Diabetic Ketoacidosis as an Effect of Sodium-Glucose Cotransporter 2 Inhibitor: Real World Insights

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Diabetic Ketoacidosis as an Effect of SGLT2 Inhibitor: Real-World Insights

Patients

* Three Hospital
* Mar 2015 ~ Dec 2023
* 110 cases of DKA using SGLT2 inhibitor

* Definition of SGLT2 inhibitor-associated DKA
  ✓ Prior diagnosis of type 1 or type 2 diabetes
  ✓ Administration of SGLT2 inhibitor before developing DKA
  ✓ Ketoacidosis define as pH<7.3, anion gap >12 mmol/L, and ketonemia/ketonuria

Result

	Euglycemic DKA (n=12)	Hyperglycemic DKA (n=9)	
Age (median), years	46	47	
Sex, men (%)	4 (33.3)	4 (44.4)	
Type 2 diabetes, n (%)	12 (100.0)	8 (88.9)	
Glucose, mg/dL	146	397	⬆
HbA1c, %	7.0	11.9	⬆
C-peptide <0.7 ng/mL, n (%)	3 (27.3)	7 (77.8)	⬆
eGFR, mL/min/1.73 m^2)	82.3	41.0	⬇
pH	7.2	7.0	⬇
Combined HHS, n (%)	0 (0)	4 (44.4)	⬆

Abbreviation: DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HHS, hyperosmolar hyperglycemic state; SGLT2, sodium glucose co-transporter 2.

Conclusion

* This study indicates that SGLT2 inhibitor-induced hyperglycemic DKA is more severe than euglycemic DKA.
* With increasing SGLT2 inhibitor use for cardiorenal benefits, clinicians must recognize SGLT2 inhibitor-induced DKA and its risk factors for timely management.

Highlights

* SGLT2 inhibitors are linked to both euglycemic (euDKA) and hyperglycemic DKA (hyDKA).
* More than 80% of DKA cases associated with SGLT2 inhibitors involved type 2 diabetes.
* HyDKA patients had poorer glycemic control and lower C-peptide than euDKA patients.
* HyDKA patients had lower lower pH and worse renal function than euDKA patients.
* Common triggers include starvation, infection, dehydration, and insulin deficiency.

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Diabetic Ketoacidosis as an Effect of Sodium-Glucose Cotransporter 2 Inhibitor: Real World Insights

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One of the notable adverse effects of sodium-glucose cotransporter 2 (SGLT2) inhibitor is diabetic ketoacidosis (DKA) often characterized by euglycemia. In this retrospective review of patients with DKA from 2015 to 2023, 21 cases of SGLT2 inhibitor-associated DKA were identified. Twelve (57.1%) exhibited euglycemic DKA (euDKA) while nine (42.9%) had hyperglycemic DKA (hyDKA). More than 90% of these cases were patients with type 2 diabetes mellitus. Despite similar age, sex, body mass index, and diabetes duration, individuals with hyDKA showed poorer glycemic control and lower C-peptide levels compared with euDKA. Renal impairment and acidosis were worse in the hyDKA group, requiring hemodialysis in two patients. Approximately one-half of hyDKA patients had concurrent hyperosmolar hyperglycemic state. Common symptoms included nausea, vomiting, general weakness, and dyspnea. Seizure was the initial manifestation of DKA in two cases. Infection and volume depletion were major contributors, while carbohydrate restriction and inadequate insulin treatment also contributed to SGLT2 inhibitor-associated DKA. Despite their beneficial effects, clinicians should be vigilant for SGLT2 inhibitor risk associated with DKA.

Keywords: Diabetes mellitus; Diabetic ketoacidosis; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitor constitutes a class of oral hypoglycemic agents that reduce blood glucose levels by enhancing glucosuria through inhibiting glucose reabsorption in the proximal tubules of the kidney [1,2]. There is growing evidence supporting the recommendation of SGLT2 inhibitors, particularly in patients with heart failure, cardiovascular disease, and chronic kidney disease [3-5]. Recent guidelines indicate a substantial increase in SGLT2 inhibitors not only in patients with type 2 diabetes mellitus (T2DM), but also

in those with heart or renal disease without diabetes [3,4].

