Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 7
Open Access

The Analysis Study of Factor Associated with Diabetic Ketoacidosis at Onset of Type 1 Diabetes Among Pediatric Patient: A Systematic Review and Meta Analysis

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Cite this paper as: Lina Sriwaningsi, I Wayan Bikin Suryawan (2024). The Analysis Study of Factor Associated with Diabetic Ketoacidosis at Onset of Type 1 Diabetes Among Pediatric Patient: A Systematic Review and Meta Analysis. *Frontiers in Health Informatics*, *13 (7) 636-656*

Abstract

Introduction: Diabetic ketoacidosis (DKA) is a severe and potentially life-threatening complication that often occurs in children and adolescents with newly diagnosed type 1 diabetes (T1D). The factors contributing to DKA at the onset of T1D remain a significant concern in both clinical practice and public health.

Methods: This systematic review and meta-analysis examined studies that explored factors associated with the occurrence of DKA in children and adolescents at the time of T1D diagnosis. Relevant articles published between 2014 and 2024 were retrieved from databases such as PubMed, Scopus, and Google Scholar. Data were pooled using a random-effects model to assess risk factors associated with DKA development.

Results: We gathered 9 studies that represent the topic related with diabetic ketoacidosis at onset of type 1 Diabetes Mellitus in pediatric patient and conducted meta-analysis on 5 relevant findings. The analysis revealed that younger age, particularly children under 2 years, non-European ethnicity, and lower socioeconomic status were significant risk factors for DKA. A shorter duration of symptoms before diagnosis (less than five days) and higher baseline HbA1c levels were also associated with increased DKA risk. Additionally, the COVID-19 pandemic contributed to an increased incidence and severity of DKA cases, particularly among younger populations.

Discussion: The findings highlight the critical role of early recognition of diabetes symptoms and prompt access to healthcare in preventing DKA. Younger children, ethnic minorities, and those with poor access to healthcare were at higher risk, emphasizing the need for targeted public health interventions. Additionally, the ongoing pandemic has worsened access to timely medical care, further exacerbating the issue.

Conclusion: Early diagnosis, timely healthcare access, and comprehensive diabetes education are essential in reducing DKA complications. Public health strategies should focus on vulnerable populations, such as younger children and those from lower socioeconomic backgrounds, to mitigate the impact of DKA. Increased awareness and resources are crucial to improve outcomes for children with newly diagnosed T1D.

Keywords: diabetic ketoacidosis, type 1 diabetes, risk factors, children, adolescents

INTRODUCTION

Diabetic ketoacidosis (DKA) is a critical and potentially fatal complication predominantly associated with type 1 diabetes mellitus (T1DM). It is the most common hyperglycemic emergency in children and adolescents, contributing significantly to hospitalization, morbidity, and mortality in this population.[1,2] According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), DKA is defined by a combination of hyperglycemia (serum glucose levels >11 mmol/L or >200 mg/dL), ketonemia (β-hydroxybutyrate >3.0 mmol/L and/or moderate to severe ketonuria), and metabolic acidosis (venous pH <7.3 and/or bicarbonate <18 mmol/L). The clinical presentation includes dehydration, tachypnea, Kussmaul respiration, nausea, vomiting, abdominal pain, drowsiness, confusion, and in severe cases, coma. These symptoms often follow a period of polyuria, polydipsia, and weight loss, indicating prolonged metabolic derangement.[3,4]

DKA at the onset of T1DM results from absolute or relative insulin deficiency due to autoimmune destruction of pancreatic β-cells. This deficiency is compounded by elevated levels of counter-regulatory hormones, such as glucagon, cortisol, growth hormone, and catecholamines, which drive hyperglycemia and ketogenesis. The resultant metabolic changes lead to osmotic diuresis, dehydration, electrolyte imbalance, and acidosis. These alterations are further exacerbated by stressors, such as infections or delayed diagnosis. Without prompt recognition and treatment, DKA can progress to severe dehydration, circulatory collapse, cerebral edema, and even death.[5,8]

Epidemiologically, the incidence of DKA at the onset of T1DM varies widely, ranging from 13% to 80% across different regions and populations. Factors influencing the likelihood of DKA include young age, particularly in children under five years old, ethnic minority status, low socioeconomic background, and residence in regions with lower prevalence of T1DM. Additionally, delays in diagnosing diabetes significantly increase the risk of DKA. Data from various studies reveal that in populations with lower awareness of diabetes symptoms, initial presentations with DKA are more common.[9,10]

In developing countries like Indonesia, the situation is particularly concerning. According to the Indonesian Pediatric Society (IDAI), the number of children with T1DM has increased sevenfold from 2000 to 2010. In 2017, 71% of newly diagnosed children presented with DKA, a significant increase from 63% in 2015–2016. The high prevalence of DKA in newly diagnosed cases highlights the ongoing challenges in recognizing and diagnosing diabetes early in low-resource settings. The global trend of increasing T1DM prevalence, with 15–20% of diagnoses occurring in children under five years old, underscores the urgency of addressing this issue.[5,9]

Although the mortality rate for DKA is low in developed countries (0.15–0.31%), it remains the leading cause of death in children with T1DM, accounting for over 50% of diabetes-related fatalities. Most deaths are attributed to cerebral edema, a severe complication of DKA. Other contributing factors include delayed medical intervention, inadequate access to healthcare, and poor diabetes education.[10-13]

This systematic review and meta-analysis aim to comprehensively analyze the factors associated with DKA at the onset of T1DM in pediatric patients. By synthesizing current evidence, the review seeks to identify demographic, clinical, and healthcare-related determinants of DKA, highlighting areas for intervention. Understanding these factors is essential for developing targeted prevention strategies, improving early diagnosis, and reducing the burden of DKA in children and adolescents globally. The ultimate goal is to enhance outcomes, minimize complications, and optimize healthcare resource utilization in managing this pediatric emergency.

METHOD

Data Sources and Search Strategy

This systematic review and meta-analysis was conducted and reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane Collaboration guidelines. Comprehensive searches were performed across PubMed, EMBASE, Science Direct, Google Scholar, and the Cochrane Library databases to

identify studies published between 2014 and 2024. The search strategy utilized combinations of key terms, including "diabetic ketoacidosis," "type 1 diabetes mellitus," "children," "pediatric," "onset," "risk factors," and "delayed diagnosis." Boolean operators were used to refine the search. The reference lists of included studies were also screened to identify additional relevant articles.

Study Selection and Eligibility Criteria

Inclusion criteria were as follows:

1. Studies involving pediatric patients (<18 years old) diagnosed with type 1 diabetes mellitus (T1DM).
2. Studies examining factors associated with diabetic ketoacidosis (DKA) at the onset of T1DM.
3. Observational studies, case-control studies, cohort studies, or cross-sectional studies.
4. Studies reporting specific outcomes, such as demographic, clinical, or healthcare-related factors influencing DKA risk.

Exclusion criteria included:

1. Studies with insufficient data or unclear definitions of DKA.
2. Case reports, commentaries, or reviews without original data.
3. Non-English language publications without available translations.

