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Original Research Article

Meta-analysis of decreased serum cholinesterase activity in COVID-19

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ABSTRACT

This meta-analysis aimed to determine Serum cholinesterase (ChE) activity decreases in COVID-19 patients. The final selection for the meta-analysis comprised 13 published studies that reported 17 records of serum ChE activity in 1402 patients with COVID-19 compared to 924 cohort counterparts. The meta-analysis was a randomized effects size model using percentages of mean (±SD) of serum ChE values of COVID-19 patients vs. their corresponding cohorts. This meta-analysis of serum ChE indicates that it is significantly reduced in COVID-19, which might be a valuable prognostic biomarker.

***Keywords*:** SARS-CoV-2 virus, butyrylcholinesterase, COVID-19

INTRODUCTION

Numerous hematological and blood biochemical tests are utilized to monitor the progression of coronavirus disease 2019 (COVID-19), which is caused by the SARS-CoV-2 virus [1-6]. These tests encompass a variety of biomarkers related to inflammatory responses and damages to major organ systems, including the liver, lungs, heart, kidneys, pancreas, and the immune system [1,3,7]. The specificity of biochemical tests in assessing the severity and progression of COVID-19 are still

under investigation and continuous debate [3,6-9]. Nevertheless, clinical laboratory assessments serve as vital biomonitoring tools, complementing clinical examinations to evaluate the status of COVID-19 and ensure optimal care and therapeutic approach for patients [1-7].

Recent studies from 2020 to 2024 emphasize the critical role of reduced serum cholinesterase (ChE) activity in COVID-19 patients, particularly as a prognostic indicator for disease severity and outcomes [10-22]. This association underscores the toxic impacts of SARS-CoV-2 on the cholinergic system, by disrupting the functional aspects of nicotinic and muscarinic cholinergic receptors as well as the ChE activity during COVID-19 [21,23-27]. Studies have consistently shown that serum ChE activity is significantly lower in grave COVID-19 cases compared to subjects considered as control ones or those with mild-to-moderate disease condition [10,13,20], or in cases with anemia, cytokine storm and noninvasive ventilation [12,21,22]. Additionally, patients who did not survive had even lower serum ChE activity compared to those who survived, indicating an association between low enzyme activity and mortality risk in COVID-19 patients [11,14-19]. Despite these reports, it is also possible that changes in serum ChE activity might not be feasible statistically in hospitalized COVID-19 patients under certain conditions [6,21].

Serum or plasma ChE is known as butyryl ChE (pseudo ChE; E.C. 3.1.1.8), whereas the true ChE (acetylcholinesterase; E.C. 3.1.1.7) is found in erythrocytes and neuronal tissues [28-30]. The liver synthesizes pseudo ChE, which is released into the blood [30,31]. In the blood, serum ChE is associated with cases of inflammation, liver damage, cardiovascular disorders, protein-energy malnutrition and in-hospital mortality [30-33]. Both enzymes are reliable and specific biomarkers of organophosphate and carbamate pesticides exposures [34-36]. Although previous studies have shown reduced cholinesterase (ChE) levels in patients with serious and grave COVID-19 conditions, it is not used as a biomarker because of the inconsistency in results of a consolidated analysis. Hence, the present meta-analysis aimed to determine whether serum ChE activity decreases in COVID-19 patients, particularly in the context of disease severity [10-22] as well in the light of non-significant statistical changes in the enzyme activity reported by others [6,21].

MATERIALS AND METHODS

Study endorsement

The Scientific Review Board of the College of Pharmacy at the University of Duhok, Duhok, Kurdistan Region, Iraq has approved the present meta-analysis. This study was based on data obtained from published literature, and it did not require any direct contact with COVID-19 patients.

Study duration and location

We initiated the study and meta-analysis on October 15, 2024, and they continued until the January 30th, 2025 at the Department of Pharmacology, College of Pharmacy, University of Duhok, Duhok, Kurdistan Region, Iraq.

Search strategy

We searched the following data bases for the existing literature on COVID-19 and ChE activity: Pubmed, Lit Covid of the National Library of Medicine, Google Scholars, Science Direct, Directory of Open Access Journals and Web of Science My Research Assistant till January 30, 2025. Searching keywords for COVID-19 and ChE included "cholinesterase activity", "serum cholinesterase", "plasma cholinesterase", "blood cholinesterase", "erythrocyte cholinesterase", or " acetylcholinesterase" and "COVID-19"or "SARS-CoV-2", with refinements as needed to include COVID-19 and "biomarkers", "adverse outcome", "mortality", or "clinical laboratory tests" among others. We also searched the references of articles chosen for this meta-analysis. We did not have any language restriction on searching the literature. All authors shared in searching the above-mentioned data bases.

Criteria for inclusion

Studies of the present meta-analysis were subjected to identification, screening and inclusion according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [37] (Figure 1). Published reports were included in the meta-analysis, when the ChE activities in COVID-19 patients versus (vs.) their cohorts were presented as means ± Standard Deviation (SD) or Standard Error (SE). Using the searching keywords and phrases, initial literature identification showed 216 studies. After additional search, refinement and screening according to criteria set for inclusion and exclusion, and data extractability, the final ChE records qualified to be included in the meta-analysis were 17, which were extracted from the results (texts, figures or tables) of 13 studies regardless of the statistical outcomes (Figure 1, Table 1).

Criteria for exclusion

Studies that were subjected to exclusion included those that did not present blood ChE activities of COVID-19 patients, or those from which it was not possible to extract the mean and/or SD/SE. Theses and dissertations that were eventually published as scientific articles in journals were excluded. Any discrepancy in including and excluding studies, or obtaining ChE activity values, was resolved by consensus with the first author FKM.

Extraction of data

All the authors (FKM, GAMR and MAM) shared in searching the data bases for COVID-19 and ChE activity as outlined above. Table 1 presents 17 records of serum ChE activities (mean ± SD) of COVID-19 patients vs. their cohorts, which were extracted from 13 studies. Studies chosen for the present meta-analysis have used different analytical methods, and thus reported various enzymatic units. To facilitate the meta-analysis, the serum ChE activity values of COVID-19 patients were expressed as percentages of the mean ± SD relative to their respective cohorts mean values. We also used the online tool Meta-Accelerator [38] to obtain the mean/SD values of serum ChE activity from median and quartile range of values, or from mean and ranges according to methods of Wan et al. [39].