Diabetic ketoacidosis (DKA) is a notable adverse effect of SGLT2 inhibitor use [1]. As SGLT2 inhibitor reduces the insulin-to-glucagon ratio by lowering plasma glucose levels, it increases lipolysis and ketogenesis, thereby elevating the risk of DKA [1]. Due to its glucosuria effects, SGLT2 inhibitor-induced DKA often manifests as euglycemic DKA (euDKA) [6]. A large population-based cohort study reported an approximately 3-fold increased risk of developing euDKA with SGLT2 inhibitor use versus other oral hypoglycemic agents [7]. The U.S. Food and Drug Administration issued a caution regarding

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euDKA risk associated with SGLT2 inhibitor use based on reports received via its adverse event system [8]. However, reports also indicate occurrence of hyperglycemic DKA (hyDKA) [9]. To close the existing gap in understanding the specific clinical characteristics of euDKA and hyDKA in patients with T2DM receiving SGLT2 inhibitors, we evaluated clinical characteristics of SGLT2 inhibitor-associated DKA, specifically focused on euDKA and hyDKA.

METHODS

We obtained medical records of 110 cases of DKA using SGLT2 inhibitors from three centers between March 2015 and December 2023. Furthermore, cases were representative of various settings including outpatient, inpatient, emergency rooms, and collaborative care. The diagnosis of SGLT2 inhibitor-associated DKA was established if cases met the following criteria: (1) prior diagnosis of type 1 diabetes mellitus or T2DM; (2) administration of SGLT2 inhibitor before developing DKA; and (3) ketoacidosis defined as pH <7.3, anion gap >12 mmol/L, and ketonemia/ketonuria [1]. This study was approved by the Institutional Review Boards of the Seoul St. Mary's Hospital, Seoul, Republic of Korea (KC24RASI0715), Uijeongbu St. Mary's Hospital, Uijeongbu, Republic of Korea (UC24ZASI0105), and Eunpyeong St. Mary's Hospital, Seoul, Republic of Korea (PC24 RADI0040). Informed consent was waived by the board.

We identified 21 cases as SGLT2 inhibitor-associated DKA. Patients were categorized into two groups based on initial plasma glucose level at the time of DKA occurrence: euDKA (n=12), <250 mg/dL; and hyDKA (n=9), ≥250 mg/dL [10,11]. Clinical parameters, laboratory findings, and contributing factors for developing DKA were analyzed.

All statistical analyses were conducted using R version 4.2.2 (R Project for Statistical Computing, Vienna, Austria). Continuous variables were compared using Mann-Whitney U test while categorical variables were compared using chi-square or Fisher's exact test. Data were presented as median (interquartile range [IQR]) or number (%). A P value <0.05 was considered statistically significant.

RESULTS

Demographic and biochemical characteristics
Among patients with SGLT2 inhibitor-associated DKA (eight males, 13 females), median age was 46.0 years (IQR, 41.0 to 61.0) and duration of diabetes was 5.0 years (IQR, 3.0 to 9.0) (Table 1). Median body mass index (BMI) was 23.2 kg/m^2 (IQR, 21.2 to 25.4) and all but one patient had T2DM. Concomitant acute kidney injury was observed in 12 cases (57.1%). More than one-half of patients (57.1%) had been taking an SGLT2 inhibitor for at least 1 year (Table 1). However, in one case with newly diagnosed T2DM, euDKA developed only 3 days after SGLT2 inhibitor administration (data not shown).

