OPEN ACCESS
Scholars International Journal of Traditional and Complementary Medicine
Abbreviated Key Title: Sch Int J Tradit Complement Med
ISSN 2616-8634 (Print) |ISSN 2617-3891 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

**Original Research Article**

# Prognostic Value of Inflammatory Biomarkers in COVID-19

Kouam Tasnim[1], Abdelkhaled Ilias[1], Ammor Abdesselam[1], Khalki Hanane[1]

[1]Biochemistry Laboratory university hospital of Tangier Morocco, Faculty of Medicine and Pharmacy, Universit of Abdelmalek Essaadi, Tangier, Morocco

**DOI:** 10.36348/sijtcm.2022.v05i07.003 | **Received:** 15.06.2022 | **Accepted:** 31.07.2022 | **Published:** 13.08.2022

***Corresponding author:** Kouam Tasnim
Biochemistry Laboratory university hospital of Tangier Morocco, Faculty of Medicine and Pharmacy, Universit of Abdelmalek Essaadi, Tangier, Morocco

## Abstract

***Background:*** Coronavirus disease 2019 (COVID-19) is characterized by a variable clinical picture ranging from asymptomatic to severe or even critical forms that can be life-threatening. The biological assessment can also be within the limits of normality, even little disturbed or outright witness of an excessive inflammatory response or a real cytokine storm which would follow the virological phase of the disease. The objective of our study is to evaluate the contribution of inflammatory biomarkers: LDH, procalcitonin (PCT), ferritin, C-reactive protein (CRP) and the level of lymphocytes, in the prediction of mortality in COVID-19 patients. ***Methods:*** We collected 79 patients diagnosed with COVID-19 on the basis of a set of clinical, radiological and / or biological arguments, which we divided into two groups: Survivors (N = 45) and deceased (N = 34). All these patients had all the biomarkers measured upon admission. ***Results:*** In our study, we found that the levels of the four inflammatory biomarkers studied in our series were elevated in both groups of patients (survivors and decedents), however, the decedents did not have significantly higher levels than the survivors (P >0.05).

**Keywords:** SARS-CoV-2 virus, inflammatory biomarkers, mortality, Prognosis.



## INTRODUCTION

The SARS-CoV-2 virus is the cause of Covid 19 disease, which occurred in Wuhan, China in December 2019. This disease is highly infectious and contagious [1, 2]. The clinical manifestations of this disease, which the WHO has declared as a public health emergency, are variable and severe damage can lead to hypoxia, multi-organ dysfunction or even death [1]. The disease goes through two phases: a first virological phase where the virus multiplies, activates the immune system to enter the second phase, called inflammatory, which may be exaggerated in some patients progressing to a cytokine storm and systemic damage [2]. This hyperinflammation would indicate the severity of the disease [3, 4]. Some analyzes can be useful in order to stratify the evolution and could orient and adapt the care according to the risks of complications.

The objective of our study is to evaluate the contribution of inflammatory biomarkers: LDH, procalcitonin (PCT), ferritin, reactive C protein (CRP) and lymphocyte count, in predicting mortality of patients with COVID-19 disease.

## MATERIAL AND METHOD

This is a retrospective, cross-sectional study, including patients hospitalized for covid 19, admitted to the two hospital structures (Intermediate Care Unit and Intensive Care Unit), from August 1 st to august 25 th, 2021 and whose biological assessments were analyzed by the laboratory department of the Tangier-Tetouan-Al Hoceima University Hospital in northern Morocco.

We enrolled 79 patients with COVID-19, were selected on the basis of clinical, radiological and/or biological arguments (RT-PCR and/or rapid serological tests), in which the laboratory test included: lymphocyte count, CRP, LDH, Ferritin and Procalcitonin. The values retained for these parameters measured, include only those realized at admission. Patients were divided into two groups: survivors and deceased.

