

The Fulminant Index: A Method of Rapidly Differentiating Fulminant Type 1 Diabetes From Diabetic Ketoacidosis

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Research

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Abstract

Objectives Fulminant type 1 diabetes (FT1D) usually presents with diabetes ketoacidosis(DKA) at the disease onset. Early identification of FT1D is crucial. This study was aimed at investigating whether the fulminant index (FI), including plasma glucose (PG) to glycated hemoglobin(HbA1c) ratio (PG/HbA1c), serum potassiumion (K^+) to HbA1c ratio ($K^+/HbA1c$), and serum sodiumion (Na^+) multiplied by HbA1c ($Na^+*HbA1c$), is a suitable indicator for early FT1D identification.

Methods A total of 76 subjects were enrolled, including 40 FT1D patients and 36 non-FT1D patients with DKA. We utilized receiver operating characteristic (ROC) curve analysis to determine the FI cut-off values between FT1D and non-FT1D groups.

Results ROC curve analyses showed that the maximum Youden's index for PG/HbA1c bonding to a cut-off value of 4.39, with the sensitivity of 75.0% and specificity of 77.8% in identifying FT1D from DKA. And optimal $K^+/HbA1c$ cut-off value was 0.85 with the sensitivity of 77.5% and specificity of 94.4%. For $Na*HbA1c$, the best cut-off value was 923.65, and its sensitivity and specificity were 85% and 69.4%, respectively.

Conclusions These results suggested FI could work as a suitable and convenient indicator for differentiating FT1D from initial DKA patients, among which the FI ($K^+/HbA1c$) presented the best .

Introduction

Fulminant type I diabetes mellitus (FT1D) is a subtype of type 1 diabetes mellitus characterized by aggressive disease progression. FT1D was first reported in Japan by Imagawa et al¹ and was gaining increasing attention around the world in the past few years²⁻⁴. Diabetic ketoacidosis (DKA), as an acute, life-threatening diabetic complication, requires prompt identification and proper management by all physicians in clinical practice. Comparing with traditional autoimmune type 1 diabetes, FT1D could generate more severe metabolic derangement. As observed in the previous study⁵ and our clinical work, fulminant type I diabetes mellitus (FT1D) patients usually present rushed clinical course and may generate ketosis or DKA at their early disease onset. Early identification of FT1D cases can help timely treatment and prevent death cases. As universally agreed, as DKA arise, for the clinicians, the first priority is correcting ketoacidosis, while detecting the cause of DKA and determination of the diagnosis come to back of the pipeline. Nevertheless, since FT1D-DKA patients are highly susceptible to various lethal complications including increase in pancreatic enzymes⁶, increase of muscle enzymes and even rhabdomyolysis⁷, leukemia-like reaction⁸, sudden death, or cardiac arrest⁹, it could be necessary for clinicians to recognize FT1D early when handling DKA cases, which could help identify highly risky cases and conduct timely intervention. Besides, a fraction of FT1D cases caused by medication¹⁰ or pregnancy¹¹ also rely on early recognition to receive appropriate treatment. However, to our current knowledge, it remains a significant problem differentiating FT1D patients from general DKA patients in the emergency room. Current FT1D diagnosis mainly depends on C-peptide monitoring. However, in the

clinic, assessment of C-peptide could be infeasible under many circumstances, such as DKA emerging or patients' unconsciousness. In that way, we aimed to seek a better diagnostic pipeline for FT1D independent of C-peptide assessment, to achieve prompt differentiation and early management of potential FT1D patients showed up in the emergency room. In this study, we investigated multi-dimensional characteristics of 40 FT1D patients enrolled since 2003. And we proposed a set of quantitative diagnostic tool named fulminant index (FI), which was calculated based on plasma glucose (PG), serum potassiumion (K^+) level, serum sodiumion (Na^+) level, and glycated hemoglobin (HbA1c) level. We also calculated the estimated FI cutting-off points and verified its efficiency in differentiating FT1D from non-FT1D DKA patients through receiver operating characteristic (ROC) curve analysis.

