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Original Article

Prevalence and Risk Factors Related to Cerebral Edema Associated with Diabetes Ketoacidosis in Pediatrics with Type-1 Diabetes Mellitus

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ABSTRACT

Aim: Cerebral edema associated with diabetes ketoacidosis (CEDKA) is the most important clinical challenge in children with type-1 diabetes mellitus (T1DM). CEDKA is associated with a high rate of morbidity and mortality. We investigated the prevalence and risk factors of CEDKA in children with T1DM.

Materials and Methods: This observational study was conducted at the Children's Medical Center Hospital, Tehran, in children up to the age of 18 years with T1DM who presented with DKA from December 2022 to June 2024. All of the patients' demographic, clinical, and laboratory data were collected and analyzed. A p value <0.05 was considered significant.

Results: In total, of the 427 patients included in this study, 204 (47.8%) were male, and their mean and standard deviation (SD) age was 8.11 (4.09) years. 100 patients (23.31%) had mild DKA, 149 (34.73%) had moderate DKA, and 178 (41.49%) had severe DKA. In this study, 8 patients (1.86%) had CE, 6 of these patients (75%) were male, and 2 of them (25%) were female, and their mean ± SD age was 9.12±2.64 years. In the analysis, factors such as pH levels [odds ratio (OR): 0.001, 95% confidence interval (CI): 0.00-0.44, p=0.00] and bicarbonate levels (OR: 0.55, 95% CI: 0.36-0.83, p=0.00) had an independent and significant relationship with the incidence of CE.

Conclusion: The prevalence of CE was higher in severe DKA patients. Rapid diagnosis and management of DKA patients, especially those with neurological symptoms, is the most critical step in T1DM.

Keywords: Type-1 diabetes mellitus, ketoacidosis, cerebral edema, pediatric, Iran

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Introduction

Failure to properly manage blood glucose levels in diabetes patients can lead to critical conditions, including hypoglycemia and diabetes ketoacidosis (DKA). DKA is a combination of many pathophysiological cascades, such as hyperglycemia, insulin deficiency, metabolic acidosis, the accumulation of ketone bodies, and increased anion gap (1). Infection, female gender, newly diagnosed diabetes, lower socio-economic status, and depression are risk factors for DKA (2). Balancing fluids and electrolytes, controlling blood glucose levels, and eventually preventing complications are all crucial components of a multidisciplinary approach to DKA treatment (3).

Mismanagement or prolonged DKA leads to multi-organ damage and other life-threatening complications, such as cerebral edema (CE) (4). The prevalence of CE has been reported to be between 0.5-1%; however, some studies have reported a higher rate of 1.44% to 1.8% (5,6). CE is the most common cause of mortality in diabetic children, with a rate between 30-60% and morbidity with a rate between 21-35% (7,8). The detailed pathogenesis of CE in DKA is undetermined. However, there are some explanations in this area, including cellular osmolarity changes during fluid replacement for rehydration therapy, cerebral ischemia-hypoperfusion and reperfusion injury, and other cytotoxic and vasogenic events during DKA therapy (9-13). Unfortunately, only limited and heterogeneous information is available regarding aspects of CE, such as epidemiology and related risk factors in various ethnicities of DKA patients. Therefore, the current study aimed to investigate the prevalence of CE and its possible related risk factors in Iranian children with DKA.

Materials and Methods

Study Design and Data Gathering

This observational study was conducted at the Children's Medical Center Hospital in Tehran, Iran, from December 2022 to June 2024. All patients during this period were included as part of the census in our study. One of the inclusion criteria for patients was being aged under 18 years. Patients older than 18 years were excluded. Other conditions, including metabolic disorders and congenital abnormalities with similar manifestations of DKA, were ruled out in all age groups.

DKA was defined as a serum glucose concentration greater than 11 mmol/L (200 mg/dL), ketonemia (blood ß-hydroxybutyrate ≥3 mmol/L) or moderate or large ketonuria (urine ketones ≥2+), blood pH below 7.3, or a serum bicarbonate level below 18 mmol/L (14). Additionally, DKA can be classified into three categories based on the severity of acidosis: mild (venous pH ≤7.30; bicarbonate concentration ≤18 mmol/L), moderate (pH ≤7.2; bicarbonate ≤10), and severe (pH ≤7.1; bicarbonate ≤5) (3,13).

