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Association of Gastrointestinal Manifestations and Laboratory Abnormalities on Clinical Outcomes of COVID-19 Patients in a Tertiary Hospital

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Abstract: SARS-CoV-2, the causative agent for COVID-19 disease, initially reported in Wuhan, Hubei China as an outbreak of viral pneumonia. The presentation ranged from asymptomatic to a severe viral pneumonia which can be fatal in high-risk groups. Some patients also presented with gastrointestinal symptoms. Studies on its symptomatology had been widely discussed in various literatures but its effect on aminotransferases and gastrointestinal system in general were still underway. Hence, this study aimed to determine the prevalence of gastrointestinal and liver manifestations and corresponding laboratory abnormalities among COVID-19 patients admitted in a tertiary referral hospital, and to determine its associations with disease severity and clinical outcomes of COVID-19 infection. Cross-sectional study design was used. A 340-sample population was computed with a 95% confidence interval. The population consisted of randomly selected COVID-19 confirmed patients aged >19 years-old admitted at Baguio General Hospital and Medical Center from May 1, 2020 to July 31, 2021. Data were encoded in a spreadsheet; and were analyzed through frequencies, percentages, means and standard deviation. Kruskal-Wallis H Test, One-way ANOVA and Chi-square were used to test for association with <0.01 alpha level of significance. 18.23% COVID-19 patients had GI and liver manifestations. The presence of GI symptoms also showed an increased risk for developing abnormal laboratory parameters (aminotransferases, INR, inflammatory markers, and Procalcitonin). Symptoms and laboratory parameters were also associated with severe COVID-19 infection and abnormal laboratories were also associated with worse outcomes (recovery status, need for ICU admission, mortality and length of hospitalizations), except for GGT. Mild acute liver injury was common in COVID-19 patients and signified better recovery outcomes. In conclusion, these symptoms and laboratory tests provided significant associations which can be used by clinicians in tailoring specific diagnostics and therapeutics; and can simultaneously be used in prognostication of COVID-19 patients.

Keywords: COVID-19, Gastrointestinal Manifestations, Liver Function Test, Severity, Outcomes

1. Introduction

Coronaviruses were known to cause respiratory and intestinal infection in animals and humans, and when they target the respiratory tract, a range of illness from simple colds to more fatal types of pneumonia may result. Currently, 7 human coronaviruses have been identified and 3 of which caused epidemics in the past few years, the latest was the severe acute respiratory syndrome 2 (SARS-CoV-2) causing the dreaded COVID-19 infection. [1-3] The presentation of the COVID-19 ranged from asymptomatic to minor symptoms of cough, colds, anosmia to severe forms of viral pneumonia which can lead to death in high-risk groups. [4-6] It had been observed in literatures that fever and cough were still the most predominant symptoms of COVID-19, but was also implicated in other organ systems with more than half of

the patients showing varying levels of gastrointestinal and liver damage. [1, 7-10]

On demographics, most cases belonged to 21-40 years old (36.9%), while most deaths occurred at age group of 60-80 years. [10] The likelihood of COVID-19 also increased in patients with known co-morbid conditions such as Hypertension (17.9%), Diabetes (12.7%), Asthma (3.2%) and Cardiovascular disease (3.2%). However, undiagnosed co-morbid conditions were potentially seen as exaggerating factors of the disease causing higher death rates (35%) compared to those with stable and known co-morbid conditions. Healthcare workers (HCW) were also found likely to be infected; however, in the same study, majority of the cases studied were not related to healthcare by profession (35.8%).[10] These inferences were made from local research statistics on COVID-19 outcomes in general but associations with gastrointestinal symptoms and liver function tests were still uncertain.

While several studies about virology and other symptoms had been widely discussed, literatures concerning the gastrointestinal (GI) manifestations were still advancing. Some patients with COVID-19 also presented with GI symptoms such as vomiting, diarrhea, abdominal pain and loss of appetite. [6] The presence of GI symptoms were possibly due to the presence of COVID-19 receptors in the GI tract where the virus can enter and multiply. [6, 11-14] Studies observed that around 47% of COVID-19 patients had both GI and respiratory symptoms and only 3% of the population had GI symptoms alone, with loss of appetite as the most frequent symptom, followed by diarrhea and vomiting. [4, 6] In the Philippines, 7.1% of cases had diarrhea at the onset [10] and was considered the most prevalent GI manifestation (16.4%) followed by anorexia and dysgeusia at 13.3% and 7.7% respectively. [15] Other recent studies also found that the prevalence rate of GI manifestations in COVID-19 confirmed patients reached as high as 30.5%, and were mostly tagged under moderate disease severity at 38.38%. [15] Literatures also suggested various levels of liver damage in some patients and also showed that severe cases have increased risk of developing GI symptoms and liver damage compared to those without GI symptoms. [1, 2, 7, 8, 16, 17] This might be attributed by viral mechanisms such as direct hepatocyte injury and hypoxic ischemic injury which may further elucidate results from previous studies on SARS-CoV-2 demonstrating significant liver damage in 14-53% cases, with elevations of aminotransferases on the 4^{th} and 17^{th} day of hospitalization. [6, 12, 18-24]