Methods

Patients inclusion and data collection

Our study included FT1D patients and non-FT1D DKA patients. The FT1D patients were identified through screening of historical inpatients cases from the Department of Endocrinology in Ninth Affiliated Hospital of Guangxi Medical University from 2003 to 2019, as well as Chinese FT1D patients in online (Wanfang medical database) databases reported between 2006 to 2019. All included FT1D cases meet the diagnostic criteria composed by the Committee of the Japan Diabetes Society in 2012: diabetic ketosis or ketoacidosis occurs soon after the onset of hyperglycaemic symptoms and the patient presents with PG level ≥ 16.0 mmol/L and HbA1c level $< 8.7\%$ at the first visit and urinary C-peptide excretion < 10 ug/day, or fasting serum C-peptide level < 0.10 nmol/L and postprandial serum C-peptide < 0.17 nmol/L at onset⁶. Non-FT1D DKA patients were identified from inpatient patients in the department of Endocrinology in Ninth Affiliated Hospital of Guangxi Medical University from 2003 to 2019, Non-FT1D patients were determined following the American Diabetes Association criteria: plasma glucose > 13.9 mmol/L and high anion gap metabolic acidosis (arterial pH < 7.30 , serum bicarbonate < 18 mEq/L, or an anion gap > 10) with positive serum or urine ketones. DKA must be distinguished from other causes of ketosis or metabolic acidosis before diagnosis, including starvation ketosis, alcoholic ketoacidosis, and lactic acidosis¹². HbA1c level of more than 8.7% of DKA was excluded in our study. Our study have been approved by ethnical review by the institutional ethics review board from the Second Xiangya Hospital, Central South University.

We retrieved the following information of each patient: demographic information including the gender and age, and clinical features or indexes including date of onset of hyperglycaemic symptoms, BMI, PG (at admission), urinary ketone bodies, arterial pH, fasting serum C-peptide, β -cell autoantibodies such as glutamic acid decarboxylase (GAD) antibodies, islet-associated antigen 2 (IA-2) antibodies, and insulin cell (ICA) antibodies, serum amylase, and diabetic complications were also recorded.

Ketosis. Especially, among the parameters above, ketosis was determined by urinary ketone bodies $\geq 2+$, and β -cell autoantibodies were measured at the onset of disease. PG levels were tested using the glucose

oxidase method, and HbA1c levels were tested using high-performance liquid chromatography through an automatic biochemical analysis system.

Statistical analysis

All statistical analysis was performed using SPSS 16.0 software. Unpaired Student's t-test was used to analyze deviations of parameters between groups. Receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) were used to measure the diagnostic strength of FI. Sensitivity and specificity were assessed for the efficacy of FI in differentiating FT1D from DKA patients. We also estimated optimal IF cut-off points, which is determined by the highest Youden's index (sensitivity + specificity - 1). For all computational analyses, $P < 0.05$ was considered statistically significant. Continuous variables fitting normal distribution were described in the form of means \pm standard deviations (SDs).

Results

Clinical features of FT1D and non-FT1D DKA patients

The clinical features of FT1D or non-FT1D DKA are shown in Table 1. The mean age of FT1D patients was 39.38 ± 16.38 and the mean age of non-FT1D DKA patients was 44.50 ± 15.48 . Among the two groups, FT1D patients showed more severe metabolic disorders than non-FT1D DKA patients. Compared with those in non-FT1D DKA patients, FT1D have significant higher PG (40.50 ± 15.28 mmol/L vs. 27.86 ± 8.55 mmol/L; $P < 0.001$) and serum K^+ (6.27 ± 0.93 mmol/L vs 4.78 ± 1.12 mmol/L; $P < 0.001$) levels. HbA1c ($6.76 \pm 0.76\%$ vs $7.45 \pm 0.91\%$; $P = 0.01$), serum Na^+ (125.09 ± 7.73 mmol/L vs 132.49 ± 9.20 mmol/L; $P < 0.001$) and HCO_3^- (6.44 ± 2.93 mmol/L vs 8.76 ± 4.56 mmol/L; $P = 0.016$) were significantly lower in FT1D patients than in non-FT1D DKA patients.

