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Original Article ANESTHESIOLOGY & REANIMATION

Evaluation of immunomodulatory nutrients in critically ill patients in the intensive care unit

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ABSTRACT

OBJECTIVE: Glutamine and omega-3 fatty acids have been shown to decrease infection rates, antibiotic use, and hospital length of stay. However, whether giving immunonutrients to critically ill patients is beneficial remains controversial. In our study, we aimed to look at the effectiveness of parenteral unsaturated (omega-3) fatty acids and amino acid glutamine in patients with serious conditions in the intensive care unit (ICU).

METHODS: The data of patients, who received parenteral amino acid glutamine and unsaturated fatty acids (omega-3) in the ICU, were retrospectively analyzed. Eighty-four patients were classified with regard to the length of the immune modulatory nutrient treatment. Groups were constructed according to the length of the treatment in days: 9 days or more (Group I), 3–9 days (Group II), and <3 days (Group III). Demographic data, Acute Physiologic Assessment and Chronic Health Evaluation II Scores (APACHE-II), ICU and hospitalization periods, inotropic medication, 60th-day mortality, serum biochemistry, and bacterial culture results were recorded. 60th-day mortality, bacterial culture results, and number of days stayed in ICU were primary outcomes of interest.

RESULTS: Demographic data of the patients and APACHE-II scores among the groups were not significantly different from each other. ICU stay length, hospitalization length, positivity in bacterial cultures, and use of inotropic agents were significantly higher in Group I compare with other groups.

CONCLUSION: In the ICU, it was observed that patients with multiorgan failure using parenteral unsaturated fatty acids and amino acid glutamine had longer hospital and intensive care stay. It can be said that long-term use of antioxidants and immunonutrition does not have a beneficial effect in patients with multiple organ failure with high APACHE-II scores.

Keywords: Glutamine; immunomodulatory nutrient; omega-3 fatty acid.

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Immune system dysfunction and protein-energy malnutrition are two common problems encountered in patients who have serious surgical or medical illnesses. Several clinical trials have demonstrated that in certain patient groups, nutritional supplements, including immune-enhancing mixtures (branched-chain amino acid, glutamine, arginine, unsaturated fatty acids (omega-3), and beta-carotene), might be beneficial. During critical diseases, the inflammatory response develops uncontrolled. Surgical damage occurs due to the severity of surgical stress and

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a systemic inflammatory response occurs. Omega-3 fatty acids and glutamine have both been added to enteral and parenteral nutrition due to their anti-inflammatory properties and have been investigated several times.

Reportedly, glutamine levels get lower during critical diseases and these values are associated with poor clinical outcomes [1, 2]. Enteral glutamine addition has been declared to improve outcomes in burn and trauma patients [3].

Long-chain polyunsaturated fatty acids, linoleic acid (omega-6), and alpha-linoleic acid (omega-3) cannot be synthesized in human body and hence, called as essential fatty acids. Omega-3 fatty acids reduce the production of cytokines and eicosanoids either by inhibiting arachidonic acid metabolism directly or by modifying inflammatory gene expressions indirectly [4]. In patients vulnerable to hyperinflammation and sepsis, the strong anti-inflammatory and immune-modulatory effects of omega-3 fatty acids may prove beneficial [5, 6].

This study has aimed to look the effects of the use of immunonutrition in critically ill patients in the intensive care unit (ICU); morbidity, mortality, length of hospital and ICU stay, and the effects of infection on patients.

MATERIALS AND METHODS

This retrospective study had inclusive those patients who had been hospitalized in the ICU and were parenterally administered with glutamine and/or omega-3 fatty acids between January 2016 and September 2018. The study was confirmed by the Institutional Ethical Committee (no: 2018-09/2018-09-01). The study included critically ill patients aged older than 18 years. The patients had been divided into three groups with respect to the period of the administration of glutamine and omega-3 fatty acids: Who used for 9 days or more (Group I), used for 3–9 days (Group II), and used <3 days (Group III). The data of 84 patients were examined, and 35 patients were included in Group I, 20 patients in Group II, and 29 patients in Group III.

