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Markers of Disease Severity and Prolonged Length of Stay for Paediatric Diabetic Ketoacidosis

Nursuhairi Muhammad [1,2]* Jeremy S. Mong,[1,2] Haikel A. Lim,[3] Sashikumar Ganapathy[4]

[1]Medical Officer, Dept. of Children's Emergency, Kandang Kerbau Women's and Children's Hospital; 100 Bukit Timah Rd, Singapore

[2]Medical Officer, Dept. of Accident and Emergency, Tan Tock Seng Hospital; 11 Jalan Tan Tock Seng, Singapore

[3]Post-Graduate Medical Student, Duke-NUS Graduate Medical School; 8 College Road, Singapore

[4]Consultant, Dept. of Children's Emergency, Kandang Kerbau Women's and Children's Hospital; 100 Bukit Timah Rd, Singapore

*Address for Correspondence: Dr. Muhammad Nursuhairi, Medical Officer, Department of Accident and Emergency, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore, Tel: +65 90880764, Fax: +65 6250 2573

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ABSTRACT- **Introduction:** Paediatric Diabetic Ketoacidosis (DKA) studies are limited in Asia and none have investigated markers of disease severity or prolonged hospital length of Stay (LOS). We investigated the predictors of disease severity and prolonged hospital LOS by analysing the demographics and signs and symptoms of patients with DKA.
Methods: We conducted a retrospective study of the medical records of patients, who presented to the emergency department of a tertiary paediatric hospital in Singapore between 2012 and 2013 and were diagnosed with DKA, obtaining demographics, signs, symptoms, serum pH levels, precipitating causes, and hospital LOS for the 67 eligible patients.
Results: Total 82.1% of patients were tachycardic, 44.8% tachypneic and 20.9% febrile; none were hypotensive. The most common symptoms were nausea and vomiting (56.7%), polyuria and polydipsia (50.7%), lethargy (34.3%), and fever (22.4%). Half had mild DKA (48.5%), while a quarter of patients each had moderate (24.2%) and severe DKA (27.3%). A higher proportion of those with severe DKA presented with tachypnea (p=.007). Prolonged LOS patients were younger at presentation (p=.010), and a higher proportion had no prior history of DM (p=.061), presented with polyuria or polydipsia (p=.062) and had a lower pH on presentation (p=.056).
Conclusion: Paediatric patients with DKA present with non-specific symptoms. Patients with tachypnea were more likely to have a worse disease severity. Younger patients, those without a history of DM, or had a lower serum pH, and polyuria and polydipsia were more likely to have a prolonged hospital LOS.

Key-Words: Diabetic Ketoacidosis, Child, Emergency Medicine, Length of Stay, Severity of Illness Index

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INTRODUCTION

The prevalence of diabetes mellitus (DM) among the paediatric population is steadily increasing worldwide.[1,2] This increase is mirrored in Indonesia whereby the overall incidence of Type 1 DM has increased from 000,383 per 100,000 in 2000 to 002,819 per 100,000 in 2010.[3] As a consequence, complications such as diabetic ketoacidosis (DKA) are also expected to increase.

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However, paediatric patients with DKA tend to present with non-specific signs and symptoms and diagnosis can be difficult and delayed, especially among those not previously diagnosed with DM.[4]

Worldwide, there are papers that examine the demographics and common signs and symptoms among paediatric patients with DKA.[5–7] A systematic review, which included 65 studies on over 29,000 children from 31 countries, was conducted to determine the frequency of DKA at first presentation of Type 1 DM in children. This review only included 2 studies from Asia and no studies from South-East Asia were available.[8] To the best of our knowledge, there are no Asian studies analysing predictors of disease severity and hospital length of stay (LOS).

The aim of this retrospective study was twofold: (1) to identify demographic and medical variables in paediatric patients diagnosed with DKA; and (2) to identify predictors of disease severity and prolonged hospital LOS so that aggressive treatment and the proper monitoring of such patients can be instituted early. Because of the lacuna in the extant literature amongst the Asian population, we were unable to generate any *a priori* hypothesis to guide the analyses and this study remained exploratory.

MATERIALS AND METHODS

Procedures and Participants

In this retrospective study, information from the medical records of patients who presented to the Children's Emergency department of a large tertiary paediatric hospital in Singapore and were diagnosed with DKA between 1st January 2012 and 31st December 2013 were reviewed. In accordance with the American Diabetes Association (ADA), we defined our inclusion criteria as DKA with a venous pH ≤7.3 in the presence of hyperglycaemia and ketonemia or ketonuria.