All procedures were performed based on the ethical standards of the institutional and national research committees. Written informed consent was obtained retrospectively from the parents or legal guardians of the pediatric patients included in the study and was documented in the patients' medical records. Ethical approval was obtained from Research Ethics Committees of Children's Medical Center-Tehran University of Medical Sciences (approval no.: IR.TUMS.CHMC.REC.1400.202, date: 23.12.2021).

Study Protocol

The medical records of those patients admitted to the hospital based on a diagnosis of ketoacidosis were used to collect the data. These medical records included all of the information we needed for our analysis. In order to extract the information required for this study, we designed a special form. We then completed the patients' hospital records, extracted the relevant information from our medical records, and entered it into the designed form. Finally, we transferred the data to a statistics software package. All of the patients included had venous blood lab tests assessing their baseline biochemical parameters carried out before any therapeutic intervention was provided.

CE Determination and Assessment

The diagnostic criteria for DKA were based on a paper from 2004 by Muir et al. (14). The determination of CE in the presence of DKA was conducted according to one diagnostic criterion, two major criteria, or one major and two minor criteria. The diagnostic criteria was abnormal motor or verbal response to pain, decorticate or decerebrate posture, cranial nerve palsy (especially III, IV, and VI), or abnormal neurogenic respiratory pattern (i.e. grunting, tachypnea, Cheyne-Stokes respiration, or apneusis). The major criteria were altered mental status, fluctuating levels of consciousness, sustained heart rate deceleration (a decrease of more than 20 beats per minute) not due to improved hydration or sleep, and age-inappropriate incontinence. The minor criteria were vomiting, headache, lethargy, diastolic blood pressure >90 mmHg, or age <5 years (14).

Fluid and Electrolyte Administration

In those children with volume depletion, fluid resuscitation was initiated with N/S (0.9%) infusion at 10-20 mL/kg for 20-30 min. Subsequent deficit fluids were replaced with 0.45-0.9% saline. One hour after intravenous fluid therapy, insulin infusion was initiated a dose of 0.05-0.1 U/kg/h of regular (soluble) insulin (15). Glucose-corrected blood sodium in mEq/L was based on the following formula: actual sodium in mEq/L-[(blood glucose in mg/dL-100) x 1.6/100] (14).

Statistical Analysis

The Statistical Package of Social Science Software (SPSS version 21, Chicago, USA) was used to analyze the data. Continuous and categorical variables are expressed as the mean and standard deviation and frequency (percentage), respectively. An independent t-test was used to compare continuous variables between the study groups. Chi-square and Fisher's exact tests were applied to compare categorical variables appropriately. A p value ≤0.05 was considered statistically significant. Additional analyses were conducted in order to determine relationships between the demographic and laboratory variables of the patients with CE.

Results

A total of 427 DKA patients were included in this study. The laboratory and demographic information on the severity of ketoacidosis is summarized in Table I. Mild ketoacidosis was present in 100 patients (23.35%), moderate ketoacidosis in 149 patients (34.9%), and severe ketoacidosis in 178 patients (41.68%). The severity of DKA was significantly greater in the male gender ($p<0.05$). Most patients in the age groups under one year and over ten years were in the severe category ($p<0.05$) with rates of 58.33% and 45.71%, respectively. The average age of those patients in the moderate group was greater, with a mean of 8.68±3.96 ($p<0.05$). The two most common symptoms, polyuria and polydipsia, had respective rates of 65.3% and 60.7%. Of all of the patients, 54 (12.58%) experienced signs of altered mental status, featuring obtundation or lethargy. Of all of the patients, only one individual had the symptom of papilledema and was concomitantly diagnosed with a severe form of DKA. One hundred and ninety-one patients (44.7%) were admitted to intensive care units (ICU). More details are shown in Table I. Laboratory data, including pH, pCO_2, bicarbonate, sodium, potassium, glucose, creatinine, and blood urea nitrogen levels, are given in Table I based on the severity of DKA.