The tests were performed on 3 automats: Vidas 3 biomerieux (ELFA technique: Enzyme Linked Fluorescent Assay) for ferritin and procalcitonin and on BS380 from mindray by immunoturbidimetric technique for CRP and by enzymatic technique for LDH and on Mindray 5580 for lymphocyte count.

All Statistical analyses were performed by IBM SPSS version 21. Quantitative data were presented as means and standard deviations and qualitative data were presented as numbers and percentages. The univariate analysis was done for the comparison of the means of the inflammatory markers (CRP, ferritin, procalcitonin and LDH) as well as the lymphocyte count in the 2 groups of patients (survivors and deceased) by the Student's test after the verification of normality.

## RESULTS

### 1) Demographic data

A total of 79 patients with COVID-19 were included in this study, divided into two groups (34 deceased, 45 survivors). The mean age of patients was 57.51 +/- 14.31 (range, 29-91) and 49.4% of patients were male.

The mean age was (59.85 years +/- 15.81) among the deceased group and was (55.75 years +/- 12.98) among the survivors group.

### 2) Analysis of inflammatory biomarkers and blood lymphocytes

The CRP values of the patients ranged from 10.30 mg/l to 346.30 mg/l with a mean of 155.4 mg/l. For Ferritinemia, the values ranged from 27.9 ng/ml to 1200 ng/ml with a mean of 639 ng/ml. Concerning the range of values of Procalcitoninemia, its values are between 0.05 ng/ml and 205.9 ng/ml with an average of 6.57 ng/ml. About the values of LDH, they are between 211 U/L and 1512 U/L with an average of 598.10 U/L and for the rate of lymphocytes, it is between 0.25 x10^3/µL, and 6.62 10^3/µL With an average of 0.96 x103 /µL

**Table 1: CRP, LDH, PCT, Ferritin and Lymphocyte count in patients**

| | CRP | LDH | Ferritin | Procalcitonin | Lymphocyt count |
|---|---|---|---|---|---|
| Average | 155.40 | 598.10 | 639.00 | 6.57 | 0.96 |
| Standard deviation | 79.85 | 266.18 | 358.23 | 32.09 | 0.91 |
| Minimum | 10.30 | 211.00 | 27.90 | 0.05 | 0.25 |
| Maximum | 346.30 | 1512.00 | 1200.00 | 205.90 | 6.62 |

### 3) The relationship between the values of the biomarkers of inflammation, lymphocytes and the evolution towards death:

The average levels of inflammatory biomarkers and lymphocytes count measured in the two categories of patients (Dead / Survivors), are summarized in the table below:

**Table 2: Average levels of the different inflammatory biomarkers and lymphocytes measured in the two categories of patients: deceased/survivors**

| Paramètre | Survivors | Deceased | P-value* |
|---|---|---|---|
| CRP(mg/l) | 144.48+/-81.11 | 169.84 +/- 76.95 | 0.16 |
| LDH(U/L) | 593.55+/-245.34 | 604.11+/-295.20 | 0.86 |
| FERRITIN(ng/ml) | 678.46+/-412.09 | 609.19+/-313.07 | 0.41 |
| PROCALCITONIN (ng/ml) | 5.42+/-29.77 | 8.10+/-35.33 | 0.71 |
| LYMPHOCYTE COUNT(x10^3/µL) | 0.98+/-0.98 | 0.92+/-0.83 | 0.77 |

*Test used: student

The serum levels of the four inflammatory biomarkers studied in our series were increased in both groups of patients (survivors and Deceased), however, the deceased did not have significantly higher levels than the survivors (P >0.05).

Concerning the mean ferritin level in the deceased, it is 609.19 ng/ml compared to 678.46 ng/ml in the survivors. The survivors group had a mean procalcitonin level of 5.4ng/ml compared to 8.10ng/ml in the Deceased group.

For LDH, the mean level in the Deceased was 604.11 ng/ml compared to 593.55 ng/ml in the survivors. For CRP, the mean level in Deceased was 169.84 mg/L compared with 144.48 mg/L in survivors.