Derangements of aminotransferases commonly seen in severe COVID-19 pneumonia had foreboding risk on intensive care unit admission and mortality. [6, 8, 11, 20-22] Recent studies in the Philippines further suggested a worsening trend on outcomes with increasing aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], and presence of co-morbid disease increased the risk for ALT derangements. [25, 26] ALT was also used to calculate the acute liver injury (ALI) grade; further subclassified into mild, moderate and severe. ALI was further defined as mild (ALT up to 2x upper limit of the normal), moderate (ALT 2-5x upper limit of the normal) and severe (ALT >5x upper limit of the normal), with increasing severity of ALI showing worse disease outcomes. [25] Elevated AST was also found to be associated to higher risks for mortality, making aminotransferases tests, in general, good prognostic tests in COVID-19 patients. [24, 27]

In other studies, Gamma glutamyl transferase (GGT) elevations (17.6-42.2%) were also found to be a better indicator of bile duct injury in hospitalized patients compared with Alkanine Phosphatase (ALP) (4.1-6.7%). [24, 28] Reports, however, signified higher chances of progression to severe COVID-19 if patients have either elevated AST/ALT, or both AST and ALT, and ALP or GGT. [1, 24] Histopathologic examinations of autopsied patients showed microvesicular steatosis and mild lobular activity which can be attributed to its ability to deregulate liver function tests due to expression of ACE-2 receptors in cholangiocytes and hepatocyte. [1, 6, 23, 29]

Lists of international and local studies were made with contrasting results as to their association with outcomes. Studies comprehensively analyzing elevated aminotransferases and clinical characteristics of COVID-19 confirmed patients with liver failure also had different results. Local studies were made regarding the outcomes of COVID-19 patients with gastrointestinal symptoms. One local study determined the over-all prevalence of patients presenting with GI symptoms concluding that most cases with GI symptoms had moderate and critical COVID-19 severity. Other findings concluded that the presence of GI manifestations (such as anorexia and GI bleeding) significantly affected health outcomes such as the need for ICU admission and mortality. [26] Other literatures negated these findings and concluded that abnormal aminotransferases and liver injury were self-limiting and were not in any way, associated with severity outcomes of COVID-19. [30] The need for more studies on the pathogenesis of abnormal liver function tests and its correlation to GI and liver manifestations should be re-emphasized as this will later influence the patient's outcomes and prognosis. Contrasting results from various international and local studies also made the causality less certain. Hence, this study will aim to strengthen links that may help clinicians, scientists and healthcare institutions reinforce and improve their diagnostic and treatment modalities for COVID-19 confirmed patients.

1.1. Objectives

The general objective of the study is to determine the prevalence of gastrointestinal (GI) symptoms, liver manifestations and corresponding laboratory abnormalities and its association with clinical outcomes among COVID-19 confirmed cases admitted at Baguio General Hospital and Medical Center. Specific objectives included:

1) To determine the clinico-demographic profiles of COVID-19 confirmed patients presenting with GI and

liver manifestations according to age, gender, comorbid illness, exposure history, smoking history and employment status;
2) To identify the disease severity of COVID-19 and determine its association with most GI and liver manifestations and corresponding laboratory abnormalities; and
3) To determine the association of GI and liver manifestations and corresponding laboratory abnormalities to clinical outcomes such as mortality, recovery, need for ICU admission and length of hospital stay among those admitted for COVID-19 infection.