Prevalence of CE in DKA

Table II presents the complications of the patients categorized according to the severity of ketoacidosis. In all of the examined patients, 8 patients (1.87%) were diagnosed with CE, with one patient (12.5%) having moderate DKA, and 7 patients (87.5%) being diagnosed with severe DKA ($p<0.05$). Fortunately, none of the CE patients expired during this investigation. Regardless of altered mental status and ICU admission, none of the CE cases needed to be intubated. Seven patients had CE symptoms during admission, and only one patient developed CE hours after. One of the CE cases had a history of DKA ($p<0.05$). After establishing CE diagnosis, all patients received mannitol, but none of them received bicarbonate therapy. Table III shows the demographic, clinical, and laboratory factors in the DKA patients according to CE. Levels of pH were significantly related to the occurrence of CE ($p<0.05$) (Table III).

In the analysis, it was shown that only the factors of pH [odds ratio (OR): 0.001, 95% confidence interval (CI): 0.00-0.44) and bicarbonate (OR: 0.55, 95% CI: 0.36-0.83) had an independent relationship with the occurrence of CE associated with DKA (CEDKA) ($p=0.000$ for both). Additionally, the age group of patients younger than 5 years old (OR: 2.71, 95% CI: 0.33-22.28, $p=0.032$) was significantly related to CE incidence (Table IV).

Table I. Demographic, clinical symptoms, and laboratory findings of the included patients

Variable	Total (n=427)	Mild DKA (n=100)	Moderate DKA (n=149)	Severe DKA (n=178)	p value
Demographic					
Age, (mean ± SD)	8.11 (4.09)	7.17 (4.18)	8.68 (3.96)	8.17 (4.07)	<0.05
Age groups, n (%)					
<1 year	24 (5.59)	6 (6)	4 (2.68)	14 (7.86)	<0.05
1 year-less than 5 years	94 (21.91)	34 (34)	27 (18.12)	33 (18.53)	
5 years-less than 10 years	171 (39.85)	36 (36)	68 (45.63)	67 (37.64)	
10 years or older	140 (32.63)	24 (24)	50 (33.55)	64 (35.95)	
Sex					
Male, n (%)	204 (47.8)	58 (58)	52 (25.5)	94 (46.1)	<0.05
Female, n (%)	223 (52.2)	42 (42)	97 (43.5)	84 (37.7)	
Weight, (kg) (SD)	28.55 (14.16)	26.57 (13.31)	30.59 (15.37)	27.93 (13.40)	<0.05
New onset of T1DM, n (%)	291 (67.73)	72 (72)	95 (63.75)	124 (69.66)	0.334
History of DM >1 month, n (%)	136 (31.70)	28 (28)	54 (36.24)	54 (30.33)	0.381
Misdiagnosis in EM, n (%)	0	0	0	0	
Symptoms		**n=100**	**n=149**	**n=178**	
Polyuria, n (%)	279 (65.3)	56 (20.1)	85 (30.4)	138 (49.4)	<0.001
Polydipsia, n (%)	259 (60.7)	44 (17)	77 (29.7)	138 (53.3)	<0.001
Polyphagia, n (%)	191 (44.7)	20 (10.4)	56 (29.3)	115 (60.2)	<0.001
Vomiting, n (%)	55 (12.9)	7 (12.7)	21 (38.2)	27 (49)	0.128
Headache, n (%)	64 (14.9)	4 (6.2)	12 (18.7)	48 (75)	<0.001
Lethargy/obtundation, n (%)	54 (12.58)	3 (5.5)	8 (14.8)	43 (79.6)	<0.001
Fatigue/irritability, n (%)	58 (13.6)	9 (15.5)	22 (37.9)	27 (46.5)	0.332
Abdominal pain, n (%)	112 (26.2)	22 (19.6)	31 (27.6)	59 (52.6)	0.022
Papilledema, n (%)	1 (0.2)	0	0	1 (0.2)	0.421
Focal neurological signs, n (%)	0	0	0	0	
ICU admission, n (%)	191 (44.7)	20 (10.4)	56 (29.3)	115 (60.2)	<0.001
Laboratory					
pH (unit) mean ± SD	7.19±0.14	7.33±0.06	7.23±0.07	7.07±0.12	<0.001
pCO_2 (mm Hg) mean ± SD	13.2±7.02	18.2±6.32	13.6±4.57	8.7±1.84	0.005
Bicarbonate (mmol/l) mean ± SD	9.04±4.98	15.4±3.73	9.6±3.16	5.0±2.02	<0.001
Sodium (mmol/L) mean ± SD	135.35±5.03	135.06±4.82	135.70±4.72	135.22±5.40	0.553
Potassium (mmol/dL) mean ± SD	4.28±0.7	4.36±0.67	4.24±0.66	4.27±0.72	0.441
Glucose (mg/dL) mean ± SD	462.4±142.9	432±152.2	445.5±130.8	493.6±141.7	<0.001
BUN (mg/dL) mean ± SD	13±3.36	13±3.08	12±2.87	13±3.01	0.092
Creatinine (mg/dl) mean ± SD	1.06±3.84	0.8±0.22	4.24±6.48	0.9±0.32	<0.001