Table 1
Clinical characteristics of patients with DKA

	FT1D	non-FT1D	P
n	40	36	
Age (years)	39.38 ± 16.38	44.50 ± 15.48	0.166
pH	7.12 ± 0.09	7.16 ± 0.12	0.143
HCO ₃ ⁻	6.44 ± 2.93	8.76 ± 4.56	0.016
BE	-19.82 ± 6.46	-18.54 ± 6.32	0.433
PG (mmol/LI)	40.50 ± 15.28	27.86 ± 8.55	< 0.001
K ⁺ (mmol/LI)	6.27 ± 0.93	4.78 ± 1.12	< 0.001
Na ⁺ (mmol/LI)	125.09 ± 7.73	132.49 ± 9.20	< 0.001
HbA1c (%)	6.76 ± 0.76	7.45 ± 0.91	0.01
FI			
FI (PG/HbA1c) (mmol/L/%)	6.02 ± 2.19	3.79 ± 1.24	< 0.001
FI (K ⁺ /HbA1c)(mmol/L/%)	0.94 ± 0.17	0.65 ± 0.17	< 0.001
FI (Na ⁺ *HbA1c) (mmol*/%/L)	854.00 ± 102.41	985.22 ± 118.67	< 0.001
FT1D: fulminant type 1 diabetes mellitus; DKA: diabetic ketoacidosis; HbA1c: haemoglobin A1c; PG: plasma glucose (randomly measured at onset); FI: fulminant index			

ROC curve analyses on the optimal clinical parameters in differentiating FT1D from DKA

Between the groups, FI (PG/HbA1c) was significantly higher in FT1D patients (6.02 ± 2.19 mmol/L/%) than in non-FT1D DKA patients (3.79 ± 1.24 mmol/L/%; P < 0.001). ROC analyses showed that the highest Youden's index for FI (PG/HbA1c) corresponds to the optimal cut-off value of 4.39, of which the sensitivity was 75.0% and specificity was 77.8% in differentiating FT1D from general DKA (AUC: 0.818). Thirty-two out of 40 FT1D patients (80.0%) had FI (PG/HbA1c) > 4.39 mmol/L/%, while ten out of 36 (27.8%) non-FT1D DKA patients (Fig. 1).

FI (K⁺/HbA1c) was significantly higher in FT1D patients (0.94 ± 0.17 mmol/L/%) than in non-FT1D DKA patients (0.65 ± 0.17 mmol/L/%; P < 0.001). ROC analyses showed that the highest Youden's index with K⁺/HbA1c ratio cut-off value of 0.85, with a corresponding sensitivity of 77.5% and specificity of 94.4% in identifying FT1D from DKA (AUC: 0.899). Thirty-seven out of 40 FT1D patients (92.5%) had FI (K⁺/HbA1c) > 0.85 mmol/L/%, and eight out of 36 (22.2%) non-FT1D DKA patients (Fig. 1).

FI ($\text{Na}^+ \cdot \text{HbA1c}$) was significantly lower in FT1D patients ($854.45 \pm 102.98 \text{ mmol}^* \%/L$) than in non-FT1D DKA patients ($985.22 \pm 118.67 \text{ mmol}^* \%/L$; $P < 0.001$). ROC analyses showed that the highest Youden's index for FI ($\text{Na}^+ \cdot \text{HbA1c}$) bonded with a cut-off value of 923.65, with the corresponding sensitivity of 85.0% and specificity of 69.4% in identifying FT1D from DKA (AUC: 0.814). Twenty-nine out of 40 FT1D patients (72.5%) had FI ($\text{Na}^+ \cdot \text{HbA1c}$) $< 923.65 \text{ mmol}^* \%/L$, compared with six out of 36 (16.7%) non-FT1D DKA patients (Fig. 1).

Discussion

In recent years, an increasing number of FT1D cases have been reported in China, which has expanded our knowledge about the disease^{3, 13, 14}. In clinical practice, DKA is one of the most commonly encountered lethal complications, nevertheless, for many reasons, physicians may not be able to obtain the patients' previous diabetic histories in the first place. Since C-peptide level assessment could be time-consuming and could be not applicable under certain circumstances, prompt diagnosis of FT1D based on C-peptide could be impossible at this time. Alternatively, taking advantage of other accessible biomedical indexes would be an ideal solution for the timely identification of FT1D. Compared to autoimmune type 1 patients, FT1D patients showed lower levels of Na^+ and HbA1c and significantly higher levels of K^+ and PG ^{3, 5}. In the present study, we found the same deviations between FT1D and non-FT1D DKA patients.

