

Clinical Outcome of Patients with COVID Transaminitis Given Essential Phospholipids in a Tertiary Medical Center: A Retrospective Cohort Study

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Abstract: Background: The COVID-19 pandemic has been a global public health challenge since the initial emergence of the novel coronavirus. COVID-19 infections can cause multi-systemic effects, including gastrointestinal symptoms such as abdominal pain, loose bowel movement, and increased liver enzymes, leading to transaminitis. The use of essential phospholipids, with its anti-inflammatory, antioxidant, antifibrinogenic, antiapoptotic, membrane-protective, and lipid-regulating effects, may be a viable treatment option for COVID-19-induced transaminitis. Methods: This retrospective cohort study aims to evaluate the clinical outcomes of administering essential phospholipids to adult Filipino patients with COVID-19 Transaminitis admitted in a tertiary medical center from July 2021 to February 2022. A total of 238 COVID-19 patients admitted met the inclusion criteria. The primary treatment arm consists of 156 patients who received essential phospholipids during admission, while the control arm consists of the remaining 82 patients who did not receive essential phospholipids. The study's statistical analysis utilized Wilcoxon Signed Rank Test, Mann-Whitney U Test, and Chi-square test. The computed minimum sample size is 109 based on a confidence value of 95%, a margin of error of 5, 50% population proportion, and a population size of 150. Results: The study shows that the prevalence of COVID-19 Transaminitis is 70%. There is also a significant decrease from baseline to repeat serum AST and ALT levels for patients who took essential phospholipids. Although not statistically significant, there is a trend toward a decrease in mortality rate from those patients who took essential phospholipids compared to those who did not (16% vs. 24% respectively). There was also higher mortality rate for those patients with COVID-19 transaminitis (21%), from those who did not have COVID-19 transaminitis (16%), however, the study did not reach the level of significance. There is a significant difference in the number of COVID-19 critical patients with transaminitis compared to those who did not have transaminitis (51% vs 33%). Conclusion: The prevalence of transaminitis in COVID-19 infection is high. essential phospholipids may hold promise as an effective treatment option for COVID-19 transaminitis. The presence of transaminitis in COVID-19 patients appears to have a significant impact on the severity of the disease or the course of treatment.

Keywords: COVID-19, Transaminitis, Essential Phospholipids

1. Introduction

The COVID-19 pandemic is a formidable global public health challenge. Since the initial emergence of a novel coronavirus, the spread has been unrelenting, impacting nearly every aspect of society worldwide. The pandemic has required a substantial response by public health authorities at all levels. Public transportation has been reduced, and

medical consultation has been limited, and most patients who had no means to do online consultation were lost to follow-up. Upon lifting of some restrictions, we have observed cases of disseminated or fulminant diseases return to us in the hospital. With regards to patients admitted due to COVID-19, the severity of the illness ranges from moderate

to critical. The effect of the virus is multi-systemic. In particular, aside from the respiratory and cardiovascular systems, the GIT is also afflicted by the SARS-CoV-2 virus. GIT symptoms include abdominal pain, changes in bowel habits, particularly loose bowel movement, and evidence of increased liver enzymes, leading to transaminitis.

Though the mechanism of liver injury in COVID-19 infection is uncertain at this point, the expression of the ACE-2 receptor on the alimentary tract as well as the hepatic cholangiocytes and biliary epithelial cells seems to explain the viral entry and replication. A retrospective cohort study by Suresh et al defines elevated liver enzymes or transaminitis as an elevation in ALT/SGPT and/or AST/SGOT. In women, the upper limit of normal (ULN) is > 32 IU/L for AST and > 33 IU/L for ALT. In men, the ULN is > 40 IU/L for AST and > 41 IU/L for ALT [1]. One treatment that may be viable for COVID-19-induced transaminitis may be the use of essential phospholipids, which influences membrane-dependent cellular functions and shows anti-inflammatory, antioxidant, antifibrinogenic, antiapoptotic, membrane-protective, and lipid-regulating effects, hence contributing to the improvement or normalization of subjective symptoms, pathological, clinical, and biochemical findings, hepatic imaging, and liver histology. The term "essential phospholipids" refers to a highly purified extract of soybean semen (glycine max) with standardized contents of 72%–96% (3-sn-phosphatidyl) choline. This extract contains polyenylphosphatidylcholine (also called polyene phosphatidylcholine) molecules. The main molecule in EPL is 1,2-dilinoleoylphosphatidylcholine (DLPC), which accounts for up to 52% of the administered PCs. This high level of DLPC distinguishes EPL/PPC from typical phospholipids, as well as PC consumed through diet and synthesized within the body. It is therefore, justified to administer essential phospholipids [2].

