (P < 0,0001). C-reactive protein (CRP) as inflammatory indicator was elevated with a median 190.27 mg/L ((IQR 98.50–256.75) vs 146 mg/L (IQR 27.36–235.0) in lymphopenia group than non-lymphopenia group (P < 0,0001). Ferritin and fibrinogen levels on admission were also high due to inflammatory syndrome of COVID-19 infection in lymphopenia group and the median was respectively 1015 µg/L (IQR 546.0–2000.0; P < 0.0001); 6,8 g/L (IQR 5.2–7.9; P = 0.023).

According to our results, the frequency of lymphopenia was higher in the severe impairment of Covid-19 patients. Indeed, most of 357 cases of Covid-19 patients with lymphopenia were classified as severe cases with 74.3% than no lymphopenia group with 62.4% and only 25.7% patients were general cases in group with lymphopenia versus 37.6% in the other group. Indeed, a significant correlation was found between lymphopenia group and CT scan with a P value of 0.004.

The treatment of our patients was given in isolation, and received the basic treatment using azithromycin 500 mg the 1st day then 250 mg for 4 days, vitamin C 4 g per day, zinc 90 mg per day and vitamin D 25,000 IU/week for 4–6 weeks. Salicylic acid was given at a dose of 160 mg/day. Dexamethasone (6 mg/day) was used in 72 cases in the lymphopenia group (20.2% vs 22.4% in non-lymphopenia group with P = 0.51), followed by methylprednisolone relay (32 mg/day) with progressive regression. More patients received Tocilizumab in the lymphopenia group than in the non-lymphopenia group (15.7% vs 10.8%; P = 0.09). Only 3 of our patients with lymphopenia benefitted from plasma exchange (PLEX) (0.8% vs 0.4%; P = 0.48).

In this cohort, most of our patients in the lymphopenia group required higher levels of respiratory support, such as high concentration masks (81.5% vs 77.6%; P = 0.24), high-flow nasal cannula (54.9% vs 48.3%; P = 0.11), non-invasive ventilation (28.3% vs 15.9%; P = 0.01) and invasive ventilation (39.6% vs 22.4%; P = 0.0001).

The correlation between the duration of hospitalization and lymphopenia in Covid-19 patients was also analyzed. There is no difference in the median duration of hospitalization for patients in lymphopenia group and non-lymphopenia group with a median of 6 days (IQR 3.0–12.0) vs median of 6 days (IQR 3.0–10.0) respectively (P = 0.13). Among the 357 patients with lymphopenia in our study, 136 patients (38.1% vs 24.6% in patients without lymphopenia) died in the intensive care unit while 221 (61.9% vs 75.4% in non-lymphopenia group) were survived and had favorable evolution (P = 0.001). But the comparison of the Kaplan-Meier curves showed no significant difference of the survival rates between lymphopenia and no lymphopenia groups (Fig. 2).

4. Discussion

In this retrospective study performed on 589 patients during a 10-month period (from March 2020 to December 2020), we have observed that lymphopenia is associated with epidemiological characteristics, hypertension and diabetes as medical history of our patients, clinical manifestations, inflammatory biomarkers and the severity of pneumonia on CT scan images. However, prolonged hospitalization was not associated to lymphopenia.

Lymphopenia has become increasingly common in patients with Sars-COV-2 as was noted in the attack of SARS, MERS and respiratory syncytial virus and it is an important predictor of the severity of the disease [13–15]. In the current study, more than a half of our patients were presented with lymphopenia (60.6%) on their admission, which is coherent with a retrospective study by Liu K and al. in Hubei Province from December 30, 2019 to January 24, 2020 including 137 patients with Covid-19 infection (72.2% patients with lymphopenia) [16]. The results of Liu Y et al. in Shenzhen, China for 12 cases of the 2019-nCoV-infected patients, revealed that lymphopenia was positively correlated with the severity of COVID-19 [17], which agrees with the results of our study. Also, was reported in a single-centred, retrospective study of Jiheng Liu and al, for a total of 115 patients diagnosed with COVID-19 from the First Hospital of Changsha from January 17, 2020, to February 14, 2020 [18].

The main pathophysiology of SARS-CoV-2 infection in severe cases may be related to the consequences of the cytokine storm. The presence of hypercytokinemia in COVID-19 patients with lymphopenia may represent the uncontrolled progression of the pathogen that can be observed in severe patients [19,20].

Among the possible mechanisms that could explain the reduction of lymphocytes in patients with COVID-19 are the use of the main receptor for Sars-Cov-2 called the angiotensin converting enzyme (ACE2) that