Hyponatremia and hyperkalemia are commonly found in the DKA, and the serum electrolyte changes are more extensive in the FT1D patients. There is a negative correlation between Na^+ levels and PG and, conversely, a positive correlation between K^+ levels and PG . The changes are more evident in patients with insulin-dependent diabetes mellitus than in those with non-insulin-dependent diabetes mellitus. The underlying pathophysiology mechanisms may include the movement of electrolytes between intra- and extracellular spaces, impaired insulin action, as well as hyperosmolality^{15, 16}. Insulin activates Na^+/K^+ -ATPase¹⁷⁻¹⁹. The activity of Na^+ , K^+ -ATPase could be attenuated in insulin-dependent diabetic patients whose insulin secretion is impaired. In FT1D, hyponatremia and hyperkalemia could arise as a consequence of remarkably increase of plasma glucose and devastation of insulin-producing capacity^{5, 13}. Both endogenous or exogenous insulin is capable of effecting serum electrolyte levels, especially K^+ . Thus, DKA patients with insulin-dependent diabetes may not necessarily generate high serum K^+ is they received insulin therapy. Similarly, for FT1D patients, those who have been treated with insulin may experience alleviation of hyperkalemia, but the PG or serum Na^+ may not respond as good if the patient was severely dehydrated.

Improvements in technology now permit the prompt testing of HbA1c. PG , Na^+ , and K^+ are routine blood examination results. Therefore, FI ($\text{PG}/\text{HbA1c}$, $\text{K}^+/\text{HbA1c}$, $\text{Na}^+ \cdot \text{HbA1c}$) can be easily measured in clinical practice. Our results indicate FI ($\text{PG}/\text{HbA1c} \geq 4.39 \text{ mmol}^* \%/L$, $\text{K}^+/\text{HbA1c} \geq 0.85 \text{ mmol}^* \%/L$, $\text{Na}^+ \cdot \text{HbA1c} \leq 923.65 \text{ mmol}^* \%/L$) can be adopted as a new set of biomedical indexes in diagnosing FT1D. In recent

findings on the diagnosis of FT1D, GA^{20} , 1,5-anhydroglucitol (1,5-AG)/ GA^{21} , the $GA/HbA1c$ ratio²² and the $PG/HbA1c$ ratio²³ were used for screening FT1D. The $GA/HbA1c$ ratio and $PG/HbA1c$ ratio are both FI.

Compared with those of acute-onset autoimmune type 1 diabetes mellitus (T1ADM) patients, both HbA1c and GA were significantly lower in FT1D patients. In the differential diagnosis between FT1D and T1ADM, ROC analysis showed that the optimum cut-off value for GA was 33.5% with a sensitivity and specificity of 97.4% and 96.8%, respectively²⁰. And GA and 1,5-AG are indicators that reflect short-term glucose levels, 1,5-AG/GA can help facilitate the early differential diagnosis of FT1DM and T1ADM when $HbA1c < 8.7\%$, with an optimal cut-off point of 0.3²¹. FI ($GA/HbA1c$) for FT1D patients has already been reported to be higher than for patients with T2DM. ROC analyses showed that although both the specificity and sensitivity of HbA1c and those of serum GA for differentiating FT1D and T2DM were low, a cut-off value of 3.2 for FI ($GA/HbA1c$) yielded 97% sensitivity and 98% specificity for differentiating FT1D from T2DM. However, no significant differences in FI ($GA/HbA1c$) between T1ADM patients and FT1D patients were observed²². According to reported cases of FT1D in China, few primary hospitals in China monitor GA and 1,5-AG. Compared with HbA1c, GA 1,5-AG are not widely used in China. Liu L et al proposed a cutoff value of 4.2 for FI ($PG/HbA1c$), yielding 94% sensitivity and 98% specificity in differentiating FT1D from DKA²³. However, that study did not limit HbA1c in the DKA group because if HbA1c exceeded 8.7%, we could rule out FT1D without the $PG/HbA1c$. Therefore, our study established a limit for the HbA1c level in the DKA group and compared it with the level in the FT1D group to test whether the $PG/HbA1c$ ratio was effective and to explore whether there were better indicators for diagnosis.