Patients' demographic data, indications for admission to ICU, comorbidities, the period of stay in the ICU and hospital, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE-II) scores, condition at discharge from ICU, and mortality on day 60, culture growth and whether they received inotropic drug support were all screened through the patient files. Urea, creatinine, BUN, GFR, albumin, leukocyte, procalcitonin, ALT/AST, and lactate values admitted to the ICU, initiation and discontinuation of immunonutrients and discharge from ICU were recorded by screening the data in the patient files. These recorded data were compared, and the efficacy of using parenteral glutamine and omega-3 fatty acids omega-3 fatty acids in critically intensive care patients was evaluated.

Highlight key points

- The duration of administration of glutamine and omega-3 fatty acid in the Intensive Care Unit has been found to be variable.
- The period of the staying in the intensive care unit and hospital for the critical patients who received omega-3 fatty acids and glutamine more than 9 days were sta-tistically higher than those who used less than 9 days.
- It can be suggested that the use of antioxidant and immunonutrition supplementation is not of benefit in patients with multiple organ failure and high APACHE-II scores.
- If immunonutrition supplementation is required, it should be administered in stable patient groups.

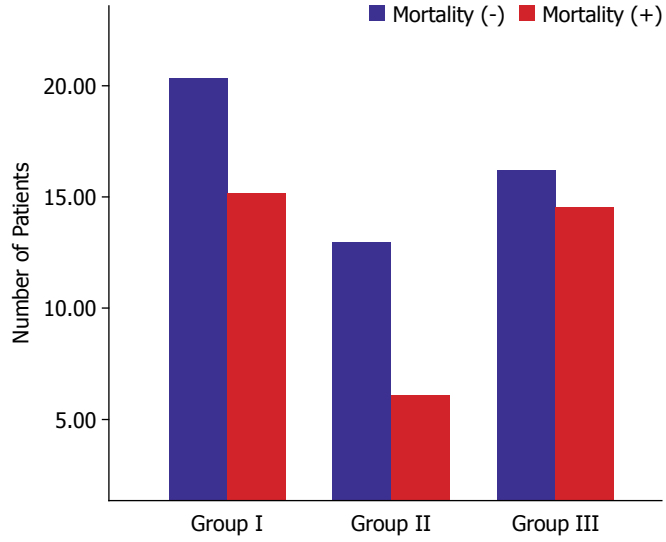

FIGURE 1. Sixty days mortality among the groups.

Statistical Analysis

The data were given as mean, median, standard deviation, minimum, and maximum and where appropriate ratios. Normal distributions of the variables were checked by Kolmogorov–Smirnov test. Groups were compared using ANOVA, Kruskal–Wallis, and Mann–Whitney U-test. Qualitative data were compared by Chi-square

TABLE 1. Demographic features and clinical outcomes of the study groups

	Immunonutrition >9 days n=35		Immunonutrition 3–9 days n=20		Immunonutrition <3 days n=29		p
Age, years	57.6±21.7		49.8±20.8		57.3±19.9		0.367[K]
Sex							0.843X²
Female (n, %)	13	37.1	9	45.0	12	41.4	
Male (n, %)	22	62.9	11	55.0	17	58.6	
Comorbidity							0.422X²
(-) (n, %)	16	45.7	11	55.0	18	62.1	
(+) (n, %)	19	54.3	9	45.0	11	37.9	
Culture							**0.014**X²
(-) (n, %)	5	14.3	10	50.0	11	37.9	
(+) (n, %)	30	85.7	10	50.0	18	62.1	
Inotropic							**0.028**X²
(-) (n, %)	9	25.7	8	40.0	17	58.6	
(+) (n, %)	26	74.3	12	60.0	12	41.4	
Mortality on day 60							0.653X²
(-) (n, %)	20	57.1	13	65.0	15	51.7	
(+) (n, %)	15	42.9	7	35.0	14	48.3	
Duration of ICU stay	59.7±88.4		20.2±26.0		16.8±15.3		**0.000**[K]
Duration of hospital stay	66.5±86.9		31.1±37.9		22.6±18.9		**0.000**[K]
APACHE scores	28.3±10.9		24.9±12.9		23.3±9.7		0.184[K]

ICU: Intensive care unit; APACHE: Acute physiology and chronic health evaluation; K: Kruskal–Wallis (Mann–Whitney U test); X²: Chi-square test.

test. P values under 0.05 were considered statistically significant. All statistical studies were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The groups were not different among themselves with regard to mean age and female/male ratios (p>0.05). The three groups were similar for 60-day mortality (p>0.05, Fig. 1). There was not also any significant difference among Groups I, II, and III in terms of the comorbidity rate (p>0.05) (Table 1). Culture positivity of patients in Group I was significantly higher than that in Groups II and III (p<0.05). In addition, there was no difference significantly between Groups II and III in terms (Table 1 and Fig. 2).