There were no differences in age, sex, BMI, diabetes type, or duration of diabetes between the two groups (Table 1). At the time of DKA diagnosis median glucose levels were significantly higher in the hyDKA group compared to the euDKA group (397.0 mg/dL [IQR, 349.0 to 695.0] vs. 146.0 mg/dL [IQR, 116.0 to 188.5], P=0.001). The hyDKA group also exhibited markedly elevated HbA1c levels (11.9% [IQR, 10.2 to 12.4] vs. 7.0% [IQR, 6.5 to 9.1], P<0.001) compared with the euDKA group. Median C-peptide levels were lower with hyDKA compared with euDKA, but not significantly (0.5 ng/mL [IQR, 0.1 to 0.7] vs. 1.0 ng/mL [IQR, 0.6 to 1.9], P=0.183). However, percent of C-peptide levels <0.7 ng/mL was greater with hyDKA compared with euDKA (77.8% vs. 27.3%, P=0.025). The hyDKA group exhibited reduced renal function by estimated glomerular filtration rate (eGFR) compared to the euDKA group (41.0 mL/min/1.73 m^2 [IQR, 25.0 to 74.0] vs. 82.3 mL/min/1.73 m^2 [IQR, 68.5 to 91.6], P=0.022). The hyDKA group also had lower pH levels compared to the euDKA group, indicating more severe acidosis (7.0 [IQR, 6.9 to 7.1] vs. 7.2 [IQR, 7.1 to 7.3], P=0.012). Two patients (22.2%) in the hyDKA group and one patient (8.3%) in the euDKA required hemodialysis (data not shown).

Although the duration of hospitalization and recovery time was slightly longer in hyDKA group, there was no significant difference between the two groups. The duration of hospitalization for the patients studied was a median 8 days, with no significant difference between those with euDKA and hyDKA (7 days vs. 8 days, P=0.695). Similarly, the median recovery time from acidosis was 31.0 hours across the board, showing no significant distinction between the euDKA and hyDKA groups (29.0 hours vs. 31.5 hours, P=0.409).

Clinical presentation and possible contributing factors to SGLT2 inhibitor-associated DKA
Nausea and vomiting were the most common presenting symptoms of SGLT2 inhibitor-associated DKA, followed by general weakness, dyspnea, abdominal pain, and mental changes (Table

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Table 1. Demographic and biochemical characteristics of SGLT2 inhibitor-associated diabetic ketoacidosis

Characteristic	Total (n=21)	euDKA (n=12)	hyDKA (n=9)	P value
Age, yr	46.0 (41.0–61.0)	47.0 (44.0–64.0)	47.5 (36.5–60.5)	0.502
Male sex	8 (38.1)	4 (33.3)	4 (44.4)	0.604
BMI, kg/m^2	23.2 (21.2–25.4)	23.2 (21.1–24.4)	25.3 (21.2–32.8)	0.248
Diabetes type (T2DM)	20 (95.2)	12 (100.0)	8 (88.9)	0.237
Duration of diabetes, yr	5.0 (3.0–9.0)	6.0 (3.0–7.0)	4.5 (3.0–15.0)	0.868
Glucose, mg/dL	233.0 (144.0–369.0)	146.0 (116.0–188.5)	397.0 (349.0–695.0)	0.001
HbA1c, %	9.2 (6.9–11.7)	7.0 (6.5–9.1)	11.9 (10.2–12.4)	<0.001
C-peptide, ng/mL	0.7 (0.2–1.9)	1.0 (0.6–1.9)	0.5 (0.1–0.7)	0.183
C-peptide <0.7 ng/mL	10 (50.0)	3 (27.3)	7 (77.8)	0.025
WBC, ×10^3 cells/mm^3	16.64 (11.45–20.75)	15.93 (13.10–19.33)	17.90 (10.61–22.63)	0.444
Segmented neutrophils, %	84.2 (73.5–88.0)	85.8 (78.4–89.5)	79.6 (70.3–84.3)	0.082
ESR, mm/hr	6.0 (2.0–22.0)	8.5 (4.0–32.0)	6.0 (2.0–14.0)	0.664
CRP, mg/dL	0.6 (0.2–2.5)	0.6 (0.1–5.8)	0.5 (0.2–1.7)	0.910
BUN, mg/dL	20.3 (13.9–43.9)	19.8 (13.4–25.6)	43.9 (16.7–53.2)	0.034
Creatinine, mg/dL	1.0 (0.9–1.4)	0.9 (0.8–1.1)	1.7 (1.0–2.1)	0.012
eGFR, mL/min/1.73 m^2	75.0 (41.0–87.0)	82.3 (68.5–91.6)	41.0 (25.0–74.0)	0.022
Concomitant AKI	12 (57.1)	5 (41.7)	7 (77.8)	0.098
Sodium, mEq/L	137.0 (134.0–140.0)	138.5 (137.0–142.5)	132.0 (129.0–134.0)	0.002
Potassium, mEq/L	4.6 (3.9–5.8)	4.4 (3.8–4.8)	5.9 (4.1–6.5)	0.057
pH	7.1 (7.0–7.3)	7.2 (7.1–7.3)	7.0 (6.9–7.1)	0.012
Bicarbonate, nmol/L	10.0 (8.6–13.0)	10.5 (9.3–15.2)	10.0 (6.7–10.0)	0.193
Anion gap, mEq/L	23.6 (19.5–32.0)	25.7 (19.1–32.5)	23.0 (20.0–29.0)	0.887
Osmol, mOsm/kg	314.0 (302.5–325.5)	305.0 (298.0–314.5)	325.0 (309.5–341.0)	0.052
HHS combined	4 (19.0)	0	4 (44.4)	0.010
Total ketone, μmol/L	3,600 (1,000–5,750)	4,205 (1,000–6,877)	3,111 (1,000–5,750)	0.661
Urine ketone				0.178
Negative	1 (4.8)	0	1 (11.1)	
1+	1 (4.8)	0	1 (11.1)	
2+	3 (14.3)	3 (25.0)	0	
3+	15 (71.4)	9 (75.0)	6 (66.7)	
SGLT2 inhibitor type				
Dapagliflozin	9 (47.4)	5 (41.7)	4 (44.4)	0.899
Empagliflozin	11 (52.4)	7 (58.3)	4 (44.4)	0.528
Ertugliflozin	1 (4.8)	0	1 (11.1)	0.237
Duration of SGLT2 inhibitor use, mo	18.0 (12.0–24.0)	18.0 (12.0–30.0)	18.0 (4.0–24.0)	0.838
SGLT2 inhibitor use ≥1 years	12 (57.1)	9 (75.0)	3 (33.3)	0.350
Other antidiabetic medications				
Insulin	5 (23.8)	1 (8.3)	4 (44.4)	0.055
Sulfonylurea	7 (33.3)	3 (25.0)	4 (44.4)	0.350
Metformin	21 (100.0)	12 (100.0)	9 (100.0)	-
DPPIV inhibitor	12 (57.1)	7 (58.3)	5 (55.6)	0.899

