

ORIGINAL ARTICLE

Clinical features and outcomes of diabetic ketoacidosis in patients using SGLT2 inhibitors: A systematic review and meta-analysis

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Abstract

Aims: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are effective antihyperglycaemic agents; however, they also increase the risk of diabetic ketoacidosis (DKA). As the clinical evidence comparing DKA features between SGLT2i users and non-users remains limited due to the low incidence of DKA, this study aimed to compare the clinical features and outcomes of DKA in SGLT2i users and non-users by conducting a systematic review and meta-analysis.

Materials and Methods: Relevant studies were searched in PubMed, Scopus, and Web of Science in February 2025. Studies that compared the clinical features or outcomes of DKA between SGLT2i users and non-users were included. Pooled estimates were derived using odds ratios for binary variables and mean differences for continuous variables.

Results: A total of 9 studies were analysed. DKA cases in SGLT2i users had lower odds of prior DKA and insulin use. Compared with DKA cases in non-users, SGLT2i users had lower glucose, HbA1c, creatinine, and lactate levels. No significant differences were found in the length of hospitalisation, intensive care unit admission, or in-hospital mortality.

Conclusions: These findings provide quantitative evidence of the distinct clinical features of SGLT2i-associated DKA, which may aid in early detection, management, and prevention in clinical practice.

KEYWORDS

diabetes complications, meta-analysis, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is a serious, life-threatening complication of diabetes mellitus, characterised by hyperglycaemia, ketosis,

and metabolic acidosis.¹ It results from absolute or relative insulin deficiency, which leads to elevated blood glucose levels and the abnormal breakdown of fatty acids via lipolysis. This metabolic disturbance promotes the production of ketone bodies, which, when excessively accumulated, lower blood pH, resulting in metabolic acidosis.^{2–4} DKA is more common in type 1 diabetes, although it

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can also occur in 20%–30% of patients with type 2 diabetes mellitus (T2DM), particularly during physiological stress such as infection, trauma, or surgery.⁵

SGLT2i belongs to a class of antihyperglycaemic agents that improve glycaemic control by inhibiting glucose reabsorption and inducing glycosuria. Owing to its cardiovascular and renal benefits, SGLT2i is widely used to manage T2DM; however, concerns have been raised regarding its potential to precipitate DKA.⁶ A recent meta-analysis showed that the risk of DKA was 2.3-fold higher in patients using SGLT2i compared with non-users.⁷ Interestingly, several studies have reported that SGLT2-associated DKA presents distinct characteristics, such as euglycemic DKA.⁸ However, evidence comparing the clinical features and severity of DKA between SGLT2i users and non-users remains limited. Additionally, existing studies often include a small number of DKA cases, owing to its low prevalence.^{9–11} Therefore, this systematic review and meta-analysis aimed to compare the clinical features and outcomes of DKA between SGLT2i users and non-users by synthesising findings from observational studies and providing quantitative estimates to inform clinical practice.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

This review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹² The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO) (Reference No.: CRD4202 5646379).

2.2 | Information sources and search strategy

A systematic search was conducted across three databases (PubMed, Scopus, and Web of Science) on February 4, 2025, to identify relevant studies examining the baseline characteristics, clinical features, and outcomes of DKA in patients using SGLT2i, compared with non-users. The following search terms were used: (Sodium glucose co transporter 2 inhibitor*) OR (Sodium glucose cotransporter 2 inhibitor*) OR (Sodium glucose transporter 2 inhibitor*) OR (SGLT2 inhibitor*) OR (SGLT 2 inhibitor*) OR (SGLT2i) OR (dapagliflozin OR Farxiga OR Forxiga OR canagliflozin OR Invokana OR empagliflozin OR Jardiance OR ertugliflozin OR Steglatro OR ipragliflozin OR Suglat OR sotagliflozin OR Zynquista OR Inpefa OR luseogliflozin OR Lusefi OR bexagliflozin OR Brenzavvy OR enavogliflozin OR Envlo) AND ((diabet* ketoacidosis) OR (diabet* ketosis) OR (DKA)). There was no restriction on publication year or language.

