

The Implication of Elevated Serum Myoglobin Level in Acute Diabetic Complications of Ketoacidosis and Hyperglycemic Hyperosmolar State: A Real-World Study

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Objective: To investigate the implications of elevated myoglobin (MYO) in acute diabetic conditions of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).

Materials and methods: This study integrates in-patient data from Shanghai Pudong Hospital from 2019 to 2023. Laboratory data were compared between stable T2D patients (without acute diabetic complications), DKA, and HHS patients. The multilinear regression explored variables relevant to the elevated MYO in DKA and HHS. The dynamics of MYO, the survival rate, and associated risk factors in HHS were determined.

Results: Except for triglyceride, procalcitonin, low-density lipoprotein, islet cell autoimmune antibodies, N-terminal Pro-brain natriuretic peptide (NT-ProBNP), and brain natriuretic peptide (BNP), there were significant differences in age, gender distribution, duration of diabetes, type of diabetes, and other referred laboratory data ($p < 0.05$). The age, gender, creatine kinase (CK), estimated glomerular filtration rate (eGFR), and free triiodothyronine (FT3) in DKA, whereas osmolar, uric acid (UA), and cardiac troponin I (cTNI) in the HHS, were significant determinants of elevated MYO, respectively ($p < 0.05$). The dynamic of MYO in HHS was in line with the survival trend, where the percentage of death was 29.73%, and aging with higher procalcitonin levels was a key risk factor. Besides, the cumulative survival rates between patients with or without bone fracture or muscle injury were substantially different.

Conclusion: This real-world study demonstrated DKA and HHS potentially have unique causes for increased MYO. By utilizing the appropriate regression parameters, we could forecast the progression of increased MYO in groups of DKA and HHS, while based on risk factors of aging, severity of infection, and different MYO sources, we could predict the prognosis of HHS.

Keywords: diabetes mellitus, diabetic ketoacidosis, hyperosmolar hyperglycemic state, myoglobin, survival

Introduction

Diabetes mellitus (DM) emerges to be the prevalent public health issue, for continually increased incidence and prevalence of DM are associated with unexpected expanded proportions of severe cardiocerebrovascular events such as acute myocardial infarction (AMI), stroke, heart failure (HF), etc.¹ According to the current epidemic survey, the major cause for death in DM is comprised mainly by macrovascular diseases such as AMI, stroke, HF s,² in contrast with the outcome of diabetic microvascular diseases such as diabetic retinopathy (DR), diabetic nephropathy (DN), which could be early prevented via intensive glycemic control.³ Therefore, the present international guidelines for the pharmacotherapy of diabetes mellitus have

been reconfigured to prioritize factors that enhance the cardiovascular outcome of individuals with diabetes, extending beyond the simple reduction of blood glucose levels.⁴

It is also acknowledged by the majority of DM patients with poor control of glycemic increases rates of acute diabetic complications, such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state or coma (HHS), both are severe conditions that are hazardous to the survival of patients.⁵ Nevertheless, the pathophysiology of these two conditions might be distinctive.⁶ In clinical settings, DKA frequently onset in younger patients who may be presented with ketosis-prone, deteriorated pancreatic islet function and extreme metabolic acidosis, while HHS often onset in the elderly, whose past illness history could deny the existence of DM and with impaired consciousness, and exaggerated osmolar pressure (defined as two folds of total concentrations of blood sodium and potassium, which plus plasma glucose level that exceeds the 320 mOsm/L).⁷ In addition, multiple studies have acclaimed that both in the treatment of DKA and HHS, there are also doubled risks for cardiovascular events.⁸ A dynamic reexamination of combined critical parameters, including but not limited to myoglobin (MYO), cardiac troponin I (cTNI), procalcitonin (Pct), D-dimers, electrolytes, electrocardiogram (ECG), and blood-air analysis, can enable endocrinologists to ascertain the most effective approach in preventing adverse death events. For most opportunities, these indicators that could exclusively forecast the crisis of certain conditions may not be completely sensitive and specific. Thus, we should re-analyze them in a comprehensive and systemic pattern.