(*Continued to the next page*)

Table 1. Continued

Characteristic	Total (*n*=21)	euDKA (*n*=12)	hyDKA (*n*=9)	*P* value
Duration of hospitalization, day	8.0 (6.0–12.0)	7.0 (4.0–12.5)	8.0 (7.0–11.0)	0.695
Recovery time from acidosis, hr	31.0 (20.0–42.5)	29.0 (18.5–35.5)	31.5 (21.0–59.0)	0.409

Values are presented as median (interquartile range) or number (%).
SGLT2, sodium-glucose cotransporter 2; euDKA, euglycemic diabetic ketoacidosis; hyDKA, hyperglycemic diabetic ketoacidosis; BMI, body mass index; T2DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; Osmol, osmolarity; HHS, hyperosmolar hyperglycemic syndrome; DPPIV, dipeptidyl peptidase 4.

Table 2. Clinical presentation and contributing factors of SGLT2 inhibitor-associated diabetic ketoacidosis

Variable	Total (*n*=21)	euDKA (*n*=12)	hyDKA (*n*=9)	*P* value
Presenting symptoms/sign				
Nausea/vomiting	9 (42.9)	5 (41.7)	4 (44.4)	0.899
General weakness	6 (28.6)	1 (8.3)	5 (55.6)	0.018
Dyspnea	6 (28.6)	3 (25.0)	3 (33.3)	0.676
Abdominal pain	5 (23.8)	4 (33.3)	1 (11.1)	0.237
Mental change	4 (19.0)	0	4 (44.4)	0.010
Seizure	2 (9.5)	2 (16.7)	0	0.198
Fever	1 (4.8)	1 (8.3)	0	0.375
Flank pain	1 (4.8)	1 (8.3)	0	0.375
Potential contributing factor				
Carbohydrate restriction/starvation	13 (61.9)	8 (66.7)	5 (55.6)	0.604
Infection	10 (47.6)	4 (33.3)	6 (66.7)	0.130
Volume depletion	9 (42.9)	4 (33.3)	5 (55.6)	0.309
Inadequate insulin treatment/insulin deficiency	7 (33.3)	4 (33.3)	3 (33.3)	-
Pancreatitis	3 (14.3)	2 (16.7)	1 (11.1)	0.719
Surgery	3 (14.3)	2 (16.7)	1 (11.1)	0.719
Alcohol	2 (9.5)	2 (16.7)	0	0.198
Steroid use	1 (4.8)	0	1 (11.1)	0.257
HF aggravation	1 (4.8)	0	1 (11.1)	0.257
GI bleeding	1 (4.8)	1 (8.3)	0	0.375