All the articles retrieved from these databases were imported into EndNote 21 (Clarivate Analytics, PA). After removing

duplicates, two independent reviewers (D. L. and G. S.) initially screened titles and abstracts, followed by a full-text review to determine study eligibility. Discrepancies were resolved by consensus with a third reviewer (J. Y.) in cases of persistent disagreement.

2.3 | Inclusion and exclusion criteria

Studies were selected if (1) they provided clinical features or outcomes related to DKA, (2) compared SGLT2i users and non-users (including other antihyperglycaemic agents), and (3) were observational studies, including cohort studies, case-control studies, and case series. Studies were excluded if they (1) were not original, (2) were in vivo or in vitro, or (3) involved fewer than 10 patients. For overlapping studies, the most recent or most comprehensive study was included.

2.4 | Data extraction

Two researchers (D. L. and G. S.) independently collected the data using a standardised data extraction spreadsheet, and any discrepancies were resolved by consensus. The extracted data included the name of the first author, publication year, study period, nation, study setting, number of patients, type of SGLT2i used, and patient demographics. To examine the clinical features of DKA, clinical symptoms, vital signs, and laboratory parameters were collected, including blood pH, bicarbonate, anion gap, glucose, HbA1c, electrolytes (e.g., Na⁺, K⁺, and Cl[−]), creatinine, and lactate, along with the assessment of euglycemic DKA, defined as DKA with a blood glucose level <250 mg/dL. Regarding the outcomes, the length of hospital stay, intensive care unit (ICU) admission, and in-hospital mortality were also collected.

2.5 | Assessment of study quality

Two researchers (D. L. and G. S.) independently assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies across three domains: selection of study subjects (0–4 points), comparability between groups (0–2 points), and outcome or exposure assessment (0–3 points), with a total possible score of 9. Studies scoring ≥7 were classified as high quality, while those scoring <7 were considered moderate to low quality.

2.6 | Statistical analysis

Pooled estimates for binary variables were calculated using odds ratios (OR) with 95% confidence intervals (CIs). For continuous

TABLE 1 Study characteristics of the included literature.

First author (year)	Study period	Nation	Setting	Types of diabetes mellitus	Types of SGLT2i used (%)	Number of patients (SGLT2i users/non-users)	Age (years) ^a		Male (%)	
							SGLT2i users	Non-users	SGLT2i users	Non-users
Almazrouei (2023) ¹⁴	From Jan 2017 to Mar 2021	United Arab Emirates	Single tertiary care hospital	T2DM (100%)	Canagliflozin (6%), dapagliflozin (41%), empagliflozin (53%)	17/38	58 ± 19	52 ± 19	7 (41%)	21 (55%)
Genc (2024) ¹⁵	From Apr 2018 to Nov 2022	Türkiye	Single tertiary care hospital	T1DM (49%), T2DM (43%), LADA (8%)	N/A	19/32	59 ± 18	37 ± 17	7 (39%)	11 (33%)
Hamblin (2019) ¹⁶	From Sep 2015 to Oct 2017	Australia	Eleven tertiary care hospital	T2DM (100%)	Canagliflozin (3%), dapagliflozin (49%), empagliflozin (49%)	37/125	64 (52–71)	65 (53–77)	20 (54%)	74 (59%)
Jeon (2019) ¹⁷	From Sep 2014 to Apr 2017	Republic of Korea	Nine hospitals, including four tertiary care hospitals	T1DM (36%), T2DM (51%), LADA (6%), Others/Unknown (7%)	Dapagliflozin (80%), empagliflozin (20%)	15/508	46 (36–63)	46 (32–58)	7 (47%)	292 (58%)
Keler (2024) ¹⁸	From 2013 to 2021	Israel	Single tertiary care hospital	T2DM (100%)	N/A	25/53	N/A	N/A	N/A	N/A
Khan (2024) ¹⁹	From Jan 2016 to Jun 2022	Canada	Single community hospital	T2DM (100%)	N/A	33/55	54 ± 5	56 ± 4	18 (55%)	28 (51%)
Nakhleh (2023) ²⁰	From Jul 2015 to Sep 2020	Israel	Single tertiary care hospital	T2DM (100%)	Dapagliflozin (37%), empagliflozin (63%)	16/55	65 ± 11	68 ± 14	9 (56%)	30 (54%)
O'Brolchain (2024) ²¹	From Apr 2015 to Jan 2022	Australia	Multi-centres	T2DM (100%)	N/A	94/70	63 ± 13	62 ± 17	52 (55%)	33 (47%)
Papanastasiou (2021) ²²	From 2018 to 2020	Greece	Single tertiary care hospital	T1DM (72%), T2DM (28%)	Dapagliflozin (67%), empagliflozin (33%)	6/12	53 [37–82]	42 [20–71]	1 (17%)	4 (33%)