Meta-analysis and statistics

We applied the online tool of meta-analysis (Meta-Essentials, Version 1.5 of the Erasmus Research Institute of Management, Rotterdam, Netherlands) [40] to perform randomized effects size analysis using percentages of mean ± SD of serum ChE values of COVID-19 patients vs. their corresponding cohorts (Table 1). The main meta-analysis output was the forest plot to estimate the combined effect size (% serum ChE activity) with 95 % Confidence Intervals (CI) and % weight of individual effect sizes. The statistical analysis supportive of the forest plot included Z-test at p value of < 0.05 [40,41]. Heterogeneity analysis was assessed by calculating Higgins's I^2 value (< 25 %= low, 25 %-50 %= moderate, >75 %= high level of heterogeneity), and Cochrane Q-test at a p value of < 0.10 [40-43]. Another output of the Meta Essentials tool was analysis of publication bias by the funnel plot to visually examine effect size against the SE, and the quantitative Egger's regression test at $p<0.05$ [40,42,44]. Galbraith regression plot is an alternative output of the Meta Essentials tool [40] for the assessment of heterogeneity among

studies [45], as it depicts Z score against inverse SE to present homogeneity of data points within the lower and upper limits of the regression line.

Assessing study quality

Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of studies chosen for the present met-analysis [46]. Two reviewers independently scored each study according to three categorical criteria of NOS, namely, the selection (4 stars could be allocated), comparability (2 stars) and outcome (3 stars) with a maximum possible score being nine [46]. The scoring range was from 0 to 9, with quality assessment based on the following ratings: 0-2 indicates poor quality; 3-5 represents fair quality, and 6-9 signifies high quality. Any discrepancy during the scoring process was resolved with consensus and discussion. All reviewers approved final study NOS scores. NOS scores of the 13 studies were also evaluated by one-group proportions meta-analysis using the online software OpenMetaAanalyst. Additional statistical analyses such as the median and interquartile percentages were calculated by the statistical software Past5.0.2.

RESULTS

Extraction of serum ChE activity records

According to criteria set for including studies, the PRISMA flow chart (Figure 1) outlines the search results of studies that reported serum ChE of COVID-19 patients in comparison with their respective cohorts. Initially, we identified 216 studies, and after subjecting them carefully to selection criteria, the final number of ChE records included for the present meta-analysis was 17; they were extracted from texts, figures and tables of 13 studies, which were published between 2020 to end of 2024 (Figure 1, Table 1). These records consisted of serum ChE activity of COVID-19 patients (n=1402) versus their cohort counterparts (n=924).

Meta-analysis: Forest plot and statistical evaluation

Using the random effects model of the meta-analysis, the forest plot showed that the combined effect size depicting % serum ChE activity of COVID-19 patients vs. their cohorts was 77.21 % (SE= 2.48, 95 % C.I.= 71.96, 82.47) (Figure 2). The 22.79 % reduction in serum ChE activity of COVID-19 patients was highly significant at a *Z* value of 31.15, with a two-tailed p value <

0.0001. Weights of study records varied from 2.58 % to 13.08 % (Figure 2).

Analysis of heterogeneity

The data did not show heterogeneity as shown by the Cochrane *Q* statistical test (*Q*= 3.03, p=1), with corresponding zero values for heterogeneity indices (I^2, T^2, T). To this end, we did not conduct subgroup analysis because of the homogeneity of the data.

Table 1. Changes reported in serum cholinesterase (ChE) activity among COVID-19 patients compared to respective cohorts

Authors [reference]	**Code**	**ChE activity unit**	**Cohort/Control ChE**	**n**	**COVID-19 ChE**	**n**	**% of respective cohort (Mean±SD)**	**Notes**
Xiang et al. 2020 [10]	A	kU/L	6.611 ± 2.204	20	5.222 ± 1.829	8	78.990 ± 27.666	Severe vs. mild
Wang et al. 2021 [11]	B	U/L	7075 ± 1680	63	5082 ± 1566	37	71.830 ± 22.134	Death vs. survival
Bergamaschi et al., 2021 [12]	C	U/L	6970 ± 1995	80	5698 ± 2169	126	81.750 ± 31.119	Anemic vs. non-anemic
Nakajima et al. 2021 [13]	D	U/L	316.0 ± 140.81	11	227.33 ± 76.88	15	71.940 ± 24.329	Severe vs. mild-moderate
Zeng et. 2021 [14]	E	U/L	6886.67 ± 1516.96	357	5275.67 ± 1257.79	75	76.607 ± 18.264	Death vs. discharged
Bahloul et al. 2022 [15]	F	UI/L	6242 ± 1763	49	5471 ± 1723	47	87.648 ± 27.603	On admission, death vs. survival
Bahloul et al. 2022 [15]	G	UI/L	6059 ± 1628	49	4574 ± 1821	47	75.491 ± 30.054	Lowest ChE, death vs. survival
Bahloul et al. 2022 [16]	H	IU/L	6273 ± 1823	63	5138 ± 1655	74	81.907 ± 26.383	Death vs. survival
Bahloul et al. 2022 [16]	I	IU/L	5960 ± 2008	63	4091 ± 1111	74	68.641 ± 18.641	Nadir ChE, death vs. survival
Espeter et al., 2022 [17]	J	U/L	2970.67 ± 404.46	40	2238.0 ± 468.14	52	75.337 ± 15.759	Day 7, patients vs

								healthy controls
Sipahioglu et al.2022 [18]	K	ng/ml	21.9 ± 19.51	62	15.23 ± 7.77	85	69.543 ± 35.479	Severe pneumonia vs. mild-moderate pneumonia
Markuskova et al., 2023 [19]	L	ΔmO.D.	222.7 ± 83.1	21	147.6 ± 53.9	20	66.278 ± 24.203	Death vs. discharged (females)
Markuskova et al., 2023 [19]	M	ΔmO.D.	210.4 ± 67	25	124.4 ± 53.5	33	59.125 ± 25.428	Death vs. discharged (males)
Wang et al., 2023 [20]	N	U/L	5820.4 ± 2012.6	55	4503.8 ± 1662.1	102	77.380 ± 28.556	Severe vs. non-severe
Raouf et al. 2024 [21]	O	Δ pH/20 min	1.10 ± 0.20	50	1.16 ± 0.25	15	105.455 ± 22.727	Cytokine storm vs non-cytokine storm (males)
Raouf et al. 2024 [21]	P	Δ pH/20 min	1.08 ± 0.23	61	0.92 ± 0.23	18	85.185 ± 21.963	Cytokine storm vs non-cytokine storm (females)
Chen et al 2024 [22]	Q	U/L	5595.33 ± 1882.98	333	4645.67 ± 1368.34	96	83.028 ± 24.455	NIV requirement vs. none

NIV= Noninvasive ventilation

When ChE activity was reported as median and quartile range of values, or mean and ranges, the SD was calculated by using the online tool Meta-Accelerator [38] according to methods of Wan et al. [39].