1.2. Significance of the Study

The aim of this study was to determine the prevalence of GI and liver manifestations and corresponding laboratory abnormalities in patients admitted for COVID-19. This was so to identify high-risk groups for developing GI symptoms which can provide clinicals prognostic cues to improve their outcomes and reinforce better treatment modalities among institutions. Furthermore, this study can reinforce tertiary hospitals and COVID-19 referral centers to improve hospital services, tailor diagnostic tests, and provide additional medications for patients with COVID-19. With better knowledge of its pathogenesis, course and outcomes, more treatment and diagnostic options can be improved and developed to prevent multi-organ failure in COVID-19.

1.3. Limitation of the Study

The associations deduced were based on retrospective observational data which may be subjected to biases, incomplete data and influenced by confounding variables. Undiagnosed and/or unstable pre-morbid conditions and pre-morbid liver problems can also complicate COVID-19 illness and may over-estimate the results of the study. Other laboratory tests such as liver biopsy, ultrasound and fecal RNA detection was not included since it was not routinely done in all patients.

The population selected was also not representative of the general population of COVID-19 patients, which may underestimate the results. Majority of the mild cases were sent home for quarantine or to community isolation facilities and do not have baseline laboratory work-ups.

This study also focused on determining prevalent gastrointestinal symptoms and laboratory abnormalities at the outset (or during admission). Other symptoms and clinical syndromes unrelated to the GI system were not included. Similarly, GI manifestations as part of the disease's complications were also not included in the study.

2. Methodology

2.1. Study Design

This is a cross-sectional study which evaluated the presence of GI and liver manifestations among adult COVID-19 patients admitted at a tertiary hospital. It also assessed associations of these symptoms, laboratory abnormalities with disease severity, and clinical outcomes such as mortality, recovery status and need for ICU admission. The research was approved by the Institutional Review Board of Baguio General Hospital Medical Center and was conducted in the same institution.

2.2. Study Population

The study included all COVID-19 confirmed patients admitted at Baguio General Hospital and Medical Center from May 1, 2020, to July 31, 2021 aged >19 years old fulfilling the case definition of COVID-19 infection. Excluded from the study were COVID-19 confirmed patients under the pediatric age group (<18 years old), COVID-19 confirmed cases who arrived dead, or died before any diagnostic modalities can be performed, COVID-19 suspects, possible and probable cases with negative COVID-19 RT-PCR results, and COVID-19 patients who were sent home or to an isolation facility for quarantine and do not have baseline liver function tests or work ups. The population size was derived from the available census of adult COVID-19 cases admitted at Baguio General Hospital and Medical Center as per IPCC report on August 31, 2021. Using the OpenEpi application, a sample proportion of 340 was computed, with a confidence interval of 95%.

2.3. Data Collection

With the supervision of the Data Privacy Officer, a complete list of admitted patients for COVID-19 was obtained from the Medical Records, listed in excel form. The study employed a simple random sampling technique upon access to the list of COVID-19 confirmed cases. Random number and Function were done to generate number codes assigned to corresponding hospital numbers. Once finalized, even numbers were picked out from the roster until a sample of 340 was obtained. The selected population were listed with their corresponding hospital numbers and inclusive dates of admission and were sent to the Data Privacy Officer to grant electronic access to the charts. The data were collected in a Data Abstraction Form, summarized and encoded in Microsoft Excel. The following independent variables were collected: age, gender, exposure history, smoking, co-morbid conditions, present symptoms, and laboratory abnormalities of AST, ALT, acute liver injury grading, ALP, GGT, international normalized ratio (INR), and inflammatory markers such as ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP) and procalcitonin. Outcomes or dependent variables were determined through recovery rates, mortality, disease severity, length of hospital stay and need for ICU admission.

2.4. Statistical Analysis

Frequencies and percentages were used to describe discrete variables. Means and standard deviations were used for continuous data. Data were analyzed through IBM SPSS Version 25. Kruskal-Wallis H Test and One-way ANOVA was used to test for the association of GI and liver

manifestations and laboratory abnormalities with COVID-19 severity and outcomes such as the need for ICU admission, mortality, and recovery status. Chi-square was used to determine the association between GI and liver manifestations and laboratory parameters with the length of hospital stay. Pearson correlation, and an alpha level of significance of < 0.01 was used to determine strong associations on the outcomes.