Though in theory, essential phospholipids have been used in liver injury of all causes in general, its use in COVID-19-induced transaminitis is also becoming common². However, it is still largely unknown if the improvement of transaminases in adult patients is due to the use of essential phospholipids, or if the natural course of the disease allows the liver function to improve over time. A study by Gundermann et al in 2016 showed that essential phospholipids accelerate the improvement or normalization of subjective symptoms and pathological findings, such as pain in the right hypochondrium, dyspeptic symptoms, and hepatomegaly, in nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease [2]. Please note that this study was conducted before the COVID-19 pandemic and only addresses the use of essential phospholipids for liver disease. On the other hand, it may be prudent to administer essential phospholipids in adult patients as early as transaminitis is documented and/or established, as elevated transaminases on admission are associated with severe clinical outcomes, and other studies suggest that transaminases may act as a surrogate marker for disease severity and a predictor of mortality [3].

The evidence in other studies lean towards improving serum transaminase levels in the use of essential phospholipids. It is therefore, the aim of this study to establish if the use of essential phospholipids will improve the liver transaminases in adult patients with COVID-19-induced transaminitis, and furthermore, answer the question of essential phospholipids may be used routinely in such patients.

This research aims to establish the clinical outcomes of the use of essential phospholipids in improving the serum transaminase levels in COVID-19 transaminitis. We also aim to determine the prevalence of COVID-19 transaminitis in patients diagnosed with COVID-19 and to determine if elevated transaminases can be an indicator of severity among COVID-19 patients.

2. Methodology

This is a retrospective cohort study of patients admitted at Quirino Memorial Medical Center, Quezon City, Philippines from July 2021 to February 2022.

2.1. Definition of Terms

1. COVID 19 infection – patients who have positive RTPCR SARS-CoV-2 result.
2. Transaminitis - elevations of either AST or ALT more than the upper limit of normal.
3. COVID-19 Transaminitis – transaminitis in COVID-19 patients.
4. Essential Phospholipids - a well-defined, highly purified extract of glycine max with standardized contents of 72%-96% (3-sn-phosphatidyl) choline.

2.2. Inclusion Criteria

1. All laboratory confirmed COVID-19 positive patients diagnosed through RT-PCR SARS-CoV-2 test.
2. Age 19 to 59 years old.
3. Elevated serum glutamate pyruvate transaminase (SGPT/ALT) and/or serum glutamic-oxaloacetic transaminase (SGOT/AST) levels (Normal Values: SGPT/ALT: <35, SGOT/AST 15-46).
4. Admitted in the Quirino Memorial Medical Center.
5. Admitted from July 2021 to February 2022.

2.3. Exclusion Criteria

1. Pediatric patients aged 18 years and below and elderly patients aged 60 years and above.
2. Those with comorbidities such as known hepatic failure, hepatitis, cancer patients, pregnant patients, immunocompromised hosts, known liver pathologies (i. e., NAFLD, Hepatic Nodules or Malignancy etc).
3. Those without baseline AST and ALT, or repeat AST and ALT.
4. Patient who has history or currently taking supplements, vitamins, or medications for liver.
5. COVID-19 reinfection admission.