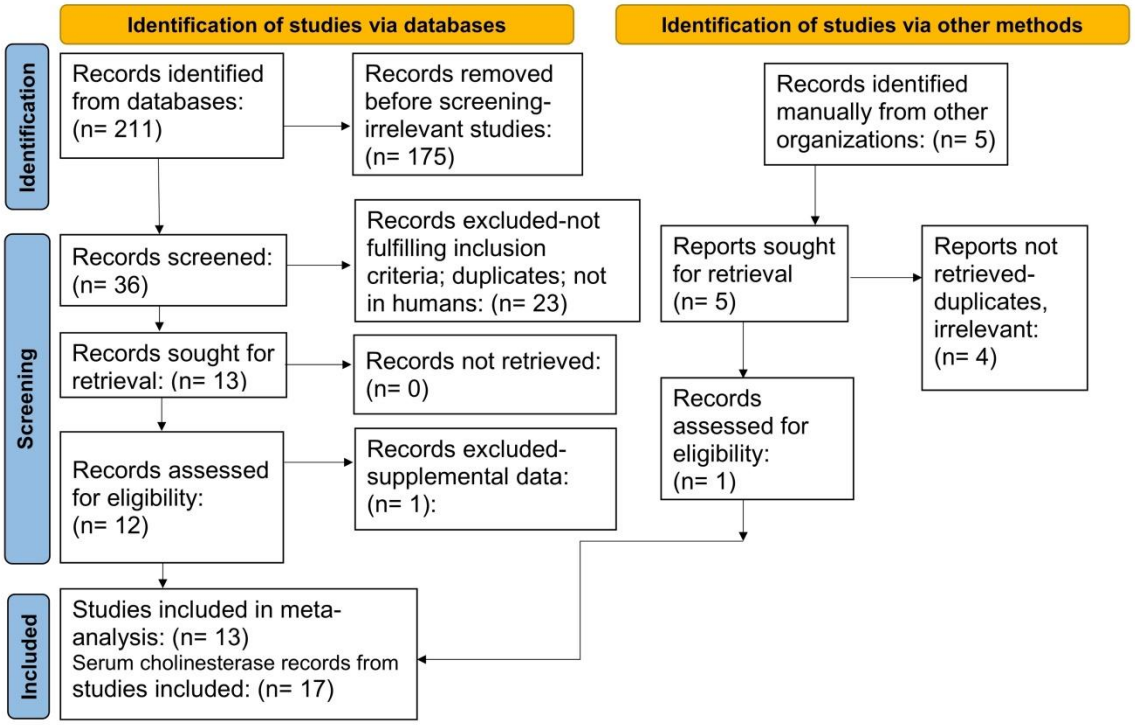

Figure 1. Selection of meta-analysis studies on serum cholinesterase activity in COVID-19 patients according to Application of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

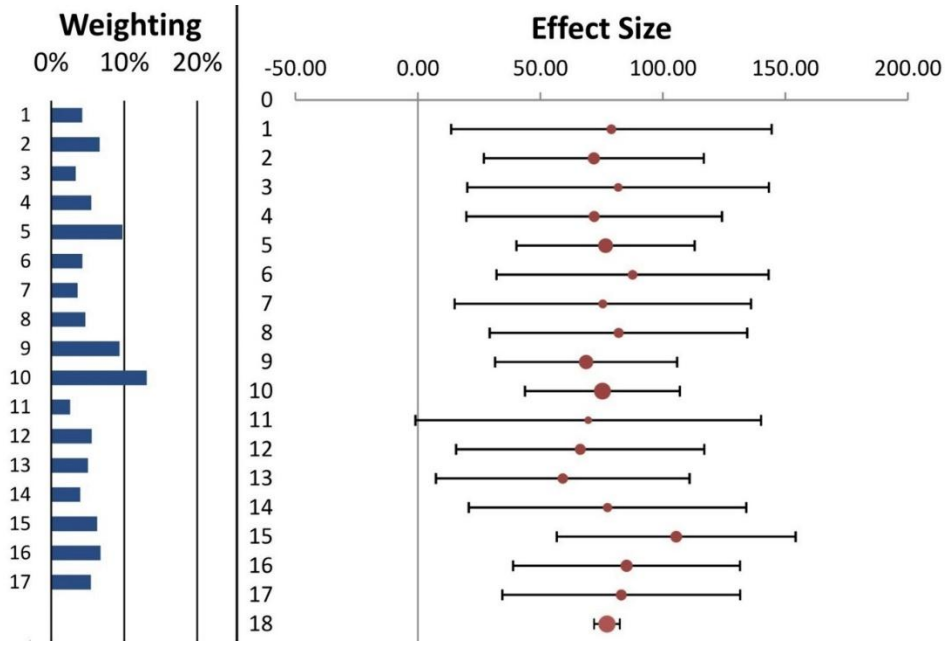

Figure 2. Forest plot of serum cholinesterase activities and their weightings in COVID-19 patients. Effect sizes were expressed as percentages of respective cohorts.

Publication bias

Visual inspection of the funnel plot (Figure 3), which was created using data points representing SE vs. effect size, revealed no evidence of publication bias. Additionally, the subsequent trim-and-fill analysis did not show imputed points. Egger's regression analysis, which showed non-significant results (t= 0.28, p= 0.782), also confirmed the absence of any publication bias. Further, the Galbraith regression analysis of Z scores plotted against their corresponding inverse SE values revealed that the effect size points were distributed uniformly (no heterogeneity) within the 95% lower and upper limits of the regression line, with no outliers (Figure 4). Notably, none of the points fell below the zero no-effect line (y= 0).