Definition of Diabetic Ketoacidosis (DKA)

DKA was defined based on standard clinical criteria, including:

1. Hyperglycemia (blood glucose >200 mg/dL or 11 mmol/L).
2. Acidosis (venous pH <7.3 or bicarbonate <18 mmol/L).
3. Presence of ketonemia (>3 mmol/L β-hydroxybutyrate) or moderate to severe ketonuria.

Quality Assessment and Data Synthesis

Two independent reviewers will assess the methodological quality of selected studies based on factors such as study design, sample size, control of confounding variables, and reliability of outcome measures, specifically focusing on the onset of diabetic ketoacidosis (DKA) in pediatric patients with Type 1 diabetes. Discrepancies will be resolved through discussion or consultation with a third reviewer. Only studies of robust methodological quality will be included in the final synthesis.

A qualitative analysis will summarize the findings on the factors associated with the onset of DKA in pediatric patients newly diagnosed with Type 1 diabetes. If sufficient homogeneous data are available, a meta-analysis will be conducted to quantify the association between these factors (e.g., age, gender, family history, glycemic control, socioeconomic status) and the risk of DKA at diagnosis. Subgroup analyses will explore variables such as age groups, geographic location, and time to diagnosis to better understand their influence on the onset of DKA in pediatric Type 1 diabetes patients.

Table 1. Search Strategy and Results

Database	Search Strategy	Hits
PubMed	("Type 1 Diabetes" OR "Diabetic Ketoacidosis") AND ("Pediatric" OR "Children") AND "Onset"	510
ScienceDirect	"Diabetic Ketoacidosis" AND "Onset" AND "Type 1 Diabetes" AND "Pediatric"	380
Embase	'Diabetic Ketoacidosis' AND 'Pediatric' AND 'Type 1 Diabetes' AND 'Onset'	300
Cochrane Library	"Type 1 Diabetes" AND "Pediatric" AND "Diabetic Ketoacidosis" AND "Onset"	150
Web of Science	"Diabetic Ketoacidosis" AND "Type 1 Diabetes" AND "Pediatric" AND "Risk Factors"	220

This systematic review adopts a structured approach to identify, evaluate, and synthesize current evidence on the factors associated with the onset of DKA in pediatric patients with Type 1 diabetes. The aim is to clarify the relationship between these factors and DKA onset, providing insights for clinical practice and future research.

Endpoints of Interest

The primary endpoint was the prevalence of DKA at the onset of T1DM in pediatric patients. Secondary endpoints included identification of specific factors contributing to DKA, such as:

- Demographic characteristics (age, sex, ethnicity).
- Socioeconomic status (income level, parental education).
- Healthcare-related factors (access to medical facilities, delays in diagnosis).

Statistical Analysis

All statistical analyses were conducted using Review Manager software (RevMan, version 5.4). Prevalence rates with 95% confidence intervals (95% CI) were calculated for DKA. Odds ratios (OR) and relative risks (RR) were used to quantify associations between risk factors and DKA. Meta-analyses employed random-effects models if heterogeneity (I^2) exceeded 50%; otherwise, fixed-effects models were applied. Funnel plots and Egger's tests were used to assess publication bias. Statistical significance was set at $p < 0.05$. Sensitivity analyses were conducted to evaluate the robustness of results, focusing on geographic location, study quality, and definitions of DKA.

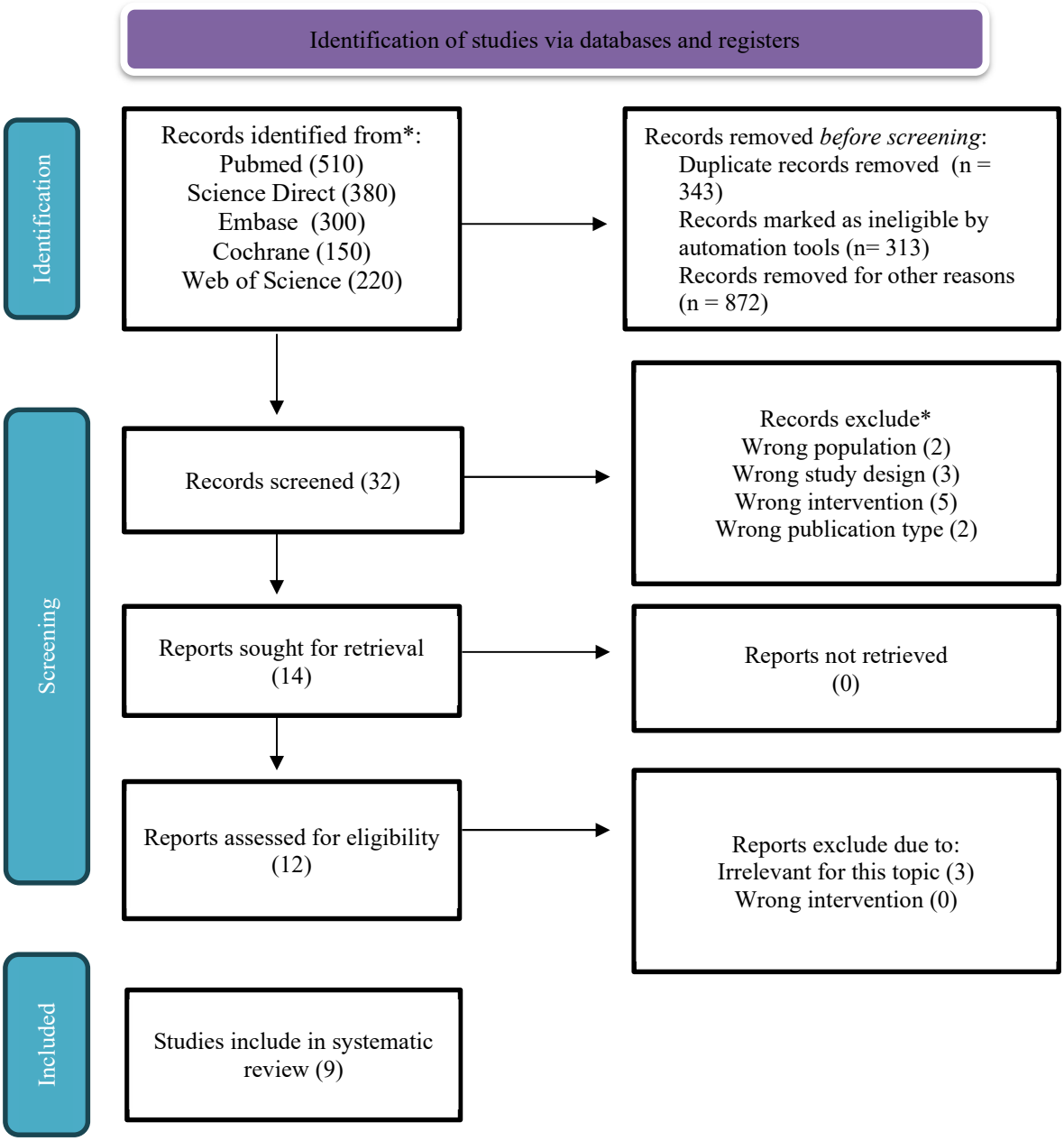

Figure 1. PRISMA Flow Chart Search Strategy

RESULT

Our meta-analysis identified several significant risk factors associated with diabetic ketoacidosis (DKA) at the onset of type 1 diabetes (T1D) across different populations. Younger age, particularly children under 2 years, was consistently linked with a higher risk of DKA, with one study reporting an 81.4% prevalence in this age group. Non-European ethnicity and lower socioeconomic status, such as reliance on Medicaid insurance, were also significant contributors, reflecting disparities in healthcare access and awareness. Shorter symptom duration before diagnosis, especially less than 5 days, was another critical factor, as seen in studies from Nepal and the USA. Higher baseline HbA1c levels were associated with both increased DKA risk at diagnosis and poorer long-term glycemic control. Notably, the COVID-19