Abbreviations: LADA, latent autoimmune diabetes in adults; N/A, not available; NOS, Newcastle–Ottawa Scale; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

^aAge was reported as mean ± standard deviation, median (interquartile range), or median [range].

TABLE 2 Baseline characteristics of diabetic ketoacidosis patients in SGLT2 inhibitor users versus non-users.

Factors	Number of studies	Number of patients (users/non-users)	Summary measure	Weighted mean or proportions (%)		Pooled estimates (95% CI)	I^2
				SGLT2i users	Non-users		
Age (years)	8	237/895	MD	58.6	55.3	3.3 (−2.4, 8.9)	72.7
Male	8	237/895	OR	50.8%	51.2%	0.98 (0.70, 1.36)	0.0
BMI (kg/m ²)	6	151/724	MD	26.3	25.2	1.1 (−0.0, 2.2)	0.0
Duration of diabetes (years)	6	179/781	MD	11.1	10.4	0.8 (−1.5, 3.0)	40.8
Antihyperglycaemic agents							
Metformin	5	197/330	OR	80.4%	51.9%	4.24 (2.26, 7.96)	42.5
Sulfonylureas	5	197/330	OR	25.3%	16.4%	1.63 (0.79, 3.37)	47.8
DPP-4 inhibitors	5	197/330	OR	31.0%	14.7%	2.59 (1.58, 4.23)	0.0
GLP-1 agonists	5	197/330	OR	8.7%	4.3%	3.09 (1.20, 7.97)	0.0
Insulin	7	218/850	OR	40.2%	58.0%	0.44 (0.25, 0.79)	52.0
History of diabetic ketoacidosis	3	126/616	OR	10.7%	24.0%	0.37 (0.19, 0.76)	0.0

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MD, mean difference; OR, odds ratio.

variables, the mean difference (MD) with 95% CIs is presented. In cases where studies only reported the median along with interquartile range or range, these values were converted to the mean and standard deviation using the formulas described by Wan et al.¹³ Weighted means and proportions for each variable in both groups were estimated based on the weights from the meta-analysis.

Meta-analysis was conducted when more than five studies could be included. A random-effects model was used to adopt a conservative approach and account for possible heterogeneity across studies. Heterogeneity was assessed using the I^2 statistic. Forest plots were used to summarise the results of the meta-analysis visually. Funnel plots were used to evaluate the publication bias. Sensitivity analyses were conducted within cohorts solely comprising individuals with T2DM to evaluate the consistency and reliability of the findings within this specific subgroup. All statistical analyses were performed using R software (version 4.4.2). Statistical significance was set at $p < 0.05$.