Measures

The following information was collected from patients' medical records: basic demographics, history of DM, vital signs, symptoms, venous pH, known precipitating cause of DKA and hospital length of stay. A median split was used to segregate patients into normal or longer than normal LOS. Venous pH was used to determine DKA severity: mild (pH 7.20–7.30), moderate (pH 7.10–7.19), and severe (pH <7.10)[4].

Data Analyses

Data was analysed using the Statistical Package for Social Sciences Version 21 (Chicago, IL, USA), and all significance levels were set at 0.05 unless stated. Univariate analyses were conducted to ascertain the demographic and clinical profile of the sample of patients diagnosed with DKA during the specified time period. Bivariate analyses, such as t-test, Chi-square, and Fisher's exact tests, were employed to determine if there are group differences or relationships of the demographic or clinical variables that may be related to DM status, severity of DKA, or LOS. Since continuous variables proved to be non-normal, non-parametric analogues of the aforementioned tests were employed.

RESULTS AND DISCUSSION

Patient Demographics

Of the 207 patients reviewed, 67 patients met the inclusion criteria (inclusion rate 32.3%). Table I demonstrate the demographics of the total sample and divided by known DM status. A majority were female (60%, *n*=40), of Chinese ethnicity (57%, *n*=38), and nearly half were previously not known to have DM (47.7%, *n*=32). The mean age at presentation was 11.69±4.58 years (Range: 2–25 years). Venous pH of patients at presentation ranged from 6.85 to 7.30, with a mean of 7.16±0.14.

Patient Presentation

Table I also detail the frequencies of patients' vital signs and presenting symptoms for the total sample and divided across known DM. Of the 67 patients, 82.1% were found to be tachycardic (*n*=55), 44.8% tachypneic (*n*=30), and 20.9% were febrile on arrival to the Children's Emergency (*n*=14). None were found to be hypotensive.The most common symptoms were nausea and vomiting (56.7%; *n*=38), followed by polyuria and polydipsia (50.7%; *n*=34), lethargy (34.3%; *n*=23), and fever (22.4%; *n*=15). Nearly half of all patients had mild DKA (48.5%; *n*=32; pH 7.20–7.30) while a quarter of the patients each had either moderate (24.2%; *n*=16; pH 7.10–7.19) or severe DKA (27.3%; *n*=18; pH <7.10).The mean LOS was 95.7 hours (range =16–250).

Table 1: Demographic and Medical Variables of the Total Sample and Across Known Diabetes Mellitus Status

Variable	Total (*N* = 67)	Known DM (*N* = 35)	Unknown DM (*N* = 32)
Age	11.69 ± 4.58	13.60 ± 4.15	9.59 ± 4.14
Female	40 (59.7)	24 (68.6)	16 (50.0)
Ethnicity			
Chinese	38 (56.7)	17 (48.6)	21 (65.6)
Malay	13 (19.4)	10 (28.6)	3 (9.4)
Indian	14 (20.9)	7 (20.0)	7 (21.9)
Others	2 (3.0)	1 (2.9)	1 (3.1)

Prior Healthcare Visit	–	–	25 (78.1)
Vitals			
Febrile	14 (20.9)	9 (25.7)	5 (15.6)
Hypotensive	0 (0)	0 (0)	0 (0)
Tachycardic	55 (82.1)	32 (91.4)	23 (71.9)
Tachypneic	30 (44.8)	17 (48.6)	10 (31.3)
Presenting Symptoms			
Fever	15 (22.4)	10 (28.6)	5 (15.6)
Nausea/Vomiting	38 (56.7)	27 (77.1)	11 (34.4)
Lethargy	23 (34.3)	11 (31.4)	12 (37.5)
Polyuria/Polydipsia	34 (50.7)	5 (14.3)	29 (90.6)
pH on Arrival	6.85 ±0.14	6.85 ±0.13	6.86 ±0.15
DKA Severity			
Mild	32 (47.8)	16 (45.7)	16 (50.0)
Moderate	16 (23.9)	10 (28.6)	6 (18.8)
Severe	18 (26.9)	8 (22.9)	10 (31.3)
Hospital Length of Stay (hours)	95.72 ±102.74	96.66±101.75	94.69±105.44

DM= Diabetes Mellitus. DKA= Diabetic Ketoacidosis.
Data are presented either as *M* ±*SD* or as Frequency (%).