As shown in the above figure and table, FI ($PG/HbA1c$) can differentiate FT1D from DKA. ROC analyses showed that the highest Youden's index for FI ($PG/HbA1c$) was a cutoff value of 4.39, with a corresponding sensitivity of 75.0% and specificity of 77.8% in identifying FT1D from DKA (AUC: 0.818). FI ($PG/HbA1c$) at a cutoff value of 4.39 mmol/L/% among DKA patients was the best predictor of FT1D in China. Since K^+ and PG were both higher in FT1D than in DKA, we used the ratio of these two parameters to HbA1c to construct the FI. Na^+ and HbA1c were lower in FT1D than in DKA, so we constructed the FI by multiplying both to increase the difference between the two diseases.

$K^+/HbA1c$ and $Na^+*HbA1c$ were additionally constructed FIs. ROC analyses showed that the highest Youden's index for FI ($K^+/HbA1c$) was a cut-off value of 0.85, with a corresponding sensitivity of 77.5% and specificity of 94.4% in identifying FT1D from DKA (AUC: 0.899). FI ($K^+/HbA1c$) at a cutoff value of 0.85 mmol/L/% among DKA patients was the best predictor of FT1D in China. ROC analyses showed that the highest Youden's index for FI ($Na^+*HbA1c$) was a cut-off value of 923.65, with a corresponding sensitivity of 85.0% and specificity of 69.4% in identifying FT1D from DKA (AUC: 0.814). FI ($Na^+*HbA1c$) at a cutoff value of 923.65 mmol/L/% among DKA patients was the best predictor of FT1D in China. We can also construct other FIs based on the differences in the data for the two diseases, but they are too complex and no better than these. The $K/HbA1c$ ratio is the best FI for predicting FT1D from DKA according to the AUC (0.899). Since insulin can reduce K^+ , it is best to use K^+ to create the FI before insulin intervention to more accurately reflect the real situation of patients.

Improvements in technology now permit the rapid testing of HbA1c. PG, Na⁺, and K⁺ are routine blood examination results. Therefore, FI (PG/HbA1c, K⁺/HbA1c, Na⁺*HbA1c) can function as a simple tool that may be useful to identify FT1D in DKA patients. FI (PG/HbA1c \geq 4.39 mmol/L/%, K⁺/HbA1c \geq 0.85 mmol/L/%, Na⁺*HbA1c \leq 923.65 mmol*%/L) can be adopted as a new clinical parameter in diagnosing FT1D. As mentioned in previous paragraphs, early diagnosis of FT1D could set alert for high-risk cases, or direct appropriate clinical intervention, and may help early management of drug-induced FT1D or pregnancy-associated FT1D cases.

Our study proposed a more convenient quantitative tool to help distinguish FT1D from DKA secondary to other types of diabetes. This tool could achieve early screening of FT1D prior to C-peptide assessment and DKA correction. Besides these advantages, there are still limitations in this study. Limited by the rareness of FT1D cases, our sample size is relatively small. An increase of observations on FT1D cases would provide more abundant data to verify the capacity of FI as a diagnostic index in the future. Also, our study focuses on the Chinese FT1D population, while how FI works in the population of other ethnicities remains unclear. Besides, our analysis did not involve other clinical factors that could also be susceptible to serum electrolyte, such as insulin usage and diarrhea of the patient. Therefore, if physicians apply FI in clinic, we suggest taking the effects of diarrhea and insulin usage into additional consideration.

Conclusion

Our study suggested that the FI could work as a potential indicating index for identifying FT1D from general DKA patients. And our study determined the estimated thresholds of FI (PG/HbA1c \geq 4.39 mmol/L/%, K⁺/HbA1c \geq 0.85 mmol/L/%, Na⁺*HbA1c \leq 923.65 mmol*%/L) on differentiating FT1D from non-FT1D DKA. The K⁺/HbA1c ratio presented the best diagnostic strength with AUC 0.899, sensitivity 77.5%, and specificity 94.4%. FI helps realize quick diagnosis of FT1D in clinical practice and may also help FT1D patients acquire appropriate management on their early disease onset.