Values are presented as number (%).
SGLT2, sodium-glucose cotransporter 2; euDKA, euglycemic diabetic ketoacidosis; hyDKA, hyperglycemic diabetic ketoacidosis; HF, heart failure; GI, gastrointestinal.

2). General weakness was more frequently observed in the hyDKA group compared with the euDKA group (55.6% vs. 8.3%, *P*=0.018). Mental changes were seen only in the hyDKA group, but two patients presented with seizures in the euDKA group (Table 2).

Potential contributing factors for SGLT2 inhibitor-associated DKA are presented in Table 2. Overall, carbohydrate restriction/starvation (61.9%) was the most common contributing factor. Most patients were unable to eat due to secondary causes including gastrointestinal symptoms or surgery while in the euDKA group, intentional carbohydrate restriction was reported in three patients (25%). Infection (47.6%), volume depletion (42.9%), and inadequate insulin treatment/deficiency (33.3%) also contributed. Other major contributing factors included acute pancreatitis, surgery, alcohol use, steroid use, heart failure aggravation, and gastrointestinal bleeding (Table 2) with no differences between the two groups.

Re-introduction of SGLT2 inhibitor after DKA recovery

Four of the total study patients restarted SGLT2 inhibitors after recovery from DKA. All patients belonged to the euDKA group. One patient who experienced euDKA while using dapagliflozin 10 mg was restarted on empagliflozin 10 mg. Another patient experienced euDKA while using empagliflozin 10 mg and was restarted on dapagliflozin 5 mg. In particular, this patient experienced worsening heart failure while discontinuing SGLT2 inhibitor. The other two patients used the same SGLT2 inhibitor and doses as previously used. No patients experienced the DKA after re-introduction of SGLT2 inhibitors.

DISCUSSION

We observed that SGLT2 inhibitor-induced both euDKA and hyDKA with the latter presenting distinct manifestations including poor glycemic control, low C-peptide levels, reduced eGFR, and lower pH levels. Our study emphasizes a potential association between insulin deficiency and SGLT2 inhibitor-associated hyDKA evidenced by high glucose levels and decreased C-peptide concentrations. Furthermore, hyDKA represented a more advanced DKA state compared to euDKA characterized by more severe acidosis and concomitant acute kidney injury. However, clinical course after adequate management was similar between two groups. Carbohydrate restriction, prolonged fasting, infection, volume depletion, and inadequate insulin treatment, along with nausea/vomiting, general weakness and dyspnea, figured prominently in SGLT2 inhibitor-associated DKA.

Due to glucosuria effect attention (particularly for euDKA induced by these inhibitors) is ongoing from physicians and regulatory authorities [1,8,12] despite the similar number of hyDKA and euDKA cases we observed. To the best of our knowledge, only one study compared the characteristics of euDKA and hyDKA associated with SGLT2 inhibitor [9]. They reported 43 cases of SGLT2 inhibitor-associated DKA (euDKA, $n=25$; hyDKA, $n=18$). In contrast to our study, theirs reported similar HbA1c and pH levels between the two groups, possibly due to different ethnicities (Middle East and North Africa), higher BMI (mean BMI 29.8 kg/m^2), and higher proportion of insulin users (67.4%). Of note, they did not investigate duration of diabetes or C-peptide levels, which reflects the β-cell reserve of each individual.

