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Research Paper

Biologist's Statement of Biomarkers Variations between Two Covid-19 Waves in Mohammed VI University Hospital of Tangier

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ABSTRACT

Introduction

The Covid-19 pandemic continues to evolve in successive epidemic waves with the appearance of new variants of the SARS-Cov-2 virus. Several biological markers are disrupted and some of them are known to be associated with the severity and unfavorable clinical course of the disease. Regular monitoring of these biomarkers is essential to improve clinical outcomes.

Objective

Our study aim to compare biological outcomes of two waves of the covid-19 pandemic, to reveal a relationship between biological severity and the possible role of the SARS-cov2 variant predominant in the wave.

Methods

It is a retrospective and a descriptive study, including patients with COVID-19, hospitalized in the different hospital structures of the city of Tangier and whose biological workup was performed at the biochemistry laboratory of the UHC TTA, over two periods from December 23, 2020 to January 29, 2021 (first wave), and from August 1 to September 3, 2021 (second wave).

Results

One hundred and forty patients were included, 70 for each wave. The mean age was 65 for the first wave and 59 for the second wave. Male gender predominated in the first and second waves with a sex ratio of 1.59 and 1.12, respectively. The mortality rate was 35.7% in the first wave and 30% in the second wave. Only 38.6% of patients in the second wave were vaccinated.

The results of the biological assessment at admission showed that for all participants, the mean values of the hematological markers were respectively in the first and second waves: 9.05 $.10^3$ Cells/µl versus 7.71 $.10^3$ Cells/µl (p=0.12) for neutrophils (PNN) and 0.82 $.10^3$ Cells/µl versus 0.91 $.10^3$ Cells/µl (p=0.54) for lymphocytes.

Regarding biochemical markers, the means were respectively at the first and second wave: C-reactive protein (CRP) 140.81 mg/L versus 160.73 mg/L (p=0.24), lactate dehydrogenase (LDH) 442.58 U/L versus 594.10 U/L (p=0.45), ferritinemia 711 ng/mL versus 727.86 ng/mL (p=0.98), D-dimers 2344.58 ng/mL versus 1779.06 ng/mL (p=0.47), troponin (TN Ihs) 76.79 ng/L versus 34.10 ng/L (p=0.12), serum creatinine 11.12 mg/L versus 16.87 mg/L (p=0.15), serum urea 0.56 g/L versus 0.64 g/L (p=0. 38), natraemia 137.25 mmol/L versus 136.34 mmol/L (p=0.38), kalemia 4.17 mmol/L versus 3.74 mmol/L (0.01), and chloraemia 99.84 mmol/L versus 97.77 mmol/L (p=0.03).

Blood tests were performed in all patients. For the comparison of the data of the two waves, the threshold of significance retained was $p < 0.05$.

Conclusion

Hospitalized patients with SARS-Cov-2 frequently present biological disturbances. The results of this study show an elevation of the means of CRP (12.5%) and LDH (25%) in the second wave. While the first wave was marked by elevated mean D-dimer (30%), troponin (100%) and deeper lymphopenia.

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I. INTRODUCTION

COVID-19 was declared a global pandemic by the WHO on March 11, 2020 (1). This viral infection can give clinical pictures ranging from minimally symptomatic to acute respiratory distress syndrome (ARDS) or septic shock with multivisceral failure (2). It is caused by the novel coronavirus SARS-CoV-2, whose high virulence and contagiousness have necessitated extreme social distancing measures worldwide to avoid overwhelming health care facilities.

The greatest impact appears to be on the elderly and those with co-morbidities such as diabetes and obesity. This is an unpredictable and unprecedented upheaval that is severely affecting humanity, the economy and health systems worldwide.

Given the high incidence and mortality rates, there is reason to fear that this virus will persist for several months or years to come. Thus, a rapid and unprecedented global mobilization has been provided to identify effective treatments and develop vaccines, in order to address this scourge.

Understanding the dynamics of the spread of the pandemic and the effectiveness of interventions is essential to predict its future evolution (3–7). In fact, several countries have experienced the evolution of the pandemic in waves of iterative epidemics with varying characteristics between waves (8). This model of spread was supported by a study analyzing data from 18 countries (9).

INTEREST OF THE BIOLOGICAL ASSESSMENT

COVID-19 is considered a multisystemic disease, caused by a diffuse systemic process, involving a complex interplay of immunological, inflammatory and coagulation cascades that are closely linked.