The mean lymphocyte count in the Deceased was 0.92 x10^3/µL, compared with 0.98 x10^3/µL in the survivors.

## DISCUSSION

The inflammatory response plays a central role in COVID-19. Evidence is accumulating to suggest that the cytokine storm is involved in the progression to the most severe forms of the disease. This uncontrolled hyperinflammatory response is thought to lead to acute respiratory distress syndrome (ARDS), which can lead to multi-organ failure and death [5]

In the present retrospective study, the serum levels of LDH, CRP, Procalcitonin and ferritin of the patients who died were not significantly higher than those of the group of patients who survived (P >0.05), but were still increased in both patient groups.

We first evaluated serum ferritin levels, which were elevated in both the surviving and deceased patient groups. Ferritin, is an iron storage protein, whose serum level reflects the martial reserve level, it's also a protein of the acute phase of inflammation. Indeed, it plays an anti-inflammatory role by sequestering iron, thus limiting oxidative stress. Its synthesis is strongly increased under the influence of interleukins and TNF [6, 7]. It may also reflect a viral macrophagic activation syndrome [8]. Several studies have demonstrated the prognostic value of ferritin in Covid 19. In fact, the increase of ferritinemia is associated with the severity and the negative evolution of this disease [9, 10]. However, in our study, the mean ferritin level was increased in both the surviving (678.46 ng/ml) and deceased patients (609.19 ng/ml), which does not allow us to say that the increase in ferritin level is correlated with death in our series.

As we know, CRP is also a protein of the acute phase of inflammation whose expression depends on IL6. Its interest as a predictive marker of severe forms of COVID-19 has been clearly demonstrated by many studies [9, 11, 12]. However, contradictory results have been reported. In particular, it has been shown that an increase in CRP level in SARS-CoV-2 infected individuals may not be a good indicator of the severity of Covid 19 infection [13, 14], which is in agreement with the results obtained in our study, Indeed, the mean CRP level is slightly higher in deceased patients (169.84 mg/l) compared to a mean level in survivors 144.48 mg/l , which doesn't allow us to link an increase of CRP level with the fatal process of Covid 19.

Serum levels of procalcitonin, which is a glycoprotein, pro hormone and precursor of calcitonin, are usually very low or undetectable [5]. It is normally synthesized and released by parafollicular C cells of the thyroid, however, it can also be synthesized in many extra-thyroid tissues during bacterial infections, mediated by increased levels of tumor necrosis factor alpha and interleukin 6. On the other hand, it is only slightly increased during viral infections, which makes it a marker for differential diagnosis between bacterial and viral infection [5, 15]. In the Chinese study of Fang Liu *et al*., [1], involving 140 patients with Covid 19, IL-6, CRP and Procalcitonin levels were increased in 95 (67.9%), 91 (65.0%) and 8 (5.7%) patients respectively upon admission. The proportion of patients with increased IL-6, CRP and Procalcitonin levels was significantly higher in patients with more severe forms of the disease. In our sample, the mean procalcitonin level in the group of patients who died was higher than in the group of patients who survived 8.10 ng/ml vs. 5.4ng/ml, however this elevation was not significantly associated with increased mortality ($p = 0.71$).

About lactate dehydrogenase (LDH), it is an important enzyme in the metabolism of sugars and is present in almost all tissues and organs of the human body. An increase in the level of this enzyme in the blood testifies to tissue damage in the organism, although it is not possible to determine the source [16]. According to two systematic reviews with meta-analyzes, this level would be 3 to 6 times higher in patients who have developed a severe form of Covid 19 compared to those who have a less severe form [10, 17]. and nearly 16 times higher in deceased patients [10] .The results of our study do not support this data, in effect, the average level of LDH in the deceased is 604.11 ng / ml compared to 593.55 ng / ml in survivors, which is explained by the selection of our sample which comes from Intermediate Care Unit and Intensive Care Unit which hospitalize patients with severe form.