In the current study, we retrospectively investigated the pathological role of MYO in DKA and HHS, for it is often detected to rise rapidly (within 2 hours after a specific injury) during our clinical observations. Previous studies have already found that MYO is an integral component of striated muscle, including skeletal muscle and myocardium, and it could be found in the central nervous system. When our heart or skeletal muscles experience an injury, these cells could release myoglobin into our bloodstream; the elevated MYO detected in our blood or urine can be traced to the injury of these striated muscles, indicating the potentiality of the condition, such as acute myocardial infarction (AMI), or acute cerebral infarction. The level of MYO in the blood can rise very quickly (within 2–3 hrs) with severe muscle damage so that it can be measured within a few hours following an injury. Therefore, its rapid elevation in circulation could help physicians implement practical actions to prevent adverse outcomes of AMI or acute cerebral infarction and help them monitor the progression of these conditions. Thus, during the treatment, the evolution of MYO could be indicators to assist in judging the condition of certain patients, for exclusion of undesired AMI or stroke, both of which are severe sequelae. Moreover, many causes could lead to the rise of MYO in an individual patient, such as rhabdomyolysis and bedsores. Therefore, our study compared the laboratory data of DKA, HHS, and T2DM only, which will help construct the profile of these cohorts, and most importantly, we determined the parameters related to the MYO elevation, linked the MYO changes with the possibilities of survival in HHS, and identified risk factors associated with the adverse outcome of HHS patients, the results of which could help predict the progression and prognosis of HHS patients.

Materials and Methods

Source of Patient Data

We collected data on 433 adult diabetic patients admitted to the Department of Endocrinology between 2019 and 2023 from the inpatient record system of Shanghai Pudong Hospital. Typical type 2 patients (n=300) met the diagnostic criteria for DM according to established World Health Organization (WHO) and American Diabetes Association (ADA) guidelines and were included in a randomized manner and compared with the other 2 groups.⁹ The diagnostic standards for diabetes (DM) include at least one of the symptoms of hyperglycemia, such as dry mouth, polydipsia, polyuria, unknown reasons for bodyweight rapid reduction, etc, or hyperglycemic crisis. The random plasma glucose value exceeds 200mg/dL (11.1mmol/L), or fasting (no caloric intake for at least eight h) plasma glucose value exceeds 126mg/dL (7.0mmol/L), or 2 hours post oral glucose challenge by oral glucose tolerance test (OGTT), shows exceeding 200mg/dL. Those results examined at least two different single days, or an HbA1c real value exceeds 6.5%. The diagnostic evidence for type1 diabetes (T1DM) encompasses onset at the early age of a person, with or without immunoreactive for diabetes-related antibodies, concurrently showed sparse pancreatic insulin secretion represented by extremely lower C-peptide levels, who often exhibited ketone-prone characteristics, whereas type 2 diabetes (T2DM) onset latently with strong genetic background on adults with relatively insulin

insufficiency, and frequently with comorbidity of overweight or obesity or other metabolic disorders, who might exhibit as overt insulin resistance.

Patients who fulfilled the international diagnostic criteria for diabetic ketoacidosis (DKA) (n=59) (blood glucose >200 mg/dL or known to have DM, with ketonemia (>3.0mmol/L) or ketonuria (2+ or more on standard urine sticks), and pH < 7.3 or HCO₃⁻ <15 mmol/L determined by blood-air analyses, anion gap >10mmol/L), hyperosmolar hyperglycemic state (HHS) (n=74) (blood glucose >599.4mg/dL, with hyperosmolar state defined as >320mOsm/L, pH >7.3 or HCO₃⁻ >15 mmol/L determined by blood-air analyses, urinary glucose showed strong positive, without or weak positive for ketonemia or urine ketone, anion gap <12mmol/L). All DKA or HHS patients received hydration treatment and a continuous low intravenous dose of rapid-acting insulin (0.1 U/kg) until the normalization of pH, ketone, or blood osmolar. T2DM only patients received either oral anti-diabetic medication, such as metformin, sulfonylurea, glinides, pioglitazone, sodium-glucose co-transporter inhibitors (SGLT-2i), α -glucosidase inhibitors and dipeptidyl peptidase-IV inhibitors (DPP-IV inhibitors), or injectables such as glucagon-like peptide-1 receptor agonists (GLP-1RA), and insulin (basal insulin or combined with prandial insulin or premixed insulin), based on disease progression, glycemic control, and complications such as liver or kidney insufficiency.

