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Assessing Serum Asprosin Levels among Iraqi Individuals Diagnosed with Acromegaly

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Abstract

Objective: Asprosin (ASP) is a modern adipokine produced from white adipose tissue that is linked to metabolic disorders such as obesity and diabetes. Acromegalic syndrome results from excessive pituitary growth hormone (GH) secretion, leading to increased insulin-like growth factor-1 (IGF-1) production, usually due to a pituitary adenoma. The serum ASP levels were higher in acromegaly patients (AC-PTs) than in healthy controls. The aim of the study was to explore ASP levels in AC-PTs compared with healthy controls, considering gender, diabetes status, treatment duration, and hypertension.

Materials and Methods: Fifty AC-PTs with different body mass index, sex, age, diabetes, and blood pressure were enrolled in this study. IGF-1, GH, and fasting blood glucose (FBG) levels were measured alongside 30 healthy controls. In addition, enzyme-linked immunoassay (ELISA) was used to measure ASP.

Results: There was no significant difference in ASP levels between AC-PTs and healthy controls ($p>0.05$). Moreover, the current study showed no statistically significant difference in ASP levels among the subgroups categorized according to the patient's gender, diabetes status, hypertension, and treatment course.

Conclusion: ASP levels revealed no difference between Iraqi AC-PTs and control group; ASP is not affected by hormonal changes that are typically associated with acromegaly.

Keywords Acromegaly · Adipokine · Asprosin · GH · IGF-1 · Pituitary Adenoma

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INTRODUCTION

Acromegaly is a slowly developing disorder resulting from the raised secretion of insulin-like growth factor-I (IGF-I) and growth hormone (GH). Acromegaly patients (AC-PTs) are commonly induced by a growth hormone-secreting pituitary adenoma, which causes the extra production of IGF-1 (1). It may result in musculoskeletal, endocrine, and metabolic comorbidities. The global annual incidence is up to 13 cases per 100,000 people (2). Premature diagnosis and cure are important to relieve the extra mortality linked with AC-PTs (3, 4). Correspondingly, AC-PTs are personified by unproportioned growth of the organs, tissues, and skeleton (5, 6). In response to GH, IGF-1 is produced by the liver (7). Excess spread of IGF-I and GH levels in acromegaly includes harmful influences on various physiological processes and tissues. Patients typically share abnormal enlargements of soft tissue and bone, and have dysregulated glucose metabolism, with an increased risk of cardiovascular disease, which may influence mortality chance (8). In adipose tissue, GH action (catabolic) induces the decomposition of accumulated triglycerides into free fatty acids (FFA). GH provokes insulin action via different biomolecular pathways. Long-lasting GH secretion suppresses the anti-lipolytic effect of insulin. It raises FFA changes in the blood, thus enabling lipotoxicity and insulin resistance, which can lead to certain pathophysiological complications (9). AC-PTs have irregular glucolipid metabolism, which involves diabetes and insulin resistance; it may be linked with high GH levels, leading to adipose tissue dysfunction and the imbalances of adipocytokine production (10). Multiple research studies have investigated the serum levels of various adipokine between AC-PT and the control group. In addition, correlations between glucolipid metabolism indexes and adipokine have been reported (11). IGF-1 has been a biomarker of acromegaly since the turn of the millennium. The levels of circulating IGF-I are considered as critical biochemical means because of their prolonged half-life of 18–20 h (stability throughout the day) (12). An elevated IGF-I level and an incapability to lower GH levels <1 μg/L in an oral glucose tolerance test (OGTT) are considered influential standards for diagnosing acromegaly (13). IGF-I levels are influenced by multiple physiological characteristics, such as body mass index (BMI), sex, and age, and these should be considered during data performance (14).