Upon admission, baseline Serum ALT and AST levels, along with other laboratory parameters and co-morbidities were determined. COVID-19 Transaminitis was diagnosed base on elevated ALT and AST in COVID-19 patients during admission. VITROS ® 5600 is used for the determination of ALT and AST levels. Essential phospholipids 300 mg, 1 cap twice daily were given to SARS-CoV-2 positive patients with elevated ALT and AST. A portion of COVID-19 Transaminitis patients were not able to take Essential phospholipids due to financial constraints since this drug is

not included in the Philippine National Drug Formulary, hence need to be bought outside the institution.

Admitted Covid Transaminitis patients who took the Essential Phospholipids were compared to those who were not able to take the medication. Routine laboratory parameters were done at 5th to 7th hospital days, ALT & AST levels were included. Laboratory outcome parameter is noted for resolution of elevated ALT and AST. The standard of care for COVID-19 infection management was given to both groups.

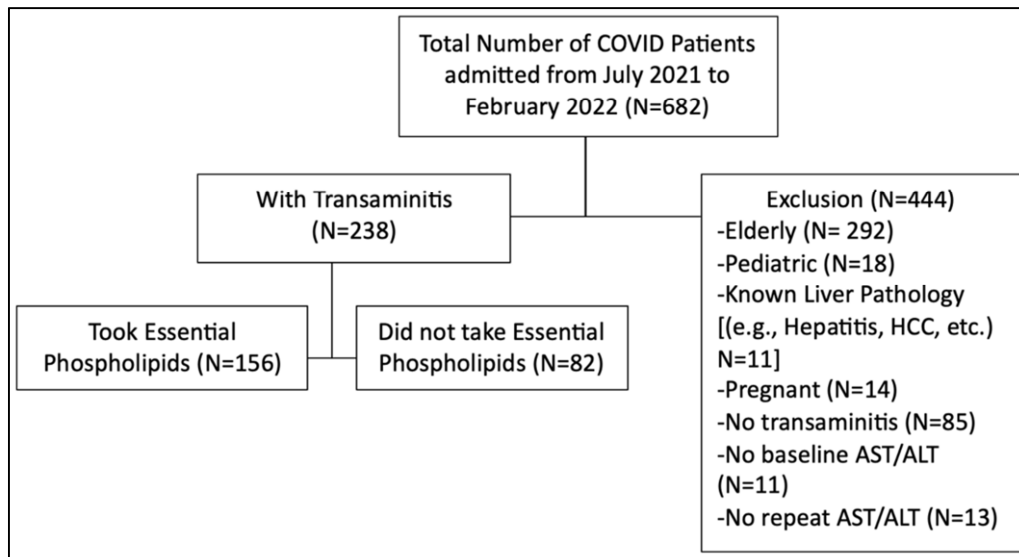


Figure 1. Flow chart of inclusion and exclusion criteria.

2.4. Statistical Analysis

Data were encoded and tallied in SPSS version 29 for Windows. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean, median, \pm SD were generated. Analysis of the different variables was done using the following test statistics: Wilcoxon Signed Rank Test, Mann-Whitney U Test, and Chi-square test. The computed minimum sample size is 109 based on a confidence value of 95%, a margin of error of 5, 50% population proportion, and population size of 150.

3. Results

In this section, we aim to present the significant findings of the study based on the specific objectives declared in this research paper. The chapter includes the presentation, interpretation, and analysis of data. The primary purpose of this section is to provide a comprehensive overview of the research results, and to communicate the main findings to the readers.

Through careful analysis of the data, we were able to identify key patterns and trends that are relevant to the research objectives. We have also included graphical representations of the data.

Table 1. Prevalence of COVID-Induced Transaminitis.

	N
Total number of admitted patients with COVID-19-induced Transaminitis	238
Total number of admitted COVID-19 patients	337
Prevalence rate	70.62%

Table 1 shows the prevalence of COVID-induced transaminitis in COVID-19 confirmed patients admitted to Quirino Memorial Medical Center during the period of July 2021 to February 2022. The study included a total of 337

COVID-19 patients who met the inclusion criteria, out of which 238 patients were identified. The prevalence rate is 70.62%.