Other acidosis disorders, including lactic acidosis, shock, hypoperfusion of circulation, hypoxia such as chronic obstructive pulmonary disease (COPD), asthma, uremia, intestinal obstruction, and severe sepsis, were excluded from the study according to the information of diagnoses and history as well as evidence from certain examinations or maneuvers such as enhanced computed tomography (CT), magnetic resonance imaging (MRI), etc. in our recording system. The clinical characteristics of the three groups are represented in Table 1.

Table 1 The Metabolic Profile of T2DM Only, DKA, and HHS on Demographic Data, Diabetic Background, Electrolyte, Osmolar, and Lipid Profile

	Total (n=433)	T2DM Only (n=300)	DKA (n=59)	HHS (n=74)	P Value (Total)
Age	65.03±15.82	64.85±13.91	50.36±14.97	77.46±13.42	<0.0001
Gender (Male/Female)	232/201	168/132	38/21	26/48	0.002
Duration (years)	9.92±8.32	10.50±8.38	5.73±5.87	11.11±8.82	<0.0001
Type of DM (unidentified/II/III)	4/30/399	0/0/300	0/26/33	4/4/66	<0.0001
GAD (U/mL)	2.74±13.57	1.46±8.71	8.52±27.43	2.11±3.29	0.042
ICA (COI)	1.80±6.58	1.87±6.76	1.14±4.59	2.74±8.73	0.575
IAA (COI)	0.83±3.87	0.16±1.34	0.85±1.95	4.70±9.72	<0.0001
FPG (mmol/L)	12.46±7.58	9.02±3.63	22.84±8.96	17.05±7.31	<0.0001
FPCP (nmol/L)	0.35±0.31	0.41±0.34	0.12±0.15	0.34±0.22	<0.0001
2hPPCP (nmol/L)	0.67±0.59	0.77±0.63	0.27±0.35	0.49±0.31	<0.0001
HbA1c (%)	10.13±2.78	9.57±2.43	11.58±2.67	10.89±3.41	<0.0001
GA (%)	18.77±15.24	10.22±4.36	39.80±15.95	32.81±11.44	<0.0001
Sodium (mmol/L)	143.17±9.60	140.81±4.30	135.07±6.98	158.72±9.78	<0.0001
Potassium (mmol/L)	3.95±0.61	3.97±0.50	4.19±0.93	3.70±0.59	<0.0001
Chlorine (mmol/L)	107.84±9.77	105.46±5.37	100.78±7.00	122.64±10.50	<0.0001
Phosphorus (mmol/L)	1.07±0.34	1.14±0.25	0.85±0.49	0.98±0.38	<0.0001
Osmolar (osmo)	350.10±262.51	283.28±64.66	300.99±16.31	660.14±522.25	<0.0001
LDL (mmol/L)	2.63±1.01	2.67±1.01	2.66±0.88	2.46±1.14	0.361
HDL (mmol/L)	0.98±0.33	1.03±0.31	1.01±0.39	0.78±0.27	<0.0001
TC (mmol/L)	4.34±1.24	4.35±1.13	4.66±1.32	4.04±1.50	0.026
TG (mmol/L)	2.03±1.81	1.94±1.66	2.44±2.44	1.98±1.64	0.446

Abbreviations: T2DM only, stable type 2 diabetic patients; DKA, diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; DM, diabetes mellitus; GAD, glutamic acid decarboxylase; ICA, islet cell autoimmune antibody; IAA, Insulin autoimmune antibody; FPG, fasting plasma glucose; FPCP, fasting plasma C-peptide; 2hPPCP, 2 hours postprandial C-peptide; HbA1c, Glycated hemoglobin A1c; GA, glycated albumin; LDL, low density lipoprotein; HDL, high density lipoprotein; TC, total cholesterol; TG, triglyceride.