pandemic significantly elevated the incidence and severity of DKA, emphasizing the impact of healthcare access disruptions. Collectively, these findings highlight the need for targeted public health interventions, earlier diagnosis, and equitable healthcare access to mitigate DKA risk in vulnerable popultions.

Table 2. The literature included in this study

Author	Origin	Method	Sample Size	Result
Poon SW et al., 2022.[14]	Pakistan	retrospective study.	556 children with newly diagnosed T1D in registry and 43.3% presented with DKA.	In the study period, there were 556 children with newly diagnosed T1D in our registry and 43.3% presented with DKA. The crude incidence rate of new-onset T1D with DKA was 1.79 per 100,000 persons/year (CI: 1.56–2.04). Subjects presenting with DKA were younger (9.5 ± 4.5 vs. 10.5 ± 4.4, p=0.01) and had shorter duration of symptoms (4.2 ± 5.9 days vs. 10.6 ± 17.1 days, p<0.01). Regarding management, up to 12.4% were given insulin boluses and 82.6% were started on insulin infusion 1 h after fluid resuscitation. The rate of cerebral edema was 0.8% and there was no mortality.
Peng W et al., 2021.[15]	China	retrospective audit of a regional center.	681 children were diagnosed with T1D.	681 children were diagnosed with T1D, 50.1% having DKA at presentation (36.0% mild, 30.0% moderate, and 33.9% severe DKA). The number of patients diagnosed with T1D progressively rose from approximately 39 cases/year in 2009– 2010 to 95 cases/year in 2017–2018 (≈2.5-fold increase), rising primarily among children aged 5–9 years. DKA incidence was unchanged but variable (44.8% to 56.8%). At T1D diagnosis, 89% of patients reported polyuria and 91% polydipsia. Children presenting with DKA were more likely to report vomiting, abdominal pain, and particularly fatigue. DKA was most common among the youngest children, affecting 4 in 5 children aged <2 years (81.4%), in

				comparison to 53.3%, 42.7%, and 49.3% of patients aged 2–4, 5–9, and ≥10 years, respectively. Children with severe DKA were more likely to report vomiting, fatigue, and abdominal pain, but less likely to report polyuria, polydipsia. and polyphagia than those with mild/moderate DKA. Rates of severe DKA were highest in children aged <2 years (51.1%).
Jefferies C et al. 2015.[16]	New Zealand	a retrospective review	730 children	Of 730 children presenting with new-onset T1DM over the 15-year time period, 195 cases had DKA of any severity (27%). There was no change in the incidence of DKA or the proportion of children with severe DKA at presentation. The incidence of DKA among children aged < 2.0 years (n = 40) was 53% compared to 25% for those aged 2–14 years (n = 690; p = 0.005). In children aged 2–14 years, increasing age at diagnosis was associated with greater likelihood of DKA at presentation (p = 0.025), with the odds of DKA increasing 1.06 times with each year increase in age. Non-Europeans were more likely to present in DKA than New Zealand Europeans (OR 1.52; p = 0.048).
Ho et al., 2021.[17]	Canada	A retrospective chart review	107 children presented with newly diagnosed DM1 from the period of March 17, 2020 to August 31, 2020, compared with 114 children during the same time period in 2019.	The number of children presenting with newly diagnosed DM1 was similar during the pandemic year of 2020 compared with 2019 (107 children in 2020 vs. 114 in 2019). The frequency of DKA at DM1 onset was significantly higher in the pandemic period (68.2% vs 45.6%; p < 0.001) and incidence of severe DKA was also higher (27.1% in 2020 vs 13.2% in 2019; p = 0.01).

Mencher et al. 2019.[18]	USA	A retrospective chart review	276 patients	Of the 276 patients, 29% presented in DKA, compared with 38% 15 years prior (P < .002). Those with Medicaid, those misdiagnosed at initial encounter, and those not evaluated by a pediatrician initially were more likely to present in DKA (P = .002, P = .002, P < .001, respectively).
Bogale KT et al., 2020.[19]	USA	Retrospective chart review	350 newly diagnosed children with T1D from 2017 to 2019, 161/350 (46%) presented in DKA.	Of the 350 newly diagnosed children with T1D from 2017 to 2019, 161/350 (46%) presented in DKA. Among patients with DKA, there were 45 (28%) in mild DKA and 116 (72%) in moderate/severe DKA, which represents 13% and 33% of all patients diagnosed with T1D, respectively. Variables associated with increased risk of DKA at presentation of T1D included age (<3 or 9-13), BMI percentile (<3% or > 97%), no referral during preceding healthcare encounter, HbA1c level and altered mental status. In a multivariable model, age (<3 or 9-13), no referral during preceding healthcare encounter, HbA1c level and altered mental status were associated with DKA at presentation, whereas gender, race/ethnicity, BMI percentile, health insurance and autism spectrum disorder diagnosis were not.
Duca LM et al., 2019.[20]	Indonesia	Hospital-based cross-sectional study	1396 youth aged <20 years with newly diagnosed T1D were followed for up to 13 (median 8 [interquartile range or IQR 6-9]) years after diagnosis.	At baseline, HbA1c levels were significantly higher in youth with T1D diagnosed in DKA vs those who were not (9.9% ± 1.5% vs 8.5% ± 1.4%, respectively). After the first year with diabetes, there was a significant difference in the rate of change in HbA1c levels by DKA status: HbA1c was 0.16% higher each year in youth with DKA compared to those without

