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Association between Transaminitis and Myositis among Patients with COVID-19: A Case- Control Study

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Abstract

Introduction: COVID-19 has brought about a major health burden globally. There are little to no attention has been paid to muscle-related complication in patient with COVID-19. Elevated liver enzymes together with the presence of comorbidities in COVID-19 patients render greater risk for morbidity and mortality, and the phenomenon may be related to Myositis. This study aimed to describe the association between transaminitis and myositis in patients hospitalised with COVID-19 at Hospital Pontian (Malaysia). Methods: This is an observational case-control study involving patient with myositis, hospitalised due to COVID-19 infection. Descriptive and inferential statistics were computed to analyse the data. Results: Total of 60 patients by ratio of 1:1, sex-matched, were included in this study. Elevated AST (86%, p=0.037) and ALT (66.7%, p=0.038) were shown significantly more common in patients with elevated CK compared to control. Discussion: The incident rate for myositis among hospitalised COVID-19 patient was reported to be approximately 9.7%. Normal liver biomarkers such as: alkaline phosphatise, total protein and bilirubin may potentially suggest the release of ALT and AST occurs from an origin other than liver tissue. Multiorgan failure may not necessarily be the cause of myositis among patients with COVID-19. Conclusion: This study indicates that myositis in patients with COVID-19 is not an uncommon occurrence.

Keywords: COVID-19; Transaminitis; Myositis; Hospital Pontian.

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1. Introduction

The pandemic caused by Coronavirus disease 2019(COVID-19) has brought about brought about a major health burden globally [1]. COVID-19 is an infectious disease caused by the spread of severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) from person-to-person predominantly through airborne droplets [2]. Infected individuals can manifest variable clinical states, ranging from being asymptomatic to experiencing mild, moderate or severe illness [3]. The majority of patients with confirmed COVID-19 only show minor symptoms, such as a fever, or flu-like symptoms, but a subset of COVID-19 patients can progress to experiencing a life-threatening critical illness with or without complications [4]. Various manifestations of the disease process arising from SARS-CoV-2 infection have been reported, including but not limited to pulmonary, cardiovascular, hematologic, renal and neurologic disorders [5]. However, little to no attention in the literature has been paid to muscle-related complications [6].

Myositis refers to a group of conditions that share the common feature of chronic muscle inflammation, resulting in muscle weakness and damage [5]. In such a condition, creatine kinase (CK) enzyme levels are elevated, and this biomarker may be used to detect inflammation of the muscles (myositis) or muscle damage due to muscle disorders [7]. Elevated CK levels in combination with other signs of myositis, such as rash or weakness, have been reported in as many as 16% to 33% of COVID-19 patients [8]. Meanwhile, in the setting of myositis, elevated levels of liver enzymes, especially aspartate aminotransferase (AST), are also not uncommon [9]. A follow-up study conducted over a 27-year period, which identified 16 patients who had elevated aminotransferase levels following muscle injury, reported that the recorded AST elevations were often greater than the recorded ALT elevations [10]. There has been a suggestion made that elevated liver enzymes together with the presence of co-morbidities in COVID-19 patients render them at greater risk for morbidity and mortality, and this phenomenon may be related to myositis [11]. However, no current evidence has been offered regarding the incidence or direct association between transaminitis and myositis in COVID-19 patients [4]. The question remains as why do patient experience myositis without the involvement of multiorgan failure? To contribute in solving the dilemma, this study aimed to describe the association between transaminitis and myositis in patients hospitalised with COVID-19 at Hospital Pontian.

2. Materials and methods

This is observational case-control study design involving unvaccinated patient with COVID-19 prior admission to Hospital Pontian Johor, Malaysia. We selected all survivors with normal electrocardiogram and age more than 20 years with confirmed positive real-time polimerase chain reaction (RT-PCR) on nasopharyngeal swabs amongst 291 hospitalized patients during the peak of fourth wave of the COVID-19 pandemic (from 1st August to 30th September 2021). Myositis complicated COVID-19 was defined as elevated Creatinine Kinase (CK) value >235 U/L with positive RT-PCR result prior to admission in which 30 cases fulfill criteria were included.

We selected a control population consisting in 30 sex-matched COVID-19 patients who have normal CK value ≤ 235 U/L. In both groups, cycle threshold value (Ct) of less than 40 was considered as a positive diagnosis for COVID-19. Excluded from this study, patients with history of recent trauma/massage, using traditional

medication/prolong steroid used, received at least one-dose COVID-19 vaccination or having more than one of secondary infection. Characteristics of patient (age, gender, co-morbidities, liver function test, and oxygen requirement) were obtained retrospectively from electronic medical records. Elderly in this study was defined as age >50 years old, while hypoxia was defined as fraction of inspired oxygen (FiO2) >40%. The study was registered under Malaysian National Medical Research Register and obtains related Ethic Committee approval. The statistical analysis was performed using Open source Epi Info™ Software (Centers for Disease Control and Prevention, released on 2018, Version 7.2.2.6). Continuous variables were expressed as means standard deviation (SD) and were compared by t-test or parametric tests as appropriate. The categorical variables were expressed in number (%) and compared by chi-square ($\chi 2$) or Fisher exact test as appropriate. Significant risk factors for myositis among COVID19 patients were identified using univariate analyses and the significance level of the hypothesis tests of *p*-value was set at less than 0.05 (2-sided).