Table 1. *Clinico-demographic Characteristics and Outcomes of the Sample Population.*

Clinicodemographic Factor		Mean (SD)	n (340)	%	With GI Symptoms n=62			Without GI Symptoms n=278			p-value
					Mean (SD)	n	%	Mean (SD)	n	%	
Age (Years)		53 (±18)			56 (±17)			51 (±18)			0.076
Sex	Male		147	43.2		32	51.6		115	41.4	0.141
	Female		193	56.8		30	48.4		163	58.6	
Exposure	HCW		15	4.4		3	4.8		12	4.3	*<0.01**
	Symptomatic		220	64.7		55	88.7		165	59.4	
	Contact Traced		46	13.5		3	4.8		43	15.5	
	Travel		59	17.4		1	1.6		58	20.9	
	Others		0	0		0	0.0		0	0.0	
Smoking history	Non-smoker		245	72.1		43	69.4		202	72.7	0.851
	Current		6	1.8		1	1.6		5	1.8	
	Former/Quit		89	26.1		18	29.0		71	25.5	
Employment	Unemployed		159	46.8		25	40.3		134	48.2	0.878
	Professional		53	15.6		12	19.4		41	14.7	
	Clerical		44	12.9		10	16.1		34	12.2	
	Agriculture		17	5.0		4	6.5		13	4.7	
	Craft		24	7.1		4	6.5		20	7.2	
	Elementary		34	10.0		5	8.1		29	10.4	
	Armed Forces		8	2.3		2	3.2		6	2.2	
	Others		1	0.2		0	0.0		1	0.4	
Co-morbidities	Hypertension		149	48.8		31	50.0		118	42.4	0.278
	Diabetes Mellitus		88	25.9		17	27.4		71	25.5	0.760
	Heart Disease		75	22.1		16	25.8		59	21.2	0.431
	Chronic Kidney Disease		28	8.2		4	6.5		24	8.6	0.572
	Cancer		16	4.7		2	3.2		14	5.0	0.543
	Cerebrovascular Disease		14	4.1		0	0.0		14	5.0	0.071
	Pregnancy		45	13.2		1	1.6		44	15.8	*0.003**
	Liver Disease		12	3.5		3	4.8		9	3.2	0.537
	Hematologic Disorder		4	1.2		1	1.6		3	1.1	0.742
	Respiratory Disease		30	8.8		6	9.7		24	8.6	0.739
	None		35	10.3		12	19.4		24	8.6	0.452
Severity	Mild		82	24.2		7	11.3		75	27.0	
	Moderate		98	28.8		16	25.8		82	29.5	*0.023**
	Severe		125	26.8		30	48.4		95	34.2	
	Critical		35	10.2		9	14.5		26	9.4	
Clinical Outcomes	ICU admission		34	10.0%		9	14.5		25	9.0	0.190
	Mortality		26	7.6%		6	9.7		20	7.2	*<0.01**
	Recovered With Clinical Improvement		267	85.0%		46	74.2		221	79.5	0.504
	Recovered With Residual Organ Damage		47	15.0%		10	16.1		37	13.3	
Days of Illness		15.27 (±5.93)			15.79 (±5.99)			15.15 (±5.92)			0.446
Length of Hospital Stay (Days)		11 (±7.24)			10.73 (±5.5)			11.20 (±7.6)			0.641

3. Results

The chart review of the patients admitted for COVID-19 from May 1, 2020 to July 31, 2021 yielded 340 participants qualifying the inclusion criteria. No records were removed from the study after the data gathering period. All participants were included in the analysis of the data.

From Table 1, 340 participants had a mean age at diagnosis of 53 years old (SD=18) with age ranging from 22-92 years old. The population consisted of females (56.8%) and the most common mode of exposure observed was from a symptomatic individual (64.7%). Out of the 340 participants, 72.1% were non-smokers and mostly were unemployed (46.8%). Most patients had hypertension (48.8%) and diabetes (25.9%), while 10.3% had no co-morbid conditions. 34 participants (10%) in general, required ICU admission. While 7.6% of the participants died of the disease, 85.03% clinically recovered from COVID-19 illness, 14.97% of which had residual organ damage (e.g. pulmonary fibrosis and cerebrovascular disease). Overall, majority had moderate COVID-19 disease (28.8%), followed by severe (26.8%), mild (24.2%) and critical (10.2%). Mostly were diagnosed at an average of 11 days or 15th day of illness (SD=5.93) and had an average hospital stay of 11 days (SD=7.24).