Quality of studies

The 13 studies were of high quality, as demonstrated by individual NOS scores ranging from 6 to 8, with a median score of 8 and 25 and 75 interquartile values of 8. Furthermore, one-group proportions meta-analysis of NOS scores of the 13 studies produced a standardized proportion mean (95 % CI) of 0.875

(0.816, 0.935) with no heterogeneity (Q= 2.443, df=12, p= 0.998; I^2 = 0 %) (Figure 5).

DISCUSSION

Among numerous clinical manifestations of COVID-19, patients have been found to suffer from hepatic dysfunction [4] with altered cholinergic anti-inflammatory pathways [24,26], neuronal complications [47,48] and potential risks of adverse neuronal responses to medications [21,49] and toxicants [50]. The role of butyryl ChE found in the plasma or serum is well documented in the context of biomonitoring exposure to ChE inhibitors such as organophosphates and carbamates [29,34-36], as well as in assessing systemic inflammatory responses involving the CNS, liver, cardiovascular and endocrine systems [28,30-33]. In the light of numerous reports indicating decreased serum ChE activity in patients with COVID-19 (compiled in Table 1), the present meta-analysis reports and ascertains reduced serum ChE (22.79 %) among these patients. It is therefore conceivable to further ascertain and support previous studies about the biomonitoring role of serum ChE as an added advantage in the assessment of COVID-19 risks and prognosis, particularly in hospitalized patients [10-22]. The observed reduction in serum ChE activity among COVID-19 patients is clinically significant and calls for further investigations.

Notably, reduced serum ChE activity in COVID-19 patients was identified clinically as a potential predictor of the severity of the disease and associated mortality risks in terms of cytokine storm and multi-organ failure [10,11,13-16,19,21]. As an additional support for this notion, a study has considered a reduction of 20 % or more in the enzyme activity a possible risk for poor outcome (death) in COVID-19 patients with cytokine storm [21]. Similarly, reduced serum ChE activity has been reported in COVID-19 patients with severe pneumonia [13,18,22], anemia [12], or elevated markers for inflammation such as C-reactive protein and interleukin-6 [13,19], particularly in terminally ill patients. This meta-analysis indicates that a reduction of approximately 20% in ChE activity could be a key marker for identifying patients at a greater risk of COVID-19 illness or death. These findings are in accordance with other studies, which have shown that patients who did not survive COVID-19 had consistently lower ChE levels compared to those who recovered. Regular monitoring of ChE activity could become

an essential tool for clinicians, helping them evaluate risk in hospitalized patients, and prioritize intensive care for individuals with critically low enzyme activity. While studies cited above support the predictive clinical value of reduced serum ChE activity, two others have indicated no changes in the enzyme activity during COVID-19 [6,21]. One of these studies did not show significant statistical changes in serum ChE activity in COVID-19 patients during admission, hospitalization, and at discharge as well as when compared with normal range of enzyme activity (mean and SD/SE were not extractable though), but without any cohorts to compare with [6]. Therefore, his study was not included in the present meta-analysis. While, the second study, did not find significant statistical change in serum ChE of male COVID-19 patients, in contrast to females [21]. Both gender results were included in the meta-analysis (Table 1). This discrepancy in serum ChE activity of COVID-19 patients could be ascribed among other factors to the severity of the condition, frequency of blood sampling, gender of the patient, comorbidities and duration of hospitalization. It was striking to note that the above-mentioned studies did not report erythrocyte ChE in COVID-19 patients, as this enzyme mirrors that of the CNS in response to biological, pharmacological and toxicological impacts [29,51,52].

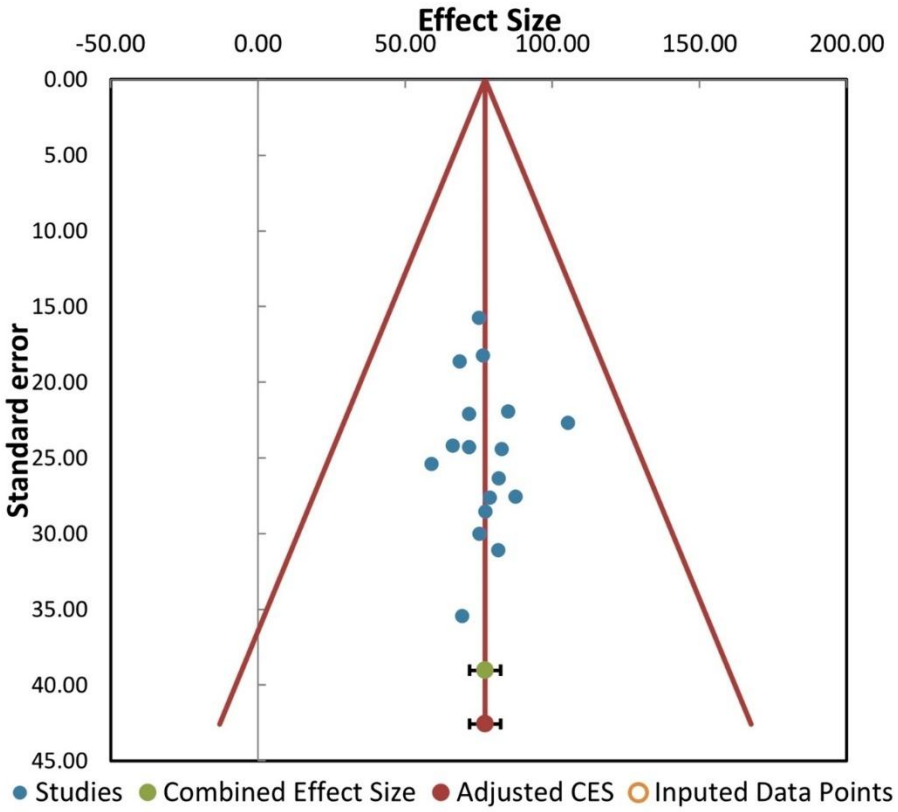

Figure 3. Funnel plot to visualize publication bias of serum cholinesterase activities in COVID-19 patients.

