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Liver Injury as Mortality Risk Factor in Sars-Cov-2

Sandoval L*, Sanchez A, Samayoa A, Hernandez E and Choco A

Internal Medicine Department, Gastroenterology Unit, Hospital Roosevelt, Universidad de San Carlos de Guatemala, Guatemala

***Corresponding author:**

Luis Fernando Sandoval García, Internal Medicine MSc, Senior Gastroenterology Resident, Hospital Roosevelt, Universidad da San Carlos de Guatemala. Guatemala, Tel:(502)30342311, E-mail: lufesandoval@ufm.edu

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1. Abstract

1.1. Background: The current COVID-19 pandemic has put all health units in crisis. The easy transmissibility facilitated the fast spread to all countries, and Guatemala was not the exception. By May 2020 almost 229 thousand cases were reported, with 3.2% of case fatality. Among the principal mortality risks factors there are: advance age, diabetes mellitus, cardiovascular disease, etc. Due to the systemic injury associated with moderate to severe SARS-CoV2, the clinic presentation is not limited to fever and lung lesion, but neurological, renal, and liver damage have been reported. Some studies have linked liver injury and mortality, so we decided to recollect data with our patients seeking for this association. Material and Methods: Data were recollected from over 18-year-old patients admitted to the COVID-19 service at Roosevelt Hospital, looking for epidemiological and laboratory data, making correlation with mortality during April – September 2020. Then logistic regression was made looking for the best variables to predict mortality. Results: The main results were mean age 48.26 and 59.2 years old for alive and deceased cases respectively, no differences in transaminases, albumin, INR nor alkaline phosphatase. The best sensibility and specificity predicting mortality were obtained with lactate dehydrogenase > 400 and bilirubin > 0.58. Conclusions: According with our data the best predictors for COVID-19 mortality were lactate dehydrogenase > 400 and Bilirubin > 0.58.

2. Introduction

The recent description of the coronavirus 19 disease (COVID-19), which causes severe respiratory distress syndrome (SARS-CoV-2), has put all private and public health units in the world in crisis. The easy transmissibility has facilitated the spread to all geographic areas. Guatemala was no exception, even though specific units were opened to care for patients with COVID-19, these could not cope, even using third-level referral hospitals to manage these cases. The Roosevelt Hospital was no exception, we found ourselves in the need to open exclusive areas for the care of this pathology and isolate them from the rest of the patient population.

By the beginning of May (2020), almost 229 thousand accumulated cases were reported, with a fatality of 3.2%, which corresponds to a rate of 45 deaths per 100 thousand inhabitants [1].

The factors commonly associated with a worse prognosis are: over 60 years of age, diabetes mellitus, cardiovascular disease and obesity [2]. Among the laboratory markers with an impact on mortality we have elevated levels of D-dimer, C-reactive protein, lactate dehydrogenase (LDH), and cardiac troponins I. [3] [4]. Multiple studies have documented the specific relationship of acute phase reactants with the severity of SARS-CoV-2, [5][6], [7], as well as with blood group A [8]. In a Latin American court of patients with COVID-19, they documented that the presence of cirrhosis increases mortality, obtaining a percentage of deaths in this population group of 47%, compared with non-cirrhotics in 16%. Associated with severity scores of chronic liver disease, obtaining as the best predictor of mortality at 28 days with CLIF-C with ROC 0.85 (0.78-0.91) [9].

Currently, fever and cough continue to be the main clinical presen-

tations. Cardiovascular and hematological disease are quite common and are associated with a worse prognosis. However, the systemic involvement makes that we also find gastrointestinal, renal, and even neurological symptoms. Liver disease continues to be of limited characterization, however, being present, it prolongs the hospital stay. It typically occurs in severe SARS-CoV2 with transaminase elevations in up to 16-53% of cases, 1.7 times more bilirubin elevations, and hypoalbuminemia. The proposed pathophysiology is the tropism of the coronavirus for angiotensin-converting enzyme 2, which is found in hepatocytes (as well as many other cell lines). Also among the associated factors are the use of antibiotics, antivirals, systemic inflammatory response, etc. [10].