From 340 participants, 62 patients of which had GI and liver manifestations (18.23%), and mostly were males (51.6%). Most were diagnosed with a mean age of 56 years old (SD=17) and tested positive due to the presence of symptoms (88.7%). Majority were non-smokers (69.4%) and were unemployed (40.3%). Most patients also had Hypertension (50.0%), and Diabetes Mellitus (27.4%), and mostly had severe COVID-19 disease. Out of 62 participants, 9 participants (14.5%) required ICU admission, 6 (9.7%) of which died. 46 (74.2%) recovered with clinical improvement, and 10 (16.1%) had residual organ damage upon discharge. Patients with GI and liver manifestations had shorter duration of hospitalization at 10 days or 16th day of illness (SD=5.99) compared with those without GI and liver manifestations at 11 days or 15th day of illness (SD=5.92).

Using the One-Way ANOVA test, associations were seen with GI and liver symptoms on exposure *(p=<0.01)*, and severity *(p=0.023)* of COVID-19 infection. Among the co-morbid conditions, a significant difference was seen among pregnant patients *(p=0.03)*. On the outcomes, the only significant association was seen in mortality *(p=<0.01)*. These results may further signify those patients with GI and liver symptoms tend to have more severe disease and worse outcomes on mortality.

Table 2. *Association of Gastrointestinal and Liver Manifestations, and Laboratory Findings on Disease Severity in COVID-19 confirmed patients admitted at Baguio General Hospital and Medical Center from May 1, 2020 to July 31, 2021.*

Patient Characteristics	**Disease Severity of COVID-19 confirmed patients**								
GI Symptoms, (n, number of patients with symptoms)	**Mild**		**Moderate**		**Severe**		**Critical**		**H**
	N		**N**		**N**		**N**		
Abdominal Pain	5		5		5		2		0.509
Vomiting	1		2		5		0		2.811
Diarrhea	1		4		4		1		1.324
Nausea	1		2		6		0		3.976
Loss of appetite	0		5		11		7		16.871
Dysgeusia	2		8		11		1		4.529
Liver Symptoms, n									
Jaundice/Icteresia	0		1		0		1		4.605
Laboratory (mean)	N	Mean	N	Mean	N	Mean	N	Mean	P value
AST	26	31.7	34	35.4	90	63.6	25	93.7	*<0.01**
ALT	20	27.8	34	36.6	74	63.8	20	67.1	*0.001**
ALP	0	0.85	0	0.00	0	3.2	1	15.1	*0.001**
GGT	0	0.00	1	0.7	2	3.3	0	0.00	0.484
Albumin	0	30.7	0	34.6	0	35.8	0	31.2	*0.035**
INR	2	0.80	1	0.9	0	0.9	4	1.07	*0.001**
LDH	19	179.3	30	232.6	96	378.9	26	529.9	*<0.01**
Serum Ferritin	2	55.4	18	264.5	40	513.3	14	721.3	*0.001**
CRP	28	11.0	49	17.8	100	57.8	30	92.2	*<0.01**
Procalcitonin	9	0.02	14	0.05	38	0.63	17	2.1	*0.036**
Acute Liver Injury Grading (n, number of patients with elevated ALT)									
Mild	15		25		49		12		*<0.01**
Moderate	6		7		21		6		
Severe	0		2		6		3		

AST: aspartate aminotransferase; ALT: alanine aminotransferase, ALP: alkaline phosphatase; PTT: partial thromboplastin time; INR: international normalized ratio; LDH: Lactate Dehydrogenase; CRP: C-Reactive protein; ULN: upper limit of the normal value
One-Way ANOVA for laboratory parameters; Kruskal Wallis H test for Gastrointestinal and GI manifestations; Significant P value=<0.01.

The most common manifestation as seen in Table 2 was loss of appetite (25.3%), followed by dysgeusia (24.2%) and abdominal pain (18.7%). The mean value obtained for each laboratory parameters were reported as above, with observable increasing trends on increasing severity of illness. Kruskal-Wallis H test was used to determine the association of severity of the COVID-19 infection with specific GI and liver manifestations. However, no significant differences were seen between the severity of the COVID-19 infection and the specific GI and liver manifestations, implying that these symptoms were non-specific and not unique to COVID-19 disease.

One-Way ANOVA test was used to determine associations of COVID-19 severity with laboratory parameters, with an alpha significant (p-value) of <0.01 indicating strong associations. From table 2, significant differences seen with severity and AST *(p=<0.01)*, ALT *(p=0.001),* ALP *(p=0.001)*, albumin *(p=0.035)*, INR *(p=0.001)*, LDH *(p=<0.01)*, serum Ferritin *(p=0.001)*, C-reactive protein *(p=<0.01)*, procalcitonin *(p=0.036)*, and Acute Liver Injury grading *(p=<0.01)*. GGT was not found to be associated with disease severity, in contrast with previous studies.