Patients with No History of DM

Among the 32 (47.8%) patients who did not have a known history of DM before attending the Children's Emergency, 78.1% were found to have had a prior healthcare visit to outpatient clinics, family physicians, private hospitals, and other restructured hospitals before arrival (n= 25). There were no significant differences in the demographics, signs and symptoms, severity of DKA, or hospital LOS between those who had a prior healthcare visit compared to those who did not.

Patients with a Known History of DM

Thirty-five patients (52.2%) were known to have had a prior diagnosis of DM before arrival at the Children's Emergency. Comparison between those with a known history of DM against those with no history of DM showed that there was a significant difference in age with known cases of DM being older than unknown (13.60±4.15 vs. 9.59±4.14, p< .01).

Statistically significant differences in heart rate and respiratory rate were also found with a higher proportion of patients with a history of DM presenting with tachycardia (χ^2[1,67]= 4.35, p= .037) and tachypnea (χ^2[1,67] = 4.53, p = .033).

There were also statistically significant differences in symptoms, with a higher proportion of known cases of DM presenting with nausea or vomiting (χ^2[1,67]= 12.46, p< .001) and a lower proportion presenting with polyuria or polydipsia (χ^2[1,67]= 38.98, p<.001).

Excluding non-compliance, significant differences in precipitating cause of DKA were also found, with a higher proportion of known DM having pneumonia or an upper respiratory tract infection (p= .003).

Markers of Disease Severity

The study objective included the search for markers of disease severity. Unsurprisingly, we found that a higher proportion of those with severe DKA presented with tachypnea (χ^2[1,66]= 7.15, p= .007). Demographics (age, gender, ethnicity), prior diagnosis of DM, other vital signs (heart rate, fever, blood pressure), symptoms, and known precipitating causes were not significantly related to disease severity.

Markers of Prolonged Hospital Stay

Prolonged hospital stay was defined as >71 hours, based on the median split of the data with the median being

excluded. Analyses revealed that there was a significant difference in age with prolonged LOS patients being younger at presentation (10.21±4.41 vs. 13.16±4.46, t[63]= 2.68, p= .010). There were also a higher proportion of patients with prolonged LOS having no prior history of DM, although this difference was marginal (χ^2 [1,65]= 3.52, p= .061).

Similarly, there was a marginally significant difference with a higher proportion of prolonged LOS patients having polyuria or polydipsia (χ^2[1,65]= 3.47, p= .062) and a lower pH on presentation (7.12±0.15 vs. 7.20±0.12, t [61] = 1.95, p= .056).

DISCUSSION

The economic burden of DKA is extremely high, with an annual cost of treating DKA in all patients at diagnosis and during subsequent visits exceeding $1 billion.[5] Newly-diagnosed patients account for a quarter of this amount.[9] It has also been found in a separate study that more than half all paediatric patients newly diagnosed with DM will be hospitalized and among those hospitalized, 44% will be due to DKA.[10]In Iran, 24% of newly diagnosed Type 1 DM presented in a state of ketoacidosis and severe DKA (pH≤7.2) was observed in 54.5% of patients.[11] Given the significant worldwide economic burden of DM and that a large percentage of newly diagnosed patients present with DKA, healthcare, education aimed at increasing awareness on paediatric DM are warranted and have the potential to be effective. Interestingly, a study in the United Kingdom showed that children who were the second affected child in the family were less likely to present in DKA than first affected children.[12] This could be due to the fact that parental awareness regarding the management of DM and DKA could be higher and proper counselling regarding the need to seek early medical treatment could have been instituted. This is particularly important as our study showed that approximately half of all patients, who were diagnosed with DKA did not have a prior history of DM. Therefore, there is a significant window of opportunity at highlighting the symptoms of DM to parents so that it can be diagnosed early, reducing the risk of progression to DKA which is costly to treat and carries with it greater complications and morbidity. Other studies have also proven that DKA prevention programs are effective. In Italy, an 8-year community intervention program highlighting the signs and symptoms of childhood diabetes costing $23,470 led to a reduction in the prevalence of DKA at diagnosis from 78% to 13%. [13]

Diagnosis of DKA has also proven to be difficult, particularly in young children who may be labelled as having pneumonia, asthma or bronchiolitis instead.[4] Our study found that the most common symptoms were nausea and vomiting (56.7%), polyuria and polydipsia (50.7%) and lethargy (34.3%). This is comparable to another study that showed polyuria was observed in 96% of children at the time of diagnosis whereas fatigue was present in 52% of cases.[14] Healthcare providers should remain vigilant and maintain a high index of suspicion for DKA in the child with unexplained nausea and vomiting, polyuria and polydipsia and lethargy. This is made even more important given the fact that our study demonstrated that nearly 80% of patients with no known history of DM had a prior healthcare contact before arrival at Children's Emergency.