The inotropic drug use was significantly higher in compared with Group III (p<0.05), whereas Group II was not significantly different from the other two groups (p>0.05) (Table 1).

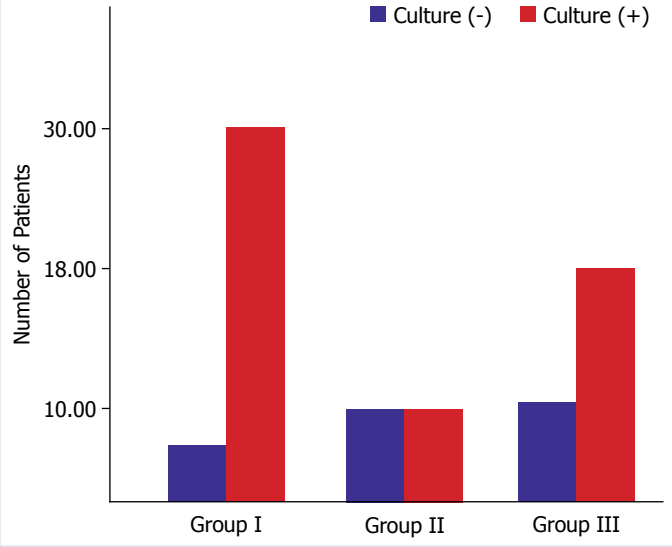

FIGURE 2. The culture positivity in Group I (immunonutrients >9 days) was significantly higher than that in Groups II (immunonutrients 3–9 days) and Group III (immunonutrients <3 days).