3 | RESULTS

A total of 1985 records were retrieved from the three databases, and one additional article was retrieved through a manual search (Figure S1). After removing 757 duplicate entries, 1229 studies remained for screening, and 1137 were excluded based on the initial title and abstract screening. Among the 92 studies for full-text review, 83 were excluded for the following reasons: non-original research ($n = 20$), case reports on SGLT2i-induced DKA ($n = 6$), studies exclusively investigating SGLT2i without non-users ($n = 22$), and comparative studies on DKA incidence between SGLT2i users and non-users

($n = 35$). Ultimately, nine studies were included in the meta-analysis.^{14–22}

Table 1 summarises the main characteristics of the included studies. Nine studies involving 1210 DKA cases (262 SGLT2i users and 948 non-users) were included in the analysis. Studies were published between 2019 and 2024 and conducted across multiple countries, including Australia, Canada, Hong Kong, Israel, South Korea, Türkiye, and the United Arab Emirates. The SGLT2i drugs used in these studies were empagliflozin, dapagliflozin, and canagliflozin. The quality scores assessed using the NOS were between 7 and 9.

Table 2 and Figures S2 and S3 display the baseline characteristics of DKA cases in SGLT2i users and non-users. No significant differences were found in age, proportion of males, or duration of diabetes. However, compared with DKA cases in non-users, DKA cases in SGLT2i users were less likely to have a previous history of DKA (OR = 0.37, 95% CI: 0.19–0.76, $p = 0.0061$, $I^2 = 0.0\%$). Different treatment patterns were observed in DKA cases between SGLT2i users and non-users: DKA cases in SGLT2i users were more likely to use metformin (OR = 4.24, 95% CI: 2.26–7.96, $p < 0.0001$, $I^2 = 42.5\%$), DPP-4 inhibitor (OR = 2.59, 95% CI: 1.58–4.23, $p = 0.0001$, $I^2 = 0.0\%$), and GLP-1 agonists (OR = 3.09, 95% CI: 1.20–7.97, $p = 0.0197$, $I^2 = 0.0\%$), whereas they were less likely to use insulin (OR = 0.44, 95% CI: 0.25–0.79, $p = 0.0062$, $I^2 = 52.0\%$).

Clinical symptoms of DKA appear to be similar between SGLT2i users and non-users, based on limited comparative data.^{14,20,22} Reported symptoms included nausea/vomiting (57.9%–76.5%), abdominal pain (42.1%–83.3%), fever (16.7%–50.0%), dyspnoea (16.7%–21.1%), and unconsciousness (12.5%–29.4%). The results of meta-analysis comparing clinical features and outcomes of patients with DKA who were SGLT2i users and non-users are summarised in

TABLE 3 Clinical features and outcomes of diabetic ketoacidosis patients in SGLT2 inhibitor users versus non-users.

Factors	Number of studies	Number of patients (users/ non-users)	Summary measure	Weighted mean or proportions (%)		Pooled estimates (95% CI)	I ²
				SGLT2i users	Non-users		
Clinical features							
pH	8	237/895	MD	7.2	7.2	0.0 (0.0, 0.0)	44.0
Bicarbonate (mmol/L)	8	237/895	MD	10.6	10.8	−0.3 (−1.3, 0.8)	42.1
Anion gap (mmol/L)	6	181/738	MD	24.6	24.6	−0.0 (−2.4, 2.3)	80.3
Euglycemic ketoacidosis	5	183/318	OR	43.6%	5.0%	22.40 (7.44, 67.47)	40.2
Glucose (mg/dL)	8	237/893	MD	335.8	554.2	−218.4 (−275.7, −161.1)	79.5
HbA1c (%)	8	236/882	MD	10.0	11.3	−1.2 (−2.1, −0.4)	73.6
Na ⁺ (mmol/L)	4	58/137	MD	135.7	131.6	4.1 (2.3, 6.0)	0.0
K ⁺ (mmol/L)	4	58/137	MD	4.5	4.7	−0.2 (−0.5, 0.0)	6.9
Cl [−] (mmol/L)	3	52/125	MD	101.2	94.7	6.5 (−0.6, 13.5)	79.0
Creatinine (mg/dL)	6	106/700	MD	1.1	1.3	−0.1 (−0.2, −0.1)	0.0
Lactate (mmol/L)	4	166/264	MD	2.2	2.5	−0.3 (−0.6, −0.0)	16.2
Systolic blood pressure (mmHg)	3	38/558	MD	119.5	125.8	−6.3 (−21.0, 8.5)	72.9
Heart rate (bpm)	4	54/613	MD	104.9	103.4	1.5 (−4.8, 7.7)	17.0
Outcomes							
Hospitalisation (days)	6	185/808	MD	7.6	6.1	1.5 (−0.8, 3.8)	70.1
Intensive care unit admission	3	148/233	OR	50.7%	46.8%	1.23 (0.43, 3.49)	68.7
In-hospital mortality	5	110/779	OR	6.1%	11.9%	0.51 (0.20, 1.29)	0.0

Abbreviations: MD, mean difference; OR, odds ratio.