The great heterogeneity in the clinical picture, evolution and outcome of patients is due to genetic and acquired differences in the immune system.

The gold standard for diagnosis of covid-19 infection is now RT-PCR, used to detect SARS-CoV-2 viral RNA. It has been indicated since the beginning of the epidemic as first choice (10).

Patient's management is essentially based on clinical evaluation at each phase of evolution with the integration of the results of biological markers, allowing the stratification of the severity of patients (Table 1).

Pro-inflammatory response phase related to the cytokine storm	
Increase	white blood cell and neutrophil counts CRP, ferritinemia, Procalcitonin, IL6, ESR
decrease	Lymphocyte, eosinophil and platelet counts,
Phase of progression to multivisceral damage or failure	
liver markers increase	ASAT, ALAT, GGT, total Bilirubin, LDH
cardiac and coagulation markers increase	Troponin, NT-proBNP, Myoglobin, CK-MB, D-dimers, PT
renal markers increase	Creatinine, Uremia

Table 1: Hematological and biochemical markers for monitoring severe forms of Covid-19 (11).

Biological markers that predict poor prognosis are : IL-6, Ferritin, LDH, CRP, PCT, Lymphocyte count, Neutrophil/lymphocyte ratio (NLR), PNN/GB, Lymphocyte/CRP ratio, Platelet count, and cardiac specific biomarkers (CK-MB, TNTc, Myoglobin, NT-pro-BNP) (12). These biomarkers can be grouped into panels to provide more reliable information compared with single biomarkers.

Studies have shown that dynamic changes in certain biological parameters, may have potential as prognostic factors for COVID-19(13–15). Also for clinical data, another study indicated the utility of including dynamic clinical measures when assessing patient mortality risk (16).

Issues of availability and cost cannot be ignored, especially in the face of more expensive markers such as interleukin and ProPNB assays.

II. OBJECTIVE

The present study aims to compare biological results between two waves of covid-19 pandemic for affected patients, in the city of Tangier in northern Morocco, in order to reveal a relationship between the severity of the disease, through the biological workup, and the possible role of the predominant SARS-cov2 virus variant of the wave.

III. MATERIAL AND METHOD

Our retrospective observational study analyzed data from a total of 140 patients with COVID-19, admitted to the Covid intermediate care unit (ICU) and the Covid resuscitation ward of the Duc de Tovar hospital

in the city of Tangier, and whose biological workups were analyzed at the biochemistry laboratory of the UHC of Tangier, Tetouan Al-Hoceima,
70 patients were compared from December 23, 2020 to January 29, 2021 (first wave), with 70 patients from August 1, 2021 to September 3, 2021 (second wave).
All patients were confirmed to be infected with SARS-CoV-2 by RT-PCR (reverse transcriptase polymerase chain reaction) analysis.
Inclusion criteria were: hospital admission, positivity for SARS-CoV-2 infection based on a combination of clinical, biological, RT-PCR, and radiological evidence, and age ≥ 18 years old. This study excluded patients in whom workup was not indicated.
Data were obtained from the laboratory information system (LIS).
Our study focused on the values of blood tests performed at admission to the Covid intermediate care unit (ICU) and Covid intensive care unit.
These parameters are: white blood cell (WBC), neutrophil (PNN), lymphocyte and platelet counts and hemoglobin levels, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, troponin Ihs, serum urea and creatinine, blood ionogram (Na+, K+ and Cl-), AST and ALT.
Each patient was sampled on 3 tubes: Red-top, EDTA and sodium citrate. The assays were performed on three automated systems: BC5380 Mindray hematology analyzer for CBC. VIDAS 3 of Biomérieux, ELFA (Enzyme Linked Fluorescent Assay) technique for D-dimer, ferritin, Genrui GE 300 analyzer for blood ionogram and troponin and the BS 380 biochemistry analyzer of Mindray for the rest of the biochemical markers.
and the BS 380 biochemistry analyzer from Mindray for the rest of the biochemical markers.

After data collection, statistical analysis was performed by SPSS version 26.0 software and a descriptive comparison was performed for these two groups of patients admitted during the two pandemic's waves.
Data were presented either as means, medians, standard deviation, range and interquartile range, minimum and maximum for continuous variables, or as percentages for categorical variables. The comparison of the means was done by the T-test.
Boxplots were also used to show the distribution of numerical data and skewness between the two waves of the COVID-19 pandemic.