Table 2. Laboratory parameters of the study groups

	Immunonutrition >9 days (n=35)		Immunonutrition 3–9 days (n=20)		Immunonutrition <3 days (n=29)		p
	Mean±SD	Med	Mean±SD	Med	Mean±SD	Med	
BUN, mg/dL							
Admission to ICU	27.7±20.5	20.1	27.0±23.0	21.0	22.1±18.0	18.2	0.460[K]
Initiation	28.5±18.2	24.8	34.0±26.2	24.1	29.9±18.7	26.2	0.851[K]
Discontinuation	48.7±40.8	38.3	49.1±40.6	31.3	31.4±25.7	27.5	0.157[K]
Discharge from ICU	76.3±163.6	41.6	51.1±44.1	31.3	34.4±28.5	28.3	0.222[K]
PCT, ng/dL							
Admission to ICU	6.1±16.5	1.3	36.5±124.0	1.6	28.4±111.4	0.7	0.623[K]
Initiation	2.0±3.6	0.6	10.3±28.7	0.8	27.7±85.4	0.5	0.858[K]
Discontinuation	25.2±105.6	1.5	19.3±43.9	1.2	8.0±17.8	0.7	0.383[K]
Discharge from ICU	30.8±106.3	2.2	18.7±43.5	1.2	17.6±36.8	0.5	0.350[K]
Leucocyte							
Admission to ICU	17660±8620	17500	14857±11322	12500	16183±9121	14770	0.217[K]
Initiation	13586±5678	12790	12383±5794	11300	13076±8713	9640	0.304[K]
Discontinuation	11404±5419	9410	14061±8122	13265	11302±4891	10910	0.299[K]
Discharge from ICU	13361±7330	11190	13349±8659	12370	11613±7047	10030	0.407[K]
Albumin, g/dL							
Admission to ICU	2.8±0.8	2.8	2.9±0.9	3.0	3.1±0.9	3.0	0.347[A]
Initiation	2.7±0.5	2.8	2.8±0.7	2.9	2.8±0.5	2.7	0.870[A]
Discontinuation	2.8±0.4	2.8	2.8±0.7	2.6	2.9±0.6	3.0	0.544[A]
Discharge from ICU	2.6±0.5	2.6	2.8±0.8	3.0	3.0±0.6	3.0	0.075[A]
Urea, mg/dL							
Admission to ICU	59.3±43.9	43.0	58.5±49.2	46.0	47.2±38.6	39.0	0.432[K]
Initiation	61.6±39.4	53.0	74.8±56.8	53.0	62.9±41.7	56.0	0.720[K]
Discontinuation	105.6±88.4	83.0	101.4±86.1	60.5	68.8±55.0	61.0	0.208[K]
Discharge from ICU	109.9±93.3	89.0	105.2±93.6	60.0	73.9±61.2	67.5	0.275[K]
Creatinine, mg/dL							
Admission to ICU	1.2±0.9	0.9	1.4±0.9	1.2	1.2±0.6	1.1	0.490[K]
Initiation	1.0±0.9	0.6	1.4±1.4	1.0	1.3±1.1	1.1	0.133[K]
Discontinuation	1.2±1.2	0.7	1.7±1.4	1.2	1.2±0.9	1.0	0.293[K]
Discharge from ICU	1.4±1.2	0.9	1.7±1.1	1.2	1.4±1.4	1.1	0.905[K]
GFR							
Admission to ICU	77.8±38.4	86.3	69.8±38.9	61.8	73.6±35.5	66.1	0.772[K]
Initiation	93.6±45.2	99.9	80.2±46.1	78.2	81.2±54.8	68.8	0.268[K]
Discontinuation	90.2±52.5	96.3	78.4±60.4	62.7	86.3±59.0	83.4	0.638[K]
Discharge from ICU	77.0±50.3	68.1	79.7±61.2	62.7	81.3±61.8	66.4	0.974[K]
AST, IU/L							
Admission to ICU	132.8±352.0	29.0	114.9±250.7	45.0	176.3±675.6	21.0	0.074[K]
Initiation	44.4±70.2	26.0	91.4±245.0	29.5	84.0±197.5	26.0	0.771[K]
Discontinuation	40.4±33.2	32.0	39.1±23.4	29.0	49.2±68.5	30.0	0.906[K]
Discharge from ICU	87.9±180.0	32.0	36.9±23.6	27.0	87.5±238.9	32.0	0.653[K]

TABLE 2 (CONT). Laboratory parameters of the study groups

	Immunonutrition >9 days (n=35)		Immunonutrition 3–9 days (n=20)		Immunonutrition <3 days (n=29)		p
	Mean±SD	Med	Mean±SD	Med	Mean±SD	Med	
ALT, mg/dL							
Admission to ICU	147.0±518.6	25.0	68.8±126.4	33.0	107.8±328.4	17.0	0.115[K]
Initiation	41.2±86.7	25.0	65.8±128.2	29.5	69.7±182.9	19.0	0.488[K]
Discontinuation	49.4±92.9	14.0	42.5±55.6	31.5	50.4±112.6	19.0	0.177[K]
Discharge from ICU	40.7±71.5	15.0	38.5±32.0	34.5	46.8±85.1	20.5	0.393[K]
Lactate, mmol/L							
Admission to ICU	2.2±1.2	2.2	2.8±2.3	1.9	2.5±1.6	2.1	0.850[K]
Initiation	1.8±1.2	1.4	1.9±1.8	1.4	2.1±1.7	1.5	0.825[K]
Discontinuation	2.5±2.1	1.7	1.8±1.3	1.3	2.1±1.3	1.8	0.211[K]
Discharge from ICU	4.2±4.7	2.0	1.9±1.3	1.4	2.4±2.1	1.5	0.052[K]

SD: Standard deviation; PCT: Procalcitonin; BUN: Blood urea nitrogen; GFR: Glomerular filtration; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; K: Kruskal–Wallis (Mann–Whitney U test); A: ANOVA (Analysis of variance); *: P<0.05 significant.

