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UTILITY OF TAU PROTEIN AND SOME ROUTINE LABORATORY BIOMARKERS TO DETECT COVID-19

Muayad AL-dulaimi * **and Nagham Qasim Kadhim**
Department of Chemistry College of Science, University of Tikrit Salah Aldeen Iraq.
*Author Corresponding: E-mail: Moaedchemistry@yahoo.com, Naghamkassim@tu.edu.iq.

Abstract

Background: The COVID-19 is a virus that results in numerous organ failure in people as well as physiological alterations in the ratios and makeup of blood and biochemical cells, including elevated AST, ALT, and LDH levels as well as Tau Protein. However, because of their association with COVID-19, they were considered to be important disease markers. **Methods:** For this research, 90 participants were chosen from 30 control groups and 60 COVID-19 patients. The research materials came from the hospitals' labs in Baqubah. **Results:** Through examining the data from the studie, we came to the conclusion that inflammatory markers, particularly Tau protein, AST, ALT, and LDH, were favorably correlated with the severity of COVID-19. Tau protein levels increased significantly between the patient group and the control groups ($P<0.001$). According to the Iraqi Ministry of Health's protocol for the severity of COVID-19 stages, the ranking of severity for patients in this research was based on those stages. **Conclusions:** There is presently indication that tau protein has practical significance. Additionally, we found a correlation between the intensity of COVID-19 and the levels of tau protein, AST, ALT, and LDH that was consistent with COVID-19 infection.

Keywords: Tau Protein, AST, ALT and LDH in COVID-19.

Introduction

The present coronavirus disease outbreak in 2019 (COVID-19) is a global emergency because of its increasing prevalence and high mortality rate **[1].** The majority of nations, including Iraq, has implemented stringent public health measures and has gone into total isolation **[2].** Since it was first reported, the novel coronavirus disease has surprisingly attracted a lot of attention globally. Early in December 2019, the WHO stated that China had reported that several patients had been hospitalized for pneumonia with an unknown etiology. This is when the epidemic first appeared in China (Hubei region). These patients were employees of a seafood market, but soon after, human-to-human transmission was verified, raising concerns for the general public's health **[3][4][5].** Soon after the patients started displaying symptoms similar to those of the SARS pandemic, the cause was identified as an emerging strain of the coronavirus family, which was given the name 2019nCoV. The ICTV changed the name to "R-CoV2" on February 11th, 2020 **[6]**. This epidemic follows the SARS outbreak from 2003 and the MER outbreak from 2012 **[7].** The epidemic has aggressively spread to almost all countries, in contrast to SARS and MERS,

leading to a global health care catastrophe **[8],** and is thought to be the seventh member of the family of viruses that can seriously illen people **[9].**

The illness quickly spread throughout the world, leading to a pandemic that put strain on all nations as they proclaimed a lockdown, social distancing laws because there are asymptomatic carriers, a dearth of targeted therapies, as well as numerous risk factor categories **[10].**

One of the most crucial proteins in the central nervous system is the tau protein. In addition to other cell compartments, they can be located in the axon, dendrites, nucleolus, cell membrane, and synapses. Tau, on the other hand, can infiltrate the cerebrospinal fluid (CSF) and is found in the interstitial fluid at concentrations of 10 to 25 pg/mL **[11].** Normal aging frequently includes tau tangle aggregation, especially in the medial temporal lobes **[12].** Due to its highly adaptable shape, the tau protein can connect with a wide range of partners and participate in a number of signaling pathways. The dark side of tau's structural range is its ability to form oligomers and filaments with other molecules, which results in a variety of neurodegenerative diseases known as "tauopathies." **[13].** Intraneuronal aggregates of neurofibrillary tangles make up neurofibrillary tangle (NFT) compositions **[10].** Alzheimer's disease (AD), frontotemporal dementia (FTD), Pick's disease, and progressive supranuclear palsy all have tau protein clusters that produce toxic-rich clumps. Tau hyperphosphorylation results in microtubule disintegration, which causes synaptic dysfunction and cell demise **[11].** The pathogenesis of misfolding-related neurodegenerative disorders is mediated by the tau protein, and oxidative stress is frequently associated with hypothyroidism **[14].**

It is well known that the liver is where the majority of medications are metabolized. Some medications, when taken by a COVID-19 patient who is ill, can put the liver under duress. The research therefore makes the assumption that the increase in liver enzymes is caused by the liver being under stress as a result of the patient receiving medications. Patients with SARS-CoV-2 had increased levels of AST and ALT, indicating that liver damage is caused by infection **[15].**