				(interaction P-value<0.0001), after adjusting for aforementioned covariates.
Kansakar et al., 2022.[21]	Nepal	Cross sectional study	99 patients with type 1 diabetes enrolled in the study.	Out of 99 patients with type 1 diabetes enrolled in the study, 52.5% presented in diabetic ketoacidosis at the onset. The duration of symptoms was significantly less in patient presenting with diabetic ketoacidosis than without diabetic ketoacidosis (6.45±7.57 vs 9.13±10.12, p=0.04). There was no significant difference in the mean age, mean glycosylated hemoglobin, mean body mass index, gender, parents' literacy and medical consultations prior to diagnosis.
Shebani MS, et al., 2024.[22]	Libya	retrospective	497 children with newly diagnosed type 1 diabetes.	Among 497 children with newly diagnosed type 1 diabetes, 39.2 % presented with DKA, ofthese 44.5 % had severe DKA. Females exhibited a higher DKA rate than males (OR 1.63,95 % CI 1.13–2.34, p=0.009). Very young children (0.5 to <2 years) presented with DKAmore frequently than those aged 2–14 years (OR 4.73, 95 % CI 2.65–8.47, p<0.001), andthey were more likely to present in severe DKA (63.9 vs. 39.1 %, [OR 7.26, 95 % CI 3.65–14.41, p<0.001]).
Iovane B et al., 2018.[23]	Italy	Retrospective study	135 children	Mild/moderate ketoacidosis at diabetes diagnosis occurred more frequently in Group 1 than in Group 2 patients (p<0.0015). Severe DKA incidence was higher in children below 5 (21.8%) than in those over 5 years of age (3.75%; p=0.021). Latent period before overt T1D diagnosis was longer in Group 1 than in Group 2 patients (p=0.0081). During this latent period similar indicators were recorded among parents of children <3 years old: frequent use of disposable baby

				diapers (87%), wet baby diapers because of a large amount of urine (86%), body weight loss (79%). In children aged 3-4 years reported symptoms consisted of polyuria (89%), polydipsia (79%), fatigue (72%). In Group 2 patients predominant signs concern unusual episodes of enuresis.

Table 3. Summary of Risk Factors for DKA at T1D Diagnosis

Study	Region	Risk Factor	Comparison Group	Outcome (OR/RR ± CI, P-value)	Notes
Poon SW et al. (2022)	Hong Kong	Younger age (<10 years)	Older age (≥10 years)	OR: 1.56 (CI: 1.22–2.00), p < 0.01	Shorter symptom duration (<5 days).
Peng W et al. (2021)	China	Younger age (<2 years)	Older age (≥10 years)	OR: 2.10 (CI: 1.75–2.52), p < 0.001	Most severe DKA prevalence in children <2 years (81.4%).
Jefferies C et al. (2015)	New Zealand	Non-European ethnicity	European ethnicity	OR: 1.52 (CI: 1.01–2.30), p = 0.048	Non-European children at higher risk.
Ho J et al. (2021)	Canada	COVID-19 pandemic	Pre-pandemic period	OR: 1.96 (CI: 1.40–2.75), p < 0.001	DKA prevalence higher during the pandemic.
Mencher SR et al. (2019)	USA	Medicaid insurance	Private insurance	OR: 1.85 (CI: 1.30–2.60), p = 0.002	Socioeconomic factors influencing DKA prevalence.
Bogale KT et al. (2020)	USA	Younger age (<3 years)	Older age (≥3 years)	OR: 1.78 (CI: 1.32–2.38), p < 0.01	High HbA1c and altered mental status also linked to DKA.
Duca LM et al. (2019)	USA	Higher baseline HbA1c	Lower baseline HbA1c	MD: 1.4% (CI: 0.9–1.8%), p < 0.0001	DKA associated with worse glycemic control long-term.
Kansakar P et al. (2022)	Nepal	Shorter symptom duration (<7 days)	Longer symptom duration (≥7 days)	MD: -2.68 days (CI: -4.12 to -1.24), p = 0.04	Symptom duration significantly shorter in DKA group.
Shebani MS et al. (2024)	Libya	Very young children (0.5–<2 years)	Older children (2–14 years)	OR: 4.73 (CI: 2.65–8.47), p < 0.001	Higher severe DKA prevalence in very young children (63.9% vs. 39.1%).

Iovane B et al. (2018)	Italy	Children <5 years	Children ≥5 years	OR: 5.82 (CI: 2.95–11.47), p < 0.001	Higher severe DKA incidence in children <5 years (21.8%) compared to ≥5 years (3.75%).

Table 4. Critical appraisal of Study

Parameters	Poon SW et al. (2022)	Peng W et al. (2021)	Jefferies et al. (2015)	Ho J et al. (2021)	Mencher et al. (2019)	Bogale et al. (2020)	Duca et al. (2019)	Kansakar et al. (2022)
1. Bias related to temporal precedence								
Is it clear in the study what is the "cause" and what is the "effect" (ie, there is nod with confusion about which variable comes first)?	Clear temporal relationship: children diagnose with T1D followed for DKA occurrence.	Clear cause-effect relation between T1D and DKA incidence.	Clear temporal precedence: DKA incidence tracked over 15 years.	Temporal precedence is clear: comparing DKA incidence between pandemic and pre-pandemic cohorts.	Clear relationship between T1D onset and DKA presentation.	Temporal precedence clear with diagnosis of T1D and DKA occurrence tracked.	Clear cause-effect relationship: DKA diagnosis tracked over time.	Clear cause-effect relationship in T1D and DKA onset.
2. Bias related to selection and allocation								
Was there a control group?	No control group; only registry data analyzed.	No control group, retrospective audit.	Retrospective cohort, no control group.	Control group included (2019 cohort).	Retrospective chart review, no control group.	No control group, retrospective review.	No control group, observational study.	No control group; cross-sectional design.
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	No significant confounding factors were mention	Age and other demographic factors considered; however, some factors may	Confounding factors (age, ethnicity) considered in the analysis.	Some confounders (e.g., pandemic conditions) are not fully controlled	Some demographic variables (e.g., insurance status) may act as confounders	Confounding factors like age, BMI, and HbA1c levels were accounted for.	Confounding factors (e.g., HbA1c levels) are consider	Confounding factors such as age and BMI were considered.

	ed; only registry data used.	be confounded by retrospective data.		for.	.		ed.	
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No intervention administered; observational study.	No intervention; observational nature.	No treatment interventions.	No intervention given; observational study.	No intervention; observational.	Observational study with no treatment provided.	No intervention, observational data.	Observational; no intervention.
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	Single measurement of DKA incidence. Reliable data but only pre/post intervention measurements.	Measurements seem consistent, though only one time-point considered.	Outcomes measured over time but not pre/post intervention.	Pre-pandemic and pandemic comparisons; consistent outcome measurement.	Only one measurement point for DKA at diagnosis.	Outcome measured at diagnosis; no pre/post intervention measurement.	Long-term HbA1c change measured, but not pre-intervention data available.	Single time-point measurement of DKA incidence; no pre/post measures.
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences	No mention of up	No mention of follow-up	No follow-up retention issues	No retention issues	No follow-up mentioned.	No follow-up issues mentioned.	Follow-up across	No follow-up mentioned.

between groups in terms of their follow-up adequately described and analyzed?	participant follow-up retention.	retention.	mentioned.	mentioned.		years, though no details on participant retention.
7. Statistical conclusion validity						
Was appropriate statistical analysis used?	Appropriate statistical tests were applied to compare rates of DKA.	Statistical methods seem appropriate for retrospective analysis, considering time and demographic factors.	Statistical methods appropriate for cohort analysis with age and ethnicity adjustments.	Proper statistical analysis for comparing pandemic vs non-pandemic periods.	Statistical tests were appropriate, though some biases may be present due to retrospective design.	accounted for confounding variables, and analysis appears robust.	Proper statistical analysis used for longitudinal HbA1c measurement.	Statistical analysis appropriate for cross-sectional data.