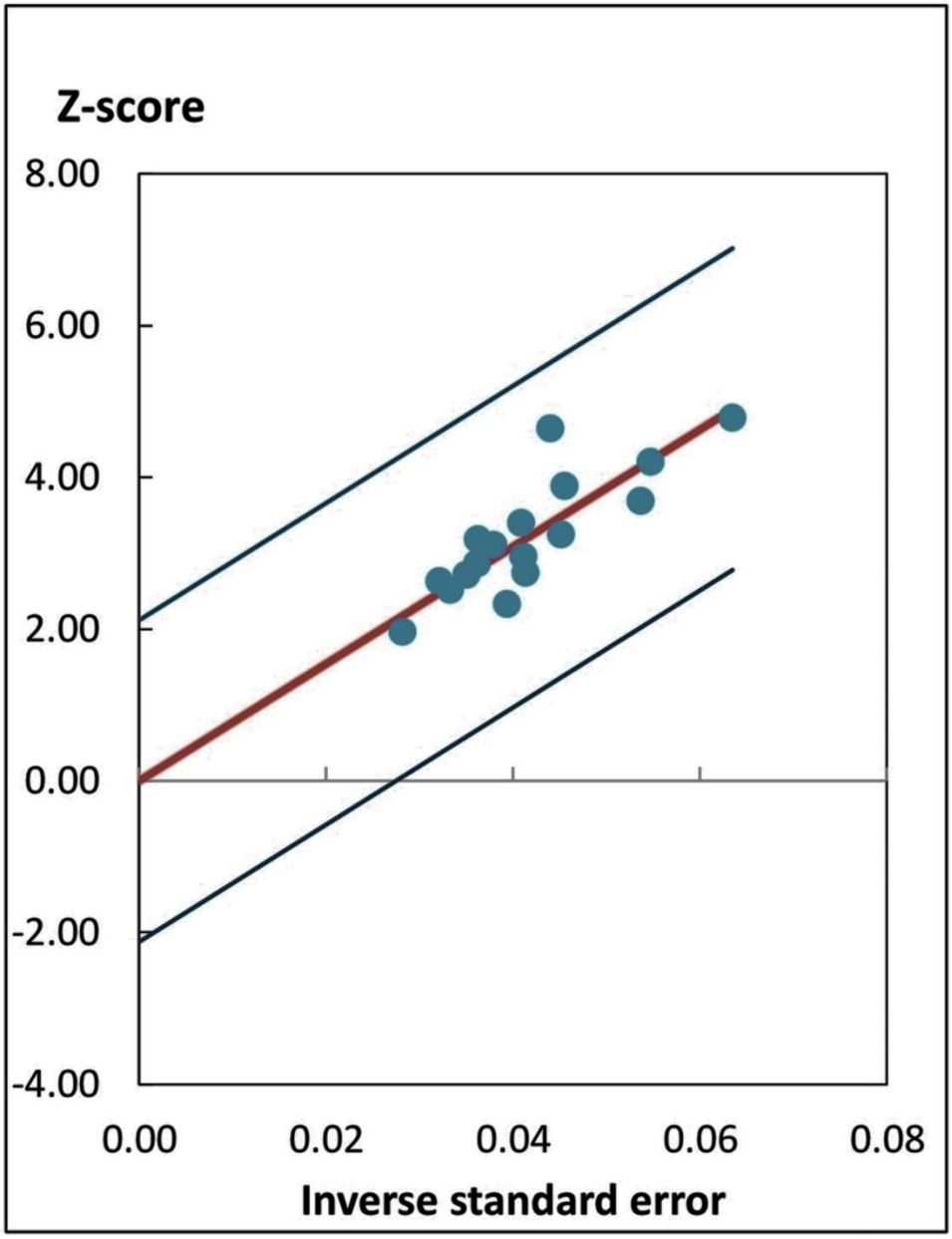

Figure 4. Galbraith regression distribution of serum cholinesterase activities in COVID-19 patients.

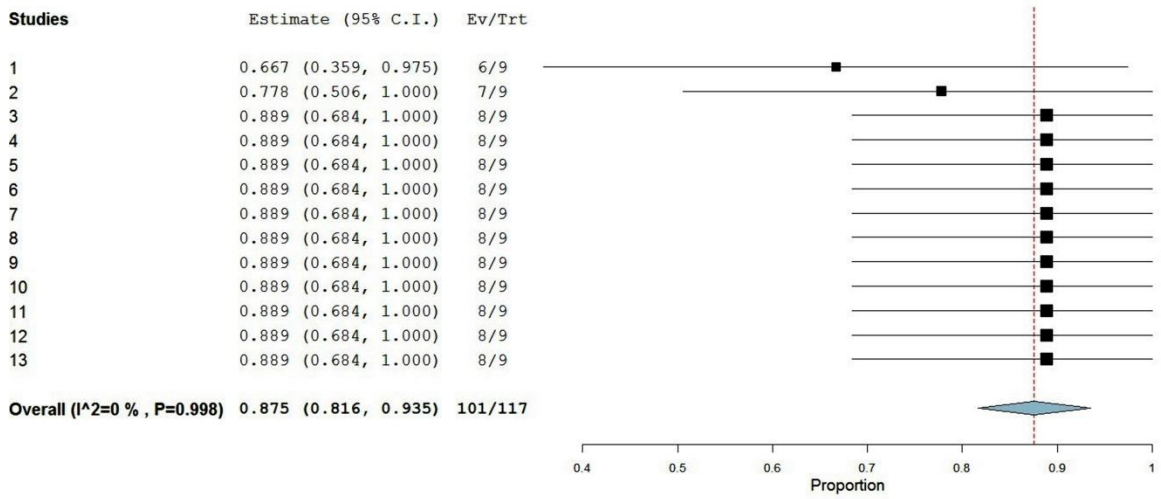

Figure 5. Forest plot of Newcastle–Ottawa Scale (NOS) scores of 13 studies shown in Table 1, consecutively, that reported serum cholinesterase activities in COVID-19 patients. NOS scores 6-9 indicate high quality studies.