Blood Sampling and Methods of Laboratory Assessment

Blood samples were obtained from patients on the first day of admission to assess the metabolic and organic parameters. These laboratory parameters include serum blood glucose, pancreatic islet function, hemoglobin A1C (HbA1C), plasma lipids, electrolytes, thyroid function, hepatic function, renal function, and cardiac function. All biochemical indicators: fasting blood glucose, lipid parameters, hepatic function, kidney function indicators, estimated glomerular filtration rate (eGFR), and creatinine were analyzed via a full-automatic biochemical analyzer (ADVIA chemistry XPT, SIEMENS, USA). HbA1C was analyzed by an HbA1C analyzer (TOSOH G8), reflecting the glycemic control level in the past three months. C-peptide and thyroid function indicators were processed via chemiluminescence methods in a full-automatic chemiluminescence immunoassay analyzer (ADIVA Centaur XPT, SIEMENS, USA). The islet cell autoimmune antibodies were assessed via another chemiluminescence analyzer (Smart 6500, Keysmile, China). Cardiac injury indicators, including brain natriuretic peptide (BNP), myoglobin (MYO), cardiac troponin I (cTNI), creatine kinase-Mb (CK-Mb), were analyzed via methods of the immunofluorescent assay (Pylon, ETHealthcare, USA).

Statistical Analyses

The statistical analyses were performed using SPSS (IBM, version 26.0) and Prism (GraphPad, version 10.0) software. To compare the groups of patients with T2D only, patients with DKA, and with HHS, all data were analyzed using standard one-way ANOVA or Brown-Forsythe and Welch ANOVA tests, depending on whether the data were fitted for normal distribution and homogeneity of variance. Tukey’s test or Dunnett T3 test was then used for the post-hoc analyses. The independent variables associated with MYO in DKA and HHS were carried out using multilinear regression analysis. The survival data, including risk factors related to HHS, were used in Cox regression analyses. All statistical analysis significance thresholds were set at $p < 0.05$. The data were shown as mean \pm standard error of mean (SEM).

Results

The Comparisons of Profiles of Cardiac Injury Markers Among T2DM Only, DKA, HHS

We compared the profiles of cardiac injury markers among three groups and found that besides the NT-ProBNP and BNP, there were significant disparities in MYO, cTNI, CKMB, and CK ($p < 0.0001$) (Table 2 and Figure 1).

Table 2 The Cardiac Injury Associated Parameters Among 3 Groups

	Total	T2DM Only	DKA	HHS
MYO (ng/mL)	165.10 \pm 349.77	74.72 \pm 174.42	139.61 \pm 198.77	491.39 \pm 604.74
P Value	Total	T2DM vs DKA	DKA vs HHS	HHS vs T2DM
	<0.0001	0.0898	<0.0001	<0.0001
cTNI (ng/mL)	0.17 \pm 0.67	0.09 \pm 0.16	0.07 \pm 0.06	0.59 \pm 1.55
P Value	Total	T2DM vs DKA	DKA vs HHS	HHS vs T2DM
	<0.0001	0.3378	0.0350	0.0452
CKMB (U/L)	12.63 \pm 10.08	15.66 \pm 9.40	6.75 \pm 9.60	6.88 \pm 8.06
P Value	Total	T2DM vs DKA	DKA vs HHS	HHS vs T2DM
	<0.0001	<0.0001	0.9967	<0.0001
CK (U/L)	196.87 \pm 408.18	123.64 \pm 245.61	118.38 \pm 109.21	571.72 \pm 767.00
P Value	Total	T2DM vs DKA	DKA vs HHS	HHS vs T2DM
	<0.0001	0.9934	0.0002	0.0002
NT-ProBNP (pg/mL)	845.27 \pm 1559.37	692.30 \pm 1408.07	884.42 \pm 1681.58	1564.12 \pm 1946.73
P Value	Total	T2DM vs DKA	DKA vs HHS	HHS vs T2DM
	0.18	0.8491	0.1556	0.3983
BNP (pg/mL)	124.40 \pm 211.23	131.28 \pm 232.15	136.02 \pm 224.51	94.60 \pm 104.96
P Value	Total	T2DM vs DKA	DKA vs HHS	HHS vs T2DM
	0.328	0.9992	0.2579	0.6412

Abbreviations: MYO, myoglobin; cTNI, cardiac troponin I; CKMB, creatine kinase-MB; CK, creatine kinase; NT-ProBNP, N terminal B-type natriuretic peptide; BNP: B-type natriuretic peptide.