Asprosin (ASP), a modern peptide recently found to be an influential regulatory adipokine, affects obesity in adult humans and animals (15, 16). Remarkably, several studies suggested that ASP as a modern fasting-induced glucogenic protein adipokine was found exalted in persons (and in rodent models) with metabolic disease (17-19). ASP is impacted by fasting and targets the liver, stimulating hepatic glucose release via the G protein cyclic adenosine monophosphate protein kinase A (cAMP-PKA) pathway (20-22). The tardy study conducted by Liu et al. (23) showed that ASP triggers agouti-related protein (AgRP) neurons, improving olfaction and facilitating appetite when attached to the central OLFR734 receptor. Recent investigations have detected that ASP levels in serum have risen in persons with metabolic disorders, such as type 2 diabetes, thyroid dysfunction, and obesity (24, 25). Other studies have suggested that ASP triggers the pathway of G-protein-linked receptor-cAMP-PKA, inducing phosphorylase activity by fast breakdown and glycogen release in the liver and increasing blood glucose (26). We know that glucose levels negatively affect GH levels, and excessive GH will raise the production of IGF-1 (27).

According to recent research, ASP plays a significant role in metabolic regulation, particularly in controlling glucose homeostasis and energy expenditure. This involvement specifically induces glucose tolerance, insulin resistance, and fasting-induced homeostasis (28). ASP is critical and essential in metabolic disorders (29).

This study is the first to evaluate serum ASP concentrations in individuals with acromegaly in Iraq. In addition, this study focuses on different subgroups, such as sex, hypertension, and diabetes mellitus (DM); thus, this work addresses a significant gap in the literature. We hypothesized that serum ASP levels are altered in AC-PT patients compared with healthy controls, and these levels may be influenced by factors such as gender, diabetes status, hypertension, and treatment duration. The findings of this study contribute to our understanding of metabolic dysregulation in acromegaly. This study provides a novel understanding of the role of ASP as a potential biomarker of acromegaly and links it to metabolic dysregulation, such as diabetes and hypertension. Thus, the present study aimed to examine serum ASP levels in Iraqi AC-PT and their correlation with elevated GH levels.

MATERIALS AND METHODS

Samples

The study enrolled individuals diagnosed with acromegaly, and healthy controls. To ensure a fair comparison, the control participants were matched with the patients based on age, gender, and BMI. Controls were selected to be within ±5 years of age and of the same gender as individuals with acromegaly.

More than 350 AC-PTs have been registered in Mustansiriyah University/National Diabetes Center (NDC) since 2003 from various provinces of Iraq; they have been regularly checked by endocrinologists clinically. Diagnosis depends on biochemical

parameters such as elevated IGF-1 levels and the absence of GH suppression after glucose management. Magnetic resonance imaging (MRI) of the pituitary in AC-PTs identifies an implied adenoma. The diagnosis and optimal administration of acromegaly comorbidities are essential for providing the best long-term outcomes for acromegaly (30). The samples of AC-PT and healthy participants were collected from September to December 2023; fifty AC-PT (female and male) with pituitary adenoma were enrolled at the NDC in Baghdad, Iraq, and considering parameters: sex, age, BMI, fasting blood glucose (FBG), hypertension, basal GH (morning), and IGF-1 levels. The age range of the AC-PT and healthy participants was 26–73 years. The patients were also administered a lanreotide injection (90 or 120 mg) intramuscularly according to their clinical status. Thus, patients were selected randomly according to their prespecified appointment. The treatment duration ranged from 1 to 10 years. Before the commencement of this trial, all patients provided written and dated consent for their participation. Furthermore, ethical approval for this study was extradited from the ethics committee of the National Diabetes Center at Mustansiriyah University in September 2023, ensuring compliance with the principles outlined in the 1964 Declaration of Helsinki and any subsequent revisions or comparable ethical standards.

Hormonal and Biochemical Assessments

Eight milliliters (mL) of peripheral blood were collected utilizing a one-use plastic needle and analyzed in a laboratory gel tube. All samples were centrifuged at 3000 rpm for 7 min to collect blood serum for laboratory examinations. The chronology of individual AC-PT and control subjects were subjected to medical estimation and physical parameters (weight, height). BMI was calculated using the following formula: BMI = weight (kg)/height² (m²). GH and IGF-1 were tested using a DiaSorin analyzer device (Elecsys hGH and IGF-1 kit-Germany), respectively. FBG levels were assayed with Gluc2 kit in a Cobas C11-1 analyzer (Roche Diagnostics, Germany).