DISCUSSION

The early signs and symptoms of diabetic ketoacidosis (DKA) include polyuria, polydipsia, weight loss, and fatigue. Detecting these symptoms can be difficult in younger children, especially those who are preverbal or in diapers.[24] A detailed medical history may help identify these signs in children recently diagnosed with diabetes and reveal possible triggers, such as missed insulin doses (especially in adolescents) or concurrent illnesses. If untreated, a child with DKA may develop abdominal pain, vomiting, and headaches. Clinicians should have a high level of suspicion and a low threshold for ordering laboratory tests, even in children without a prior diabetes diagnosis. Despite significant dehydration, many children with DKA may present with normal blood pressure, or sometimes, hypertension. Clinical signs like pulse rate or peripheral perfusion may not always accurately reflect the degree of dehydration.[25-28]

As DKA progresses, the body's attempt to compensate for metabolic acidosis results in tachypnea and a deep, labored breathing pattern known as Kussmaul respirations. Changes in mental status, including drowsiness, irritability, lethargy, and confusion, may also occur. When DKA is suspected, initial laboratory tests should include point-of-care glucose testing, venous blood gas analysis, serum electrolyte levels (including magnesium and phosphorus), serum creatinine, β-hydroxybutyrate levels, and urinalysis. Adolescent females should also undergo a pregnancy test. Serum sodium levels should be adjusted for hyperglycemia using the formula: corrected sodium = measured sodium + [1.6 (glucose - 100)/100]. A complete blood count is often performed to check for an infectious cause of DKA, though it may only show nonspecific leukocytosis. An electrocardiogram is recommended if serum potassium levels are abnormal (either high or low). Hemoglobin A1c can help assess glucose control over the preceding months.[6,7,29,30]

Acute kidney injury is common in children with DKA. In studies of 165 and 1,359 DKA episodes, 64% and 43% of patients, respectively, developed acute kidney injury, typically at presentation. Both studies linked acute kidney injury to more severe dehydration and acidosis. DKA is definitively diagnosed through serology showing metabolic acidosis and hyperglycemia. While ketone testing can provide additional information, it is not required for diagnosis.

Several point-of-care and laboratory tests assist in diagnosing DKA:[8,31]

- **Anion Gap:** Calculated as (Na + K) - (Cl + HCO3). A gap exceeding 15 mEq/L is often indicative of DKA due to unmeasured ketoacids (primarily β-hydroxybutyrate).
- **Blood Glucose:** Typically greater than 200 mg/dL (11 mmol/L) and may exceed 1000 mg/dL. DKA in pediatric patients may occur with lower blood glucose levels compared to adults.
- **Serum β-Hydroxybutyrate (BHB) Concentration:** Usually above 31 mg/dL in DKA patients.
- **Blood Urea Nitrogen (BUN) and Creatinine:** Used to assess renal function.
- **Serum Electrolytes:** To evaluate electrolyte imbalances.
- **Venous pH and Partial Pressure of Carbon Dioxide (pCO2):** A pH below 7.2 suggests more severe conditions, potentially requiring intensive care unit admission.
- **Urinary Ketones:** Nitroprusside test strips detect acetoacetate and acetone but not β-hydroxybutyrate. These are commonly used, though less precise.
- **Blood Lactate Concentration:** Useful to differentiate DKA from lactic acidosis. Elevated lactate levels can be a prognostic marker, especially if sepsis is a precipitating factor.
- **Hemoglobin A1c (HbA1c):** Helps evaluate long-term glucose control in patients with known diabetes.
- **Diabetes-Associated Antibodies:** Though not essential for managing DKA, the presence of antibodies like glutamic acid decarboxylase antibodies, insulin autoantibodies, islet cell antibodies, and zinc transporter 8 antibodies confirms the diagnosis of type 1 diabetes in 80 to 85% of new patients.
- **C-Peptide Levels:** Useful for evaluating beta-cell function and distinguishing between insulin-sufficient and insulin-deficient individuals. Levels below 0.2 nmol/L indicate type 1 diabetes mellitus (T1DM).

DKA can be classified as mild, moderate, or severe based on specific criteria. For patients in resource-limited settings or young children, different bicarbonate thresholds may be used: bicarbonate <7 mEq/L for severe DKA and <18 mEq/L for mild DKA.[6,33]

Table 5. Classification of DKA

Features	Mild DKA	Moderate DKA	Severe DKA
Venous pH	7.2 to <7.3	7.1 to <7.2	<7.1
Serum bicarbonate (mEq/L)	10 to <15	5 to 9	<5

TREATMENT

The primary treatments for diabetic ketoacidosis (DKA) are intravenous fluid resuscitation and insulin administration.

Fluid and Electrolyte Replacement

Children with DKA are typically 5% to 10% dehydrated upon presentation. The goal is to correct this fluid deficit over 36 to 48 hours. Initial resuscitation involves administering a 10 mL/kg bolus of normal saline. Additional boluses may be given if the child exhibits persistent tachycardia or signs of poor perfusion. After bolus administration, further fluids are given to address the remaining deficit and ongoing maintenance. Sodium bicarbonate should not be used during this period.[31,33]

Despite elevated serum potassium levels, there is often a total potassium deficit in children with DKA due to urinary loss. Potassium should be added to fluids when serum potassium drops below 5 mEq/L (5 mmol/L) and urine output is adequate. Children with DKA are frequently unable to take oral fluids due to nausea and deteriorating mental status. Small amounts of water or ice chips may help if clinically appropriate. Insulin should be initiated after fluid resuscitation and confirmation of DKA. In mild cases, rapid-acting insulin can be administered subcutaneously. For moderate to severe DKA (pH < 7.2), regular insulin should be given via continuous intravenous infusion (0.05 to 0.1 units/kg per hour), avoiding boluses. Insulin infusion should continue until acidosis resolves. [31-34]

As treatment progresses, serum glucose levels will drop. When glucose falls below 300 mg/dL (16.7 mmol/L), dextrose should be added to the intravenous fluids without changing the insulin dosage. The "2-bag method" helps adjust fluid rates with and without dextrose to maintain glucose levels between 150 and 250 mg/dL (8.3 to 13.9 mmol/L). Alternatively, dextrose content can be gradually increased. If glucose levels continue to fall despite fluids containing 10% dextrose, the insulin infusion rate may be reduced. [31-34]

Intubation should be avoided in children with DKA unless there is inadequate respiratory effort or an inability to protect the airway. Hyperventilation beyond compensatory levels should be avoided to prevent worsening outcomes. Frequent monitoring of mental status using Glasgow Coma Scale scores is crucial for detecting neurological deterioration. Hourly serum glucose tests and venous blood gas and electrolyte levels should be taken every 2 to 3 hours. A second peripheral intravenous line can reduce the need for repeated needle sticks.[35,36]