Liver enzymes, Alanine Amino Transferase (ALT) and aspartate amino transferase (AST), are elevated in patients with COVID-19 critical cases, with higher rates of intensive care unit transfers, mechanical ventilation, kidney failure and mortality. Hypoalbuminemia has also been implicated as an independent predictor of mortality [4]. In a recent study in a Latin American population, including Guatemala, alterations in liver function tests had an OR of 1.5 (CI 1.1-2, p 0.01) of mortality and of 2.6 (CI 2.0 -3.3 p <0.0001) of presenting severe COVID-19 [2]. Among the non-specific markers of cellular damage, we have LDH, whose increase is severely correlated, it has been suggested that it is an indirect marker of respiratory function [4].

We did not have local data on liver factors and mortality in COVID-19, so we decided to collect this information during the pandemic.

3. Materials and Methods

3.1. Design and Sample Selection

Retrospective study, carried out at Roosevelt Hospital, in the Gray Area service from May to September 2020. Records of hospitalized patients over 18 years of age, who were discharged home alive, were included, reviewed one by one to collect the login data. Demographic variables and admission laboratories were taken. Death registry at the COVID-19 morgue area was reviewed. They were compared with the electronic registry of the admission laboratories. Medical history was not obtained for the deaths. Patients older than 18 years were included and divided into 2 groups, living and deceased, for their respective analysis. The dimensions used are the following: platelets K / uL, bilirubin mg / dl, albumin g / dl, transaminases, gamma glutamyl transferase (GGT), LDH and alkaline phosphatase (ALP) U / l, and Prothrombin Time (PT) in seconds.

3.2. Statistical Analysis

The data collected were registered in SPSS 21 and Excel 2016. Categorical variables were analyzed with frequencies and percentages, and were subjected to chi square of independent samples. Numerical variables were subjected to the Shafiro Wilk normality test, they were examined with measures of central tendency and were compared according to student's t-test. Then a logistic regression was carried out for the multivariate evaluation, a sub analysis of variables total bilirubin and LDH was carried out, with new coding according to the numerical value with better sensitivity and specificity to predict mortality.

3.3. Primary Objective

Associate hepatogram alteration with mortality from the SARS-COV2 virus

Secondary Objective

- Characterize hepatogram alteration in hospitalized patients with SARS-COV2.
- Characterize hospitalized patients for SARS-COV2.

3.4. Ethical Aspects

Because it is retrospective data collection, the management of the patient is not altered or modified; therefore, no aspect is violated according to ethical criteria of the 2013 Helsinki Declaration, Nuremberg Code, Universal Declaration on Human Genome and Human Rights approved by the General Conference of UNESCO 1997. As well as the GCP (Good Clinical Practice) standards. All individual data was strictly kept confidential through encryption.

4. Results

The population cutoff of 247 patients, 119 living patients and 128 deceased, with a mean age of 48.26 years (SD 15.53) and 59.20 years (SD 14.48) respectively with a p <0.01. Within the living population: 52.94% were male; mean laboratory results were: aspartate amino transferase (AST) 89.05, alanine amino transferase (ALT) 78.34, albumin 3.93, total bilirubin (TB) 0.72, indirect bilirubin (IB) 0.33, direct bilirubin (DB) 0.39, ALP 144.21, GGT 146.96, INR 1.16, PT 12.80, platelets 277.32 and LDH 416.71; additionally, with R factor of 4.36 - cholestatic. Within the deceased population: 78.99% were male, with mean laboratory values of AST 86.36, ALT 54.34, albumin 6.05, TB 0.9, IB 0.32, DB 1.21, ALP 146.32, GGT 152.56, INR 1.23, TP 13.41, platelets 257.87 and LDH 604.99, finally with factor R of 3.64 - Mixed (Table 1). Within the initial analysis, the only variables with a statistically significant difference between alive vs. deceased were sex and age (Table 1). The most relevant past medical history of survivors gave the following results (Table 2): no past medical history 14.92%, diabetes mellitus (DM) 7.66%, hypertension (HTN) 7.66%, chronic kidney disease (7.26%), among others. Multivariate logistic regression was performed where the difference between groups was maintained for age, it was lost for sex, and LDH and TB obtained significance (Table 3). All the numerical values of these laboratory results were analyzed, finding the best sensitivity and specificity with LDH> 400 and BT> 0.5850, with an area under of the curve of 0.767 and 0.59 respectively (Graphs 1 and 2).