Among patients with a known history of DM, non compliance to medications is an important causal event leading to DKA. A quarter of such patients were found to have omitted or administered suboptimal amounts of insulin in our study. Among all patients with DKA, only 21% could be directly attributed to infective causes (respiratory and gastro-intestinal infections). Our findings are supported by other studies, which showed that an inter-current illness is seldom the cause of DKA when DM management is properly taught and families are provided with the support of a diabetes team and a 24-hour diabetic care hotline.[15-18]

Severity of DKA was significantly related to patients with tachypnea. This finding is unsurprising given the fact that patients with severe DKA have a lower venous pH with a consequent greater amount of respiratory compensation and Kussmaul's breathing. Age, gender, ethnicity, other vital signs, symptoms on arrival to Children's Emergency and known history of DM were not significant predictors of DKA severity. Our findings are in agreement with previous studies conducted in America that demonstrated that there was no racial or ethnic differences in DKA severity.[10] Thus, the emergency physician should be wary of the tachypneic child, which portends a worse disease. This clinical correlation can and should be used to ascertain disease severity even before laboratory results are available so that early and aggressive resuscitative measures and proper monitoring can be arranged in order to increase the likelihood of a good outcome for the child.

Lack of healthcare insurance was also associated with higher rates and greater severity of DKA at diagnosis.[9,19,20] This is presumed to be due to the fact that uninsured subjects tend to delay seeking medical attention. However, in our analysis, among patients with no known history of DM, those, who sought prior medical attention before attending Children's Emergency, did not demonstrate a better disease outcome compared to those who did not have a prior medical contact. We suspect that this situation is unique to Singapore as the readily accessible transport and healthcare network in combination with her small geographical size prevents significant delays from acute and emergency healthcare delivery.

Our study defined prolonged hospital stay as being more than 71 hours, based on the median split. This duration is comparable to the average length of hospital stay in children from Ontario who was hospitalized with DKA. Their average length of stay was found to be 3.2 days.[21] Based on our study; younger patients were likelier to have a prolonged hospital stay. Patients presenting with polyuria and polydipsia, low serum pH levels and those with no

history of DM were also found to have a more prolonged hospital stay even though this difference is marginal. We suspect that cultural practices within Singapore could influence the hospital LOS. This could be due to the fact that the caregivers and family members of young patients and those with no history of DM would require more time to be educated regarding DM as well as the proper administration of insulin, regular blood sugar level monitoring as well as the warning signs of DKA and this could be one reason for a delayed hospital discharge.

Strengths and Limitations

We believe we are the first Asian study that examined markers of disease severity and prolonged LOS amongst paediatric patients with DKA. However, only 67 medical records met the inclusion criteria (inclusion rate of 32.3%) for our retrospective study over a 24-month period.Among those with a prolonged hospital LOS, reasons for a delayed hospital discharge could not be accurately elicited. The relative lack of Asian studies, combined with the wide-ranging clinical implications suggests that further studies are warranted to examine reasons behind a prolonged hospital LOS.

CONCLUSIONS

Clinical Implications

Our study showed that half of all paediatric patients presenting with DKA in Singapore were not previously known to have DM. Greater efforts aimed at highlighting the signs and symptoms of paediatric DM has the potential to prevent and reduce the rates of DKA in Singapore. Eighty percent of all patients with no known history of DM had a prior healthcare contact before arrival to the Children's Emergency and the most common symptoms among all patients were nausea and vomiting, polyuria and polydipsia and lethargy. Therefore, all healthcare providers have a role to play in maintaining a high index of suspicion in the previously healthy child, who present with the above symptoms. Patients who had tachypnea were also found to be at higher risk of having severe DKA. As such, emergency personnel should be wary of the child with suspected DKA who is also noted to be tachypneic as this would signify a greater disease severity and would affect their disposition and level of monitoring. Younger patients, those without a history of DM and those with a lower serum pH and those who present with polyuria and polydipsia were likelier to have a prolonged hospital LOS. Upon admission, healthcare providers and administrators should counsel caregivers of such patients that hospital stay could be prolonged.

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ETHICS STATEMENT

This study obtained ethics approval from Singhealth Centralised Institutional Review Board (Reference number: 2014/529/E), which also approved a waiver of consent. No patient identifiers were collected and all information was collected anonymously as either categorical or ordinal variables. This study was not funded, and the authors declared no conflict of interest.

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