Enzyme-Linked Immunosorbent Assay (ELISA) for ASP Levels

The ASP levels of the control and patients' serum groups were determined using an ELISA kit (Catalog no: E-EL-H0515, E-lab science, USA) following the manufacturer's instructions. We excluded any criteria linked to endocrinopathy and autoimmune diseases. In contrast, the reagents and ELISA plates were brought to room temperature before use. Serum samples were diluted according to kit instructions, and standards were prepared to create calibration curves. The assay was initiated by coating the ELISA plates with ASP and incubating them to allow binding. After that, a buffer was used to block non-specific binding. Next, serum samples and standards were added and incubated to allow ASP binding. Detection was achieved by adding a detection antibody and streptavidin- horseradish peroxidase conjugate then, a substrate solution was added to develop a colorimetric reaction. Finally, the intensity of the color was measured at 450 nm using a microplate reader. ASP levels were quantified based on the standard curve.

Statistical Analyses

In this research, statistical data were explored utilizing the Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc, Chicago, IL, USA) software. The Shapiro-Wilk test was used to determine parametric or non-parametric analyses; all variables (except IGF-1) were determined to have non-parametric distributions. Thus, the Mann–Whitney U test was used to evaluate the significance level of the differences between the AC-PTs. Results are presented as median, minimum, and maximum. The Spearman test was used for correlation. A result was considered statistically significant when the p value was less than 0.05.

RESULTS

Fifty AC-PTs and 30 control subjects were included in this study. Half of the patients had DM, whereas the remaining had non-DM. The subjects were aged between 26 and 73 years, with a mean of 50.33 ± 13.59 years. The gender distribution of AC-PT was roughly distributed (Figure 1).

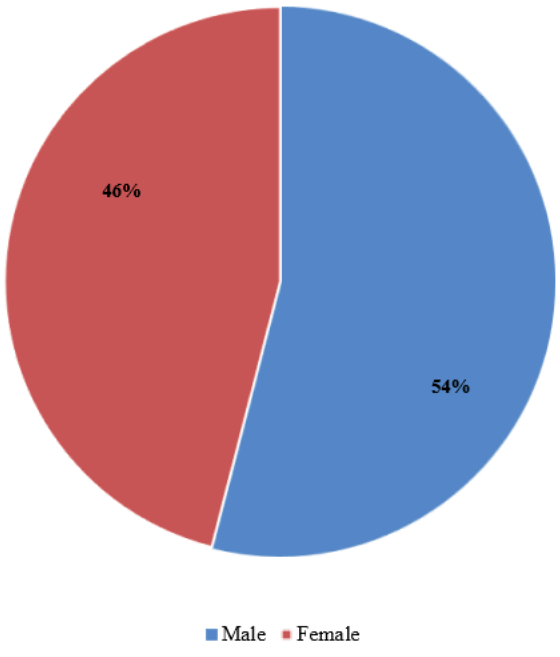

Figure 1. Gender distribution of acromegaly patients

The current study investigated the levels of ASP in AC-PT and healthy controls. Additionally, this study further explored the variations in the concentrations of ASP, GH, IGF-1, and FBG among different cohorts, categorized by gender, diabetic status, treatment course, and tension status.

When ASP levels in patients and the control group were compared, no significant differences between the patients and the controls were noted (Table 1).

Table 1. Median, minimum, maximum, and p values of study parameters between patients and control groups

Parameters	Patients Median (Min-Max)	Controls Median (Min-Max)	p value
ASP (ng/mL)	5.63 (2.88-11.67)	4.9 (3.7-6.77)	0.097
GH (ng/mL)	2.2 (0.21-54)	-	-
IGF-1 (ng/mL)	491 (105-1386)	-	-

p values calculated by Mann–Whitney U test

In this study, within AC-PT, the BMI showed no significant differences between males and females, as shown in (Table 2) and between DM and Non-DM, as shown in (Table 3).

Table 2. Median, minimum, maximum, and p values of the study parameters for male and female patients with acromegaly

Metabolites	Male Median (Min-Max)	Female Median (Min-Max)	p value
ASP (ng/mL)	5.35 (2.88-11.29)	5.93 (3.34-11.67)	0.770
GH (ng/mL)	2 (0.31-20)	3 (0.21-54)	0.247
IGF-1 (ng/mL)	450 (117-1120)	530 (105-1386)	0.403
FBG (mg/mL)	104 (60-240)	118 (60-306)	0.209
BMI (kg/m²)	27.75 (24.1-41.5)	27.9 (19.7-38.7)	0.874

p values calculated by Mann–Whitney U test.