IV. RESULTS

The analysis included a total of 140 patients, 70 patients of each wave, admitted all in ICU and Covid intensive care unit.

1- Demographics:

The average age of the patients was higher in the 1st wave where the average age of the patients was 65 years old of which 54% were > 65 years old, compared to that of the 2nd wave which was 59 years old of which 37% were > 65 years old and the gender distribution was marked by a predominance of the male gender in the first wave (sex ratio =1,59) than in the second wave (sex ratio = 1,12).
The mortality rate was 35,7% of the 70 patients in the first wave versus 30% in the second wave.
In the first wave 39,47% of the patients > 65 years died, while 31,25% of the patients < 65 years died. In the second wave 30,76% of the patients > 65 years old died, while 29,54% of the patients < 65 years old died. According to the gender of the patients, the mortality rate in the first wave was 39,53% in males and 29,62% in females while in the second wave it was 32,43% in males and 27,27% in females.
No patients were vaccinated against Covid-19 given that the national vaccination campaign was launched on January 28, 2021. The vaccinated patients of the second wave represent 38,6% out of the total of 70 patients. All received 2 doses except one patient who received only the first dose.

2- Hematological markers:

It was observed that the blood cell averages for the first wave were 10,37 $.10^3$ Cell/µl for white blood cells (WBC) (p=0,16), 9,05 $.10^3$ Cell/µl for neutrophils (NEUT) (p=0,12), 0,82 $.10^3$ Cell/µl for lymphocytes (LYMPHO) (p=0,54), 12,54 g/dL for hemoglobin (HGB) level (p=0,01) and 259,51 $.10^3$ Cell/µl for platelets (PLT) (p=0,62). For the second wave the averages are 9,03 $.10^3$ Cell/µl for white blood cells, 7,71 $.10^3$ Cell/µl for neutrophils, 0,91 $.10^3$ Cell/µl for lymphocytes, 11,13 g/dL for hemoglobin level and 250,44 $.10^3$ Cell/µl for platelets. (Table 2)

	1st wave (n=70)					2nd wave (n=70)				
	WBC	NEUT	LYMPHO	HGB	PLT	WBC	NEUT	LYMPHO	HGB	PLT
Average	10,37	9,05	0,82	12,54	259,51	9,03	7,71	0,91	11,13	250,44
Median	9,29	8,04	0,66	12,55	240,50	8,44	7,36	0,69	11,20	224,00
Standard deviation	5,59	5,50	0,54	1,87	115,38	5,70	4,71	1,06	2,61	98,95
Interval	24,77	21,98	2,19	12,70	681,00	41,33	31,97	8,51	13,60	499,00
Minimum	3,35	2,12	0,04	6,20	13,00	2,19	1,69	0,06	4,50	115,00
Maximum	28,12	24,10	2,23	18,90	694,00	43,52	33,66	8,57	18,10	614,00

Table 2: Hematological markers of the two COVID-19 waves (n = 140)

3- Inflammation markers:

Inflammation markers in the first wave were with means of 140,81 mg/L for C-reactive protein (CRP), 442,58 U/L for lactate dehydrogenase (LDH) and 711 ng/mL for ferritinemia. Second wave means were 160,73 mg/L for CRP (p=0,24), 594,10 U/L for LDH (p=0,45) and 727,86 ng/mL for ferritinemia (p=0,98). (Table 3)

		1st wave (n=70)					2nd wave (n=70)				
		CRP	LDH	FERRITIN	D-dimers	Troponin	CRP	LDH	FERRITIN	D-dimers	Troponin
N	Valid	70	70	70	70	52	70	70	70	70	53
	Missing	0	0	0	0	18	0	0	0	0	17
Average		140,81	442,58	727,86	2344,58	76,79	160,73	594,10	711,00	1779,06	34,10
Median		120,95	399,00	636,71	1273,12	15,45	170,25	568,50	602,26	1628,34	11,00
Standard deviation		115,43	221,70	460,37	2741,92	176,51	83,49	243,84	413,64	1278,02	91,69
Interval		483,80	1132,00	1909,86	13295,00	762,09	345	934,00	1470,00	7154,00	577,30
Minimum		1,20	28,00	90,14	145,00	0,003	1,00	213,00	18,00	183,00	1,50
Maximum		485,00	1160,00	2000,00	13440,00	762,10	346,00	1147,00	1488,00	7337,00	578,80

Table 3: Inflammatory markers, troponin and D-dimer in both waves of COVID-19 (n = 140)

4- D-dimer and troponin:

In the first wave, the means were 2344,58 ng/mL for D-dimer (p=0,47) and 76,79 ng/L for troponin (p=0,12). While in the second wave, the means were 1779,06 ng/mL for D-dimer and 34,10 ng/L for troponin (Table 3).

