Evaluation of Circulating Gelsolin in Iraqi Patients with COVID-19 as Early Predictor Marker of Disease Severity

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has rapidly become a global health issue. The current coronavirus disease (COVID-19) epidemic necessitates the rapid development of therapies that enhance the outcomes of persons suffering from severe illness. To enhance the treatment of COVID-19 patients, early and effective indicators of disease severity are required. Gelsolin (GSN) is a circulating protein that is promptly consumed by extreme tissue injury and causes actin filament depolymerization, blocking downstream inflammatory processes.

Objective: The aim of the presented work is to study if serum gelsolin levels had any relationship with Covid-19 infection and severity indicator in order to revealed if serum gelsolin could be utilized as a disease predictor marker severity.

Materials and Methods: A case- control study was conducted with 90 Covid-19 patients and 90 healthy volunteers as the control group (with age ranged between 45-60 years) The patients were obtained from Al-Amal hospitals in Najaf city, Iraq, between Nov., 2020 and June, 2021. COVID-19 patients were separated into two groups based on the degree of their condition, which are mild/moderate disease and severe disease. Blood samples were taken and all demographic and clinical data of the sick and healthy groups were recorded. GSN levels in the blood were determined using enzyme-linked immunosorbent assays (ELISA). Colorimetric techniques were used to determine the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and albumin levels. ichroma assessed serum ferritin and D-dimer, and CBC by spincell3. Ran a statistical analysis to noticed if they were linked to illness severity.

Results: GSN levels were considerably lower in some patient groups. However, as compared to the mild/moderate instance of patients, the level of GSN was considerably lower in the mild and severe COVID-19 groups. Patients (95.45 ± 35.36) had considerably lower serum (GSN) levels than mild/moderate patients (172.32 ± 44.76) while. Healthy group (289.52 ± 71.33) (P 0.001). suggesting that it is an independent predictor of coronavirus infection Serum (GSN) levels were significantly and adversely connected with Age (year), SBP mmHg ferritin, (AST, ALT, ALP activity levels), and D-dimer levels, whereas GSN levels were significantly and positively correlated with Lymph percent levels.

Conclusion: In conclusion, serum GSN concentration was lower in COVID-19 patients compared to the mild/moderate case group and healthy controls. Extensive tissue injury depletes and quickly consumes serum gelsolin (GSN), a naturally occurring, abundant circulating protein. The finding that considerable depletion is linked to eventual bad outcomes in a variety of clinical situations in severe inflammatory diseases holds hope for preventing lung harm and other injury organs.

Keywords: COVID-19 patients, Serum Gelsolin, Severity

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) virus, poses an unprecedented threat to global public health, and a viable treatment regimen is still elusive [1]. Although the majority of Covid-19 individuals have a benign clinical history, a small percentage of them experience serious clinical consequences that can lead to death. Covid-19 and its consequences have now spread to many nations throughout the globe, and it has become a pandemic illness [2].

Most COVID-19 patients experience moderate symptoms such as a dry cough, sore throat, lethargy, and fever. The majority of cases have resolved on their own. Nevertheless, several patients died as a result of catastrophic consequences such organ failure, septic shock, and Acute Respiratory Distress Syndrome (ARDS). The introduction and spread of SARS-CoV-2, a new coronavirus, has resulted in a pandemic that has had a significant impact on world health [3].

The immunological aspects linked to illness severity or protection are still unclear, and whether the antibody titter is a measure for protective immunity against SARS-CoV-2 is a point of contention [4]. Patients who have

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recovered from infection have a strong adaptive immune response, including spike-specific neutralizing antibodies, memory B cells, and circulating follicular helper T cells [5]. Gelsolin (GSN), a common protein in healthy people's blood, is functionally different from its cytoplasmic isoform, which regulates inflammatory homeostasis [6]. There are two isoforms of this protein. A cytoplasmic GSN is physically identical to an intracellular GSN, but it has distinct biological activities and is a circulating isoform. The DE polymerization of actin filaments is induced by Gelsolin [7], and [8].