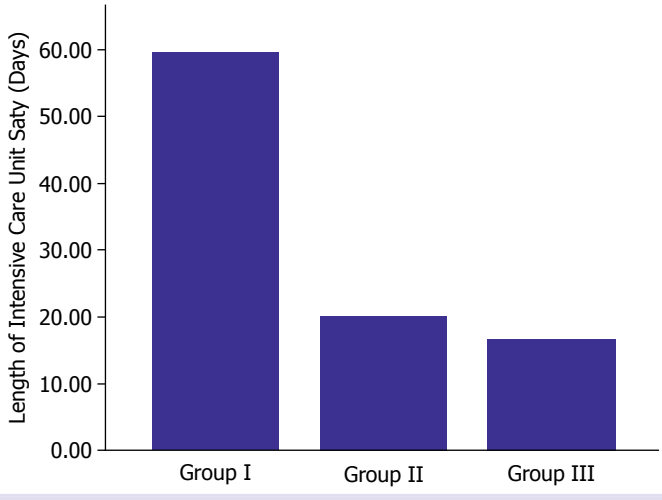

FIGURE 3. The length of intensive care unit stay among the groups.

The duration of staying in the ICU and hospital for the patients in Group I was found significantly higher than for the patients in Group II and Group III (p<0.05).

No significant difference was shown between Group II and Group III in accordance with ICU and hospital stay length (p>0.05) (Table 1 and Fig. 3). Apache-II scores was not significantly difference in Group I, Group II, and Group III (p>0.05) (Table 1). Similarly, no significant difference was observed among Groups I, II, and III in point of laboratory parameters (p>0.05) (Table 2). The diagnosis and comorbidity of the patients admitted to the ICU are given Table 3 and Table 4.

DISCUSSION

It has been shown that immunonutrition has beneficial effects on the critical patients who hospitalized in the ICU, such as less morbidity and mortality, shorter ICU, and hospital stay, reduced infection. However, it has also been stated that its inappropriate usage may have potentially harmful effects. In this study, it had been examined the effects of parenteral immunonutrition supplementation of glutamine and omega-3 fatty acids in critically ill patients who were in the ICU.

In critically ill patients, the dose and duration of glutamine administration are as important as its administration route. The recommended daily dose of parenteral glutamine is 0.2–0.4 g/kg/day, and it has been expressed that its use at a dose of 0.2 g/kg/day for <5 days has shown no effect on new infections or mortality [7].

In the study of Sheridan et al. [8], it has been stated that glutamine used for <48 h has no beneficial effects. In most studies, the duration of glutamine administration is 5–7 days. Goeters et al. [9] have also reported that 6-month survival is better when glutamine is administered for >9 days. In a multicenter study, it has been reported that the optimal dose of parenteral omega-3 fatty

Table 3. Intensive care unit admission diagnosis

Intensive care unit ad-mission diagnosis	NP	(%)
Head trauma	19	22.6
Thoracic trauma	7	8.3
Abdominal trauma	4	4.8
Post-operative	35	41.7
Respiratory failure	14	16.7
Ketoacidosis	1	1.2
Shock	3	3.6
Major bone fracture	9	10.7
Bleeding	6	7.1
Pancreatitis	1	1.2
Post CPR	6	7.1
Intracerebral hemor-rhage, subarachnoid hemorrhage, intracere-bral mass, cerebrovascular disease, meningitis, brain degenerative disease	17	20.2
Emergency abdominal disease (ileus, perforation, anastomotic leakage)	9	10.7
VAC (vacuum assisted closure)	1	1.2
Sepsis	5	6.0
Acute kidney failure	3	3.6
Liver failure	1	1.2
Only diagnosis	42	50.0
Multiple diagnosis	42	50.0

NP: Number of patients.

Table 4. Comorbidity (n=84)

Comorbidity	NP	%
No	32	38.1
Yes	52	61.9
Cardiovascular disease	26	31.0
Metabolic disease	18	21.4
Neurological disease	12	14.3
Respiratory disease	5	6.0
Urinary system disease	3	3.6
Pregnancy, preeclampsia	4	4.8
Malignancy	18	21.4
Digestive system disease	5	6.0
Single comorbidity	28	33.3
Multiple comorbidity	24	28.6

NP: Number of patients.

