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Evaluation of Biochemical Test Results in Patients with COVID-19 Infection

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ABSTRACT

***Background*: The current pandemic outbreak of COVID-19 due to SARS-CoV-2 virus, affected the health care systems, health services and economy globally. Moreover, it significantly affected the health of the population worldwide. Mortality and morbidity rates are still increasing. According to WHO, as of September 2021 there have been 224180869 confirmed cases of COVID-19, including 4621173 deaths. USA, India, and Brazil are the three world's worst-hit countries. In Greece the mortality rate is at 3%.**

***Methods*: Study population included 565 patients, who were admitted at the Emergency Department and the Pathology Department of Naval and Veterans Hospital, Athens, Greece, during a period of 3,5 months. Patients' demographic characteristics, underlying diseases, travel history, symptoms, aetiology of admission and history of contact with confirmed cases were recorded. All patients included to the study were positive for SARS-CoV-2 and characterized as COVID-19 patients. All statistical analyses were conducted using MINITAB 17.**

***Results*: Statistically significant differences in the results of albumin (marginal p-value), urea, creatinine, AST, ALT, and LDH between hospitalized and non-hospitalized patients were detected. Also, we observed statistically significant differences in the results of albumin, urea, creatinine, and ALT, between male and female patients. Moreover, patient age was statistically significant between male and female patients. The Logistic regression model of hospitalization show that statistically significant variables are ALT, LDH, age and gender.**

***Conclusions*: The rapid spreading of the new COVID-19 pandemic due to SARS-CoV-2 increased the need for the measurement of biochemical tests and the evaluation of their correlation with patient hospitalization. Biochemical monitoring of COVID-19 patients is critical for assessing disease severity and progression as well as monitoring therapeutic intervention. Several common biochemical tests have been implicated in COVID-19 infection progression, providing important prognostic information. In the present study we evaluated the test results of albumin, urea, creatinine, AST, ALT, LDH and total bilirubin in patients with COVID-19 infection.**

Keywords: biochemical tests, clinical outcomes, COVID-19 infection, hospitalization, liver function parameters, liver injury, SARS-CoV-2.

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I. Introduction

The virus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is responsible for the coronavirus disease 2019 (COVID-19) and was declared a pandemic by the World Health Organization (WHO) in early March 2020 [1], [2]. SARS-CoV-2 is a single-stranded, positive-polarity RNA virus with genome size 26-32kb, presenting extremely infectious abilities [3], [4]. It causes a wide spectrum of symptoms that vary from completely asymptomatic disease to severe infection, such as acute respiratory distress syndrome, complete respiratory failure, multi-organ failure or death. While the disease continues to spread, several clinical and biological studies take place to further understand the infection mechanism and its impact on human tissues and organs. The most suggested infection mechanism of SARS-CoV-2 is through the angiotensin-converting enzyme 2 (ACE2) receptor of human cells which are on several organs, such as the heart, the kidneys, and the liver. The Receptor Binding Domain of the spike protein (S) of the virus binds to ACE2 receptors of human cells as a key-lock mechanism [5]-[9]. Recent reports showed that COVID-19 disease has an impact on liver dysfunction as the

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virus enters in high degree through ACE2 receptors, found abundantly present on cholangiocytes [10]-[12]. This leads to liver injury and several abnormalities on albumin, ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), LDH (Lactate dehydrogenase) and TBIL (total bilirubin) values [9], [13]-[17]. Moreover, kidney is another important target organ for SARS-CoV-2, causing kidney function injury and affecting urea and creatinine levels, since recently has been demonstrated that SARS-CoV-2 can infect podocytes and tubular epithelial cells, which could contribute to the development of renal abnormalities [18]-[20].

The aim of the present study was to measure biochemical tests in patients with COVID-19 infection and to evaluate the correlation of biochemical results with gender and the need for patient hospitalization.