Table 3 described GI and liver manifestations and laboratory parameters with clinical outcomes. Chi-square was utilized and results indicated that loss of appetite was the only gastrointestinal symptom with significant associations on ICU admission, $X^2(1)=11.446$, $p=0.001$, and patient recovery, $X^2(1)=9.046$, $p=0.011$. This maybe secondary to the non-specificity of GI and liver manifestations in viral illnesses. However, the results of this study were similar with other tests, indicating more associations with loss of appetite from other GI symptoms.

Table 3. *Association of Gastrointestinal and Liver Manifestations, and Laboratory Findings on Outcomes of COVID-19 confirmed patients admitted at Baguio General Hospital and Medical Center from May 1, 2020 to July 31, 2021.*

Patient Characteristics	**Clinical Outcomes**											
GI Symptoms, (n, number of patients with symptoms)	**Mortality**		**ICU admission**		**Recovered with residual organ impairment**		**Recovered with clinical improvement**		**Length of Hospital stay**			
	n	**P value**	**n**	**P value**	**n**	**P value**	**n**	**P value**	**mean**	**SD**	**Correlation**	**Sig.**
Abdominal pain	1	0.779	1	0.561	13	0.873	3	0.873	11.065	7.253	-.032	.561
Vomiting	0	0.410	2	0.152	6	0.502	2	0.502	11.091	7.233	.075	.166
Diarrhea	1	0.776	2	0.285	8	0.911	1	0.911	11.085	7.243	.009	.865
Nausea	0	0.382	1	0.910	6	0.181	3	0.181	11.088	7.232	.076	.162
Loss of appetite	4	0.069	7	*0.001**	13	*0.011**	5	*0.011**	11.047	7.233	.054	.321
Dysgeusia	1	0.571	2	0.883	20	0.330	1	0.330	11.050	7.254	-.029	.595
Liver symptoms (n, number of patients with symptoms)												
Jaundice/icteresia	0	0.683	0	0.636	1	0.322	1	0.322	11.109	7.236	.095	.082
Laboratory (n, number of patients with elevated parameters)												
	Mean	P value	Mean	P value	Mean		Mean	P value			F	Sig.
AST	103.03	*<0.01**	108.34	*<0.01**	78.96		40.87	*<0.01**			1.272	0.152
ALT	67.94	*<0.01**	94.15	*<0.01**	86.03		38.85	*<0.01**			1.464	0.053
ALP	5.88	*0.007**	6.03	0.007	11.87		1.07	*<0.01**			1.968	*0.002**
GGT	.00	0.155	.00	0.162	2.77		1.33	0.615			0.219	1.000
Albumin	30.10	*<0.01**	31.56	*<0.01**	33.97		34.09	0.958			0.891	0.643
INR	.95	*<0.01**	.95	*<0.01**	.92		.85	0.229			1.226	0.191
LDH	610.70	*<0.01**	545.79	*<0.01**	401.17		257.20	*<0.01**			5.620	*<0.01**
Serum Ferritin	647.07	*<0.01**	976.61	*<0.01**	936.46		221.10	*<0.01**			2.189	*<0.01**
CRP	97.10	*<0.01**	82.91	*<0.01**	67.81		27.67	*<0.01**			1.500	*0.043**
Procalcitonin	2.68	0.065	2.16	0.083	1.64		0.04	0.002*			3.007	*<0.01**
Acute Liver Injury Grading	n	P value	n	P value	n		n	P value	Mean	Mean Square	F	Sig.
Mild	9	0.192	10	0.132	20		72	0.005*	11	35.224	0.670	0.571
Moderate	5		6		85		30		12			
Severe	2		3		4		5		14			

AST: aspartate aminotransferase; ALT: alanine aminotransferase, ALP: alkaline phosphatase; PTT: partial thromboplastin time; INR: international normalized ratio; LDH: Lactate Dehydrogenase; CRP: C-Reactive protein; ULN: upper limit of the normal value
One way ANOVA for laboratory parameters; Chi square for Gastrointestinal and Liver Manifestations.