acids is 0.1–0.2 g/kg/day, and the effect of infection rate, hospital stay duration, and mortality in critically ill patients is dose-dependent [10]. In this study, it has been observed that patients were given parenteral glutamine and omega-3 fatty acids at appropriate recommended doses (glutamine 0.2–0.3 g/kg/day and omega-3 0.1–0.2 g/kg/day), but the administration times were varied. Contrary to the study by Goeters et al. [9], which showed that survival is better with the prolonged use of glutamine, in our study, there has been no significant difference in terms of mortality on day 60 among the three groups. Consistent with our these findings, the study by Novak et al. [11] stated that the addition of glutamine to the nutrition in surgical or critical patients had no effect on mortality. Furthermore, Pettersson et al. [12] notified that the use of enteral and parenteral glutamine at higher doses than that recommended for critically ill patients with multiple organ failure was associated with higher mortality rates. There is no difference significantly observed in terms of APACHE-II scores among the three groups in this study. We suppose that, similarity, in mortality rate among the three groups in the study is related to the fact that glutamine and omega-3 fatty acids have been used in patients who those with multiple organ failure with an APACHE-II score >15. The con-

troversial results reported in all these studies mentioned above suggest that there is still a need for larger prospective and controlled trials to determine the efficacy of glutamine-supplemented nutrition in terms of the mortality in critical illness. In this study, we have found that the period of the staying in the ICU and hospital for the critical patients who received omega-3 fatty acids and glutamine more than 9 days was statistically higher than those who used <9 days. However, Grimble et al. [13] showed that glutamine administration had not any effect on the duration of stay in hospital. Although Wischmeyer et al. [14]and Singer et al. [15] showed that nutrition with parenteral glutamine or omega-3 fatty acid shortened the duration of hospital stay.

Current data investigating the role of glutamine and omega-3 fatty acids on immune response and infection rate in critically ill patients reveal conflicting results. Grimble et al. [13] determined that the addition of glutamine to nutrition in critically ill patients decreased the incidence of infection and inflammation. Singer et al. [15] pointed out that omega-3 fatty acids reduce the synthesis of arachidonic acid and, therefore, lead to a reduced inflammatory response. In a meta-analysis by Pradelli et al. [16], it was reported that infection rates decreased with the addition of omega-3 fatty acid to parenteral nutrition. In the study, no significant differences have been found in terms of PCT and leukocyte values (as infection follow-up parameters) among the three groups. However, culture positivity and the requirement for inotropic drugs have been significantly higher in the patients who received immunonutrients for a longer duration (Group I) than those in the other groups (Groups II and III). It has been suggested based on the results of our study that immunonutrition usage does not have an impact in reducing infection rates for the critically ill patients in the ICU and that the addition of long-term immunonutrients even increases the risk of infection and results in increasing inotropic drug usage.

Antebi et al. [17] have said that the use of omega-3 fatty acids for critically ill patients who received total parenteral nutrition could be associated with better liver function owing to their antioxidant effects. In this study, no significant difference has been found in terms of AST and ALT levels among the three groups. We believe that beyond the standard laboratory tests used to monitor liver function, cellular sampling, and pathocytologic examination could be useful in elucidating the protective role of glutamine and omega-3 fatty acids on liver cells through an antioxidant effect.

The retrospective fashion of this study is a major limitation. Critical parameters of nutrition such as the total calorie and fluid intake could not be presented as a consequence of the paucity of the information in patients' charts concerning these parameters. The lack of a control group receiving solely the standard care without any immunonutrient administration is another limitation of the study.

Conclusion

This study has demonstrated that prolonged parenteral immunonutrition has no positive effect on mortality. Based on the results of this study, it can be suggested that the use of antioxidant and immunonutrition supplementation is not of benefit in patients with multiple organ failure and high APACHE-II scores. We suggest that if immunonutrition supplementation is required, it should be administered in stable patient groups. The optimal dose and route of administration of glutamine and omega-3 fatty acids in patients in the ICU remain unclear. There is a need for larger randomized, prospective, and controlled studies to evaluate the efficacy of parenteral immunonutrition.

Ethics Committee Approval: The Kanuni Sultan Suleyman Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 01.09.2018, number: 2018-09).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – NA; Design – AD; Supervision – AD; Data collection and/or processing – NA; Analysis and/or interpretation – NA; Literature review – NA, HK; Writing – NA; Critical review – ZS.

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