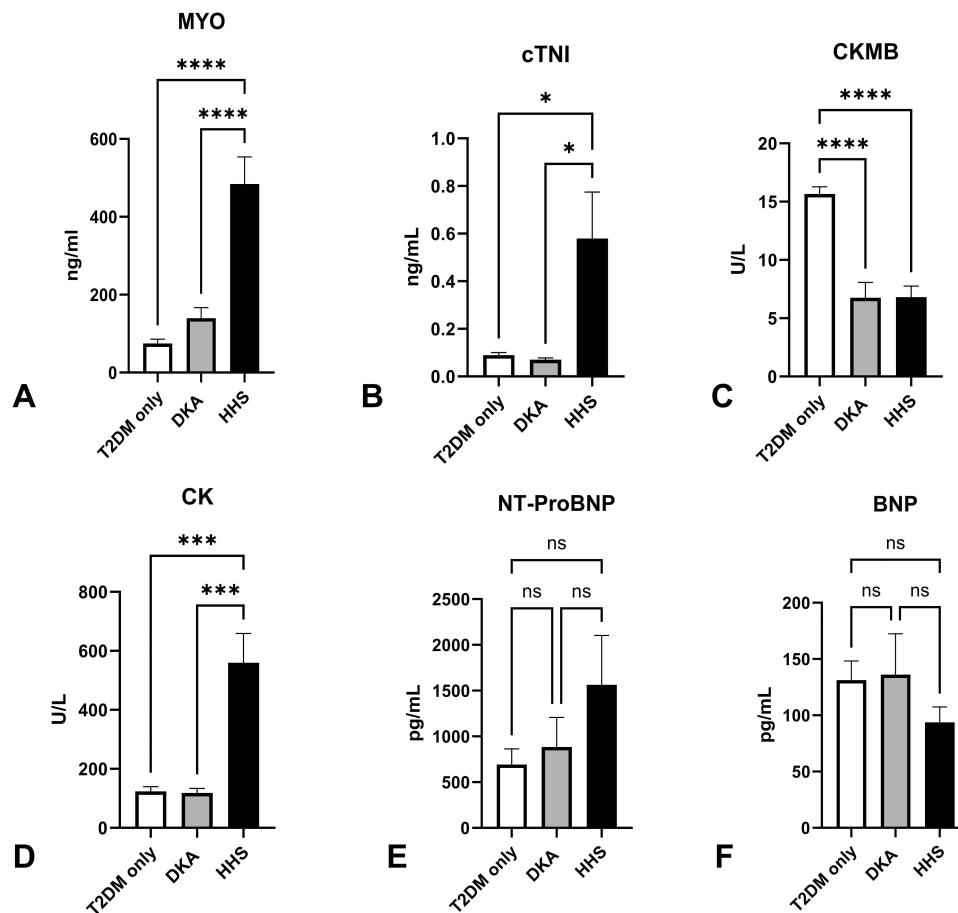


Figure 1 The significant changes in cardiac injury associated parameters: (A) MYO, (B) cTNI, (C) CKMB, (D) CK, when compared among 3 groups, whereas heart failure related markers (E) NT-ProBNP, (F) BNP did not show significant disparity.

Notes: *p<0.05; ***p<0.001; ****p<0.0001.

Abbreviations: MYO, myoglobin; cTNI, cardiac troponin I; CKMB, creatine kinase-MB; CK, creatine kinase; NT-ProBNP, N terminal B-type natriuretic peptide; BNP, B-type natriuretic peptide.

The Different Profiles of Hepatic and Kidney Injury Markers Among T2DM Only, DKA, HHS

We subsequently compared the differences among T2DM only, DKA, and HHS regarding hepatic and kidney injury markers. The results showed AST is significantly elevated in HHS (p<0.0001) when compared with DKA and T2DM only, while ALT showed no significance among the three groups. The kidney injury markers showed that SCr was substantially elevated in HHS(p<0.0001), while UA levels were higher in DKA and HHS (p<0.0001). The eGFR levels showed significantly higher in DKA while decreased in HHS (p<0.0001) (Table 3 and Figure 2).