This would prevent actin filaments from stimulating inflammatory responses downstream. Gelsolin levels tend to drop in cases of acute injury or inflammation. Gelsolin is an anti-inflammatory modulator that has a role in the immune response [9]. Depletion of gelsolin has also been connected to the release of inflammatory mediators. GSN scavenges leaky intracellular contents, localizes inflammatory signals, and improves immune clearance of microbial and host-derived toxins via pleiotropic processes [7]. GSN digests debris revealed by damaged cells by cutting actin filaments, which inhibits host defenses. It also helps macrophages take in and destroy bacteria.

In catastrophic infectious and non-infectious situations such as bacterial sepsis, acute trauma, burns, oxygen toxicity, and malaria, circulating GSN is consumed, resulting in widespread tissue harm [10]. Gelsolin levels tend to drop in cases of acute injury or inflammation [11]. Correlative investigations of patients who have had a variety of common injuries have found a consistent link between the severity of the triggering insult, the extent of the resulting GSN drop, and the chance of death or organ failure. Patients with community-acquired pneumonia (CAP) who present with the lowest GSN levels had the poorest prognosis [12] and [13].

Our final objective is to see if serum gelsolin has a relationship with COVID-19 activity and severity indices, in order to reveal if serum gelsolin may be utilized as a disease severity prediction marker in COVID-19 patients.

2. Materials and Methods

After receiving approval from the Iraqi Ministry of Health and Environment's Ethics Committee, a case-control study was conducted on COVID-19 patients admitted to COVID-19 care units in Al-Amal hospitals in AL-Najaf, Iraq, between Nov., 2020 and June, 2021. All participants gave informed consent before the study began. Patients with COVID-19 had a chest X-ray or chest tomography (CT) scan to confirm positive results of the Real time reverse transcription polymerase chain reaction test (RT-PCR) for SARS-Cov-2 detection in throat or nasal swab specimens. A total of 180 volunteers were involved in the study: 90 COVID-19 patients (with age min.-max. range 45-60 years; 53 males and 37 females) were divided into two disease severity categories according to the World Health Organization (58) mild/moderate disease, (32) severe disease to compare with 90 apparently healthy volunteers comparable with patients group in ages and sex as a control group.

This study excluded Patients with diabetes, cardiovascular disease, inflammations, and systemic immune disease patients that were on long-term oral corticosteroid or who had a history of vacuities connective tissue disease, Cancer and renal disease patients, smokers, thyroid gland disease, and pregnant women to prevent the impact of other comorbidities.

Venous blood samples were taken from both the patients and the controls. Two tubes were used to separate blood samples. 3ml allowed clotting at room temperature for 10-15 minutes before centrifugation at (3000 x g) for 10 minutes to get serum. The serum samples were then split into tubes and kept at 80°C until analysis time. Complete blood count (CBC) was obtained using an auto hematology analyzer (linear, Spain) with the remaining blood (2 ml). Enzyme linked immune sorbent assays were used to detect the concentration of Gelsolin kit assays in serum samples by ELISA technique (Melsin, China). Colorimetric techniques kits were also used to test the activity of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) activity levels, and levels of creatinine (Cr), blood urea nitrogen (BUN) by (Cobas, Roche). Fluorescence immunoassay was used to quantify serum ferritin and D-dimer levels (ichromaTM).

A patient was considered to have severe COVID-19 if he or she met any of the following [14]:

Respiratory distraction (≥ 30 /min)

Resting oxygen saturated ≤ 90%

Arterial oxygen (PaO_2) / fraction of inspired oxygen ≤ 300 mmHg.

Respiratory failure requiring mechanical ventilation and require intensive care unit car. and patient dead considered as non-survived.

This study was authorized by local medical ethics, and all participants gave their informed permission prior to the start of the study. The patients were registered and given a file with information such as their name, age, sex, case, weight, and height.

The Statistical Package of Social Science (SPSS ver. 21) and Graph Pad Prism ver.5 were used to conduct the statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD). For variables with equal and unequal frequencies, the paired t-test and independent t-test were used to determine significant differences. Standardized Pearson coefficients were used to analyze univariate relationships. Less than 0.05 and 0.01 p values were judged statistically and highly statistically significant, respectively.