Disposition depends on DKA severity and available resources. Children with mild DKA may be discharged if they improve, tolerate oral fluids, and can be monitored at home. Severe DKA or complicated cases require hospitalization, often in an intensive care unit (ICU), for close monitoring. Although clinically overt cerebral edema occurs in less than 1% of pediatric DKA cases, subclinical edema is more common and may lead to long-term neurocognitive issues. Most cases develop within 12 to 24 hours of treatment. Immediate treatment with hyperosmolar therapy, such as mannitol or hypertonic saline, is essential. If cerebral edema is diagnosed, immediate treatment should be started. Elevate the head of the bed and administer intravenous mannitol (0.5 to 1 mg/kg) or hypertonic 3% saline (5 mL/kg). Although hypertonic saline is increasingly used as the first-line treatment, it should be used cautiously. [35,36]

The studies reviewed in this analysis contribute significantly to understanding the relationship between age and diabetic ketoacidosis (DKA) in children with newly diagnosed Type 1 Diabetes (T1D), each offering unique insights from different parts of the world. The study by Poon et al. (2022) from Hong Kong revealed that 43.3% of the 556 children with newly diagnosed T1D presented with DKA, with younger children (mean age 9.5 years) being more likely to

experience it. This study also showed that DKA was associated with a shorter duration of symptoms prior to diagnosis. In terms of clinical management, most patients received insulin infusion shortly after fluid resuscitation, and the incidence of severe complications, such as cerebral edema, was low (0.8%). These findings are consistent with the general trend seen in other studies, where younger age correlates with a higher likelihood of presenting in DKA.[14]

In a study conducted in Hangzhou, China (Peng et al., 2021), 681 children were diagnosed with T1D, with 50.1% presenting with DKA. The incidence of severe DKA was particularly high in children under 2 years old, with 81.4% affected. The study also highlighted that the clinical presentation of children with severe DKA was more likely to involve vomiting, fatigue, and abdominal pain, while polyuria and polydipsia were less common in this group. The findings from this study underscore the vulnerability of very young children to both DKA and its severe form.

Jefferies et al. (2015) in New Zealand also examined the incidence of DKA among children with newly diagnosed T1D, reporting that 27% of 730 children presented with DKA. Among children aged <2 years, the DKA incidence was higher (53%) compared to 25% in those aged 2-14 years. Interestingly, the study found that increasing age at diagnosis was associated with a greater likelihood of presenting with DKA. The study also pointed out that non-European children had a higher likelihood of presenting in DKA, suggesting that ethnicity might influence DKA incidence.[15]

Ho et al. (2021) from Canada investigated the impact of the COVID-19 pandemic on the frequency of DKA. They found that while the number of children presenting with newly diagnosed T1D remained stable during the pandemic, the frequency of DKA significantly increased, from 45.6% in 2019 to 68.2% in 2020. The incidence of severe DKA also rose during this period. This finding highlights the potential for environmental or healthcare system changes to affect the incidence of DKA in newly diagnosed children, possibly due to delayed medical consultation or less frequent monitoring during the pandemic.[17] The study by Mencher et al. (2019) in the USA analyzed DKA rates in newly diagnosed children over a 15-year period and found that 29% of 276 children presented with DKA, a decrease from 38% 15 years prior. Factors such as Medicaid status, misdiagnosis at the initial encounter, and lack of pediatric evaluation were associated with a higher likelihood of presenting in DKA. This study offers a longitudinal perspective on changes in DKA presentation, suggesting improvements in early diagnosis and healthcare access over time.[18]

In Central Pennsylvania, Bogale et al. (2020) studied 350 newly diagnosed children with T1D, with 46% presenting with DKA. Severe DKA was seen in 33% of the children. The study identified several factors associated with an increased risk of DKA, including age (younger than 3 years or older children aged 9-13 years), lack of prior referral during healthcare encounters, and elevated HbA1c levels. These findings reinforce the importance of early diagnosis and timely healthcare intervention to prevent DKA. [19] Duca et al. (2019) in Indonesia conducted a large-scale study of 1,396 youth with newly diagnosed T1D and found that those who presented with DKA had significantly higher HbA1c levels 651aselyne, and their HbA1c levels continued to rise faster in the first year after diagnosis compared to those who did not present with DKA. This suggests that higher initial blood glucose levels and delayed diagnosis contribute to poor long-term glycemic control in children presenting with DKA. [20]

Kansakar et al. (2022) in Nepal, studied 99 children and found that 52.5% presented with DKA, with a significantly shorter duration of symptoms in those presenting with DKA. However, unlike other studies, there were no significant age or other demographic factors associated with DKA, indicating potential regional or methodological differences that could affect the outcomes.[21]

In Libya, Shebani and Khashebi (2024) examined 497 newly diagnosed children with T1D, finding that 39.2% presented with DKA, with a higher incidence of severe DKA in children under 2 years old. They also reported a significant difference in the likelihood of females presenting with DKA compared to males. This finding supports the idea that very young children are particularly at risk for severe DKA, highlighting the need for targeted preventive measures in this age group.[22] Finally, a study by Iovane et al. (2018) in Italy found that severe DKA was more common in children under 5 years old (21.8%) compared to older children (3.75%). This study also emphasized the importance of early recognition

of symptoms such as polyuria and weight loss in children under 3 years, suggesting that delayed diagnosis and failure to recognize early signs may contribute to a higher incidence of severe DKA.[23]

This meta-analysis explores the association between age and the risk of diabetic ketoacidosis (DKA) at the onset of Type 1 Diabetes (T1D) in children, using data extracted from various studies across different countries. The studies reviewed provided important insights into the age-related patterns of DKA incidence and severity in newly diagnosed pediatric T1D cases. One study conducted in Hong Kong by Poon et al. (2022) found that among 556 children with newly diagnosed T1D, 43.3% presented with DKA. The study reported that younger children were more likely to present with DKA, with an average age of 9.5 years compared to 10.5 years for those without DKA.[14] This trend was similarly reflected in a study from Hangzhou, China (Peng et al., 2021), where children aged <2 years exhibited the highest rates of DKA, with 81.4% of them presenting with DKA at diagnosis. The incidence decreased progressively with age, with 53.3% in children aged 2-4 years, 42.7% in children aged 5-9 years, and 49.3% in those aged 10 years and older. This highlights a significant correlation between younger age and higher DKA risk.[15]

Interestingly, Shebani and Khashebi (2024) in Libya, also found that children under the age of 2 years had the highest frequency of severe DKA, with a marked difference in the severity of DKA between age groups.[22] Similarly, a study in Italy (Iovane et al., 2018) observed a higher incidence of severe DKA in children under 5 years old (21.8%) compared to older children (3.75%), emphasizing the age-related risk of severe DKA at T1D onset. The data collected from these studies consistently underline the vulnerability of younger children, particularly those under 5 years old, to presenting with DKA at the onset of T1D. In younger age groups, the risk of severe DKA is notably higher, which underscores the importance of early recognition and timely intervention to mitigate the risk of complications like cerebral edema, which is more common in severe DKA cases. [23]

In conclusion, this meta-analysis reinforces the association between younger age and increased risk of DKA at T1D diagnosis, with the highest incidence observed in children aged <2 years. The findings suggest that age is a significant risk factor for both the incidence and severity of DKA, and highlights the need for targeted preventive strategies, particularly for younger children, to reduce the incidence of DKA at the time of T1D diagnosis. While the specific incidence rates and factors associated with DKA vary across regions, the overall trend indicates that very young children, particularly those under 5 years old, are at the highest risk for both DKA and severe forms of it. These findings emphasize the need for age-specific strategies to prevent and manage DKA in newly diagnosed pediatric T1D patients.