Table 3 The Profiles of Hepatic and Renal Injury Parameters Among 3 Groups

	Total	T2DM Only	DKA	HHS	P Value (Total)
AST(U/L)	30.40±59.35	25.21±14.69	21.62±19.12	57.31±134.10	<0.0001
ALT(U/L)	28.09±32.93	27.60±25.28	19.46±12.00	37.03±58.29	0.55
Scr(μmol/L)	91.37±72.23	82.57±67.68	74.42±39.41	136.51±89.86	<0.0001
eGFR(mL/min*1.73m ²)	81.91±31.95	85.00±28.23	99.91±32.20	52.79±27.64	<0.0001
UA(μmol/L)	392.55±181.79	330.76±125.87	528.47±199.62	508.52±221.85	<0.0001

Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; SCr, Serum creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid.

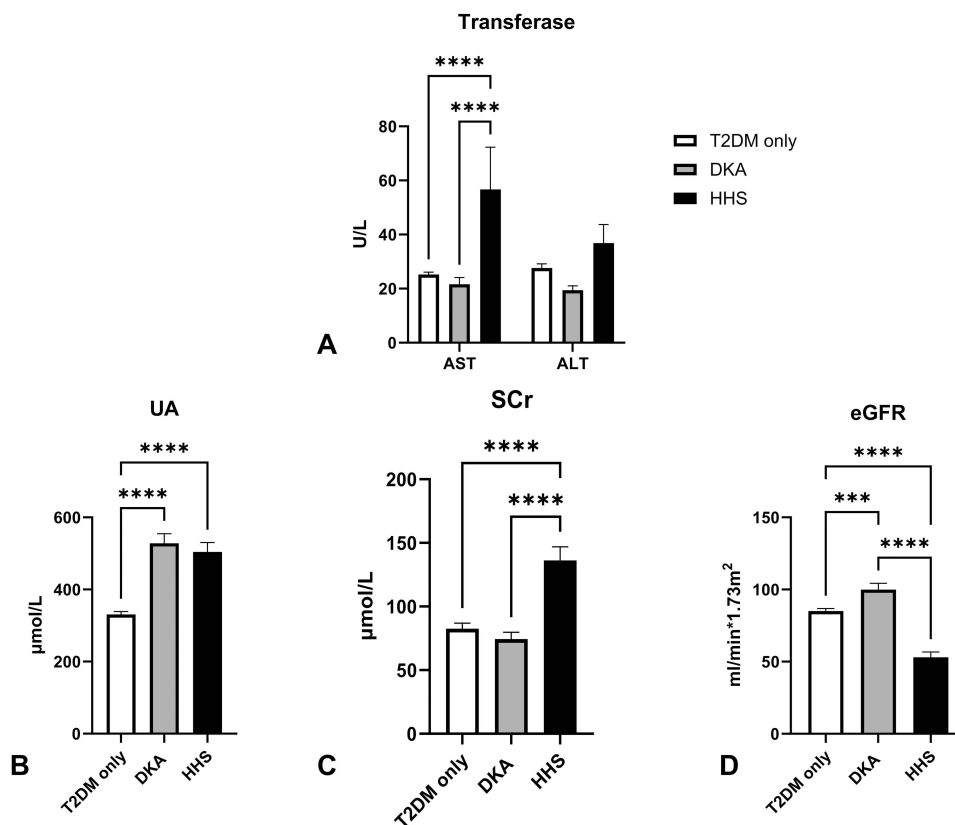


Figure 2 The comparisons show the distinct changes in hepatic (A) and renal injury (B) UA, (C) SCr, (D) eGFR markers.

Notes: ***p<0.001; ****p<0.0001.

Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; SCr, Serum creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid.

The Thyroid Function Status Comparison Among T2DM, DKA, and HHS

In the next step, we compared the status of thyroid function and observed a unique discrepancy in FT3, FT4, and TSH, where FT3 of DKA and HHS were lower than T2DM only, and FT4 of HHS was remarkably decreased in the other two groups (p<0.05). In addition, the level of TSH is significant (Table 4 and Figure 3).

Multilinear Regression Analyses of DKA and HHS Groups Reveal Different Determinants of the MYO Change

We then analyzed the determinant factors that predict the change of MYO in DKA and HHS. After performing the multilinear regression analyses, we found that CK, eGFR, FT3, gender variation, and age were determinants of the MYO change in DKA (R square: 0.543, adjusted R square: 0.500) (Table 5 and Figure 4). However, the Osmolar, cTNI, and UA levels in HHS were significantly associated with MYO change (R square: 0.249, adjusted R square: 0.217) (Table 6 and Figure 5).