3. Result

A total of 60 patients by ratio of 1:1 (30 cases and 30 controls) were included in this study. Demographic and clinical characteristics between case (elevated CK value >235 U/L) and control (normal CK) are summarized in Table 1.

Table 1: Demographic and clinical characteristics among COVID-19 patients

Variable on Admission	MYOSISTIS [Case = 30] *N* (%)	NO MYOSITIS [Control = 30] *N* (%)	*p*-value	
Age (years)	Mean: 48.3 SD: 16.4	Mean: 55.4 SD: 14.4	0.492	
Gender			1.000	
Male	18 (60.0)	18 (60.0)		
Female	12 (40.0)	12 (40.0)		
Co-morbidities				
Diabetes	6 (20.0)	10 (33.3)	0.243	
High Blood Pressure	10 (33.3)	16 (53.3)	0.118	
Obesity	5 (16.7))	1 (3.3)	0.085	
Elderly	12 (40.0)	18 (60.0)	0.121	
Liver Function Test				
Aspartate Aminotransferase (AST)	26 (86.7)	19 (63.3)	**0.037**	*
Alanine Aminotransferase (ALT)	20 (66.7)	12 (40.0)	**0.038**	*
Alkaline Phosphatase (ALP)	3 (10.0)	6 (20.0)	0.278	
Total Bilirubin	1 (3.3)	3 (10.0)	0.301	
Total Protein	3 (10.0)	4 (13.3)	0.688	
Oxygen Requirement				
Hypoxia	10 (33.3)	7 (23.3)	0.390	
Lactate Dehydrogenase (LDH)	27 (90.0)	21 (70.0)	0.053	

**indicates p<0.05 statistically significant result.*

Amongst basal and previous conditions, there were no significant differences in sex, age, co-morbidities. In respect to liver function test prior to admission, there were no significant different in total protein, total bilirubin or alanine phosphatise (ALP). However, elevated level of AST (86%, p=0.037) and ALT (66.7%, p=0.038) were significantly more common in patients with elevated level of CK compared to control. Odd ratios between

different age group with transaminitis are summarized in Table 2. Although majority of patient were >70 years old but our study showed that transaminitis occurred 5 times more likely in age group between 30-50 years old.

Table 2: Odd Ratios between Age Groups and Transaminitis

Age (Years)	Transaminitis		Odd Ratios	95% Confidence Interval
	Yes	No		
Less than 30	5	1	1.5	0.1 - 14.8
30-50	22	2	**5.5**	**1.1 - 27.4**^
50-70	16	6	0.7	0.2 - 2.4
More than 70	9	40	0.2	0.1 - 1.1

^*indicates statistically significant result.*

In respect to oxygen requirement prior to admission, there were no significant differences seen in level of hypoxia and Serum Lactate Dehydrogenase (LDH) based on Table 1. The proportions of medical device used for Oxygen therapies are depicted in Figure 1. Majority of patients admitted required Nasal Prong 3 Litres (n=38, 68%). Nearly a third required non-invasive-controlled oxygen therapy such as: High Flow Mask, Venturi Mask 60% and Venturi Mask 40%, forming classes of hypoxia requiring FiO2 >40% (n=17, 28%). In the rest of patients do not required oxygen therapy (n=5, 8%).