Finally, the hematological changes accured during SARS-CoV-2 infection are frequent and mainly concern leukocytes and platelets. In the meta-analysis of Celestin Danwang *et al*., [18] of 31 studies, lymphopenia and thrombocytopenia are associated with a severe form of the disease.

The immune response marked by profound lymphopenia seems to be a complication that occurs after an early and massive release of cytokines during the lung injury caused by SARS-CoV-2 [19]. The effects of the virus on lymphocytes can be explained by direct and/or indirect mechanisms. The direct action could be associated with the cytotoxicity of the virus, supported by active viral replication in the infected lymphocyte pool [20]. We also found that lymphopenia is a biological manifestation present in more than half of the patients with Covid-19. It was observed in 52.94% of the patients who died and in 51.11% of the patients who survived, with no significant difference between the 2 groups. Thus, the results of our study indicate that although the inflammatory role in the fatal process of Covid-19 has been described in several studies, there are other factors affecting the prognosis of patients with Covid-19, such as cardiovascular risk factors or certain underlying pathologies that could not be evaluated in our study.

Indeed, the patient's medical history and it's comorbidities play a major prognostic role in the risk of developing a severe form or dying from SARS-CoV-2 infection. For example, in the meta-analysis of 32 articles by Fatemeh Javanmardi *et al*., the comorbidities most frequently identified as being associated with a risk of developing a severe form or dying from the infection were hypertension, diabetes, cardiovascular disease, liver disease, lung disease, malignancy, neurovascular disease, COPD and asthma [21].

Our study has some limitations that must be taken into account. Firstly, we only observed biomarkers of inflammation in a limited COVID-19 patients hospitalized in Intermediate Care Unit and intensive care units, structures that receive patients of significant severity. And Also, the medical history of

the patients could not be exploited to correlate them with mortality. In addition, the effect of various therapies, including anti-inflammatory drugs and other supportive therapies, such as antibiotics, vasopressors, etc., could not be studied, as this was a retrospective study and, therefore, it was impossible to randomize the study participants to different treatment protocols.

With more clinical and paraclinical information acquired from COVID-19 patients and a larger sample size, we could better identify the involvement of inflammatory markers as risk factors for Covid 19 mortality, so as to make fast and correct clinical decisions.

## CONCLUSION

In our series, we studied markers of inflammation and lymphocyte levels in COVID- 19 patients, including serum levels of CRP, Procalcitonin, ferritin, and LDH, and their relationships with the progression of these patients to death. Our study showed that in this sample of patients from the Intermediate Care Unit and intensive care units, patients who died did not have significantly higher plasma levels of the four inflammatory biomarkers compared with the group of patients who survived. For lymphocyte levels, more than half of our series had thrombocytopenia without its depth being related to poor prognosis. According to our results, we can deduce that it is necessary to take into consideration the medical history of the patient so we could predict the evolution of the disease of Covid 19 and to define the clinico-biological factors of poor prognosis. Nevertheless, the course of the stay in these categories of care units also plays an important role in the evolution of patients.

- The author(s) declare(s) that there is no conflict of interests regarding the publication of this article.
- I have read and understood the IJMS rules on plagiarism.
- I hereby declare that this piece of written work is the result of my own independent scholarly work and that in all cases material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, and quotations and paraphrases are clearly indicated.
- No material other than that listed has been used.
- This written work has not been published previously.