II. Materials and Methods

The population under study consisted of 565 patients, who were admitted at the Emergency Department and the Pathology Department of Naval and Veterans Hospital, Athens, Greece, during a period of 3,5 months. All patients were informed about the study and gave their consent. The study was approved by the Hospital's Ethics Committee and has been carried out in accordance with Declaration of Helsinki. On admission, patients were asked about travel history, symptoms, contact with confirmed positive COVID-19 cases, and underlying diseases. Data were collected between October 2021 and January 2022. RT-PCR tests for SARS-CoV-2 detection were performed on Cepheid Inc GeneXpert®. Cepheid Inc. has developed an automated molecular test for the qualitative detection of SARS-CoV-2 (CE IVD) based on cartridge technology, in which multiple regions of the viral genome are targeted. The test can provide rapid detection of the current coronavirus SARS-CoV-2 in as soon as 30 minutes for positive results. For Quality Control of the assay, we used both Internal Controls, since each cartridge includes a Sample Processing Control (SPC) and Probe Check Control (PCC), as well as External Controls (AccuPlex™ SARS-CoV-2 Reference Material 0505-0126). Specimens were collected by doctors, stored in viral transport medium or saline, at room temperature (15-30 °C) were transported within 15-30 minutes at the molecular laboratory, according to the WHO Laboratory Biosafety Guidance Related to the Coronavirus Disease 2019 (COVID-19) [21].

All patients included in the study were positive for SARS-CoV-2 and characterized as COVID-19 patients. Measurements of AST, ALT, LDH, albumin, urea, creatinine and TBIL were performed by the Abbott Architect C8000 automated biochemistry analyzer. Albumin was measured by the BCG method (normal range 3,5-5,2 g/dL). The BCG (Bromocresol Green) albumin assay kit is designed to measure albumin directly without any pretreatment of samples, such as serum, plasma, urine. The intensity of the color, measured at 620 nm, is directly proportional to the albumin concentration in the sample. AST and ALT were measured by the IFCC method (normal range 5-45 U/L), total bilirubin by the DPD method (normal range 0,3 -1,2 mg/dL). Total bilirubin is coupled with the 3,5- dichlorophenyl-diazonium-tetrafluoroborate (DPD) to yield the corresponding azobilirubin. The absorbance of this dye at 546 nm is directly proportional to the total bilirubin concentration in the sample.

LDH was measured by the IFCC method (normal range 80-248 U/L), creatinine by the Jaffe method (normal range 0,70-1,30 mg/dL) and urea by the urease method (normal range 18-50 mg/dL).

All statistical analyses were conducted using MINITAB 17. Categorical variables were expressed with frequencies and percentages. All continuous variables were expressed as mean, standard deviation and medians with interquartile ranges. Continuous variables used the Anderson-Darling test to confirm normal distribution. All statistical significance level was presented with 95% confidence intervals and a p-value < 0.05 was considered to be statistically significant. Continuous variables were analyzed through ANOVA and multivariate logistic regression models.

III. Results

The population under study consisted of 565 patients, both male (362/565; 64,0%) and female, (203/565; 36,0%), aged between 12 and 94 years. Out of them, 428 patients were hospitalized (75,7%), while 137 (24,2%) were not, according to the severance of their symptoms. Descriptive statistics of test results in the population under study are presented in Tables I and II.