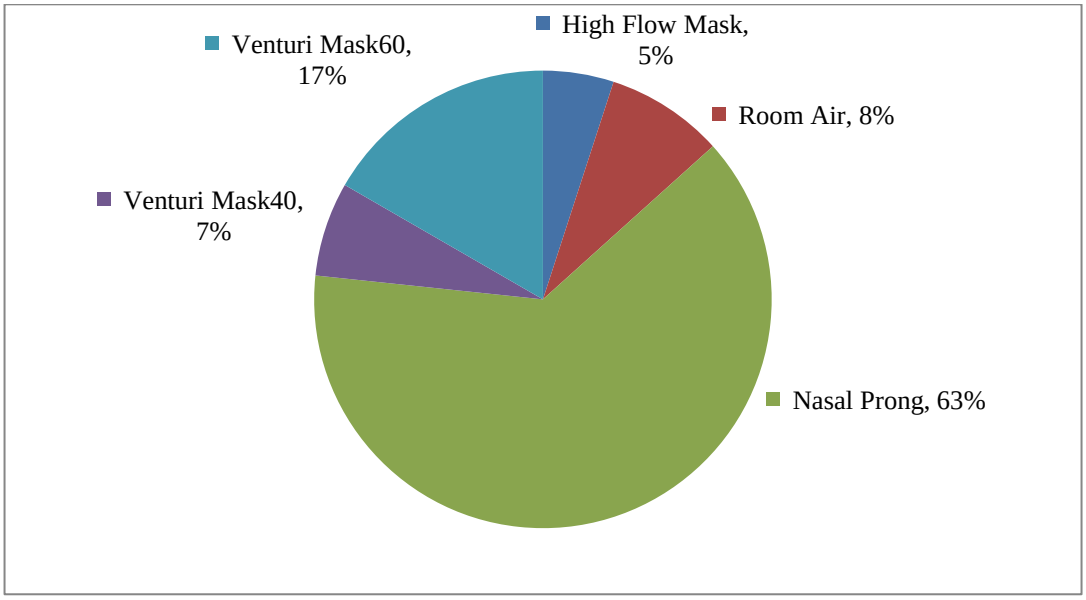

Figure 1: Device used for Oxygen therapy prior to hospital admission

4. Discussion

Muscle cell injury

We report the details of an observational case–control study, which suggests that transaminitis is associated with

myositis among COVID-19 patients. Transamines, such as AST and ALT, are present in cytosolic and mitochondrial isoenzymes and are found primarily in the liver but also in skeletal and cardiac muscle; white and red cells; and the kidneys, brain, pancreas and lungs but at much lower concentrations [9]. In contrast, CK is an enzyme necessary for the conversion of creatine that uses Adenosine Triphosphate found abundant in skeletal, cardiac and smooth muscle [7]. CK also can be found in brain cells, photoreceptor cells of the retina and hair cells of the ears [12]. Elevated CK may suggest an inflammation to muscle cells which is call Myositis while elevated AST/ALT may suggest transaminitis [8]. As muscle cell injury can also be another source of increased aminotransferase activity apart from the liver, we inferred that the possible pathophysiology might be due to infected cells may cause sudden hypoxia of localised muscle tissue which then possible trigger the release of a modest amount of ALT and AST into the blood circulation. Furthermore, we argue from the evidence that normal liver biomarkers, such as alkaline phosphatise (ALP), total protein and bilirubin, during the early stage of SARS-CoV-2 infection may potentially suggest the release of ALT and AST occurs from an origin other than liver tissue. However, a degree of uncertainty regarding our observed COVID-19 patient with elevated CK levels persists as an isolated increase in AST and ALT can arise from either the liver, muscle or both or even from other parts of the body [9].

Low oxygen requirement

We documented the incidence rate of Myositis in this study to be approximately 9.7% among our hospitalised patients with COVID-19, which highlights the potential implications of SARS-CoV-2 infection with respect to skeletal muscle. In contrast, multiorgan failure due to severe acute respiratory distress syndrome can sometimes lead to myositis [5]. We found the age between 30-50 years are 5 times more likely to experience transaminitis as there is age dependency of liver enzymes activities which support by other study [13]. We report that the majority of our patients only required limited oxygen therapy, such as 3L delivered by nasal prong. Such a low requirement of oxygen suggests multiorgan failure may not necessarily be the cause of myositis among patients with COVID-19 [14].

Muscle related hypoxia

Myositis manifestation of COVID-19 is shown in figure 2. The SARS-CoV-2 seems to employed mechanism to enter our body using spike protein to ACE2 receptor from the lungs cell and subsequently breaches into extrapulmonary circulation [15]. The viremia become more apparent as the virus being mechanically pumped by the heart into systemic circulation and possibly induced the cytokines storms. The virus infects all the cells including muscle tissues which leads to its inflammation and causes abnormal CK, transaminitis and other cells parameter [16]. This process may trigger the liver cells such as hepatocytes and cholangiocytes activities to increase [5]. Subsequently, the inflammation in the liver potentially induced the increases of right atrial pressure and impeding venous return to the heart which subsequently reduced the gas exchanged in the lungs [5]. This process may possibly cause patient to experience mild hypoxia which support our finding. Our current understanding on SAR-CoV-2's pathophysiology includes: direct cytotoxic effects, dysregulation of renin-angiotensin-aldosterone system (RAAS), endothelial cells damage with thrombo-inflammation and dysregulated immune response are indirectly supporting the possibility of systemic response by the muscle tissue [15].