Table 1: Baseline characteristics

Alive vs Deceased						
Variables		Alive (119)		Deceased (128)		*p*
		Frequency	%	Frequency	%	
Sex	Male	63	52.94	94	78.99	<0.01
	Female	56	47.06	34	28.57	
R Factor	Cholestatic	43	43.4	42	38.9	0.575
	Mixed	36	36.4	47	56.6	
	Hepatocellular	20	20.2	19	17.6	
Variables		Mean	SD	Mean	SD	*p*
Age		48.26	15.53	59.2	14.48	<0.01
AST		89.05	228.47	86.36	232.83	0.655
ALT		78.34	201.04	54.34	119.88	0.09
Albumin		3.93	2.2	6.05	25.64	0.07
TB		0.72	0.61	0.9	1.04	0.34
IB		0.33	0.29	0.32	0.23	0.08
DB		0.39	0.39	1.21	6.72	0.05
ALP		144.21	82.46	146.32	125.09	0.4
GGT		146.96	177.27	152.56	141.98	0.32
INR		1.16	0.18	1.23	0.23	0.3
PT		12.8	1.99	13.41	2.42	0.58
PLT		277.32	128.25	257.87	108.86	0.08
LDH		416.71	356.95	604.99	332.43	0.3
R Factor		4.36	7.3	3.64	7.29	0.21

Abbreviations: SD Standard deviation; AST Aspartate aminotransferase; ALT Alanine aminotransferase; TB Total bilirubin; IB Indirect bilirubin; DB direct bilirubin, ALP alkaline phosphatase; GGT gamma glutamyl transferase; PT Prothrombin time; LDH Lactate dehydrogenase, PLT platelet

Source: data collection

Table 2: Past Medical History

Variables		Frequency	%
Past Medical History	None	37	14.92
	DM	19	7.66
	HTN	19	7.66
	Heart disease	3	1.21
	Cirrhosis	5	2.02
	Rheumatic	2	0.81
	CKD	18	7.26
	Cancer	3	1.21
	Obesity	1	0.4
	HIV	3	1.21
	EtOH	1	0.4
	Neurologic	3	1.21
	Asthma	1	0.4
	Chronic lung disease	1	0.4
	Puerperium	3	1.21

Abbreviations: DM diabetes mellitus; HTN arterial hypertension; CKD Chronic Kidney Disease; HIV Human Immunodeficiency Virus; EtOH Alcoholism