Table 2. Comparison of Demographics & Clinical Characteristics Between Patients Who Took Essential Phospholipids from Patient Who Did Not.

Variable	Took Essential Phospholipids						Total	Chi-Square	p-value
	NO		YES						
	Category	Freq	Percent	Freq	Percent	Freq	Percent		
Sex	F	38	46.34	53	33.97	91	38.24	3.48	0.06
	M	44	53.66	103	66.03	147	61.76		
	Total	82	100.00	156	100.00	238	100.00		
Number of co-morbidities	1	26	31.71	39	25.00	65	27.31	23.19	0.62
	2	34	41.46	36	23.08	70	29.41		
	3	4	4.88	3	1.92	7	2.94		
	4	5	6.10	5	3.21	10	4.20		
	5	1	1.22	0	0.00	1	0.42		
	6	1	1.22	1	0.64	2	0.84		
	7	1	1.22	0	0.00	1	0.42		
	8	3	3.66	3	1.92	6	2.52		
	9	2	2.44	2	1.28	4	1.68		
	10	2	2.44	0	0.00	2	0.84		
	>10	11	13.41	15	9.62	26	10.92		
	Total	60	73.17	74	47.44	134	56.30		
	Normal	9	10.98	10	6.41	19	7.98		
Baseline AST	Not Normal	73	89.02	146	93.59	219	92.02	1.53	0.22
	Total	82	100.00	156	100.00	238	100.00		
	Normal	13	15.85	3	1.92	16	6.72		
Baseline ALT	Not Normal	69	84.15	153	98.08	222	93.28	15.93	0.10
	Total	82	100.00	156	100.00	238	100.00		
	Normal	52	63.41	106	67.95	158	66.39		
Baseline Crea	Not Normal	30	36.59	50	32.05	80	33.61	0.50	0.48
	Total	82	100.00	156	100.00	238	100.00		
	Critical	47	57.32	71	45.51	118	49.58		
COVID Classification	Mild	1	1.22	3	1.92	4	1.68	4.07	0.25
	Moderate	11	13.41	19	12.18	30	12.61		
	Severe	23	28.05	63	40.38	86	36.13		
	Total	82	100.00	156	100.00	238	100.00		

*p-value <0.05- Significant

Table 2 is a comparison between the treatment arm and the control arm. Out of the 238 patients, 156 (65.54%) received Essential Phospholipids, while the remaining 82 (34.34%) did not. There are more male patients (61.76%) than female

patients (38.24%). There is no significant difference in baseline AST, ALT, creatine levels, number of co-morbidities and COVID-19 classification.

Table 3. Comparison of SGPT and SGOT Levels with & without Essential Phospholipids.

	Took Essential Phospholipids						Mann-Whitney U	p-value
	NO			YES				
	Mean	Median	SD	Mean	Median	SD		
Number of Hospital Days	10.378	10.000	6.679	11.090	11.000	6.416	5918.000	0.343
Age	45.512	47.000	10.732	42.487	42.500	10.889	5344.000	0.037
Baseline AST	69.728	67.040	22.074	193.359	98.240	804.403	3070.000	0.000
Repeat AST	59.006	47.650	45.964	78.755	55.410	70.616	4638.000	0.004
DIFF_AST	-10.874	-16.890	44.710	-115.458	-34.100	807.445	4113.000	0.000
Baseline ALT	60.496	57.180	25.553	150.022	101.000	287.653	2287.500	0.000
Repeat ALT	66.126	52.185	55.052	106.061	83.250	81.134	3703.000	0.000
DIFF_ALT	5.257	-7.145	54.903	-44.431	-17.740	286.221	4629.000	0.004
Baseline Crea	143.574	72.160	275.972	88.983	71.795	95.860	6154.500	0.632
Repeat Crea	112.428	70.000	128.963	83.176	67.000	72.688	4645.500	0.141
DIFF_Crea	-2.821	-3.000	121.132	-2.051	-5.050	59.691	4821.500	0.284
CRP_less	32.193	24.000	29.473	30.267	24.000	25.289	4679.500	0.647
D Dimer less	1118.03	532.880	1588.47	1264.15	551.065	1657.34	3882.000	0.565