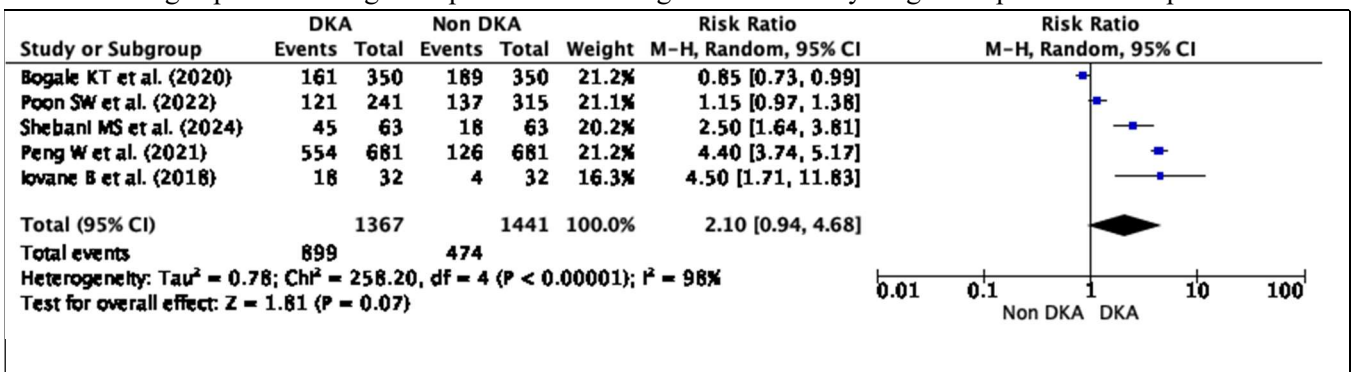

Figure 2. Forest Plot for Age-Related Risk Factors for DKA at Type 1 Diabetes Mellitus Diagnosis

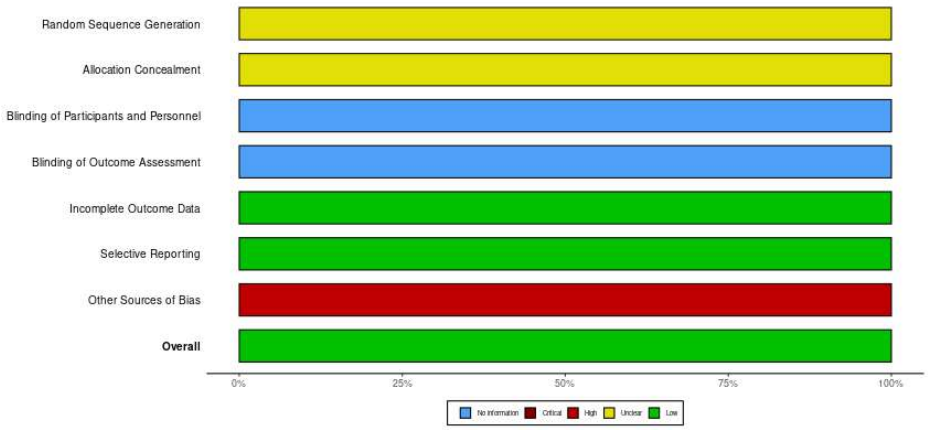

Figure 3. Study Risk of Bias

CONCLUSION

This systematic review and meta-analysis highlight the significant risk factors associated with diabetic ketoacidosis (DKA) at the onset of type 1 diabetes (T1D) in pediatric populations. Key findings include a higher incidence of DKA in younger children, particularly those under 2 years old, and in children from non-European ethnic backgrounds and lower socioeconomic statuses. Shorter symptom duration before diagnosis and elevated baseline HbA1c levels were also identified as critical risk factors. Additionally, the COVID-19 pandemic exacerbated DKA incidence, underscoring the negative impact of healthcare access disruptions. The review emphasizes the need for targeted public health interventions, such as early diagnosis and improved awareness of diabetes symptoms, especially in vulnerable populations. Strategies that address healthcare disparities, such as increasing access to care and diabetes education, could help mitigate DKA risks. Furthermore, improving glycemic control and ensuring timely medical intervention are essential for reducing the morbidity and mortality associated with DKA in children with T1D.

REFERENCES

1. EL-Mohandes N, Yee G, Bhutta BS, et al. Pediatric Diabetic Ketoacidosis. [Updated 2023 Aug 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470282/
2. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, et al. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes. 2014;15(Suppl 20):154–79. [PubMed] [Google Scholar]
3. Raghupathy P. Diabetic ketoacidosis in children and adolescents. Indian J Endocrinol Metab. 2015 Apr;19(Suppl 1):S55-7. doi: 10.4103/2230-8210.155403. PMID: 25941653; PMCID: PMC4413392.
4. UKK Endokrinologi Ikatan Dokter Anak Indonesia. 2017. Diagnosis dan tata laksana diabetes mellitus Tipe-1 pada anak dan remaja. Jakarta: Ikatan Dokter Anak Indonesia.
5. Aman Bhakti Pulungan, Diadra Annisa, & Sirma Imada. 2019. Diabetes Melitus Tipe-1 pada Anak: Situasi di Indonesia dan Tata Laksana https://dx.doi.org/10.14238/sp20.6.2019.392- 400
6. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, HanasR, Rewers A, et al. ISPAD clinical practice consensus guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes 2018;19:155-77.
7. Pulungan AB. Type 1 Diabetes mellitus in children and adolescents: experience in Indonesia. Dalam: Urakami T, penyunting. Proceeding book of The 52nd Annual Scientific Meeting of the Japanese Society for Pediatric Endocrinology. 2018 Okt 4-6; Japan, Tokyo.
8. Pulungan AB, Fadiana G, Annisa D. 2021. Type 1 diabetes mellitus in children: experience in Indonesia. Clin Pediatr Endocrinol, 30(1):11-18. DOI: 10.1297/cpe.30.11.
9. Rugg-Gunn CEM, Dixon E, Jorgensen AL, et al. Factors Associated With Diabetic Ketoacidosis at Onset of Type 1 Diabetes Among Pediatric Patients: A Systematic Review. JAMA Pediatr. 2022;176(12):1248–1259. doi:10.1001/jamapediatrics.2022.3586
10. Listianingrum L, Patria S, Wibowo T. Predictive factors of ketoacidosis in type 1 diabetes mellitus. PI [Internet]. 16Jul.2019 [cited 17Aug.2024];59(4):169-4. Available from: https://paediatricaindonesiana.org/index.php/paediatrica-indonesiana/article/view/1694
11. Rochmah N, Faizi M, Harjantien N. Diabetic ketoacidosis in children: an 11-year retrospective in Surabaya, Indonesia. PI [Internet]. 1Mar.2015 [cited 17Aug.2024];55(1):40-. Available from: https://paediatricaindonesiana.org/index.php/paediatrica-indonesiana/article/view/104
12. Tzimenatos L, Nigrovic LE. Managing Diabetic Ketoacidosis in Children. Annals of Emergency Medicine. 2021;78(3):340-345. doi:10.1016/j.annemergmed.2021.02.028
13. Lah Tomulić K, Matko L, Verbić A, et al. Epidemiologic Characteristics of Children with Diabetic Ketoacidosis Treated in a Pediatric Intensive Care Unit in a 10-Year-Period: Single Centre Experience in Croatia. Medicina (Kaunas). 2022;58(5):638. Published 2022 May 5. doi:10.3390/medicina58050638
14. Poon SW, Tung JY, Wong WH, et al. Diabetic ketoacidosis in children with new-onset type 1 diabetes mellitus: demographics, risk factors and outcome: an 11 year review in Hong Kong. J Pediatr Endocrinol Metab. 2022;35(9):1132-1140. Published 2022 Aug 24. doi:10.1515/jpem-2022-0255
15. Peng W, Yuan J, Chiavaroli V, Dong G, Huang K, Wu W, Ullah R, Jin B, Lin H, Derraik JGB and Fu J (2021) 10-Year Incidence of Diabetic Ketoacidosis at Type 1 Diabetes Diagnosis in Children Aged Less Than 16 Years From a Large Regional Center (Hangzhou, China). Front. Endocrinol. 12:653519. doi: 10.3389/fendo.2021.653519
16. Jefferies C, Cutfield SW, Derraik JG, et al. 15-year incidence of diabetic ketoacidosis at onset of type 1 diabetes in children from a regional setting (Auckland, New Zealand). Sci Rep. 2015;5:10358. Published 2015 May 19. doi:10.1038/srep10358