DKA: Diabetic ketoacidosis, SD: Standard deviation, T1DM: Type 1 diabetes mellitus, DM: Diabetes mellitus, EM: Emergency department, ICU: Intensive care unit, pCO_2: Partial pressure of carbon dioxide, BUN: Blood urea nitrogen

Table II. Prognosis of DKA patients

Variable	Total n=427	Mild DKA n=100	Moderate DKA n=149	Severe DKA n=178	p value
Hospitalization duration (days), mean ± SD (range)	3.39±1.6 (range: 1-16)	2.88±1.46 (1-9)	3.2±1.21 (1-8)	3.86±1.81 (1-16)	<0.001
DKA resolution, (days), mean ± SD (range)	1.53±0.85 (range: 0.5-9)	1.22±0.6 (0.5-4)	1.43±0.7 (1-4)	1.8±1.02 (1-9)	<0.001
ICU admission, (days) mean ± SD (range)	0.93±1.41 (range: 0-10)	0.38±0.9 (0-4)	0.72±1.11 (0-5)	1.42±1.7 (1-10)	<0.001
Cerebral edema, n (%)	8 (1.87%)	0	1 (12.5%)	7 (87.5%)	0.023
Death, n (%)	0	0	0	0	

DKA: Diabetic ketoacidosis, ICU: Intensive care unit, SD: Standard deviation

Table III. Prevalence of cerebral edema according to treatment fluid protocol

Variable	Absent CE (n=419)	Present CE (n=8)	p value
Sex Male, n (%) Female, n (%)	 198 (47.25) 221 (52.74)	 6 (75) 2 (25)	0.115
Age, mean ± SD	8.09±4.11	9.12±2.64	0.481
Age range years, n (%) 1-5 years, n (%) 5-10 years, n (%) 10-18 years, n (%)	 24 (5.72) 93 (22.19) 167 (39.85) 135 (32.21)	 0 1 (12.50) 4 (50) 3 (37.5)	0.782
New cases of diabetes, n (%)	286 (68.25)	5 (62.5)	0.490
Altered mental status, n (%)	46 (10.97)	8 (100)	<0.001
BS reduction of more than 100, n (%)	207 (49.40)	5 (62.5)	0.354
BS less than 70 (mg/dL), n (%)	48 (11.45)	2 (25)	0.233
Initial insulin (IU/kg/h) 0.01-0.02, n (%) 0.03-0.05, n (%) 0.06-0.08, n (%) 0.09-0.1, n (%)	 3 (0.71) 88 (21) 45 (10.73) 283 (67.54)	 0 0 0 8 (100)	0.286
Na quartile (mmol/L) 110-134, n (%) 135-145, n (%) 146-160, n (%)	 174 (41.52) 234 (55.84) 11 (2.62)	 6 (75) 2 (25) 0	0.163
pH quartile 6.6-7.1, n (%) 7.11-7.2, n (%) 7.21-7.3, n (%)	 82 (19.57) 114 (27.20) 223 (53.22)	 7 (87.5) 1 (12.5) 0	<0.001
HCO_3 quartile (mmol/L) 1-4, n (%) 5-9, n (%) 10-25, n (%)	 357 (85.20) 47 (11.21) 15 (3.57)	 8 (100) 0 0	0.501
Potassium quartile (mmol/L) 1.0-3.5, n (%) 3.6-5.5, n (%) 5.6-15, n (%)	 51 (12.17) 362 (86.39) 6 (1.43)	 2 (25) 6 (75) 0	0.524