Increased liver enzymes in SARS-CoV-2 patients could have several potential causes, including direct liver injury, associated inflammatory responses, and congestive heart failure. Drug-induced liver injury, muscle harm, and liver damage are all referred to as hepatopathy, hepatic ischemia, and hepatopathy, respectively. **[16]**, reasons of liver damage when Covid-19 is present. Hepatotoxic medications may cause the elevated AST and ALT: In the past, COVID-19 or its effects have all been treated with antipyretics, antibiotics, antivirals, and steroids. While some of these medications have shown promise, others have produced conflicting outcomes. Some of the COVID-19 liver anomalies have been connected to drug-induced liver damage **[17].**

The role of various biomarkers in predicting prognosis in COVID-19 patients is presently being investigated. One such biomarker of interest is lactate dehydrogenase (LDH), particularly given that higher LDH levels have previously been linked to worse results in patients with other viral infections **[18].** There are substantial differences in LDH levels between individuals with and without severe disease, according to early data in COVID-19 patients **[19].**

Materials and methods

The materials that were used to process the samples that were gathered and the various instruments and pieces of chemicals are mentioned in the table (1).

Chemicals:

Table (1): The chemicals were used and companies supplied

No	Chemicals	Supplier Company
1	Human Tau Protein	My Biosource-USA
2	AST, ALT and LDH	Human-Germany

- COVID-19 patients

On 70 COVID-19 patients admitted to hospitals in Diyala (Baqubah General Hospital) during the period from august -2021 to march-2022, a case-control analysis was done. The Iraqi National Guidelines for the diagnosis and treatment of COVID-19 were used to diagnose all COVID-19 patients enrolled in this research, and informed permission was obtained from the participants before any data or samples were taken. Using nasopharyngeal swabs and a molecular test, the patients were identified as COVID-19 positive cases. Common complaints included dizziness, headache, shortness of breath, runny nose, sore tongue, diarrhea, and reduced appetite.

Venous blood of 10 ml were taken from patients who were laying in the isolation room with 19 other patients. The blood was split into 4 tubes: an EDTA tube for hematology testing, a Gel tube for biochemistry testing, a sodium citrate tube for coagulation testing, and a second EDTA tube for 3 mL of blood. After being divided into aliquots and placed in Eppendorf tubes, the ELISA test sera were stored frozen at -20 C. (0.3 ml each).

-Controls

A control sample of 30 people who appeared to be in good condition was also used. Their blood profile for anti-infectious pathogens antibodies was negative, and they were from my lab. They had an ESR of less than 20 mm/h and negative CRP serum condition. Additionally, they underwent testing using the COVID-19 IgG/IgM by AFIAS-6 New device (boditech, company) for anti-COVID-19 IgM and IgG antibodies, but the findings were negative.

-Statistical methods

Graph Pad Prism version 8.0, were used to conduct the statistical study. The Student's t-test was used to establish the distribution's normality. $P > 0.05$ is considered non-significant, $P < 0.05$ is considered significant, and $P < 0.001$ is considered extremely significant.

Results and Discussion

- Human Tau Protein Elevated in COVID-19 patients.

Table 2 shows the median and standard range for TAU in the control and COVID-19 patient groups.

Table (2): Median for Control and Patients.

Parameter	Median		Reference range
	Control	Patients	
Tau protein	72.5 (65.7-75.2)	153.0 (139 -163)	49 — 85

The (mean ±SD&SE) levels of TAU (pg/ml) in patient and control according to gender were illustrated in table (3) and figure (1).

There was no significant differences (P>0.05) in the levels of TAU between M2 and F2 in patient group. While there was a highly significant increase (P<0.001) in serum levels of TAU in T2 compared with T1, M2 compared with M1, M1 compared with F1 and in F2 compared with F1.

Table (3): Serum Level of TAU According to Gender.

Mean(±SD&SE)						
TAU pg/ml	Group	Gender	No	Mean± SD	Mean ± SE	
	Control	T1	30	70.4 ± 7.1	70.4 ± 1.3	
		M1	15	69.6 ± 7.2	69.6 ± 1.6	
		F1	15	72.2 ± 6.9	72.2 ± 2.2	
	Patients	T2	70	150.5 ± 14.9	150.0 ± 1.9	
		M2	48	146.7 ± 12.9	146.7± 2.0	
		F2	22	158.5 ± 16.1	158.5 ± 3.7	
	P-value					
	T1 Control T2 Patients	M1 Control M2 Patients	F1 Control F2 Patients	M1/F1 Control	M2/F2 Patients	
	P < 0.001	*P < 0.001*	*P < 0.001*	*P < 0.001*	*P >0.05*	