The present meta-analysis unequivocally demonstrated reduced serum ChE activity in COVID-19 patients by analyzing 17 enzyme records of 13 high quality studies (Figure 2). The study records were homogenous as their weight varied only between 2.58% to 13.08 % with no heterogeneity as judged by the statistically insignificant Cochrane *Q* test (*Q*= 3.03, p=1), and zero values for the heterogeneity indices I^2, T^2, and T. This result of no-heterogeneity nullified the need for further subgroup analysis [40,44,45]. The present meta-analysis did not show any publication bias as judged by visual inspection of the funnel plot and by the insignificant Egger's regression analysis (t=0.28, p=0.782). Furthermore, the NOS scoring and the standardized proportion mean of 0.875 out of 9 indicated high quality studies. Further support for this notion, as well as the homogeneity of serum ChE records, is depicted by the Galbraith regression analysis, which indicated that the data points were homogeneous and contain no outliers.

The underlying mechanism(s) behind the reduced serum ChE activity is somewhat

unclear and requires additional investigations. Currently, suggested mechanisms of altered ChE activity in COVID-19 patients include, but are not limited to, enhanced capillary permeability seen in hepatitis and septic conditions [14-20], mediation of ChE inhibition by inflammatory biomarkers such as cytokines and disruption of immune response and cholinergic anti-inflammatory pathway [24,30]. The attachment of SARS-CoV-2 spike glycoprotein to nicotinic Acetyl-Choline Receptors (nAChRs) is an intriguing mechanism that is under considerable debate as it needs further exploration [24,26,53-56]. SARS-CoV-2 spike protein could act as a binding neurotoxins to nAChR in the neuronal system [26,53,54,56]. It has been postulated that the generation of small neurotoxic peptide (conotoxin) can bind the nAChRs instead of spike glycoproteins resulting in reduced serum ChE activity in conjunction with other systemic clinical changes [53-55,57]. Mirroring contoxins, a recent study identified toxin-like peptides in the plasma and as outputs in the urine and fecal samples from patients with COVID-19, stressing the need for further studies on the neurotoxic potential of these peptides and their possible connections to neurological disorders manifested in COVID-19 patients [58]. At a molecular enzymatic level, challenging the serum ChE activity of gravely ill COVID-19 patients suffering from the cytokine storm with the irreversible ChE inhibiting organophosphate dichlorvos showed alteration in enzyme inhibition kinetics (e.g. half-life of inhibition and the inhibition rate) [21]. Interestingly, viral sepsis that might also occur has been reported to be associated with lower butyryl ChE activity too [59].These findings potentially suggest possible changes in ChE functional aspects within the cholinergic neuronal pathways [24,26] as well as altered response to ChE inhibiting toxicants [21,50] or drugs used against dementia [60]. The responses of the ChE of COVID-19 patients to reversible ChE inhibitors such as carbamate insecticides or other CNS active medications are not known at present.

CONCLUSION

The meta-analysis of serum ChE activity in COVID-19 patients indicates that this enzyme is significantly reduced, particularly in those with severe outcomes and poor prognosis. This reduction may serve as a valuable prognostic biomarker for assessing COVID-19 severity and potential risk of death.

REFERENCES

[1]. Celik Tellioglu E, Oncul A, Diktas H, Atasoy Tahtasakal C, Aktas E, Genc Yaman I, Yildiz Sevgi D, Dokmetas I. The role of dynamic changes in hematologic and biochemical parameters in predicting mortality in Covid-19 patients. *Sisli Etfal Hastan Tip Bul*. 2024; 58(3): 371-80.

[2]. Ghoreshi ZA, Abbasi-Jorjandi M, Asadikaram G, Sharif-Zak M, Haddad MK, Afgar A, Arefinia N, Dabiri S, Rosen C. Time course of biochemical and metabolic parameters during and after COVID-19. *Curr Med Chem.* 2024.

[3]. Dos Santos Medeiros SMFR, Sousa Lino BMN, Perez VP, Sousa ESS, Campana EH, Miyajima F, Carvalho-Silva WHV, Dejani NN, de Sousa Fernandes MS, Yagin FH, Al-Hashem F, Elkholi SM, Alyami H, Souto FO. Predictive biomarkers of mortality in patients with severe COVID-19 hospitalized in intensive care unit. *Front Immunol.* 2024; 15: 1416715.

[4]. Mahmood N, Abdulghany Z. Parameter changes of COVID-19 incidence in Baghdad/Iraq in 2020: Infected and cured individuals: A retrospective single center study. *Health Biotechnol Biopharma.2024;* 7(4): 44-62.

[5]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395(10223): 497-506.

[6]. Nie XB, Shi BS, Zhang L, Niu WL, Xue T, Li LQ, Wei XY, Wang YD, Chen WD, Hou RF. Epidemiological features and dynamic changes in blood biochemical indices for COVID-19 patients in Hebi. *World J Clin Cases.* 2022; 10(8): 2404-19.

[7]. Letelier P, Encina N, Morales P, Riffo A, Silva H, Riquelme I, Guzmán N. Role of biochemical markers in the monitoring of COVID-19 patients. *J Med Biochem.* 2021; 40(2): 115-28.

[8]. Narvel H, Sayed A, Narvel N, Yakkali S, Katchi T. Do certain biomarkers predict adverse

outcomes in coronavirus disease 2019? *J Clin Med Res.* 2021; 13(4): 195-203.

[9]. Mussap M, Fanos V. Could metabolomics drive the fate of COVID-19 pandemic? A narrative review on lights and shadows. *Clin Chem Lab Med.* 2021; 59(12): 1891-1905.

[10]. Xiang J, Wen J, Yuan X, Xiong S, Zhou X, Liu C, Min X. Potential biochemical markers to identify severe cases among COVID-19 patients. *medRxiv.* 2020; 2020.03.19.20034447.

[11]. Wang H, Hu L, Bai GQ, Liu Z, Yu GG, Wang W, Sun L. [Serum C-reactive protein, cholinesterase and prealbumin are correlated with prognosis of severe coronavirus disease 2019 patients]. *Zhonghua Nei Ke Za Zhi.* 2021; 60(2): 134-38.

[12]. Bergamaschi G, Borrelli de Andreis F, Aronico N, Lenti MV, Barteselli C, Merli S, Pellegrino I, Coppola L, Cremonte EM, Croce G, Mordà F, Lapia F, Ferrari S, Ballesio A, Parodi A, Calabretta F, Ferrari MG, Fumoso F, Gentile A, Melazzini F, Di Sabatino A. Internal Medicine Covid-19 Collaborators. Anemia in patients with Covid-19: pathogenesis and clinical significance. *Clin Exp Med.* 2021; 21(2): 239-46.