CE: Cerebral edema, SD: Standard deviation, BS: Blood sugar, IU: International unit, Na: Sodium, HCO_3: Bicarbonate, pH: Potential of hydrogen

Table IV. Adjusted odds ratios and 95% confidence intervals with significant statistical results (p<0.050) for cerebral edema occurrence

Risk factor	OR (95% CI)	p value
New case of type-1 diabetes	0.77 (0.18-3.29)	0.496
Sex	3.34 (0.66-16.78)	0.115
Age <5-year-old	2.71 (0.33-22.28)	0.032
Weight	1.02 (0.97-1.07)	0.381
Insulin	2.02 (0.00-8.21)	0.224
pH	0.001 (0.00-0.44)	<0.001
HCO_3	0.55 (0.36-0.83)	<0.001
pCO_2	0.83 (0.78-1.12)	0.980
BS less than 70 mg/dL	0.39 (0.076-1.98)	0.238
Hyponatremia (Na <135 mmol/L)	0.23 (0.05-1.18)	0.063
Hypokalemia (K <3.5 mmol/L)	0.416 (0.08-2.11)	0.261

OR: Odds ratio, CI: Confidence interval, HCO_3: Bicarbonate, pCO_2: Partial pressure of carbon dioxide, pH: Potential of hydrogen, BS: Blood sugar

Discussion

As noted, despite extensive research on CE in DKA patients, the evidence from several domains including epidemiology and risk factors associated with the incidence of CEDKA is markedly variable. This variability leads to challenges in managing this patient group. As of the time of writing, no specific study had focused on the incidence of CEDKA in Iran, making this a relatively comprehensive report on Iranian children with DKA in this field. In the current study, we investigated the prevalence of CEDKA among children under 18 years and its association with various risk factors. We reviewed data from 427 patients with DKA, with an average age of 8.11 years and a female predominance. Most of these cases, 291 (67.73%), were of new-onset diabetes. The severity of DKA was significantly associated with male gender, age, and weight. In this study, 8 patients (1.87%) experienced CEDKA; of these, 7 had severe DKA, and one had moderate DKA. Loss of consciousness, being aged <5 years, bicarbonate levels and pH levels were significantly related to CE incidence in this study.

Age is one of the significant factors in DKA occurrence. The mean age in our study was 8.11 years, consistent with other findings: Del Pozo et al. (16) reported an average age of 7.2 years, and Sultana et al. (17) in Pakistan reported 7.86 years. Conversely, an Indian study noted an average DKA onset age of 9.5 years (18). The average age in another study in Jordan was reported to be 11.03±3.88 (19). Furthermore, a Polish investigation demonstrated that children aged 0-2 years had the highest incidence of DKA and that age was one of the factors linked to DKA (20).

Various rates of new cases of diabetes have been reported in different articles. For instance, 28.7% of patients newly diagnosed with type-1 diabetes mellitus (T1DM) had DKA in the study by McKenna et al. (21). In other studies, with findings similar to ours, Del Pozo et al. (16) and Aminzadeh et al. (22) reported DKA rates of 67.4% and 67.3% in newly diagnosed patients, respectively. New onset of T1DM has been highlighted as one of the risk factors for CEDKA in the literature (23,24); however, our analyses showed that there was no association between them. A study by Sultana et al. (17) also reported a 59% rate of new onset diabetes with no association between the incidence of new cases of diabetes and CE (p=0.27) (17).

Aligning with our results, Sehgal et al.'s (25) study emphasized a positive relation for the age group of younger than 5 years with CEDKA. Also focusing on the issue of age, Edge et al. (24) found an average patient age of 8.5 years as being an independent risk factor.

The prevalence of CEDKA reported in previous studies varies. For example, in Edge et al.'s (24) study of 2,940 DKA cases, 34 (1.15%) had CE. Another study reported prevalence rates of 1.44% (15). González Pannia et al. (5) studied 693 DKA patients aged 1-18 years and found 10 cases of CE. Totally, CE occurs in about 0.3% to 1% of DKA cases (26). In Iran, no large-scale studies on DKA and CE in pediatrics have been conducted, so comparisons are limited. The different prevalence rates across studies are likely due to heterogeneity in risk factors. Our study aimed to explore most of these factors, including demographic, clinical, and laboratory data. Additionally, as an academic referral center, we see the most complex

cases from across the country, which may have influenced our findings.