5- Other biochemical markers:

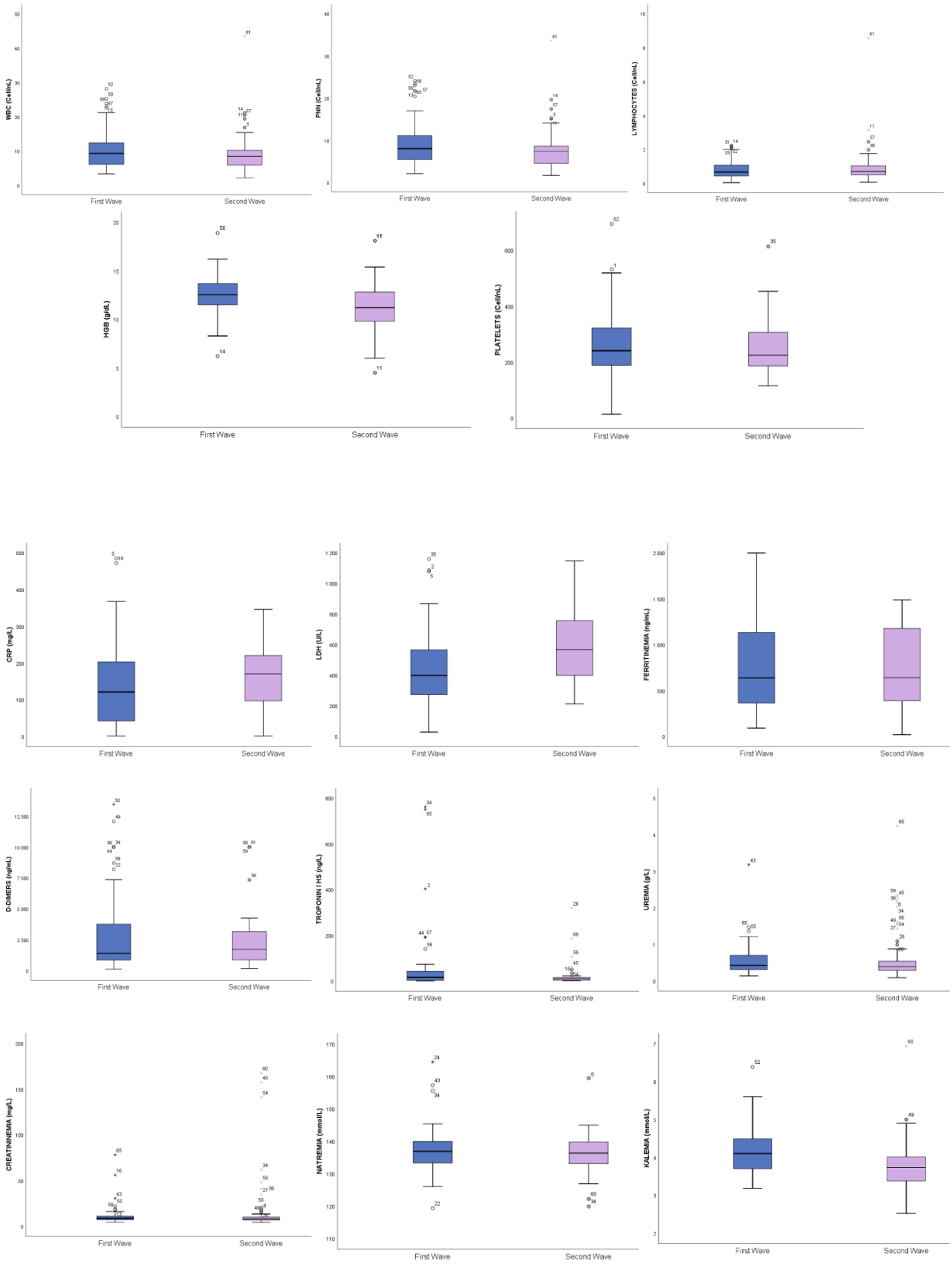
Regarding the renal function biomarkers and blood ionogram, the averages for the first wave were 11.12 mg/L for serum creatinine (p=0,15), 0,56 g/L for serum urea (p=0,38), 137,25 mmol/L for natremia (p=0.38), 4,17 mmol/L for kalemia (0,01) and 99,84 mmol/L for chloremia (p=0,03). In the second wave, the means were 16.87 mg/L for serum creatinine, 0.64 g/L for urea, 136,34 mmol/L for natremia, 3,74 mmol/L for kalemia and 97,77 mmol/L for chloremia.