TABLE I: Distribution of Test Results according to Gender

Variable	Gender	N	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
ALB	F	203	0	3,6524	0,0437	0,6226	1,7000	3,3400	3,6000	4,0000	5,3000
	M	362	0	3,8584	0,0344	0,6543	1,9700	3,4800	3,8100	4,3800	5,6000
UREA	F	203	0	47,69	2,59	36,86	12,00	28,00	37,00	56,00	299,00
	M	362	0	54,02	2,58	49,15	7,00	31,00	40,00	53,00	373,00
CREAT	F	203	0	0,9534	0,0551	0,7854	0,3000	0,7000	0,8000	1,0000	10,1000
	M	362	0	1,1463	0,0382	0,7260	0,4800	0,8375	1,0000	1,1800	7,0000
SGOT	F	203	0	52,30	5,37	76,55	12,00	22,00	31,00	47,00	635,00
	M	362	0	52,01	4,23	80,39	5,00	24,00	35,00	55,00	1009,00
SGPT	F	203	0	46,75	3,75	53,38	7,00	21,00	30,00	46,00	400,00
	M	362	0	63,28	4,64	88,23	9,00	26,00	39,00	71,00	1137,00
LDH	F	203	0	371,3	20,7	294,5	119,0	216,0	299,0	413,0	2695,0
	M	362	0	356,9	16,2	307,3	89,0	199,0	269,0	413,3	3395,0
TBIL	F	203	0	0,7562	0,0814	1,1600	0,1800	0,3800	0,5200	0,7200	14,4000
	M	362	0	0,7478	0,0318	0,6059	0,1100	0,4100	0,5900	0,8725	7,2600
AGE	F	203	0	60,17	1,31	18,60	16,00	48,00	61,00	74,00	94,00
	M	362	0	51,06	1,01	19,26	12,00	39,00	48,00	65,25	94,00

TABLE II: DISTRIBUTION OF TEST RESULTS ACCORDING TO HOSPITALIZATION

Variable	HOSP	N	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
ALB	1	137	0	3,8801	0,0483	0,5655	2,8000	3,5000	3,6700	4,3350	5,6000
	2	428	0	3,7538	0,0325	0,6727	1,7000	3,3425	3,7950	4,1800	5,3000
UREA	1	137	0	37,41	2,58	30,20	16,00	28,00	33,00	41,00	360,00
	2	428	0	56,34	2,33	48,17	7,00	31,00	42,00	63,00	373,00
CREAT	1	137	0	0,9139	0,0188	0,2197	0,3000	0,7450	0,9000	1,0350	1,5000
	2	428	0	1,1292	0,0411	0,8498	0,4000	0,8000	0,9150	1,1500	10,1000
SGOT	1	137	0	36,66	3,78	44,23	12,00	21,00	26,00	36,50	448,00
	2	428	0	57,06	4,19	86,67	5,00	24,00	36,00	57,75	1009,00
SGPT	1	137	0	38,80	2,70	31,55	9,00	23,00	31,00	44,50	279,00
	2	428	0	63,27	4,20	86,89	7,00	24,00	38,00	72,00	1137,00
LDH	1	137	0	261,5	10,8	126,3	89,0	186,5	217,0	294,5	805,0
	2	428	0	394,2	16,1	334,0	90,0	218,0	315,0	451,8	3395,0
TBIL	1	137	0	0,6993	0,0386	0,4519	0,2000	0,4100	0,5800	0,7850	2,8400
	2	428	0	0,7673	0,0454	0,9385	0,1100	0,3900	0,5600	0,8000	14,4000
AGE	1	137	0	44,58	1,46	17,05	12,00	33,50	44,00	54,00	86,00
	2	428	0	57,449	0,929	19,228	15,000	44,00	56,00	73,00	94,00

(1)=No, (2)=Yes.

We observed statistically significant differences in the results of albumin (marginal p-value), urea, creatinine, AST, ALT, and LDH between hospitalized and non-hospitalized patients. Moreover, patient age was statistically significant between hospitalized and non-hospitalized patients. The results are presented in Table III:

TABLE III: OBSERVED P-VALUES <0,05 FOR ALBUMIN, AST, ALT, LDH, UREA, CREATININE AND AGE

	P-value	Correlation
ALBUMIN	0,048	YES
AST	0,001	YES
ALT	0,001	YES
LDH	0,001	YES
TOTAL BILIRUBIN	0,413	NO
UREA	0,008	YES
CREATINIE	0,001	YES
AGE	0,001	YES

We performed chi–quare test in order to evaluate if gender is statistically significant for hospitalization. We observed that gender is not statistically significant for hospitalization (Table IV).