The acidosis mechanisms proposed include hypercapnia caused by metabolic acidosis, leading to vasoconstriction, dehydration, reduced cerebral blood flow, and cytotoxic edema, as well as reperfusion injury and vasogenic edema during rehydration (27,28). Laboratory studies support these mechanisms, showing that hypoperfusion and reperfusion during DKA treatment can alter diffusion-weighted imaging (DWI) in magnetic resonance imaging (MRI), indicating vasogenic edema (29). DWI-MRI changes related to vasogenic edema have been observed in children with DKA, supporting the concept of reperfusion injury.

In our study, pH (OR: 0.001, 95% CI: 0.00-0.44) and HCO_3 (OR: 0.55, 95% CI: 0.36-0.83) were associated with increased CEDKA risk. All patients with CEDKA had bicarbonate levels between 1-4 mmoL/dL. A body of literature has reported a similar relation between acidosis and CEDKA. For instance, Yaneva et al. (30) studied 256 children with DKA and found a direct relationship between acidosis severity and CE, although their reported prevalence was 8.6%, higher than most other studies, with unclear reasons. Also, their research showed that the severity of DKA was significantly associated with low bicarbonate levels and with higher initial blood glucose (30). Kumar et al. (31) reported that CEDKA was significantly associated with pH and bicarbonate levels. Prior studies, such as Marcin et al. (32), found that the severity of neurological complications was related to low bicarbonate levels, and other factors, such as low pCO_2 (<22 mmoL/dL), influenced outcomes. Glaser et al. (33) also reported similar findings in 2001 with 6,977 children: 0.9% experienced CE, and factors such as high initial nitrogen, low pCO_2, and bicarbonate therapy were related to CEDKA. Regarding fluid therapy, our analyses showed no significant relationship between therapy duration and CEDKA occurrence, consistent with the studies by Kadhim (28) and Lam et al. (29), which also found no significant link.

While hypoperfusion and cerebral ischemia are considered primary mechanisms for CE, the precise pathogenesis remains unclear. The roles of fluid therapy and osmotic shifts have been investigated with conflicting results. Some studies, such as Glaser et al. (34) in 2008, suggest that osmotic changes contribute to CE, whereas others highlight widespread osmolality alterations in DKA patients (35), with hyperosmolar states leading to CEDKA (36). Rapid and precise fluid management is crucial, yet no comprehensive protocol exists, as fluid therapy varies in type, tonicity, dose, and duration across studies, complicating the assessment of osmolality and volume effects in these patients (37).

There is a strong link between CE and ICU admission in DKA patients ($p<0.001$). Patients who present with severe metabolic disturbances, dehydration, and altered mental status require ICU care. Other studies have emphasized that CEDKA patients require longer hospital stays (31,38).

Study Limitations

For the first time in Iran, we investigated the prevalence of CE in a relatively large-scale cohort of children with DKA. In this study, a relatively large number of risk factors for CE, including low sodium levels, acidosis, low bicarbonate levels, and serum urea nitrogen concentrations, were examined. Among the limitations of our study, firstly, we could not establish a cause-and-effect relationship or analyze changes over time due to this study's cross-sectional design. Additionally, the lack of a control group limited the ability to better compare results, and the single-center population prevented us from exploring the effects of different protocols and patient demographics on the occurrence of CE.

Conclusion

The predominance of CE is higher in severe DKA patients. In this study, pH levels and bicarbonate levels had an independent and significant relationship with the incidence of CE. Conducting large-scale epidemiologic and multicenter studies may shed further light on this field, as well as help in developing a comprehensive treatment protocol for fluid therapy and determining the exact prevalence of CE and other complications of DKA.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Research Ethics Committees of Children's Medical Center-Tehran University of Medical Sciences (approval number: IR.TUMS.CHMC.REC.1400.202, date: 23.12.2021).

Informed Consent: Written informed consent was obtained retrospectively from the parents or legal guardians of the pediatric patients included in the study and was documented in the patients' medical records.

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Footnotes

Authorship Contributions

Concept: M.S., M.S.M., Design: M.S.K., Analysis or Interpretation: R.M., Literature Search: Mae.S., Writing: Mae.S.

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