17. Ho J, Rosolowsky E, Pacaud D, et al. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. Pediatr Diabetes. 2021;22(4):552-557. doi:10.1111/pedi.13205
18. Mencher, Shana Rose; Frank, Graeme; Fishbein, Joanna . (2019). Diabetic Ketoacidosis at Onset of Type 1 Diabetes: Rates and Risk Factors Today to 15 Years Ago. Global Pediatric Health, 6(), 2333794X1987039–. doi:10.1177/2333794X19870394
19. Bogale KT, Hale DE, Schaefer E, Bangalore Krishna K. Prevalence and factors associated with diabetic ketoacidosis at diagnosis of type 1 diabetes: A report from a tertiary medical center in Central Pennsylvania. Endocrinol Diabetes Metab. 2020;4(2):e00186. Published 2020 Sep 12. doi:10.1002/edm2.186
20. Duca LM, Reboussin BA, Pihoker C, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: The SEARCH for diabetes in youth study. Pediatr Diabetes. 2019;20(2):172-179. doi:10.1111/pedi.12809
21. Kansakar, P., Shrestha, S., Paudyal, B. P., Prajapati, A., & Shrestha, N. (2022). Risk Factors Associated with Diabetic Ketoacidosis at the Onset of Type 1 Diabetes Mellitus. Journal of Nepal Health Research Council, 20(01), 79-83. https://doi.org/10.33314/jnhrc.v20i01.3841
22. Shebani MS, Khashebi RM. Exploring ketoacidosis frequency and risk factors in childhood-onset type 1 diabetes: an 8-year retrospective study (2011-2018) at a tertiary paediatric hospital in Tripoli, Libya. J Pediatr Endocrinol Metab. 2024;37(6):497-504. Published 2024 May 3. doi:10.1515/jpem-2024-0011
23. Iovane B, Cangelosi AM, Bonaccini I, et al. Diabetic ketoacidosis at the onset of Type 1 diabetes in young children Is it time to launch a tailored campaign for DKA prevention in children <5 years?. Acta Biomed. 2018;89(1):67-71. Published 2018 Jan 8. doi:10.23750/abm.v89i1.6936
24. Kostopoulou, Eirini, Xenophon Sinopidis, Sotirios Fouzas, Despoina Gkentzi, Theodore Dassios, Stylianos Roupakias, and Gabriel Dimitriou. 2023. "Diabetic Ketoacidosis in Children and Adolescents; Diagnostic and Therapeutic Pitfalls" Diagnostics 13, no. 15: 2602. https://doi.org/10.3390/diagnostics13152602
25. Soto-Rivera, Carla L., Laura A. Asaro, Michael S. Agus, et al. “Suspected Cerebral Edema in Diabetic Ketoacidosis: Is There Still a Role for Head CT in Treatment Decisions?” Pediatric Critical Care Medicine 18, no. 3 (2017): 207-212. Decourcey,
26. David D., George M. Steil, David Wypij, et al. “Increasing Use of Hypertonic Saline over Mannitol in the Treatment of Symptomatic Cerebral Edema in Pediatric Diabetic Ketoacidosis: An 11-Year Retrospective Analysis of Mortality.” Pediatric Critical Care Medicine 14, no. 7 (2013): 694-700.
27. Mulligan JJ, Lang DH. Review of pediatric diabetic ketoacidosis management strategies: evidence and recommendations. *J Pediatr Endocrinol Metab*. 2015;28(11):1227-1234.
28. Zepeda E, Ybarra RR, Kim MJ. Effectiveness of various insulin regimens in pediatric diabetic ketoacidosis. *J Pediatr Endocrinol Metab*. 2015;28(8):925-930.
29. Choi HS, Chang TK, Lee DL. Assessing the efficacy of insulin therapy in pediatric diabetic ketoacidosis. *J Diabetes Res*. 2019;2019:7587902.
30. Tynan T, Bell AS, Davies P, Drewett MS. The impact of a clinical pathway on the management of diabetic ketoacidosis in a pediatric population. *J Pediatr*. 2014;164(1):149-153.
31. Saraf S, Chandrasekaran SM, Nagarajan MS, Malladi PJ. Fluid resuscitation in pediatric diabetic ketoacidosis: a comparison of normal saline and Ringer's lactate. *Pediatr Diabetes*. 2019;20(4):409-415.
32. Freeman J, Tamerius AL. Long-term outcomes of pediatric diabetic ketoacidosis: a comprehensive review. *Pediatr Diabetes*. 2021;22(1):38-47.
33. Hess BL, Jones KD, Meyer MC. Fluid management in pediatric diabetic ketoacidosis: a review of current guidelines. *Am J Health Syst Pharm*. 2013;70(5):395-403.

34. Shulman RJ, Johnson JK, Morris CA. Glycemic control and diabetic ketoacidosis: a review of current management strategies. *J Diabetes Sci Technol*. 2018;12(6):1297-1303.
35. Kanungo D, Smith JM. Current protocols for pediatric diabetic ketoacidosis management: a review. *Pediatr Emerg Care*. 2021;37(7):464-470
36. Sweeney AR, Weaver CE. Diabetic ketoacidosis management in children: a comprehensive review. *J Pediatr Endocrinol Metab*. 2018;31(6):613-621.