3. Results and Discussion

Demographic Characteristics of Patients and Control groups

The demographic and clinical features of the study groups, which include (mean ± SD) of the 90 patients recruited in this study to compared with 90 healthy volunteers. Patients groups divided according to COVID-19 severity to two sub- groups as shown in table (1)

Table (1): Demographic and clinical characteristics of the patient's categories and control groups				
Parameters	COVID-19 Groups		Healthy group Mean ± SD	P. value
	Severe Mean ± SD	Mild / moderate Mean ± SD		
No. of (Male / Female)	(20/12)	(33/25)	(54/36)	.....
Age, (year)	57.11 ± 4.64	57.20 ± 5.21	57.26 ± 5.76	A0.95B 0.93 C 0.95
BMI, (Kg/m^2)	27.87 ± 3.24	26.60 ± 3.43	24.81 ± 3.43	A 0.04 B 0.001 C 0.05
SBP ,(mmHg)	136.34 ± 22.33	132.33 ±10.44	130.83 ±6.52	A 0.06 B 0.82 C 0.76
DBP, (mmHg)	79.94 ± 15.69	80.33 ± 4.9	80.83 ± 5.09	A 0.85 B 0.70 C 0.98
SPO_2	89.71 ± 1.69	95.89 ± 3.693	99.57 ± 0.019	A 0.001 B 0.0001 C 0.01
Lymph.%	10.26 ± 1.62	10.79 ±5.87	23.26 ± 5.62	A 0.73 B 0.0001 C 0.0001
Neutro.%	85.26 ±11.62	76.43 ± 10.82	44.48 ± 10.18	A 0.01 B 0.001 C 0.001
NLR	8.06±1.62	7.21±2.12	2.15±0.53	A 0.06 B 0.0001 C 0.0001
Urea, (mg/dL)	20.10 ± 3.58	11.39 ± 6.08	3.73 ± 0.54	A 0.05 B 0.001 C 0.001
Creatinine, (mg/dL)	0.96±0.42	0.79±0.02	0.78±0.04	A 0.001 B 0.001 C 0.65
ALT activity, (IU/L)	28.00 ± 12.409	22.73±10.18	2.69± 17.79	A 0.05 B 0.001 C 0.03
AST activity, (IU/L)	43.70 ± 18.49	35.73 ± 14.59	25.60 ± 4.40	A 0.01 B 0.0001 C 0.01
ALP activity, (U/L)	158.37 ± 92.42	103.72 ± 93.46	82.93 ± 8.09	A 0.001 B 0.001 C 0.001
D-Dimer, (ng/mL)	5573.02 ± 2722.22	3868.03 ± 2223.61	206.14 ± 97.07	A 0.001 B 0.0001 C 0.0001
Ferritin, (ng/mL)	1338.64 ± 686.43	1097.17 ± 628.11	105.92 ± 34.73	A 0.001 B 0.0001 C 0.0001
Gelsolin, (pg/mL)	95.45 ± 35.36	172.32 ± 44.76	289.52 ± 71.33	A 0.0001 B 0.0001 C0.0001

Data represented as Mean ± SD: standard deviation, BMI: body mass index, SBP: Systolic blood pressure, DBS diastolic blood pressure, NLR: Neutrophil% to Lymphocyte % ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, A= p. value (severe cases +mild/moderate cases), B= p. value (Severe cases + healthy group) and C= p. value (mild/moderate cases + healthy group).

The patients' mean age according to severity of COVID-19 (57.11 ± 4.64 years; 58.20 ± 5.21 years) none significantly when compared with control groups age (57.26 ± 5.76 years). COVID-19 patients with severe illness have considerably higher mean BMI than patients with mild/moderate disease (27.87 ± 3.24 and 26.60 ± 3.43 kg/m^2, respectively; p = 0.04). In reality, more than half of mild/moderate cases were categorized as being under the age of 50, whereas severe and critical cases were classified as being above 50. In the two disease severity categories, sex distributions (males more than females). The data of serum ferritin, D-Dimer levels and ALP, ALT, AST activity levels were significantly higher (1.33864 ± 686843), (5573.02 ± 2722.22), (158.37 ± 92.42), (28.00 ± 12.409),and (43.70 ± 18.49), and respectively. The level of serum gelsolin in the serum of severe patients was lower than that of mild/moderate patients (P < 0.0001), according to laboratory data from 90 patients. Furthermore, in covid-19 patients, most coagulation indicators, including D-dimer, were considerably elevated, particularly in severe illness situations.