One-Way ANOVA was used to determine associations of laboratory parameters with ICU admission, mortality and recovery. From the same table, significant differences were seen in AST levels of those patients who did or did not require ICU admission *(x=108.34, p=<0.01)*, those who recovered with or without residual organ damage *(x=40.87, 78.96) p=<0.01)*, and mortality *(x=103.03, p=<0.01).* ALT levels were found to be more significant in terms of ICU admission *(x=94.15, p=<0.01)*, recovery *(x=38.85, 86.03, p=<0.01)*, and mortality *(x=67.94, p=<0.01)*. ALP levels were found to be significant between in mortality *(x=5.88, p <0.007)*, recovery *(x=1.07, 11.87, p=<0.01)* and length of hospitalization *(F=1.968, p=0.002)*. No significant differences were seen between GGT and the outcomes measured. Albumin was significant in mortality *(x=30.10, p=<0.01),* but not on other parameters of outcomes. Significant differences were found in INR on ICU admission *(x=0.95, p=<0.01)*, and mortality *(x=0.95, p=<0.01).* The inflammatory markers had significant differences when grouped by ICU admission, recovery, length of hospitalization and mortality [LDH: ICU admission *(x=545.79, p<0.01)*, recovery, *(x=257.20, 401.01, p=<0.01*), mortality *(x=610.70, p=<0.01),* and length of hospitalization *(F=5.620, p=<0.01)*; Ferritin: ICU admission, *(x=976.61, p=<0.01)*, recovery, *(x=221.10, 936.46, p=<0.01)*, mortality *(x=647.07, p=<0.01)* and length of hospitalization *(F=2.189, p=<0.01)*; C-reactive protein: ICU admission *(x=82.91, p=<0.01*), recovery *(x=27.67, 67.81, p=<0.01)*, mortality (x=*97.10, p=<0.01),* and length of hospitalization *(F=1.500, p=<0.01)*]. Procalcitonin levels were only significant when grouped by recovery outcome *(x=0.04, 1.64, p<0.002),* and length of hospitalization *(F=3.007, p=<0.01).*

Acute liver injury grade was further sub-classified into mild (up to 2x ULN), moderate (2-5x of ULN), and severe (>5x of ULN), and was found to be statistically significant in terms of the patient's recovery status *(p=0.005),* indicating that milder levels of ALT elevations were somewhat associated with less residual organ dysfunction on discharge. This was contrasted with one local study revealing that severe acute liver injury grades were associated with worse outcomes.

4. Discussion

Based on the results, the prevalence of GI and liver manifestations at the outset of COVID-19 disease was at 18.23% which was comparable to previous local studies done Among the patient characteristics, no differences were noted in terms of age, sex, employment status and smoking history. These findings contrasted other studies yielding more severe courses with the elderly and smokers. The presence of co-morbid illnesses did not have associations with GI and liver

manifestations as well, however, associations were seen in pregnant patients which were probably secondary to their hypercoagulable state (pregnancy). This finding was contrasted by other studies concluding that pre-existing liver diseases were more associated with GI and liver symptoms.

The most common GI and liver symptom was loss of appetite followed by dysgeusia and abdominal pain. Findings were compared with other literatures, revealing similar results. [16, 17] The symptomatology might be due to the presence of infection itself and might also be affected by the viral carriage and replication in the GI system.

The presence of GI and liver symptoms was significantly associated with severity and mortality status, and may further suggest a prolonged course of illness, possible disease progression or higher chances of mortality in more severe forms of COVID-19 infection. Results were similar in other studies and was postulated to be possibly due to the virus' ability to replicate in the digestive tract. [1, 4-6, 8] Although non-specific, these symptoms in general tend to increase risk for liver impairment and worse outcomes. [1, 2, 4, 5, 8, 16, 24]

With the outcomes, patients GI and liver manifestations were observed to have shorter lengths of hospitalization. However, no associations were seen in this regard. The results may be contrasted by international studies suggesting longer hospitalizations with significant GI and liver involvement. [1, 4-6] Specific GI and liver symptoms did not yield any association except for loss for appetite. This might be because GI symptoms in general were non-specific and can also be present in other viral illnesses aside from COVID-19 infection, hence cannot solely be used as specific predictors for disease severity