## REFERENCES


1. Liu, F., Li, L., Xu, M., Wu, J., Luo, D., Zhu, Y., ... & Zhou, X. (2020). Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *Journal of clinical virology*, *127*, 104370.
2. Shi, Y., Wang, Y., Shao, C., Huang, J., Gan, J., Huang, X., ... & Melino, G. (2020). COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation*, *27*(5), 1451-1454.
3. Sayah, W., Berkane, I., Guermache, I., Sabri, M., Lakhal, Z., & Rahali, S. Intérêt pronostique des biomarqueurs inflammatoires dans le COVID-19, 7.
4. Li, X., Geng, M., Peng, Y., Meng, L., & Lu, S. (2020). Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of pharmaceutical analysis*, *10*(2), 102-108.
5. Intérêt pronostique des biomarqueurs inflammatoires dans le COVID-19.pdf.
6. Torti, F. M., & Torti, S. V. (2002). Regulation of ferritin genes and protein. *Blood*, *99*(10), 3505-3516.
7. Bardou-Jacquet, É. Hyperferritinémie non hémochromatosique: diagnostic et prise en charge, 9.
8. McGonagle, D., Sharif, K., O'Regan, A., & Bridgewood, C. (2020). The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmunity reviews*, *19*(6), 102537.
9. Zhou, B., She, J., Wang, Y., & Ma, X. (2020). Utility of Ferritin, Procalcitonin, and C-reactive Protein in Severe Patients with 2019 Novel Coronavirus Disease [Internet]. In Review; 2020 mars [cité 9 déc 2021]. Disponible sur: https://www.researchsquare.com/article/rs-18079/v1
10. Henry, B. M., De Oliveira, M. H. S., Benoit, S., Plebani, M., & Lippi, G. (2020). Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clinical Chemistry and Laboratory Medicine (CCLM)*, *58*(7), 1021-1028.
11. Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive care medicine*, *46*(5), 846-848.
12. Zhu, Z., Cai, T., Fan, L., Lou, K., Hua, X., Huang, Z., & Gao, G. (2020). Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. *International Journal of Infectious Diseases*, *95*, 332-339.
13. Muller, M., Bulubas, I., & Vogel, T. (2021). Les facteurs pronostiques dans la Covid-19. *NPG Neurologie - Psychiatrie - Gériatrie*, 21(125), 304-312.
14. Ferrari, D., Motta, A., Strollo, M., Banfi, G., & Locatelli, M. (2020). Routine blood tests as a potential diagnostic tool for COVID-19. *Clinical chemistry and laboratory medicine (CCLM)*, *58*(7), 1095-1099.
15. Netgen. Procalcitonine : doser ou ne pas doser ? [Internet]. Revue Médicale Suisse. [cité 8 mai 2020]. Disponible sur:

https://www.revmed.ch/RMS/2013/RMS-N402/Procalcitonine-doser-ou-ne-pas-doser

16. Institut national d'excellence en santé et en services sociaux (INESSS). COVID-19, anomalies et analyses de laboratoire chez l'adulte. Québec, Qc: INESSS; 2020. 72 p.
17. Ali, A. H., Mohamed, S. O. O., Elkhidir, I. H., Elbathani, M. E. H., Ibrahim, A. A., Elhassan, A. B., ... & Abuzied, A. I. H. (2020). The association of lymphocyte count, crp, d-dimer, and ldh with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Sudan Journal of Medical Sciences*, *15*(2), 9-23. Disponible sur: http://medrxiv.org/lookup/doi/10.1101/2020.04.20.20072801
18. Danwang, C., Endomba, F. T., Nkeck, J. R., Wouna, D. L. A., Robert, A., & Noubiap, J. J. (2020). A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). *Biomarker research*, *8*(1), 1-13.
19. Laing, A. G., Lorenc, A., Del Molino Del Barrio, I., Das, A., Fish, M., Monin, L., ... & Hayday, A. C. (2020). A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nature medicine*, *26*(10), 1623-1635.
20. Li, H., Liu, L., Zhang, D., Xu, J., Dai, H., Tang, N., ... & Cao, B. (2020). SARS-CoV-2 and viral sepsis: observations and hypotheses. *The Lancet*, *395*(10235), 1517-1520.
21. Javanmardi, F., Keshavarzi, A., Akbari, A., Emami, A., & Pirbonyeh, N. (2020). Prevalence of underlying diseases in died cases of COVID-19: A systematic review and meta-analysis. *PloS one*, *15*(10), e0241265.