Hepatic cytolysis biomarkers's means in the first wave were 50,67 u/L for AST (p=0,45) and 41,91 u/L for ALT (p=0,27), while in the second wave the means were 55 u/L for AST and 50,48 u/L for ALT (Table 4).

	1st wave (n=70)							2nd wave (n=70)						
	Urea	Creatinine	Na+	K+	Cl-	ASAT	ALAT	Urea	Creatinine	Na+	K+	Cl-	ASAT	ALAT
Average	0,56	11,12	137,2	4,17	99,84	50,67	41,91		16,87	136,3	3,74	97,77	55,	50,48
Median	0,43	8,71	5	4,10	100,05	35,40	28,15	0,64	8,00	4	3,75	98,20	50	38,29
Standard	0,43	10,71	136,9	4,49	226,58	40,33	37,62	0,39	31,12	136,3	11,88	13,02	45,70	47,00
deviation	3,04	73,64	0	38,2	1908,0	213,3	208,3	0,70	163,10	5	100,4	116,7	35,72	275,4
Interval	0,14	4,40	6,61	2	0	8	5	4,15	4,34	5,45	8	0	211,33	2
Minimum	3,18	78,04	45,20	3,18	87,00	11,35	4,77	0,09	167,44	39,60	2,52	1,30	16,57	8,82
Maximum			119,3	41,4	1995,0	224,7	213,1	4,24		119,9	103,0	118,0	227,90	284,2
			0	0	0	3	2			0	0	0		4
			164,5							159,5				
			0							0				

Table 4: Hepatic and renal biomarkers in COVID-19 waves (n = 140).

The following figure shows the whisker boxes that reflect the skewness of the distribution of laboratory markers between the two waves of COVID-19 patients (figure 1).


WBC (Cell/mL)
PNN (Cell/mL)
LYMPHOCYTES (Cell/mL)
HGB (g/dL)
PLATELETS (Cell/mL)
CRP (mg/L)
LDH (U/L)
FERRITINEMIA (ng/mL)
D-DIMERS (ng/mL)
TROPONINI HS (ng/L)
UREMIA (g/L)
CREATININEMIA (mg/L)
NATREMIA (mmol/L)
KALEMIA (mmol/L)
First Wave
Second Wave

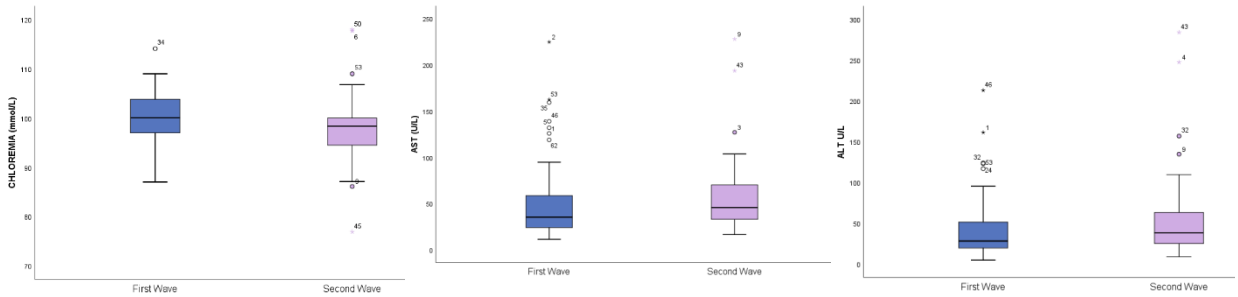


Figure 1. Boxplots of hematological and biochemical markers compared in two waves of COVID-19.