TABLE IV: CHI-SQUARE TEST FOR ASSOCIATION: GENDER; HOSP (ROWS: GENDER COLUMNS: HOSP)

	1	2	All
F	58	145	203
	49,22	153,78	
M	79	283	362
	87,78	274,22	
All	137	428	565

Pearson Chi-Square = 3,225; DF = 1; P-Value = 0,073.
Likelihood Ratio Chi-Square = 3,177; DF = 1; P-Value = 0,075.

We observed statistically significant differences in the results of albumin, urea, creatinine, and ALT, between male and female patients. Moreover, patient age was statistically significant between male and female patients. The results are presented in Table V:

TABLE V: OBSERVED P-VALUES <0,05 FOR ALBUMIN, UREA, CREATININE, ALT AND AGE

	P-value	Correlation
ALBUMIN	0,001	YES
AST	0,051	NO
ALT	0,000	YES
LDH	0,108	NO
TOTAL BILIRUBIN	0,090	NO
UREA	0,043	YES
CREATINIE	0,003	YES
AGE	0,001	YES

A. Logistic Regression of Hospitalization

A logistic regression model was fitted, with response variable the hospitalization (yes, no), numerical variables albumin, urea, creatinine, AST, ALT, LDH, TBIL, patient age and categorical variable gender. Regression was fitted three times, one with all the variables included, one with the method of foreword selection and once with the method of backward elimination. In all cases, statistically significant variables are ALT, LDH, age and gender, table 6. The estimated model was the following:

1) Gender

F

$$Y' = -2,345 + 0,008032\ ALT + 0,002647\ LDH + 0,03653\ AGE$$

M

$$Y' = -1,639 + 0,008032\ ALT + 0,002647\ LDH + 0,03653\ AGE$$

TABLE VI: OBSERVED P-VALUES<0,05 FOR ALT, LDH, AGE AND GENDER AFTER LOGISTIC REGRESSION MODEL OF HOSPITALIZATION

Coefficients	P-value
ALT	0,006
LDH	0,001
AGE	0,000
GENDER	0,002

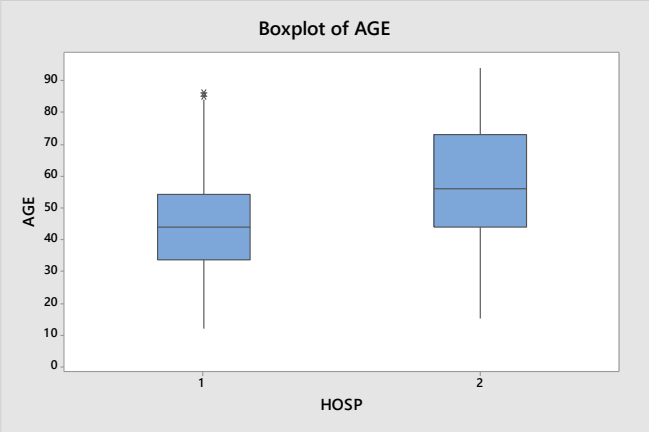

Fig. 1. Boxplot of age in non-hospitalized (1) and hospitalized patients (2).

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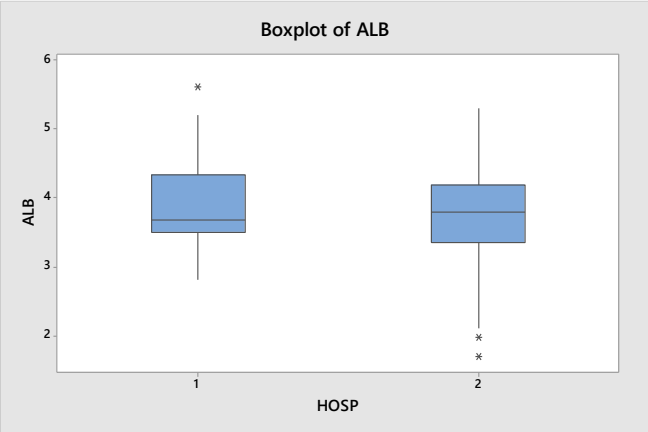

Fig. 2. Boxplot of albumin (ALB) in male and female patients.