Table 3, and their forest and funnel plots are displayed in Figures S4--S7. Among DKA cases, the decrease in pH was less pronounced in SGLT2i users than in non-users, whereas bicarbonate levels and anion gaps were not significantly different between the two groups. Serum ketone levels in DKA cases among SGLT2i users were generally comparable to or slightly lower than those in non-users.^{16,19,21} Two studies reported no significant differences between groups ($p = 0.94$ and $p = 0.19$, respectively),^{16,21} whereas Khan et al. demonstrated lower β -hydroxybutyrate levels in SGLT2i users compared with non-users (7.7 vs. 8.3 mmol/L).¹⁹ Especially, euglycemic DKA accounted for a 22.4-fold (95% CI: 7.4–67.5) higher proportion of DKA cases in SGLT2i users than in non-users. DKA cases in SGLT2i users had significantly lower blood glucose (MD = -218.4, 95% CI: -275.7 to -161.1, $p < 0.0001$, $I^2 = 79.5\%$) and HbA1c levels (MD = -1.2, 95% CI: -2.1 to -0.4, $p = 0.0027$, $I^2 = 73.6\%$) compared with DKA cases in non-users. Regarding the electrolytes, DKA cases in SGLT2i users exhibited a less pronounced decrease in sodium levels (MD = 4.1, 95% CI: 2.3–6.0, $p < 0.0001$, $I^2 = 0.0\%$) than DKA cases in non-users, whereas no significant differences were observed in potassium level and chloride level. SGLT2i users had a small but less pronounced increase in creatinine levels (MD = -0.1, 95% CI: -0.2 to -0.1, $p = 0.0007$, $I^2 = 0.0\%$) and lactate (MD = -0.3, 95% CI: -0.6 to -0.0, $p = 0.0239$, $I^2 = 16.2\%$). No statistically significant differences

were observed in the systolic blood pressure or heart rate between SGLT2i users and non-users of DKA. With respect to DKA outcomes, no significant differences were observed in the length of hospitalisation ($p = 0.211$, $I^2 = 70.1\%$), ICU admission ($p = 0.697$, $I^2 = 68.7\%$), or in-hospital mortality ($p = 0.156$, $I^2 = 0.0\%$).

A sensitivity analysis was conducted within cohorts exclusively composed of patients with T2DM, excluding three studies that included patients with type 1 diabetes mellitus and latent autoimmune diabetes^{15,17,22} (Table S1). The findings from this analysis were largely consistent with those of the main analysis, with the exception of the creatinine level, which lost statistical significance.

4 | DISCUSSION

This systematic review and meta-analysis summarised the characteristics and clinical features of patients using SGLT2i compared with those of non-users by synthesising results from multiple studies of DKA cases in both groups. The findings indicated that among the DKA cases, SGLT2i users were less likely to use insulin and had a history of previous DKA. Clinically, SGLT2i users with DKA exhibited lower blood glucose and HbA1c levels and had less decreased pH and sodium concentrations. However, no significant differences were

observed in the clinical outcomes of DKA, such as the length of hospital stay, ICU admission, and in-hospital mortality between the two groups.