* p-value <0.05- Significant

Table 3 describes the comparison of SGPT and SGOT levels with and without Essential Phospholipids. In both arms, there is no significant difference in the number of hospital days as well as the age. There is a significant difference in both the baseline and repeat AST and ALT levels for those patients who took Essential phospholipids compared those

who did not. There is no significant difference in the other laboratory parameters (Creatinine, CRP, D-Dimer), this could indicate that essential phospholipids do not have a significant impact on these parameters, or that these parameters are not directly related to liver function.

Table 4. Comparison of Disposition COVID Transaminitis with & without Essential Phospholipids.

Variable	Took Essential Phospholipids						Total	Chi-Square	p-value
		NO		YES					
	Category	Freq	Percent	Freq	Percent	Freq			
Disposition	Died	20	24	25	16	45	18.91	2.453	0.117
	Discharge improved	62	76	131	84	193	81.09		
	Total	82	100	156	100	238	100.00		

Table 4. Although not statistically significant, there is a trend toward a decrease mortality rate from those patients

who took Essential phospholipids compared to those who did not (16% vs. 24% respectively).

Table 5. Comparison of Length of hospital stay of COVID-19 with and without Transaminitis.

Variable	No Transaminitis			With Transaminitis			Mann-Whitney U Test	p-value
	Mean	Median	SD	Mean	Median	SD		
Number of Hospital Days	9.976	9.000	6.1759	10.355	10.000	6.765	10129	0.4858

* p-value <0.05- Significant

Table 5 shows the comparison between the length of hospital stay of COVID-19 patients with and without COVID

transaminitis. There is no significant difference in the number of hospital days between the two groups.

Table 6. Comparison of Disposition of With and Without COVID Transaminitis.

Variable	Category	Transaminitis				Total		Chi-square	p-value
		NO		YES					
		Freq	%	Freq	%	Freq	%		
Disposition	Died	14	16.28	53	21.12	67	19.88	0.941	0.332
	Discharge improved	72	83.72	198	78.88	270	80.12		
Total		86	100.00	251	100.00	337	100.00		
COVID Classification	Critical	29	33.72	128	51.00	157	46.59	17.091	0.001
	Mild	8	9.30	4	1.59	12	3.56		
	Moderate	19	22.09	31	12.35	50	14.84		
	Severe	30	34.88	88	35.06	118	35.01		
Total		86	100.00	251	100.00	337	100.00		

* p-value <0.05- Significant

Table 6 shows that there was a higher mortality rate for those patients with Covid transaminitis (21%), from those who did not have Covid transaminitis (16%), however, the study showed no significant difference with the 2 groups with a p value of 0.33. There were also many Covid critical patients with transaminitis compared to those who did not have transaminitis (51% vs 33%) and this showed a statistical significance with a p value of 0.001.

4. Discussion

COVID-19 was initially thought to affect primarily the lungs, leading to symptoms such as cough, shortness of breath, and fever. However, further research has indicated that the virus can cause extrapulmonary complications,

including those affecting the gastrointestinal system.

The gastrointestinal complications associated with COVID-19 can range from mild symptoms such as nausea, vomiting, and diarrhea to more severe conditions like acute liver injury and intestinal ischemia. It is believed that the virus can enter the body through the ACE2 receptors present in the intestines, leading to inflammation and damage to the gastrointestinal system.

A study conducted by Cheung et al. found that 17.6% of COVID-19 patients experienced gastrointestinal symptoms [3]. This highlights the importance of considering gastrointestinal symptoms as a potential indicator of COVID-19 and not just relying on pulmonary symptoms. Additionally, patients with severe COVID-19 are at a particularly high risk for developing gastrointestinal

complications. Critically ill patients with COVID-19 have exhibited complications ranging from transaminitis and feeding intolerance to life-threatening mesenteric ischemia [4, 5].