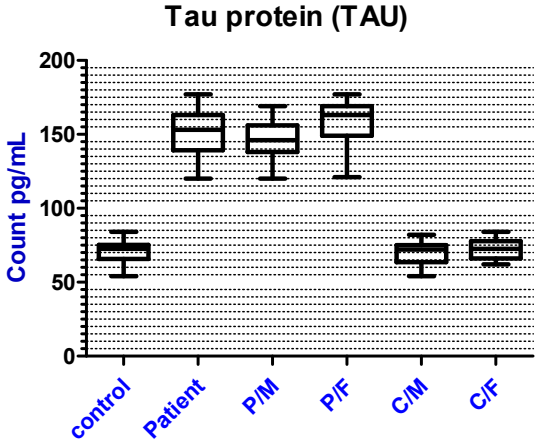

Figure (1): Levels of TAU of patients and Control Groups.

Under typical physiological circumstances, the microtubule-associated protein tau is necessary for anchoring neuronal microtubules and preserving the structural integrity of axons.

Neuronal growth, axonal sprouting, cell proliferation, signal transduction, and synaptic transmission are among the other crucial cellular processes. However, neurofibrillary degeneration is linked to hyperphosphorylation of tau protein in neurons in some abnormal circumstances. Pathogenesis of several neurological diseases, including FTD, AD, and other tau apathies, is caused by this mechanism **[20].**

The majority of people with coronavirus disease 2019 also have neuropsychiatric symptoms from post-acute COVID-19. Utilizing CNS biomarkers like total tau, one can examine objective indications of central nervous system (CNS) damage (t-tau). In severely ill COVID-19 patients, CNS biomarkers can predict fatigue and cognitive impairment 3–6 months after ICU release **[21].**

The concentration of the neuronal biomarker t-tau was higher at the follow-up ($p < 0.01$), but the variations were marginal. Patients with COVID-19 had high amounts of t-tau, which was linked to cognitive dysfunction **[22].** Elevated Tau concentrations were found in patients with encephalopathy and ADEM when the CSF profiles of patients with SARS-CoV-2 illness were examined. They suggested that SARS-CoV-2 infection causes host inflammation to be stimulated, which in turn causes immune cells to infiltrate the brain and cause damage to neurons **[23].** The TAU is therefore COVID-19 virus compatible.

- Liver Enzymes in COVID-19 Patients

Table 4 shows the median and standard range for AST (U/L) and ALT (U/L) in the control and COVID-19 patient groups.

Table (4): Median for Control and Patients.

Parameter	Median		Reference range
	Control	Patients	
AST(U/L)	**40.00 (38.0- 43.0)**	**49.5(47.0-52.0)**	**36— 43**
ALT(U/L)	**34.0 (30.0- 38.0)**	**43.0(40.0-45.0)**	**29— 40**

The (mean ±SD&SE) levels of AST (U/L) in patient and control according to gender were illustrated in table (5).

There was no significant differences ($P>0.05$) in the levels of AST between M2 and F2 in patient group and between M1 and F1 in control groups. While there was a significant increase ($P<0.001$) in serum levels of AST in T2 compared with T1, M2 compared with M1 and in F2 compared with F1.

Table (5): Serum Level of AST According to Gender.

Mean(±SD&SE)					
	Group	**Gender**	**No**	**Mean± SD**	**Mean ± SE**
AST U/L	**Control**	**T1**	**30**	**43.7 ± 3.30**	**43.7 ± 0.61**
		M1	**15**	**44.7 ± 3.2**	**44.7 ± 0.99**
		F1	**15**	**43.2 ± 3.2**	**43.2 ± 0.73**
	Patients	**T2**	**70**	**49.4 ± 4.08**	**49.4 ± 0.52**
		M2	**48**	**49.8 ± 3.60**	**49.8 ± 0.50**
		F2	**22**	**48.5 ± 4.7**	**48.5 ± 1.05**

	P-value				
	T1 Control T2 Patients	**M1 Control M2 Patients**	**F1 Control F2 Patients**	**M1/F1 Control**	**M2/F2 Patients**
	P < 0.001	***P < 0.001***	***P < 0.001***	***P >0.05***	***P >0.05***

The (mean±SD&SE) levels of ALT (U/L) in patient and control according to gender were illustrated in table (6).

There was no significant differences (P>0.05) in the levels of ALT between M2 and F2 in patient group. While there was a significant increase (P<0.001) in serum levels of ALT in T2 compared with T1, M2 compared with M1, F2 compared with F1, and in M1 compared with F1.