Table 3. Median, minimum, maximum, and p values of the study parameters between patients with and without DM acromegaly

Metabolites	DM Median (Min-Max)	Non-DM Median (Min-Max)	p value
ASP (ng/mL)	5.35 (2.88-11.67)	6.04 (3.4-11.22)	0.938
GH (ng/mL)	2.6 (0.21-46.8)	2 (0.4-54)	0.884
IGF-1 (ng/mL)	480 (153-1386)	503 (105-1120)	0.923
FBG (mg/mL)	136 (60-306)	94 (60-136)	0.000*
BMI (kg/m²)	28.125 (19.7-41.5)	27.4 (24.1-39.8)	0.271

p values calculated by Mann–Whitney U test, * significant difference <0.05

The results obtained in the Mann-Whitney U test to evaluate the level of significance between male and female AC-PT showed that all the parameters had no significant values (p>0.05) (Table 2). Between the DM and non-DM AC-PTs, FBG showed a significant difference (p=0.000) while all other study parameters showed no significant differences (p>0.05) (Table 3).

A sub-group of patients with acromegaly based on their treatment duration with somatostatin analogous (Lanreotide) was conducted. Of the 50 AC-PT, 28 patients have been under treatment for >7 years and 22 patients have been under treatment for <7 years. The results revealed no significant differences in ASP, GH, and IGF-1 levels (Table 4).

Table 4. Median, minimum, maximum, and p values of the study parameters between the treatment course groups of acromegaly patients

Metabolites	<7 years Median (Min-Max)	>7 years Median (Min-Max)	p value
ASP (ng/mL)	5.81 (3.4-10.31)	5.35 (2.88-11.67)	0.377
GH (ng/mL)	3.8 (0.4-54)	1.4 (0.21-13.4)	0.014*
IGF-1 (ng/mL)	521 (105-1386)	480 (117-966)	0.491

p values calculated by Mann–Whitney U test, * significant difference <0.050

The blood pressure in AC-PTs was measured (28 with hypertension and 22 with normal tension), and the results indicated no significant differences in ASP and IGF-1 levels. Nevertheless, there was a considerable difference in GH levels (p=0.004) (Table 5).

Table 5. Median, minimum, maximum, and p values of patients with acromegaly between blood pressure groups

Metabolites	Hypertension Median (Min-Max)	Normal tension Median (Min-Max)	p value
ASP (ng/mL)	6.01 (2.88-11.67)	5.2 (3.34-10.31)	0.197
GH (ng/mL)	1.7 (0.21-7.2)	4.2 (0.6-54)	0.004
IGF-1 (ng/mL)	506.5 (117-1386)	455 (105-1120)	0.953

Positive correlations between GH and IGF-1 (p=0.000, r=0.578), FBG and BMI (p=0.016, r=0.359), weight and height (p=0.000, r=0.537), and weight and BMI (p=0.000, r=0.787), and a negative correlation between GH and weight (p=0.003, r=-0.434) were observed. Other correlation results showed no relationship between parameters. The correlation results are presented in Table 6.

In this study, linear regression analysis was performed to determine the relationship between ASP and various independent variables like GH, IGF-1, and FBG. The test showed a weak relationship between the independent variables and serum ASP levels, as indicated by an r^2 value of 0.059, meaning that only 5.9% of the variance in ASP levels could be explained by the model. The overall regression did not show a significant value (p=0.537). Between predictor variables, FBG had the highest standardized coefficient (Beta=0.235), followed by IGF-1 (Beta=0.081) and GH (Beta=-0.065); however, none of these predictors showed a statistically significant