According to a study by Zhao et al., approximately two-thirds of severe COVID-19 patients develop high levels of liver transaminases [6]. The mean values of aspartate aminotransferase and alanine aminotransferase exceed 400 units per liter of serum. In some cases, liver injury can progress to liver ischemia. The cause of acute liver injury in COVID-19 patients is not yet clear, but it is likely due to multiple factors. Several studies suggest that the degree of transaminase elevation is an indicator of disease severity and an independent predictor of mortality [1, 7, 8].

A study by Gundermann et al. found that Essential Phospholipids can speed up the improvement or normalization of subjective symptoms and pathological findings in liver disease [2].

According to a cross-sectional local study by Rodriguez and Abola, COVID-19 patients commonly have elevated transaminase levels. Most patients with elevated enzymes have levels that are less than two times the upper limit of normal, and levels of ALT and AST are not significantly higher in severe cases. Although a greater proportion of patients with severe disease have elevated ALT and AST levels compared to those with non-severe disease, this difference is not statistically significant. Additionally, the presence of comorbid conditions is associated with elevated ALT levels, but not with elevated AST levels [9]. In a study in China, Covid transaminitis were reported in 14%–58% of hospitalized patients with COVID-19 [8, 10].

According to a local retrospective cohort study by Pizarra et al., gastrointestinal symptoms are common in COVID-19 patients, the most common symptom is diarrhea. Patients who have higher ALT, AST, creatinine and CRP levels are associated with moderate and critical disease, but do not increase the risk of death [11]. This is somewhat similar to our study, wherein ALT and AST levels were seen more in COVID-19 critical disease.

In our research, investigators found that most COVID-19 patients admitted had transaminitis, and the majority of these patients were classified as having Severe or Critical COVID-19. Most patients with transaminitis were started on Essential Phospholipids. There was a significant decrease from baseline to repeat ALT and AST levels. This finding suggests that essential phospholipids may have a positive impact on the liver function of COVID-19 patients with transaminitis.

5. Conclusion

Based on our research findings, we can conclude the following:

1. The prevalence of transaminitis in COVID-19 infection is high, and it indicates how common and significant COVID-induced transaminitis is among COVID-19 patients.

2. The presence of transaminitis in COVID-19 patients appears to have a significant impact on the severity of the disease or the course of treatment.
3. Patients with COVID transaminitis who received Essential Phospholipids had a significant decrease in repeat SGPT and SGOT levels compared to baseline.

In conclusion, our research findings have shown that many COVID-19 patients experience transaminitis. We found that patients who were treated with Essential Phospholipids experienced a significant decrease in repeat SGPT and SGOT levels when compared to their baseline levels. This suggests that Essential Phospholipids may be an effective treatment option for COVID transaminitis.

6. Recommendations

Based on our research findings, we have several recommendations for healthcare providers, researchers, and policymakers:

1. Healthcare providers should be aware of the high incidence of transaminitis in COVID-19 patients and take this into account when assessing the severity of the disease. Given that most patients who were identified with transaminitis are classified as COVID-19 Critical, it is important for healthcare providers to monitor liver function in these patients to ensure that they receive the appropriate care.
2. Healthcare providers can consider Essential Phospholipids as a potential treatment option for COVID transaminitis, given its demonstrated efficacy in reducing AST and ALT levels.
3. Further research is needed to fully understand the impact of transaminitis on COVID-19 patients and to identify potential treatment options that may improve patient outcomes. While our study provides valuable insight into the prevalence and impact of transaminitis in COVID-19 patients, further research is necessary to fully understand this condition and its impact on patient outcomes. Future studies should focus on larger sample sizes and include other populations, such as the geriatric population and those with pre-existing liver conditions, to better understand the prevalence of this condition and identify potential treatment options that may be effective in managing it.

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