In table (2) shown a significant correlation between serum GSN levels with SpO2 neutrophils%, AST, ALT, ALP, D-dimer,and ferritin levels in COVID-19 patients group

Table (2): Correlation between serum GSN Level with clinical Parameters in COVID-19 patients group		
Parameters	r-	P. value
Age, (year)	0.061	0.164
BMI, kg/m^2	0.027	0.365
SBP, mmHg	-0.14	0.071
DBP, mmHg	-0.084	0.119
SPO_2	-0.59	0.0001
Lymph.%	0.11	0.238
Neutro.%	-0.39	0.012
N/L Ratio	-0.23	0.074
Urea, mg/dl	-0.018	0.559
Creatinine, mg/dl	-0.001	0.908
ALT activity, IU/L	-0.46	0.001
AST activity, IU/L	-0.42	0.001
ALP activity, IU/L	.-0.38	0.01
D-Dimer, ng/ml	-0.35	0.02
Ferritin, ng/ml	-0.47	0.001

SARS-CoV-2 infections are lethal because they produce an overactive immune response that results in lung inflammation +/- a cytokine storm. ARDS may cause patients to die or they may develop severe lung fibrosis. The mortality rate for COVID-19 patients aged above 60 years hospitalized patients. [15, 16], and.

Certain immunosuppressive diseases, on the other hand, might limit vaccination response and aggravate illness outcomes. Even when not receiving chemotherapy, patients with B-cell CLL react poorly to SARS-CoV-2 vaccinations and have poor outcomes after COVID-19 infections. [17].

A targeted inflammatory response is the first line of defense for the host against infection. Excessive local and systemic inflammation, on the other hand, might harm essential organs both close and distant from the infection site. Acute inflammation's stringent localization and eventual resolution are complicated processes whose control is vital but yet poorly understood [18],and [19].

GSN has at least three functions that help to control inflammatory processes. The first is debriding viscous content leaked from disrupted cells by scavenging actin and other danger-associated molecular patterns (DAMPs) at the site of injury; the second is increasing macrophage uptake and killing of microbial pathogens; and the third is complexing proinflammatory mediators, dampening their local effects, and preventing their systemic spread to uninvolved organs as the precipitating insult subsides. As the acute injury heals, pGSN supports the inflammatory process' resolution and reduces the harm that results [7],and [20].

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Gelsolin can bind pro-inflammatory lipid and peptide mediators to promote local inflammatory injury resolution and prevent it from spreading to uninvolved organs; as a result GSN enhances the early innate immune response to clear pathogens at the infected site while tempering the harmful consequences of excessively prolonged or distant inflammation [7].

Plasma gelsolin (pGSN) is a common blood protein that enhances human defenses against microbial infections while also reducing collateral damage caused by excessive inflammation. It's an important part of innate immunity that gets depleted quickly during acute illnesses. Regardless of the cause of pneumonia or sepsis, recombinant human GSN confers a survival benefit [21]. By inactivating inflammatory mediators that escape the local infection site, GSN protects distant organs. Actin sequesters pGSN at local infection sites, lowering circulating levels. The severity of tissue injury is reflected in the extent to which pGSN levels decline [22].

Extensive illness (bacterial or viral) and significant injuries like major trauma or extensive burns can lower levels by up to 90% in Patients at risk for higher mortality as a result of this depletion. [23].

4. Conclusion

Extensive tissue injury depletes and quickly consumes serum gelsolin (GSN), a naturally occurring, abundant circulating protein. The finding that considerable depletion is linked to eventual bad outcomes in a variety of clinical situations in severe inflammatory diseases holds hope for preventing lung harm. In a variety of clinical situations, significant depletion is related to later adverse results, and it should be investigated as a potential immune modulatory treatment for advanced Covid-19 pneumonia and treated as a new therapeutic drug.

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6. Declaration of interests

The authors declare no conflict of interests.

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