[13]. Nakajima K, Abe T, Saji R, Ogawa F, Taniguchi H, Yamaguchi K, Sakai K, Nakagawa T, Matsumura R, Oi Y, Nishii M, Takeuchi I. Serum cholinesterase associated with COVID-19 pneumonia severity and mortality. *J Infect.* 2021; 82(2): 282-327.

[14]. Zeng HL, Lu QB, Yang Q, Wang X, Yue DY, Zhang LK, Li H, Liu W, Li HJ. Longitudinal profile of laboratory parameters and their application in the prediction for fatal outcome among patients infected with SARS-CoV-2: a retrospective cohort study. *Clin Infect Dis.* 2021; 72(4): 626-33.

[15]. Bahloul M, Kharrat S, Chtara K, Hafdhi M, Turki O, Baccouche N, Ammar R, Kallel N, Hsairi M, Chakroun-Walha O, Hamida CB, Chelly H, Mahfoudh KB, Karoui A, Karray H, Rekik N, Bouaziz M. Clinical characteristics and outcomes of critically ill COVID-19 patients in Sfax, Tunisia. *Acute Crit Care.* 2022; 37(1): 84-93.

[16]. Bahloul M, Kharrat S, Makni S, Baccouche N, Ammar R, Eleuch

A, Berrajah L, Chtourou A, Turki O, Ben Hamida C, Chelly H, Chtara K, Ayedi F, Bouaziz M. Prognostic value of serum cholinesterase activity in severe SARS-CoV-2-infected patients requiring intensive care unit admission. *Am J Trop Med Hyg.* 2022; 107(3): 534-39.

[17]. Espeter F, Künne D, Garczarek L, Kuhlmann H, Skarabis A, Zivkovic AR, Brenner T, Schmidt K. Critically ill COVID-19 patients show reduced point of care-measured butyrylcholinesterase activity-a prospective, monocentric observational study. *Diagnostics* (Basel). 2022; 12(9): 2150.

[18]. Sipahioglu H, Esmaoglu A, Kiris A, Dursun ZB, Kuzuguden S, Cavus MA, Artan C. Does serum butyrylcholinesterase level determine the severity and mortality of COVID-19 pneumonia? prospective study. *Front Med*. 2022; 9: 940533.

[19]. Markuskova L, Javorova Rihova Z, Fazekas T, Martinkovicova A, Havrisko M, Dingova D, Solavova M, Rabarova D, Hrabovska A. Serum butyrylcholinesterase as a marker of COVID-19 mortality: results of the monocentric prospective observational study. *Chem Biol Interact.* 2023; 381:110557.

[20]. Wang L, Liu T, Yue H, Zhang J, Sheng Q, Wu L, Wang X, Zhang M, Wang J, Wang J, Yu W. Clinical characteristics and high risk factors of patients with Omicron variant strain infection in Hebei, China. *Front Cell Infect Microbiol*. 2023; 13: 1294904.

[21]. Raouf GAM, Mohammad FK, Merza MA. The potential risk of reduced serum cholinesterase activity in COVID-19 patients suffering from cytokine storm. *Cureus.* 2024; 16(5): 60417.

[22]. Chen Z, Zha L, Hu B, Xu B, Zuo L, Yang J, Chu Z, Ma L, Hu F. Use of the serum level of cholinesterase as a prognostic marker of nonfatal clinical outcomes in patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease. *Can Respir J.* 2024; 2024: 6038771.

[23]. Fu Y, Xu X, Du J, Huang T, Shi J, Song G, Gu Q, Shen H, Wang S. Using machine learning algorithms based on patient admission laboratory parameters to

predict adverse outcomes in COVID-19 patients. *Heliyon.* 2024; 10(9): 29981.

[24]. Kopańska M, Batoryna M, Bartman P, Szczygielski J, Banaś-Ząbczyk A. Disorders of the cholinergic system in COVID-19 era-a review of the latest research. *Int J Mol Sci.* 2022; 23(2): 672.

[25]. Kattner S, Müller J, Glanz K, Manoochehri M, Sylvester C, Vainshtein Y, Berger MM, Brenner T, Sohn K. Identification of two early blood biomarkers ACHE and CLEC12A for improved risk stratification of critically ill COVID-19 patients. *Sci Rep.* 2023; 13(1): 4388.

[26]. Nadwa EH, Al-Kuraishy HM, Al-Gareeb AI, Elekhnawy E, Albogami SM, Alorabi M, Batiha GE, De Waard M. Cholinergic dysfunction in COVID-19: frantic search and hoping for the best. *Naunyn Schmiedebergs Arch Pharmacol.* 2023; 396(3): 453-68.

[27]. Sridhar GR, Lakshmi G. Influence of butyrylcholinesterase on the course of COVID-19. *Biomed Rev.* 2021; 32: 37-46.

[28]. Santarpia L, Grandone I, Contaldo F, Pasanisi F. Butyrylcholinesterase as a prognostic marker: a review of the literature. *J Cachexia Sarcopenia Muscle.* 2013; 4(1): 31-39.

[29]. Wilson BW. Cholinesterase inhibition. In: Wexler P (ed.). Encyclopedia of Toxicology. 3rd ed. Amsterdam; Elsevier: 2014, 942-51.

[30]. Sridhar GR, Gumpeny L. Emerging significance of butyrylcholinesterase. *World J Exp Med.* 2024; 14(1): 87202.

[31]. Abbas M, Abbas Z. Serum cholinesterase: a predictive biomarker of hepatic reserves in chronic hepatitis D. *World J Hepatol.* 2017; 9(22): 967-72.

[32]. Zhang YN, Xiao P, Zhang BF. The association between preoperative serum cholinesterase and all-cause mortality in geriatric patients with hip fractures: a cohort study of 2387 patients. *Perioper Med*. 2024; 13(1): 82.

[33]. Mohammad FK, Mohammed AA, Garmavy HM, Rashid HM. Association of reduced maternal plasma cholinesterase activity with preeclampsia: a meta-analysis. *Cureus.* 2023; 15(10): 47220.