Declarations

Ethical Approval and Consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Our study have been approved by ethnical review by the institutional ethics review board from the Second Xiangya Hospital, Central South University.

Consent for publication

Not applicable.

Availability of supporting data

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests The authors have declared that no competing interest exists.

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Authors' Contributions J.Q. and X.L. researched data and wrote manuscript, S.L. researched data and contributed to discussion, Z.Z. reviewed manuscript and contributed to discussion, W.C. and X.M. researched data and edited manuscript, Z.X. and G.H. reviewed/edited the manuscript and contributed discussion.

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Figures

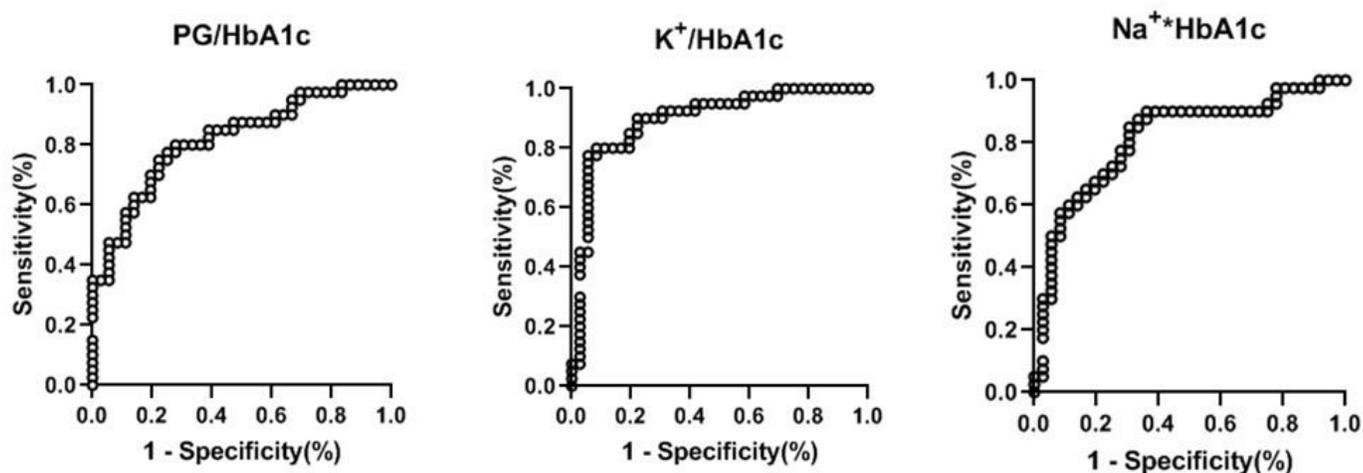


Figure 1

Receiver operating characteristic (ROC) curves for the fulminant index (PG/HbA1c, K⁺/HbA1c, Na⁺*HbA1c) in the differential diagnosis between severe fulminant type 1 diabetes mellitus (FT1D) and diabetic ketoacidosis (DKA).