V. DISCUSSION

Several studies have shown that advanced age is associated with an increased risk of death in patients with COVID-19 (17–20). The average age of our patients was 65 and 59 years in the 1st and 2nd waves, respectively, with a high percentage of older patients (≥ 65 years) in the first wave (54% versus 37%). Indeed, these patients (age ≥ 65 years) have a lower percentage of death at second wave (30,76% versus 39,47%), whereas for patients (age < 65 years) this percentage is almost similar (29,54% versus 31,47%) which is consistent with the results of a large cross-sectional survey (13 U.S. states and 14 countries), where people younger than 65 years of age have 16 to 100 times lower risk of death from COVID-19 than older people (21).

The percentage of males in our patients was 61,4% and 52,9% in waves 1 and 2, respectively. Similarly, the results of a large study in Peru, (n=961.894) which show a higher incidence rate in men than in women (22).

The mortality rate in our patients was high in the first wave (35,7% versus 30%) especially in men reaching 39,53% versus 29,62% in the first wave and 32,43% versus 27,27% in the second wave. Similar results have been reported in studies of European COVID-19 patients, which also find that men are at greater risk than women (23,24). Also a large worldwide meta-analysis (n=3.111.714) performed by Peckham et al. confirmed that male patients required almost three times more intensive care (OR = 2,84) and had a higher risk of death compared to women (OR = 1,39) (25).

In addition, disease severity has been shown to be associated with greater abnormalities in biological findings, including markers of inflammation and those assessing organ damage (26–29).

For hematological markers: At the onset of the disease and during the incubation phase, WBC and lymphocyte counts remain normal or slightly reduced. This lymphopenia persists thereafter with the onset of symptoms. Studies show that lymphocyte cells possess the ECA2 receptor which the virus attacks, leading to their lysis (30). The results of our patients show that WBC numbers are high in both waves at the expense of PNNs while lymphocyte numbers are decreased in both waves, with averages of 9,05 $.10^3$ Cell/µl and 7,71 $.10^3$ Cell/µl for PNNs and 0,82 $.10^3$ Cell/µl and 0,91 $.10^3$ elements/µl for lymphocytes in the first and second waves respectively. While a similar comparative study in Spain showed lymphocytes and platelets at lower concentrations (31). Studies have shown that the degree of lymphopenia is higher in patients with severe form and is an important prognostic factor (32,33).

Regarding the markers of inflammation, after the incubation period of the virus, a systemic increase of inflammatory mediators and cytokines begins to appear, especially interleukins (IL-6, IL-2, IL-7) that we didn't measure in our case.

C-reactive protein (CRP) is a protein of the acute phase of inflammation that increases rapidly in the circulation under conditions of infection. Studies have shown the early increase of CRP during Covid-19 infection and have recommended its use for disease's monitoring. Indeed, a systematic review of 61 articles (n=13.891), showed that the severity of Covid-19 disease is associated with high levels of CRP and that its measurement is important to monitor the severity (34).

In our patients the CRP level was clearly elevated in both waves, with a 12,5% elevation of the mean in the second wave (160,73 mg/L versus 140,81 mg/L). This is consistent with the results of a similar comparative study in northern India, where CRP was particularly high in the second wave, at about one and a half times that of the first wave (35). However, in a similar South African study, the CRP level was almost the same in both waves (36).

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme. Its role is to catalyze the reversible oxidation of l-lactate to pyruvate by transferring hydrogen. In case of tissue damage, LDH is easily released into the plasma. This enzyme lacks organ specificity because it is present in all tissues. Thus, to approach a diagnosis it is interesting to associate it with other parameters. Its significant contribution has been proven in defining the severity of COVID-19 (37). Henri et al. showed that high lactate dehydrogenase (LDH) values were associated with a 6-fold higher probability of severe COVID-19 (38).

Similarly, serum LDH of our patients also reached higher levels in both waves and a 25% elevation of the mean in the second wave was noted (594.10 U/L versus 442.58 U/L). The same Indian study found that LDH was significantly higher in the 2nd wave (35).

Serum ferritin is known as a protein used to store iron in the liver. But in addition to that, it is considered as one of the markers of the inflammation's acute phase. There was an elevation of ferritin in our patients in both waves with a slightly higher average in the second wave 727,86 ng/mL versus 711 ng/mL. In a study in Italy, they found that its increase is significantly proportional to the increase in severity and mortality rate, and therefore, it is considered a very good marker for follow-up (39). A meta-analysis objectified that ferritin is associated with a poor prognosis and could predict worsening in COVID-19 patients (40).