[34]. Chen Y, Yang Z, Nian B, Yu C, Maimaiti D, Chai M, Yang X, Zang X, Xu D. Mechanisms of neurotoxicity of organophosphate pesticides and their relation to neurological disorders. *Neuropsychiatr Dis Treat.* 2024; 20: 2237-54.

[35]. Sepahi S, Gerayli S, Delirrad M, Taghavizadeh Yazdi ME, Zare-Zardini H, Bushehri B, Ghorani-Azam A. Biochemical responses as early and reliable biomarkers of organophosphate and carbamate pesticides intoxication: a systematic literature review. *J Biochem Mol Toxicol.* 2023; 37(3): 23285.

[36]. Mohammad FK, Mohammed AA, Odisho SK. Changes of blood cholinesterase activities among pesticides-exposed agricultural workers in Iraq: a meta-analysis. *Toxicol Rep.* 2024; 13: 101830.

[37]. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* 2021; 372: 160.

[38]. Abbas A, Hefnawy MT, Negida A. Meta-analysis accelerator: a comprehensive tool for statistical data conversion in systematic reviews with meta-analysis. *BMC Med Res Methodol.* 2024; 24(1): 243.

[39]. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* 2014; 14: 135.

[40]. Suurmond R, van Rhee H, Hak T. Introduction, comparison, and validation of Meta-Essentials: A free and simple tool for meta-analysis. *Res Synth Methods.* 2017; 8(4): 537-53.

[41]. Buccheri S, Sodeck GH, Capodanno D. Statistical primer: methodology and reporting of meta-analyses. *Eur J Cardiothorac Surg.* 2018; 53(4): 708-13.

[42]. Nakagawa S, Noble DW, Senior AM, Lagisz M. Meta-evaluation of meta-analysis: ten

appraisal questions for biologists. *BMC Biol.* 2017; 15(1):18.

[43]. Clephas PRD, Heesen M. Interpretation of meta-analyses. *Interv Pain Med.* 2022; 1: 100120.

[44]. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics.* 2018; 74(3):785-94.

[45]. Ballarini NM, Chiu YD, König F, Posch M, Jaki T. A critical review of graphics for subgroup analyses in clinical trials. *Pharm Stat.* 2020; 19(5): 541-60.

[46]. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Accessed*, 2024.

[47]. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020; 77(6): 683-90.

[48]. Bayat AH, Azimi H, Hassani Moghaddam M, Ebrahimi V, Fathi M, Vakili K, Mahmoudiasl GR, Forouzesh M, Boroujeni ME, Nariman Z, Abbaszadeh HA, Aryan A, Aliaghaei A, Abdollahifar MA. COVID-19 causes neuronal degeneration and reduces neurogenesis in human hippocampus. *Apoptosis.* 2022; 27(11-12): 852-68.

[49]. Kumar D, Trivedi N. Disease-drug and drug-drug interaction in COVID-19: risk and assessment. *Biomed Pharmacother.* 2021; 139: 111642.

[50]. Rajak P, Roy S, Podder S, Dutta M, Sarkar S, Ganguly A, Mandi M, Dutta A, Nanda S, Khatun S. Synergistic action of organophosphates and COVID-19 on inflammation, oxidative stress, and renin-angiotensin system can amplify the risk of cardiovascular maladies. *Toxicol Appl Pharmacol.* 2022; 456: 116267.

[51]. Assis CRD, Linhares AG, Cabrera MP, Oliveira VM, Silva KCC, Marcuschi M, Maciel Carvalho EVM, Bezerra RS, Carvalho LB Jr. Erythrocyte acetylcholinesterase as biomarker of pesticide exposure: new and forgotten insights. Environ Sci Pollut Res Int. 2018;25(19):18364-18376.

[52]. Strelitz J, Engel LS, Keifer MC. Blood acetylcholinesterase and butyrylcholinesterase as biomarkers of cholinesterase depression among pesticide handlers. *Occup Environ Med.* 2014; 71(12): 842-47.

[53]. Cafiero C, Micera A, Re A, Postiglione L, Cacciamani A, Schiavone B, Benincasa G, Palmirotta R. Could small neurotoxins-peptides be expressed during SARS-CoV-2 infection? *Curr Genomics.* 2021; 22(8): 557-63.

[54]. Cafiero C, Micera A, Re A, Schiavone B, Benincasa G, Palmirotta R. Comment on Kopańska et al. Disorders of the cholinergic system in COVID-19 era-a review of the latest research. *Int J Mol Sci.* 2022; 23(5): 2818.

[55]. Kopańska M, Szczygielski J, Bartman P, Banaś-Ząbczyk A. Reply to Cafiero et al. Comment on "Kopańska et al. Disorders of the cholinergic system in COVID-19 era-a review of the latest research. *Int. J. Mol. Sci.* 2022, 23, 672". *Int J Mol Sci.* 2022; 23(5): 2822.

[56]. O'Brien BCV, Weber L, Hueffer K, Weltzin MM. SARS-CoV-2 spike ectodomain targets α7 nicotinic acetylcholine receptors. *J Biol Chem.* 2023; 299(5): 104707.

[57]. Shahcheraghi SH, Hamidfar M, Heidari F, Shahmohammadi S, Akhondimeybodi Z, Fallah T, Aliakbarzade Yazdani Y. Evaluation of ESR, CRP, LDH, CPK, D-Dimer, BS and FBS levels in hospitalized COVID-19 patients with mucormycosis. *Health Biotechnol Biopharma.* 2022; 6(2): 43-51.

[58]. Brogna C, Cristoni S, Petrillo M, Querci M, Piazza O, Van den Eede G. Toxin-like peptides in plasma, urine and faecal samples from COVID-19 patients. *F1000Res.* 2021; 10: 550.

[59]. Neu C, Esper Treml R, Baumbach P, Engelmann M, Gebhardt C, Götze J, Coldewey SM. Cholinesterase activities and sepsis-associated encephalopathy in viral versus nonviral sepsis. *Can J Anaesth.* 2024; 71(3): 378-89.

[60]. Simões JLB, Sobierai LD, Leal IF, Dos Santos MVR, Coiado JV, Bagatini MD. Action of the purinergic and cholinergic anti-inflammatory pathways on oxidative stress in patients with

Alzheimer's disease in the context of the COVID-19 pandemic. *Neuroscience.* 2023; 512: 110-32.