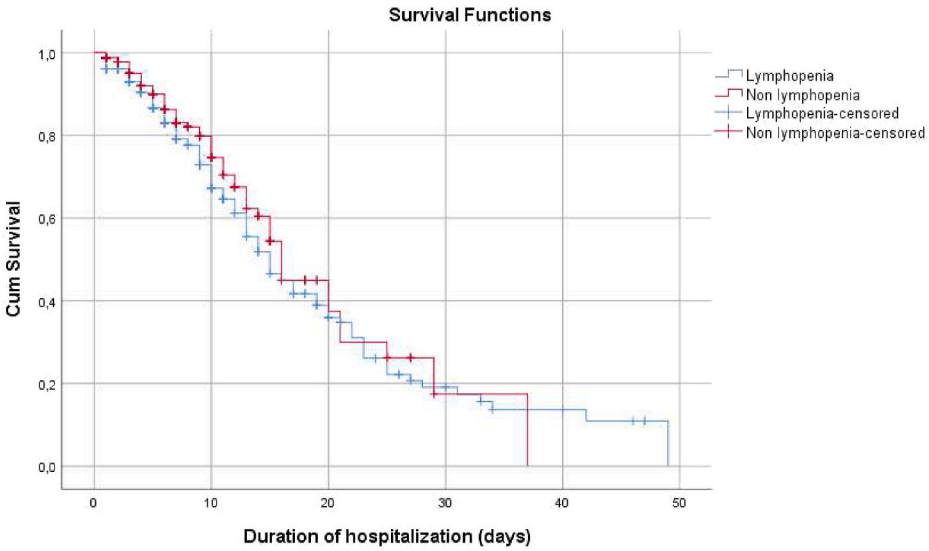

Fig. 2. Kaplan-Meier survival curves according to the presence or no of lymphopenia and no lymphopenia groups.

penetrate human cells as well as T lymphocytes, as shown in Sars-Cov [21]. Lymphopenia is strongly linked to the inflammatory cytokine storm which lead to multi-organ failure and death. The latter can affect the behavior of T lymphocytes and natural killer (NK) cells during viral infection by their exhaustion [22]. It was noted in our study that most markers of inflammation in laboratory findings were correlated with lymphopenia, confirming its severity in COVID-19 infection.

Based on our study, in the elderly, lymphopenia occurs more frequently and were significant. Tavakolpour and al. in their study shows the same results, especially in severe cases [23]. However, men were predominant in our cases.

In our series, patients with underlying chronic diseases represent the majority of COVID-19 patients with lymphopenia, which joins the other cohorts reported in Wuhan such as in a retrospective, multicentre cohort study by Zhou F and all including 191 patients from Dec 29, 2019 to Jan 31, 2020 [24–26]. More patients with lymphopenia had hypertension as main medical history as reported in data from Jiheng Liu and al [18]. The reason for this association depends on the presence of ACE2 which is a surface molecule found on arterial and venous endothelial cells, arterial smooth muscle cells and airway cells [27]. Lymphopenia is more common in diabetes also in this study.

COVID-19 infection may be asymptomatic in same cases. Indeed, our cohort found that 19.3% patients with lymphopenia were presented in our unit without fever, comparing to the retrospective cohort study of Jiheng Liu and al for a total of 115 patients who found approximately same results (25% patients with lymphopenia without fever on admission) [18], which means that the COVID-19 disease remains difficult to identify, hence a close diagnosis of any patient presenting to the emergency room with minimum symptoms in order to better control the pandemic.

We demonstrated in our study an association with the degree of impairment on the CT scan due to COVID-19 infection and lymphopenia. It was reported in the study of Tan and al.; the lymphocytes count can be considered as an accurate indicator for the classification of COVID-19 patients in severe and critical cases [28].

It was observed in this study that the use of dexamethasone as corticosteroids in the treatment of patients with COVID-19 was not correlated with lymphopenia. However, it should be borne in mind that treatment with corticosteroids could have an impact on the number of lymphocytes. The use of Tocilizumab in our patients with lymphopenia according to international recommendations has shown its benefits on the recovery of the lymphocyte count, which confirms the good practical approach. A multicenter, randomized controlled trial among patients with COVID-19 pneumonia with cytokine storm syndrome has been licensed to use the tocilizumab (IL-6 receptor blockade) in China [29]. More investigations into the therapeutic approach are needed in the prospective sense to provide evidence for large-scale use and to predict the severity of COVID-19 disease.

Our series found that lymphopenia was associated with mortality and was significant. As reported in other studies such as Zheng et al. lymphopenia was associated with mortality [30]. Hence the early recovery of lymphocytes, before other biological and radiological parameters in severe cases, which suggests its predictive value for the improvement of our patients.

Our study has several limitations. Certain data were not available and were missing during the collection of files such as biological tests, CT scan, treatments and outcomes because this study was retrospective. Thus, it is not possible to predict the severity of COVID-19 disease. Therefore, it is important to lead a more complete and thorough investigation in the future in a prospective sense.

In order to confirm our results led on 589 cases on the association between lymphopenia and the severity of COVID-19, it is necessary to early identify the risk factors associated with lymphopenia and to focus on additional studies to better study the behavior of lymphocytes counts during illness as well as the severity of ARDS due to COVID-19.

5. Conclusion

Lymphopenia is an important feature and common in severe COVID-19 patients especially with co-morbidities and high age, which can predict disease severity. In order to confirm the predictive severity in Covid-19, several studies are needed in this regard. Lymphocyte count has been associated with increased disease severity in COVID-19. The majority of our patients who died from COVID-19 had significantly lower lymphocyte counts.

Ethical approval

This is a retrospective case series that does not require a formal ethical committee approval. Data were anonymously registered in our database. Access to data was approved by the head of the department.

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Consent

Obtained.

Author contribution

EL AIDOUNI Ghizlane: Study concept, Data collection; data analysis; writing review & editing MERBOUH Manal: Contributor El Kaouini Abderrahim: Contributor Elrhalete Abdelilah: Contributor Maarad Mohammed: Contributor Alkouh Rajae: Contributor Bouazzaoui Mohammed Amine: Contributor, Data analysis BKIYAR Houssam: supervision and data validation ABDA Naima: Study concept, Data collection; data analysis, editing and supervision and data validation HOUSNI Brahim: supervision and data validation.

Trial registry number

Research registry 7098.

Guarantor

EL Aidouni Ghizlane.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors state that they have no conflicts of interest for this case series.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102816.

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