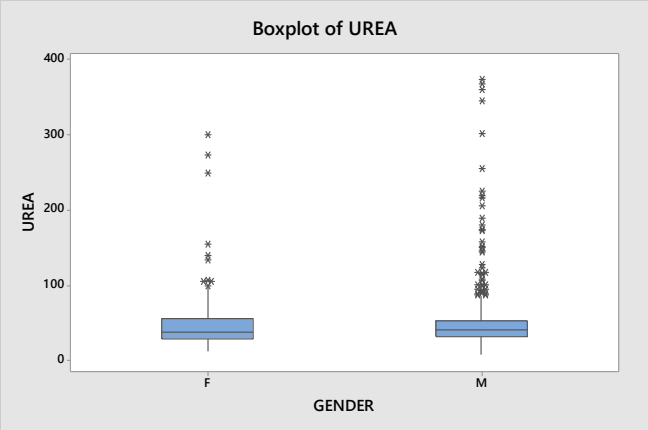

Fig. 3. Boxplot of urea in male and female patients.

Fig. 4. Boxplot of creatinine in male and female patients.

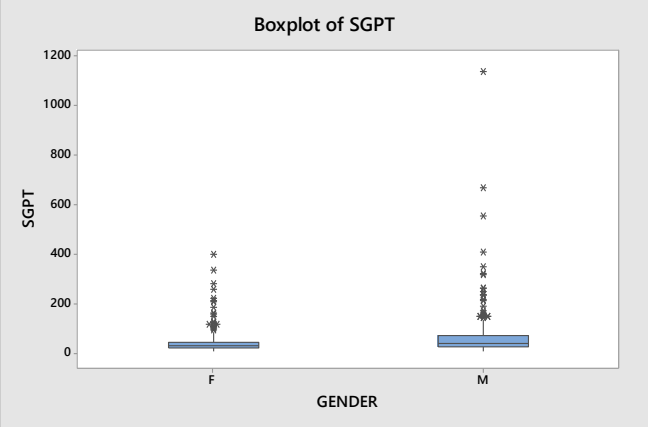

Fig. 5. Boxplot of ALT (SGPT) in male and female patients.

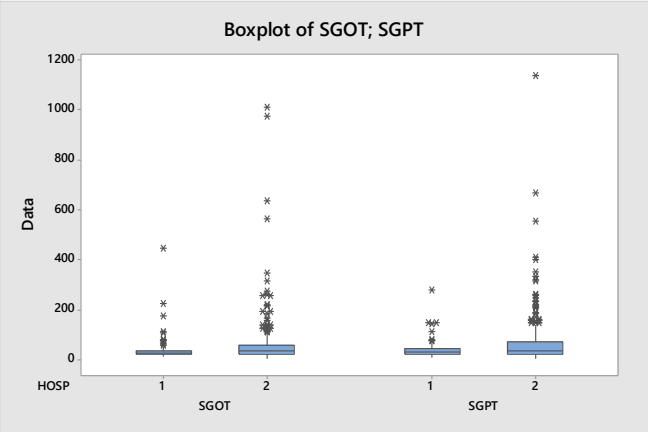

Fig. 6. Boxplot of AST (SGOT) and ALT (SGPT) in non-hospitalized (1) and hospitalized patients (2).

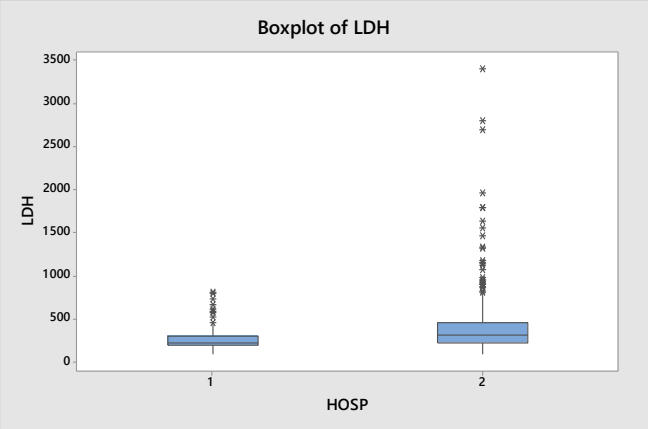

Fig. 7. Boxplot of LDH in non-hospitalized (1) and hospitalized patients (2).