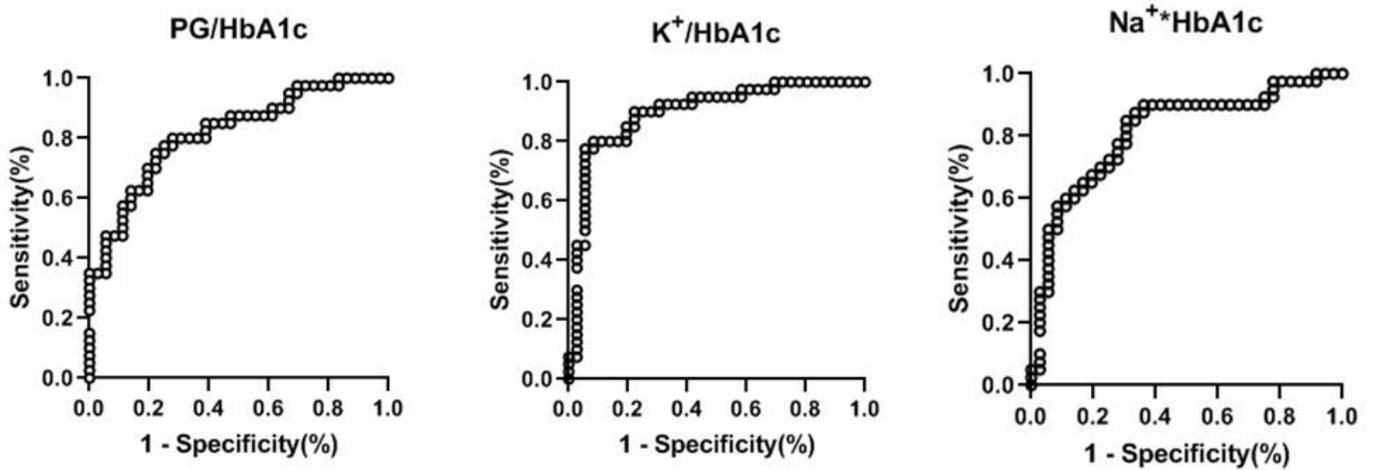


Figure 1

Receiver operating characteristic (ROC) curves for the fulminant index (PG/HbA1c, K/HbA1c, Na*HbA1c) in the differential diagnosis between severe fulminant type 1 diabetes mellitus (FT1D) and diabetic ketoacidosis (DKA).

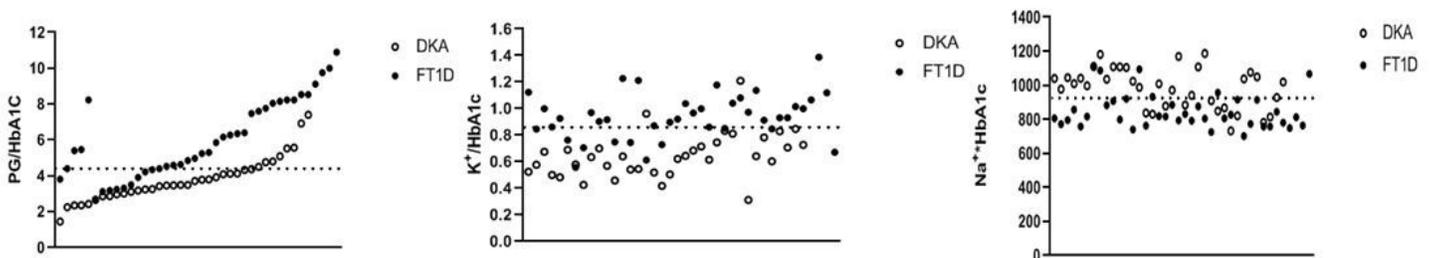


Figure 2

A comparison of the fulminant indexes (PG/HbA1c, K/HbA1c, Na*HbA1c) of patients with fulminant type 1 diabetes mellitus (FT1D) in solid circles and of patients with diabetic ketoacidosis (DKA) in open circles. The dotted lines represent the cutoff values of the fulminant index (PG/HbA1c: 4.39, K/HbA1c: 0.85, Na*HbA1c: 923.65, respectively) that best differentiate FT1D from DKA.

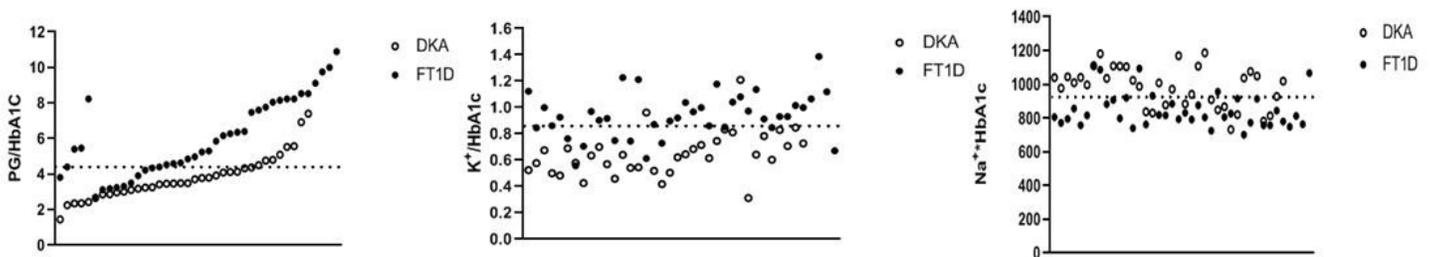


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