The potential mechanisms underlying SGLT2 inhibitor-induced DKA primarily involve the glucosuric effects of SGLT2

inhibitors. Consequently, SGLT2 inhibitors reduce blood glucose levels, lower insulin secretion, and increase glucagon secretion [6]. This, in turn, triggers lipolysis, elevating free fatty acids and leading to increased β-oxidation and ketone body accumulation [13]. These processes can contribute to the development of ketoacidosis with relatively normal blood glucose levels, known as euDKA. External factors such as carbohydrate-restricted diets, trauma, illness, or surgery can exacerbate these effects by stimulating lipolysis and ketosis due to increased counter-regulatory hormones.

As acetic acid was not measured separately, our study focused on total ketone bodies including beta-hydroxybutyrate (BHB). As BHB is the predominant ketone in blood, the measurement of ketones including BHB is helpful to assess of acidosis associated with alcohol use or SGLT2 inhibitor use [14]. On the other hands, elevations in BHB have been reported to prevent or improve the symptoms associated with various diseases that commonly occur with aging [15]. Recent perspectives suggest that the cardioprotective effects of SGLT2 inhibitors may be mediated through the increase in BHB levels: This rise in ketone bodies is thought to act as a signal that enhances the heart's resistance to oxidative and inflammatory stress, while also optimizing energy utilization, thereby contributing to the overall protective mechanism through a hormetic response [16]. In our study, ketone levels were slightly higher in the euDKA group, although there was no statistical significance. The elevation of ketone bodies, particularly BHB, underscores a pivotal aspect in understanding both the risks of SGLT2 inhibitor-associated DKA and their potential cardioprotective benefits, highlighting the necessity for further research in this area to unravel the complex mechanisms involved.

The diagnosis of SGLT2 inhibitor-associated DKA can be challenging, often resembling conditions like infection, seizures, or alcoholic ketoacidosis [11]. Given the diverse triggers for DKA in our study, clinical awareness is paramount. Notably, two recent ketoacidosis cases, occurring even without diabetes [17], alongside a recent surge in SGLT2 inhibitor prescriptions, warrant attention. According to the guidelines, SGLT2 inhibitors should be discontinued before surgery and avoided during severe illness until their safety and effectiveness are firmly established [12].

Re-introduction of SGLT2 inhibitor after DKA resolution is another issue. Cautious re-introduction of these agents may be considered in situations where there is a compelling indication

for their use, such as heart failure or chronic kidney disease. Four patients in our study cohort were re-introduced with SGLT2 inhibitor, and they did not experience DKA again. In particular, one patient experienced the worsening heart failure during SGLT2 inhibitor cessation. However, the small number of people included in the study makes it difficult to generalize. To the best of our knowledge, there is a lack of studies that address the resumption of SGLT2 inhibitors after recovery from DKA. Further research on this subject would be necessary.

While our study is limited by a small sample size and retrospective data collection procedure, we nonetheless thoroughly investigated clinical and biochemical data and compared the clinical features of euDKA and hyDKA. In addition, our study has a limitation regarding the standardization of C-peptide measurement. Although the C-peptide measurements were primarily obtained in a fasting state, either upon presentation to the emergency room or within 1 to 2 days of hospital admission, there was a lack of standardization in the timing and conditions, which influence the assessment of insulin secretion status within our cohort. Therefore, future prospective studies with standardized protocols for C-peptide measurement are warranted to further elucidate the pathophysiology of SGLT2 inhibitor-associated DKA.

Considering the anticipated rise in SGLT2 inhibitor use due to their cardiorenal protective effects, heightened awareness of SGLT2 inhibitor-mediated DKA and its predisposing factors is crucial to prevent DKA development. Clinicians should remain vigilant for DKA to ensure timely management. This research highlights that hyDKA induced by SGLT2 inhibitors presents more severe symptoms and complications compared to euDKA. It underscores the critical role of insulin deficiency in exacerbating the condition, pointing out the need for careful monitoring of patients on SGLT2 inhibitors, especially regarding their insulin levels and potential triggers such as dietary habits and infections.

CONFLICTS OF INTEREST

AUTHOR CONTRIBUTIONS

Conception or design: H.S.B., E.Y.L.
Acquisition, analysis, or interpretation of data: H.S.B., C.J., Y.Y., J.L., J.L., E.Y.L.
Drafting the work or revising: H.S.B., S.H.L., J.H.C., T.S.S., H.S.S., K.H.Y., E.Y.L.
Final approval of the manuscript: H.S.B., E.Y.L.

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