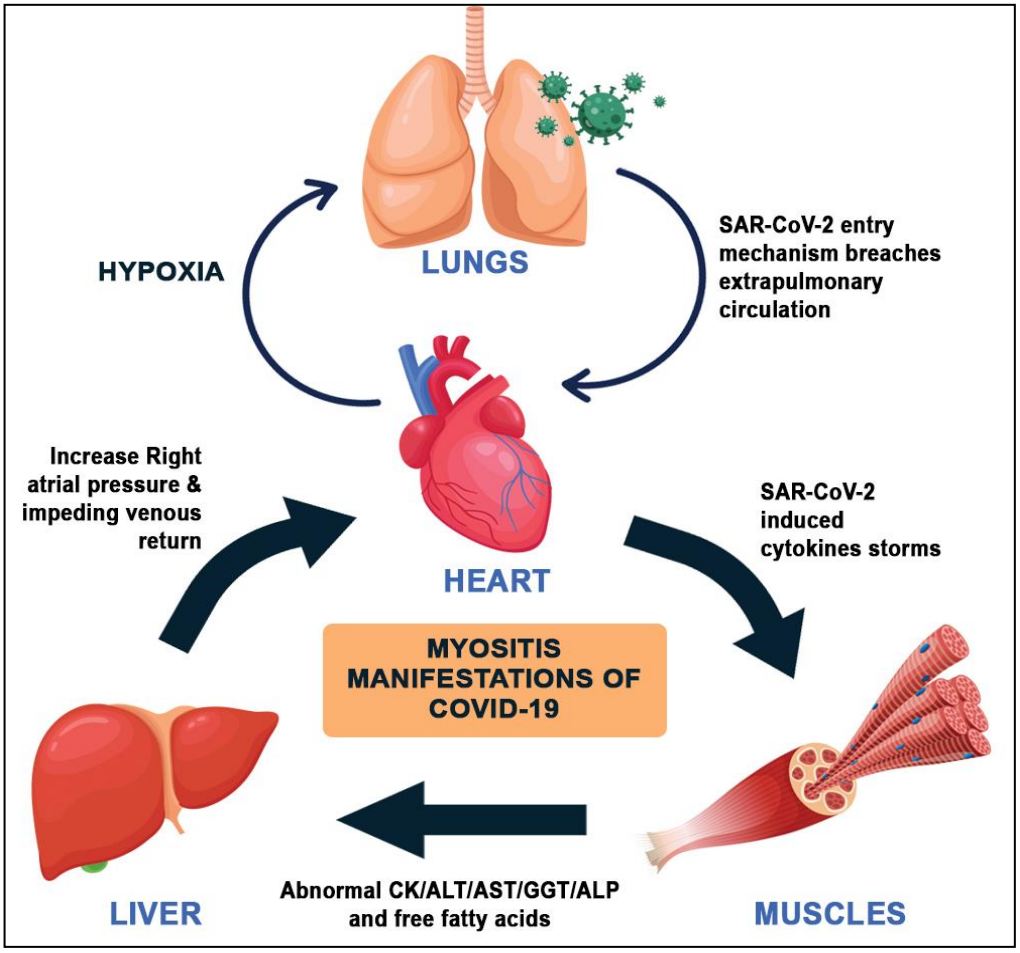

Figure 2: Myositis Manifestation of COVID-19

There are many potential implications when recognising transaminitis and myositis in patients with COVID-19. First, the use of medications that are hepatotoxic can safely be administered with appropriate caution. This also implies that development of newer COVID-19 oral medications or vaccines, which are seldom metabolised by the liver, are potentially safer. Furthermore drugs targeting muscle cells can obtain more roles, eventually providing an opportunity for newer novel biomarkers from muscle to be explored especially in patient with COVID-19.

Degree of infectivity

Our study had some limitations. First, a diagnosis of COVID-19 made by detection of CT value RNA level of SARS-CoV-2 through RT-PCR does not necessarily correlate with the degree of infectivity. Secondly, the accepted limits for biomarkers were depend upon current clinical practice guidelines and no muscle biopsy or any other detailed histopathology was performed, so our results may arguably not reflect the differences between myositis and rhabdomyositis. Finally, we showed that SARS-CoV-2 infection can cause myositis; however, this occurrence is also true of any other viral infection with may present during infection with COVID-19 [14]. There are still potential correlations between myositis and other risk factors like sex, hypertension, obesity and the level of oxygen requirement. Smoking including tobacco and electronic-cigarette

were not collected which may draw possible finding in the future [17]. Our study could not determine any direct effect of such risk factors in patients with COVID-19 complicated by myositis. Hence, more research using larger sample sizes is needed.

5. Conclusion

Our study findings highlight that myositis among patients with COVID-19 was associated with transaminitis using an observational case–control study design. The potential cause of this association may be due to the release of ALT and AST into the blood circulation from infected muscle tissue. Normal blood liver function testing performed apart from elevated serum tranamineses may provide a potential benefit not limited to the development of drugs or vaccines, which often metabolise in the liver. Importantly, this study indicates that myositis in patients with COVID-19 is not an uncommon occurrence.

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