The mechanisms for elevated liver function tests remained understudied. Theories on the affinity of SARS-COV-2 to ACE-2 receptors highly expressed in the GI system, [1, 4-6, 8, 20, 23] and the virus' ability to persist in the GI system caused longer fecal shedding and longer viral replication in the system [8, 16, 20] were among the postulated mechanisms for both GI, liver symptoms and laboratory derangements in COVID-19. The results of the study were significant in terms of aminotransferases (AST, ALT), ALP, INR, Inflammatory markers (LDH, Ferritin, CRP) and procalcitonin. These were not only observed to be high in severe and critical cases but was found to be related with worse clinical outcomes. Acute live injury grades were also found to be associated with disease severity, signifying that more elevations of ALT may mean more severe clinical presentations. However, fulminant acute liver injury seems to be very rare in these types of infection. [5]

Abnormal laboratory parameters were correlated with outcomes. In the study, aminotransferases were associated with ICU admission, mortality and recovery, signifying those elevated parameters increased the risk for mortality and ICU care, however, mild elevations can imply better recovery outcomes for these patients. ALP was also found to be associated with morality, recovery and length of hospital stay. Procalcitonin was associated with recovery and length of hospital stay. These further indicated that elevations of ALP and procalcitonin can be used to predict longer hospitalizations for COVID-19 patients. These were comparable with other studies further strengthening its use for prognostication.

Albumin and INR were strongly associated with mortality alone and further derangements (decrease in albumin and increase in INR) indicate worse outcomes as evidenced in other previous studies. [4, 5, 8]

Since effective treatment options were still in development for COVID-19, inflammatory markers were used to monitor progression of the disease. This can be attributed from the virus' ability to deregulate the immune system causing an aggravated immune response. [31] In the study, inflammatory markers (LDH, CRP and ferritin) were associated with worse outcomes in terms of ICU admission, mortality, length of hospitalization and recovery among patients with GI and live manifestations.

GGT showed no significant difference in terms of the outcomes for mortality, recovery, ICU admission and length of hospital stay. As mentioned, the underestimated results might be due to decreased number of admitted patients tested for GGT.

5. Conclusion

Gastrointestinal and liver manifestations are non-specific signs and symptoms of viral infection which can also coexist with respiratory symptoms of SARS-COV-2, causing a spectrum of a disease known as COVID-19. The presence of gastrointestinal and liver manifestations can be seen in all ages, irrespective of employment, smokers or nonsmokers alike and those with coexisting respiratory symptoms, with loss of appetite still being the most common non-specific symptom, followed by dysgeusia, abdominal pain and diarrhea as evidenced in other previous studies. The presence of co-morbid conditions does not generally affect the occurrence of gastrointestinal and liver symptoms; however, pregnancy may be associated to COVID-19 infection due to the innate hypercoagulable state of pregnancy itself.

The presence of gastrointestinal and liver manifestations may also indicate an increased risk for developing abnormal laboratory parameters, and in general, was found to be clinically associated with the severity of COVID-19 infection. This was due to the affinity of SARS-CoV-2 to ACE receptors which were widely expressed in the GI system. Although non-specific for COVID-19, the presence of these symptoms can facilitate early diagnosis and hence should still be considered in screening patients for the disease.

Laboratory parameters (such as aminotransferases, ALP, Albumin, INR, inflammatory markers, and Procalcitonin) had been implicated in severe and critical diseases as compared with the milder forms of COVID-19 infection, and elevated levels were associated with worst outcomes in terms of mortality, ICU admission, recovery and length of hospital stay. Lower albumin levels were more predictive of mortality. However, in contrast with previous studies done, acute Liver

Injury grading was found to significantly predict a patient's recovery, indicating that milder forms of ALT elevated may be self-limiting, and may reveal better recovery outcomes with no residual organ dysfunction. Though elevations of aminotransferases were seen in increasing severity of COVID-19 infection, fulminant acute liver injury for COVID-19 was found to be rare.

These findings can then help clinicians tailor down appropriate laboratory tests to use for diagnosis, monitoring and prognostication based on the goals set for each patient.

Despite the large sample size, the researcher recommends a bigger population to cover for milder cases which can be more representative of the local population. Other laboratory tests such as ultrasound or liver biopsy and fecal viral RNA can also be included in future studies to ascertain morphological changes and viral carriage attributed by COVID-19 infection in association with the presence of GI and liver manifestations.

This study also focused only on the symptoms and laboratory parameters upon admission and did not cover for gastrointestinal complications throughout the course of illness which may have other implications in the outcomes of a COVID-19 patient. The researcher, then, recommends future clinicians to also include gastrointestinal complications as part of predicting disease course and clinical outcomes for development of better treatment options for COVID-19 patients in the future.

Conflicts of Interest

All authors do not have any possible conflicts of interest.

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