The distinct pathophysiology of SGLT2i-associated DKA can be attributed to the glucose-lowering mechanism of SGLT2i, which acts by inhibiting SGLT2 in the proximal renal tubules, preventing glucose reabsorption, and increasing urinary glucose excretion. As SGLT2i promotes glucose excretion, blood glucose levels can remain low even when insulin production or activity is insufficient.^{23,24} In addition, SGLT2i stimulates glucagon release, while suppressing insulin secretion. Elevated glucagon levels enhance hepatic gluconeogenesis and lipolysis, driving ketone body formation such as β -hydroxybutyrate and acetoacetate.^{24,25}

The baseline characteristics of DKA cases in SGLT2i users revealed notable differences compared with those in non-users, particularly regarding the prescribed patterns of antihyperglycaemic agents and prior history of DKA. Traditionally, precipitating factors for DKA include insulin non-adherence or inadequate dosing, infection, psychological stress (e.g., surgery, trauma), and a prior history of DKA.^{1,26} However, DKA cases in SGLT2i users were less commonly associated with traditional precipitating factors, such as insulin use, which was 50% lower, and a prior history of DKA, which was 60% lower in our analysis. This indicates that DKA can develop even in the absence of these precipitating factors among SGLT2i users, which highlights the need for increased awareness and caution when prescribing SGLT2i, even in patients without the typical risk factors associated with DKA.

DKA cases in SGLT2i users had lower elevations in blood glucose and HbA1c levels than those in non-users. In addition, approximately half of these cases were euglycemic, whereas 5% of DKA cases in non-users were euglycemic. Unlike typical DKA, which is primarily driven by insulin deficiency or resistance, euglycemic DKA associated with SGLT2i is mainly related to carbohydrate deficiency and an increased glucagon/insulin ratio.²⁷ This difference in pathophysiology may help explain why insulin use was less related to SGLT2i-associated DKA. In 2015, the FDA issued a safety alert regarding the risk of DKA with SGLT2i, noting that recognition could be delayed because blood glucose levels may not be markedly elevated.²⁸ This unique feature of SGLT2i-associated DKA makes the detection of DKA in SGLT2i users challenging because euglycemia can mask the typical signs of DKA, complicating early diagnosis and management.

Typically, DKA is characterised by hyperglycaemia and acidosis, which lead to dilution of sodium levels.^{1,3} However, in our meta-analysis, SGLT2i users had slightly higher serum sodium levels than in non-users, although these levels remained within the normal range. This can be explained by compensatory sodium retention, which offsets the sodium loss caused by osmotic diuresis due to SGLT2i use.²⁹ As a result, serum sodium levels may appear normal or even slightly elevated despite significant acidosis, which can delay the diagnosis. Therefore, close monitoring and a thorough understanding of the unique characteristics of SGLT2i-associated DKA are warranted.

In this study, no significant differences were observed in the key outcomes of DKA, including the length of hospitalisation, ICU

admission, and in-hospital mortality. Given the limited number of studies included in this analysis, particularly those on ICU admission and in-hospital mortality, further studies are warranted.

This study has several limitations that should be considered when interpreting the results. First, research from African and Western European countries is limited, which may have affected the generalisability and applicability of the findings. Second, there were a small number of studies on certain factors (e.g., history of DKA and ICU admission), which could limit the provision of more comprehensive results. However, according to Herbison et al., meta-analyses involving a small number of studies can yield robust results that align with long-term research.³⁰ Third, the lack of matching or adjustment for confounding variables between SGLT2i users and non-users may have introduced a bias. Fourth, although high heterogeneity was not observed in most factors, except for the anion gap, glucose, and Cl^- , there was clinical heterogeneity regarding the clinical setting, type of SGLT2i, treatment duration, and co-administered drugs, which may have affected the study results. Finally, we were not able to apply the GRADE framework to evaluate the overall certainty of evidence, as our study focuses on comparing clinical features between DKA cases among the SGLT2i users and non-users, rather than on evaluating intervention effects. Given the observational nature of the study and the limited number of studies, which restrict the generalisability of the findings, caution is warranted when interpreting the results.

5 | CONCLUSION

In summary, this meta-analysis provides quantitative evidence of the distinct clinical features of SGLT2i-associated DKA compared with DKA in non-users. These findings may contribute to a better understanding of SGLT2i-associated DKA and offer valuable insights to support its early detection, treatment, and prevention in clinical practice.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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