A meta-analysis of a total of 16 studies (n=3962) demonstrated the association of inflammatory markers with the severity of COVID-19 and that their measurement allows monitoring and assessment of severity and prognosis (41).

D-dimers are a group of molecules that are the product of the specific degradation of fibrin under the proteolytic action of plasmin during fibrinolysis. The main indication for its measurement is thrombosis's diagnosis. Research has shown that the deaths of patients with SARS-Cov-2 result from thrombosis formation, particularly pulmonary embolism (42). D-dimer levels are generally elevated in patients with COVID-19 and correlate with disease severity and are a reliable prognostic marker of mortality (43). D-dimer values are higher in patients with SARS-Cov-2 and pulmonary embolism than those without pulmonary embolism (42).

Indeed, a meta-analysis including nine studies (n=2911) confirmed that the level of D-dimer at admission has a promising prognostic value for predicting all-cause mortality in COVID-19 patients (44).

The D-dimer level of our patients was higher and especially in the first wave with a high mean of 30% (2344.58 ng/mL versus 1779.06 ng/mL). Maslo et al. showed, through the analysis of biological parameters in the above-mentioned South African study, an increased risk of severe COVID-19 in the second wave. The D-dimer levels at admission of their patients were significantly higher in the second wave compared to the first wave (1100 versus 900 ng/mL) (36).

Troponins are a group of proteins (T, I, and C) that regulate muscle contraction and are present in skeletal and cardiac muscle fibers. The determination of heart-specific troponins (T or I) in the blood allows the detection of heart damage. In normal situations, the concentration of serum troponin is very low or undetectable; it increases in the case of myocardial damage in proportion to the extent of the damage. Indeed, cardiac involvement is frequently present in patients with SARS-Cov2. Cardiac troponin and natriuretic peptide are commonly elevated in hospitalized patients with COVID-19 and are associated with an increased risk of mortality. A multicenter study (32 hospitals) in Spain in COVID-19 patients, suggests that early measurement of cardiac troponin is useful for risk stratification (45). The mean troponin in our patients was elevated in both waves and especially in the first wave with an elevation of the mean troponin by 100% (76,79 ng/L versus 34,10 ng/L).

Regarding the renal function of patients with Covid-19, a large British cohort demonstrated the high incidence of AKI and its association with increased mortality even at stage 1 (46). Another study showed that acute renal failure (ARF) would have developed in more than a quarter of hospitalized patients with SARS-Cov-2 (47). According to the above-mentioned comparative study in Spain, the mean serum creatinine was 9 mg/L in both waves (p=0.005) and serum urea was also similar with a mean of 0,41g/L in the second wave versus 0,40 g/L (p=0.618) (31). In contrast, in our first wave's patients, the mean serum creatinine was higher compared to second wave (16,87 mg/L versus 11,12 mg/L) and similarly for the mean serum urea (0,64 g/L versus 0,56 g/L).

Early studies in patients progressing to the severe form of COVID-19 disease, reported various electrolyte abnormalities at admission of sodium, potassium, chloride and calcium (29,48) and that the more severe forms tend to have a higher proportion of hypokalemia at onset (49). In addition, a research study analyzing five studies (n=1415) confirms that the severity of COVID-19 is associated with lower serum sodium, potassium and calcium concentrations (50). In our patients the mean values of the measured ions (Na, K, Cl) were not significantly disturbed.

Liver function should be assessed in all symptomatic COVID-19 patients and especially in patients with pre-existing liver disease. In COVID-19 patients with severe disease, liver injury is common and may be caused either by direct injury to bile duct cells by the virus or indirectly by a cytokine storm (51).

In our patients, there were no significant disturbances of AST and ALT in the two waves with averages of (AST 50.67 U/L, ALT 41.91 U/L) for the first wave and (AST 55 U/L, ALT 50.48 U/L) for the second.

This study has certain limitations: it is monocentric, retrospective in design and has a limited number of patients. The patients included in the first wave were all unvaccinated. The evaluation of the severity of the disease is based on clinical, radiological and biological elements as well as on the course of the hospitalization, whereas only the biological data of admission are reported here.

VI. CONCLUSION

Biomarkers have a crucial role in patient diagnosis, monitoring, complication diagnosis, management and therapy.

Most of the inflammatory markers were raised in both waves, particularly in the second wave with elevated mean CRP (12.5%) and LDH (25%). While the first wave was characterized by a deeper lymphopenia level and an average's increase in D-dimer (30%) and troponin (100%).

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