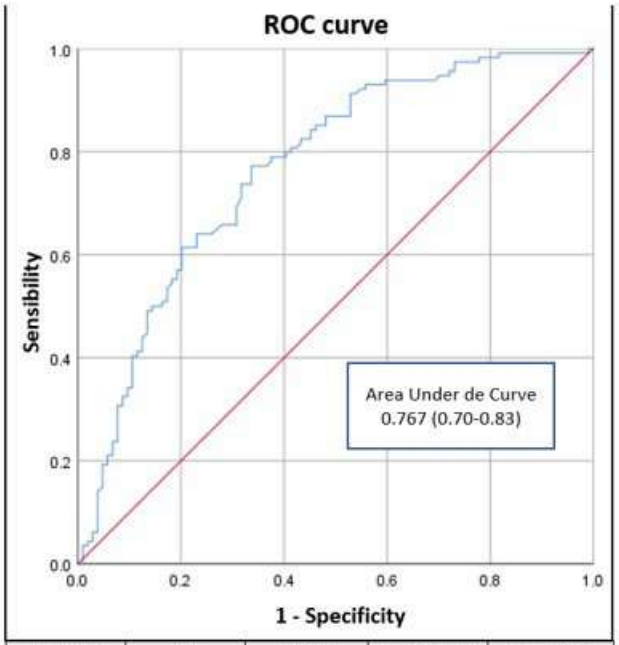
Source: data collection

Table 3: Multivariate analysis

Variables	*p*
Age	<0.01
Sex	0.06
LDH	<0.01
TB	0.01

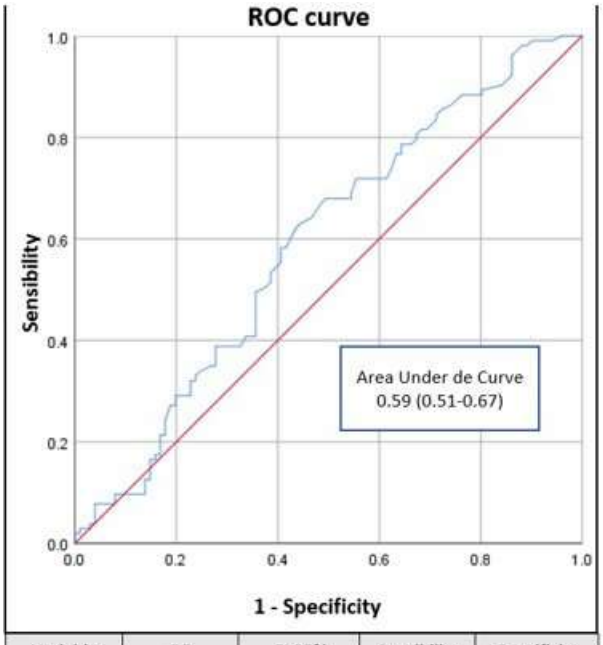
Abbreviations LDH Lactate dehydrogenase; TB total bilirubin Source: data collection

Graphic 1: Area Under de curve - LDH



Variable	OR	CI 95%	Sensibility	Specificity
LDH >400	6.67	3.672-12.126	77.19	33.65

Graphic 2: Area Under de curve – BT



Variable	OR	CI 95%	Sensibility	Specificity
BT > 0.5850	2.05	(1.169-3.592)	63.11	44.55

5. Discussion

The results of this retrospective cohort of moderate to severe SARS-CoV2 patients admitted to Roosevelt Hospital is the first data collection performed at this center. Given the health crisis presented, and the collapse of health services, there had been no opportunity to collect data and submit them to statistical analysis. Comparing a recent Latin American cohort [2], we can observe several similarities. For example, the mean age in deceased patients is 59.20 years old and 48.20 years old for alive, and in the aforementioned cohort it is 52.3 years, with a predominance of males, as in our study. Likewise, there is abundant distribution of comorbidities, and within laboratories, with similar levels of albumin, platelets, and INR. Similar results were also obtained in a Chinese cohort [11] with a predominance of the male gender and comorbidities such as hypertension, DM, heart disease, among others. Multiple clinical studies have confirmed the high prevalence of chronic degenerative comorbidities in moderate to severe COVID-19 patients [12]. In a recent meta-analysis [13] the pattern, presence of DM, HTN, cardiovascular and respiratory diseases in populations with critical presentation associated or not with mortality is repeated; with mean age between 46 to 62 years. Within the hepatogram they showed leukopenia, elevations of AST, procalcitonin, D-dimer and LDH and troponin I.

In the bivariate analysis, no significant differences were found in the laboratory results, however, within the logistic regression LDH and TB became relevant. All the values of these variables were reevaluated, and it was found that the numerical value with the best sensitivity and specificity corresponds to LDH> 400 and BT> 0.58 with areas under the curve of 0.767 and 0.59 respectively as predictors of mortality. In an Asian court [13] LDH values> 245 were associated with mortality, without documenting bilirubin data. Although there is not much data on hyperbilirubinemia in COVID-19, certain authors [14] have raised this hypothesis and have shown a correlation with time of hospitalization and mortality. In our cohort we obtained a risk association with mortality with LDH> 400 with OR of 6.67 and BT> 0.58 with OR of 2.05. Although both values are statistically and numerically relevant, we consider that clinical use is limited to the use of LDH above 400 as a predictor of mortality.

Within the main academic search engines on the web, no publications were found that characterized the alteration of the hepatogram as a whole, specifically using the Factor R. On this occasion, it was documented that the main pattern in living patients is cholestatic condition, and in the deceased mixed, with an average R factor of 4.36 and 3.64, respectively.

6. Conclusions

We can conclude that age, LDH and TB are associated with mortality in patients with moderate and severe SARS-CoV2. Liver disease in surviving patients is of a cholestatic pattern and of a mixed type in deceased patients. Hospitalized patients present multiple metabolic and cardiovascular comorbidities.

7. Limitations

Within the limitations we have that it was retrospective data collection and limited to medical records found in the hospital file. The study was conducted in a single center and includes only patients with moderate and severe SARS-CoV2, as they are the only ones who required hospitalization.

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