Table (6): Serum Level of ALT According to Gender.

Mean(±SD&SE)					
ALT U/L	**Group**	**Gender**	**No**	**Mean± SD**	**Mean ± SE**
	Control	**T1**	**30**	**38.3 ± 3.8**	**38.3 ± 0.7**
		M1	**15**	**38.4 ± 3.9**	**38.4 ± 0.8**
		F1	**15**	**38.3 ± 3.8**	**38.3 ± 1.2**
	Patients	**T2**	**70**	**43.0 ± 4.80**	**43.0 ± 0.62**
		M2	**48**	**42.5 ± 4.4**	**42.5 ± 0.6**
		F2	**22**	**44.2 ± 5.6**	**44.2 ± 1.2**
	***P*-value**				
	T1 Control T2 Patients	**M1 Control M2 Patients**	**F1 Control F2 Patients**	**M1/F1 Control**	**M2/F2 Patients**
	P < 0.001	***P < 0.001***	***P < 0.0306***	***P < 0.012***	***P >0.05***

Increased liver enzymes in SARS-CoV-2 patients could have several potential causes, including direct liver injury, associated inflammatory responses, and congestive heart failure. In addition to muscle harm, terms like hepatopathy, hepatic ischemia, and drug-induced liver injury are used to define liver damage **[24].** Speculated that elevated AST and ALT levels were seen in SARS-CoV-2 cases, indicating that liver damage is caused by infection **[25].** When the immune system works to prevent and eliminate the virus, immunopathology harm to tissues and organs develops. With increased production of inflammatory cytokines, tissue and organ damage is more severe, and mortality rates rise **[26].**

- LDH elevated in COVID-19 patients

Table 7 show the median and reference range for LDH U/L in the control and COVID-19 patient groups.

Table (7): Median for Control and Patients.

Parameter	**Median**		**Reference range**
	Control	**Patients**	
LDH U/L	**148 (138 -160)**	**573 (508 -653)**	**125 — 220**

The (mean ±SD&SE) levels of LDH (U/L) in patient and control according to gender were illustrated in table (8).

There was no significant differences (P>0.05) in the levels of LDH between M1 and F1 in control groups. While there was a highly significant increase (P<0.001) in serum levels of LDH in T2 compared with T1, M2 compared with M1, M2 compared with F2 and in F2 compared with F1.

Table (8): Serum Level of LDH According to Gender.

Mean(±SD&SE)						
	Group	**Gender**	**No**	**Mean± SD**	**Mean ± SE**	
LDH U/L	**Control**	**T1**	**30**	**148.8 ± 12.54**	**148.8 ± 2.2**	
		M1	**15**	**146.7 ± 10.6**	**146.7 ± 2.3**	
		F1	**15**	**153.0 ± 15.4**	**153.0 ± 4.8**	
	Patients	**T2**	**70**	**579.2 ± 76.1**	**579.2 ± 9.0**	
		M2	**48**	**565.7 ± 75.1**	**565.7 ± 10.5**	
		F2	**22**	**615.5 ± 68.1**	**615.5 ± 15.6**	
	***P*-value**					
	T1 Control T2 Patients	**M1 Control M2 Patients**	**F1 Control F2 Patients**	**M1/F1 Control**	**M2/F2 Patients**	
	P < 0.001	***P < 0.001***	***P < 0.001***	***P >0.05***	***P < 0.001***	

LDH is a biomarker for morbidity and mortality of patients with severe criteria and is also the parameter of interest, when increase its ranges that related with bad prognosis in infected with other preferable of virus in the past. LDH is another biochemical parameter for Prognosis of the infection outcomes in this disease need to be crucially estimated to depression the morbidity and monetary influence **[27].**

The authors added that old age and elevated LDH ranges are not related risk factors to aggravation in mild COVID-19 infected, even though doctors should be more attentive to older infected or those with elevated LDH ranges. The study that was revealed was similar to the study that found older male are more affected with increase in LDH and showed dyspnea, hypertension, and c reactive protein. The research also stated that lactate dehydrogenase is a crucial indicator of vascular permeability in the context of immune response to lung injury. Consequently, LDH is a COVID-19 contamination indicator **[28]**.

Conclusions

There is presently evidence to indicate that Tau Protein has clinical relevance, despite the intrigue surrounding the preclinical and clinical studies surrounding this protein. In addition, we discovered that COVID-19 severity was correlated with the amounts of tau protein, AST, ALT, and LDH. Strong investigations are necessary to explain the clinical Tau Protein's importance.

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