IV. Discussion

The rapid spreading of the new COVID-19 pandemic due to SARS-CoV-2 increased the need for the measurement of biochemical tests and the evaluation of their correlation with patient hospitalization. Biochemical monitoring of COVID-19 patients is critical for assessing disease severity and progression as well as monitoring therapeutic intervention [22]. Several common *biochemical* tests have been implicated in COVID-19 infection progression, providing important prognostic information [23], [24]. In the present study, we evaluated the test results of albumin, urea, creatinine, AST, ALT, LDH and total bilirubin in patients with COVID-19 infection [25]-[29].

Albumin is synthesized in the liver with a serum half-life of approximately 21 days. Albumin in COVID-19 patients is decreased as a consequence of liver function impairment [18], [19]. In the present study we observed statistically significant differences between male and female patients, as well as between hospitalized and non-hospitalized patients. The serum albumin levels <35 g/L were defined as hypoalbuminemia. Only 188 out of the 565 patients (33,3%) presented elevated albumin levels, while 377 out of 565 patients (66,7%) presented decreased albumin levels.

The mechanisms for hypoalbuminemia in COVID-19 patients have not been fully explained. According to the literature, it is a result of decreased albumin synthesis in severe COVID-19 cases, but it is also a result of systemic inflammation due to escape of serum albumin into

interstitial space as a consequence of increased capillary permeability [9], [22], [24], [30].

In the present study we observed elevated AST and ALT levels in 200 patients (35,4%), 485 patients (85,8%) presented elevated LDH levels, 60 patients (10,6%) elevated total bilirubin levels, 161 patients (28,5%) elevated urea levels and 69 patients (12,2%) elevated creatinine levels.

AST and ALT levels are elevated due to liver function impairment as well as to widespread organ damage. The virus affects liver function in various ways. Epithelial cells of the bile duct and liver express ACE2, thus providing an access point for the virus to bind to cholangiocytes and disrupt liver function. Moreover, many medications are used for the treatment of the infection, such as antipyretics, antibiotics, antivirals, and steroids, causing drug-induced liver injury. Systemic inflammatory response is also considered as a potential contributing factor for liver injury. Systemic inflammation causes overproduction of inflammatory cytokines that can injure the liver and other organs [9], [22], [31]-[33].

We observed statistically significant differences in AST and ALT levels between males and females, as well as between hospitalized and non-hospitalized patients.

Regression analysis showed that ALT levels are statistically significant for patient hospitalization.

Since LDH is present in lung tissue, it is increased in COVID-19 patients, due to pulmonary injury. Patients with severe infections release elevated amounts of LDH in the circulation, and according to many studies LDH is a predictor of worse outcomes in hospitalized patients. Moreover, LDH levels are elevated in thrombotic microangiopathy, associated with renal failure and myocardial injury, thus reflecting multiple organ failure [31]-[34].

Total bilirubin was found elevated in patients. Statistical analysis showed that total bilirubin is not statistically significant for hospitalization and that there are not statistically significant differences between genders and hospitalized patients.

Urea and creatinine are biomarkers of kidney injury and differ significantly between hospitalized and non-hospitalized patients. We also observed statistically significant differences between males and females. According to the literature hospitalized patients can develop acute kidney damage. European Renal Association European Dialysis and Transplant Association suggested that chronic kidney disease patients hold an increased risk for COVID-19 and related mortality. Kidney disease in COVID-19 patients is attributed to many factors, such as direct effects on kidney tissue, endothelial damage, deposition of immune complexes, and virus-induced cytokines or mediators [9], [35], [36].

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