Table 6. Correlations among all study parameters

Parameters	GH		IGF1		ASP		FBG		Weight		Height		BMI	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
GH (ng/mL)	1000	-	0.578**	**0.000**	−0.060	0.684	−0.183	0.208	−0.434**	**0.003**	−0.188	0.221	−0.030*	**0.046**
IGF1 (ng/mL)	0.578**	**0.000**	1000	-	−0.048	0.740	−0.055	0.704	−0.013	0.929	−0.060	0.693	0.110	0.472
ASP (ng/mL)	−0.060	0.684	−0.048	0.740	1.000	-	0.123	0.395	−0.104	0.490	0.034	0.824	−0.148	0.332
FBG (mg/mL)	−0.183	0.208	−0.055	0.704	0.123	0.395	1.000	-	0.202	0.179	−0.057	0.708	0.359*	**0.016**
Weight (kg)	−0.434**	**0.003**	−0.013	0.929	−0.104	0.490	0.202	0.179	1.000	-	0.537**	**0.000**	0.787**	**0.000**
Height (m)	−0.188	0.221	−0.060	0.693	0.034	0.824	−0.057	0.708	0.537**	**0.000**	1.000	-	−0.013	0.932
BMI (kg/m²)	−0.030*	**0.046**	0.110	0.472	−0.148	0.332	0.359*	**0.016**	0.787**	**0.000**	−0.013	0.932	1.000	-

r is Spearman's rho correlation coefficient. *Correlation was significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

association with serum ASP levels (p=0.170, p=0.663, and p=0.727, respectively).

DISCUSSION

ASP is a favorable selector share in the beginning and progress of processing endocrine or pathologic conditions, such as cancer, type 2 DM (T2DM), cardiomyopathy, polycystic ovarian syndrome, and obesity, and plays an important role in balancing energy metabolism (31).

A recent study by Lei Zhang et al. found that ASP levels were greater in adult T2DM patients than in healthy controls and might serve as a risk factor associated with the pathogenesis of T2DM; however, the researcher stated that it was not an ideal biomarker for prediction of T2DM (32). Other studies found that serum ASP levels were considerably higher in obese children than in lean and normal-weight children (33, 34). In addition, in 88 coronary artery disease patients, serum ASP were higher than that of healthy controls, suggesting a possible relation of ASP to the pathogenesis of acromegaly (35).

In 2020, Xiaoan Ke et al. revealed that ASP levels were lower in AC-PTs than in a healthy control group. Thus, we suggested the measurement of ASP levels in AC-PTs subgroups (gender, diabetes, duration of treatment course, and hypertension) (36).

The results showed no significant difference in ASP levels between AC-PTs and healthy controls. In addition, in the investigation involving 50 patients diagnosed with acromegaly, the analyses of subgroups categorized by gender, diabetes status, hypertension, and treatment course revealed no statistically significant outcomes. In the correlation study, no significant differences were found between ASP and any other parameter. In this survey, AC-PTs showed a similar gender distribution among acromegaly, analogous to that of Dal et al., 2021 which revealed a minor gender difference in the epidemiology of acromegaly.

Despite this, somatostatin (SST) drug (Lanreotide) binds to pancreatic β-cells (on SSTRs), then inhibits canals of voltage-gated calcium, leads to suppress the response of premature insulin to glucose, herewith restricting the energy transformation to adipose tissue, as we already know that ASP adipokine is a circulating hormone mainly secreted by white adipose tissue (37). The ASP in AC-PTs that course of treatment less than 7 years showed no significant difference for that in >7 years of SST treatment. This implies that the duration of treatment with SST does not directly affect ASP secretion in this research due to the regulation of ASP secretion, which includes multiple factors (38).

This study showed no correlation between disease course, FBG, GH, and IGF-1 levels, and serum ASP levels in AC-PTs. Despite past studies, ASP production is concerned with serum glucose. Nonetheless, Romere et al. presented that serum ASP levels were directly reduced with elevated serum glucose levels after feeding mice (16). After overnight fasting, the FBG was superfast, indicating that FBG plays a role in the systematization of ASP production. In addition, Wiecek et al. found that women's blood glucose levels were gradually decreased within 30 min after aerobic training, whereas serum ASP levels were gradually elevated, interpreted that reduced blood glucose might prompt increased production of ASP (39).

Our results disagree with the finding of Xiaoan Ke et al. 2020 who found lower ASP levels in AC-PTs with elevated FBG than in control individuals, although both were within the normal range (36).

This disagreement might stem from several factors, including differences in patient demographics, study designs, and methods of measuring serum ASP. It has also been suggested that the hormone ASP may not be affected by the hormonal changes typically associated with acromegaly due to genetic factors, lifestyle, or hormonal interplay mechanisms. A recent study showed that ASP is considered as an important influencer of the amelioration of metabolic disorders by

exercise and is likely to become an indispensable regulation target of exercise in forthcoming clinical practice and scientific research (40).

Another potential methodological issue is the use of measurement tools to evaluate serum ASP levels. Variability in laboratory techniques, equipment calibration, or the timing of sample collection can affect the accuracy and consistency of data. Additionally, hormonal interactions in acromegaly are complex, and ASP secretion may be modulated by multiple factors, such as insulin resistance, inflammatory cytokines, and adipokine, which were not investigated here.

Our findings might also replicate exclusive genetic or environmental characteristics of the Iraqi population, such as dietary designs or variations in GH treatment regimes, which may reduce the observed effects of acromegaly on ASP levels. These factors warrant further investigation to clarify the role of ASP in diverse populations. These suggestions may aid in clarifying ASP's role in metabolic disorders.

We studied ASP levels in diabetic and non-diabetic AC-PTs and found no notable changes in ASP levels between these groups. Because ASP possibly does not have a direct function in the diabetes of AC-PTs, indicating that metabolic conditions or hormonal changes linked with increased GH and IGF-1 could overshadow ASP secretion in diabetes or the pathophysiology of AC-PTs. This finding suggests that systemized ASP production is very complex and affected by the implicit factors of AC-PTs, not only diabetes (41). Regarding the sex group, there were no significant differences in ASP levels between males and females, possibly because the hormonal environment of AC-PTs may be a further homogenous metabolic process, where ASP secretion is regulated analogously regardless of acromegaly sex (42).

According to blood pressure in AC-PT, our results revealed no notable differences in ASP and IGF-1 levels, but there was a considerable difference in GH levels (p=0.004). This result may not be valuable because GH is normally released in pulses throughout the day and night, with peaks occurring mostly at night. As a result, it is challenging to interpret a single measure of GH in the blood, and it is not usually clinically applicable (43). The sample value may exhibit an increase when taken during a pulse and a decrease when taken between pulses.

The results of linear regression analyses displayed that FBG, GH, and IGF-1 collectively did not significantly predict serum ASP levels. Although FBG has a slightly stronger relationship with ASP than GH and IGF-1, none of these variables showed a statistical significance (p>0.05). Additionally, the model explains only 5.9% of the variance in serum ASP, indicating poor predictive power. These findings suggested that factors other than FBG, GH, and IGF-1 may play a more important role in regulating serum ASP levels. Further research is warranted to explore other potential determinants, such as adipokine, insulin resistance markers, and inflammatory cytokines.

Although our results did not reveal a significant difference in ASP levels, they provide valuable data to the literature. Further investigation of ASP as a marker of acromegaly is not necessary. Future research should focus on exploring other potential biomarkers or pathways to better understand the metabolic aspects of acromegaly and improve patient management strategies.

The limitation of this study was the relatively small sample size. However, acromegaly is a rare disease that limits the number of available patients for research. Additionally, the genetic and environmental specificity of the Iraqi population could influence the observed results, limiting their applicability to other populations. The potential influence of unaccounted factors such as diet, treatment regimens, and genetic variability may also affect these findings.

Conclusion

Levels of serum ASP have no difference between Iraqi AC-PT and the normal control group; according to this, ASP is not affected by the hormonal changes that are typically associated with acromegaly due to genetic factors, lifestyle, or patient behavior. Additionally, ASP can not be a helpful biomarker as there is no significant difference between study parameters in the DM and non-DM groups of AC-PTs. Moreover, ASP levels are not affected by long-term exposure to high GH levels and disease courses.

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Peer Review	Externally peer-reviewed.
Author Contributions:	Conception/Design of Study – O.Y.S., S.E.A., K.G., L.A., A.M.R.; Data Acquisition – O.Y.S., S.E.A., K.G., L.A., A.M.R.; Data Analysis/Interpretation - O.Y.S., S.E.A., K.G., L.A., A.M.R.; Drafting Manuscript – O.Y.S., S.E.A., K.G., L.A., A.M.R.; Critical Revision of Manuscript – O.Y.S., S.E.A., K.G., L.A., A.M.R.; Final Approval and Accountability – O.Y.S., S.E.A., K.G., L.A., A.M.R.
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