Table 4 The Profiles of Thyroid Functional Change Among 3 Groups

	Total	T2DM Only	DKA	HHS	P Value (Total)
FT3 (pmol/L)	5.37±4.16	4.11±1.08	3.22±1.94	2.63±0.71	<0.0001
FT4 (pmol/L)	13.09±4.90	15.23±2.53	14.00±4.13	13.54±2.48	<0.0001
TSH (mIU/L)	2.25±4.23	2.76±4.99	1.32±1.51	1.06±0.93	0.003

Abbreviations: FT3, Free Triiodothyronine; FT4, Free thyroxine; TSH, thyroid stimulating hormone.

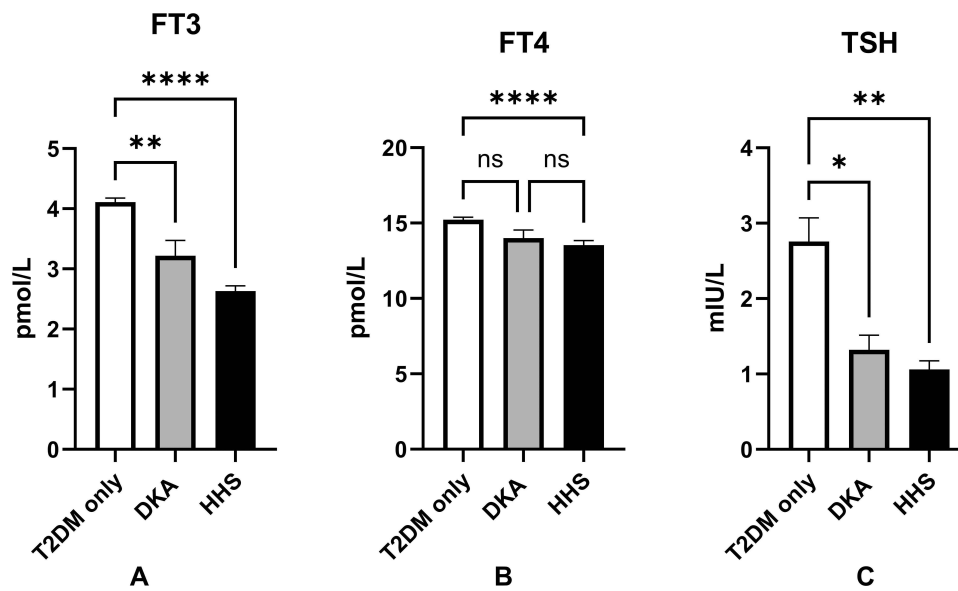


Figure 3 The comparisons reveal decline in thyroid function (A) FT3, (B) FT4, (C) TSH in DKA and HHS relative to the T2DM only. **Notes:** * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$. **Abbreviations:** FT3, free triiodothyronine; FT4, free thyroxine; TSH, Thyroid stimulating hormone.

The Dynamic of MYO and Its Relationship with the Survival Status in HHS

Moreover, an analysis of the dynamics of MYO in HHS reveals a discernible trend of reduction, as illustrated in Table 7 and Figure 6. In this dynamic, we found that MYO slightly dropped on Day 3 while continued to increase to the highest level on Day5, and sharply decreased in Day 6.

Consistent with this observation, we found a decline in the percentage of survival rate and an increase in mortality rate during Day1-Day6, with the dead patients in this study proportion to 29.73% (Figure 7). Therefore, we subsequently performed Cox regression analyses to determine the critical factors associated with the survival dynamic. We found that age and the level of procalcitonin (markers of severity of infection) were positively associated with the increased risk in mortality rate in survival analyses of HHS in this study (Figure 7 and Table 8).

In addition, we investigated the categorical variables such as clinical conditions that may be associated with elevation of MYO levels (including bedsores, bone fracture or muscle injury, acute coronary syndrome, and acute cerebral infarction), type of diabetes, and gender variation on the outcome of HHS during treatment. We found only patients with a bone fracture or muscle injury conditions potentially increased risk of death in this study. In contrast, bedsores suspected acute coronary syndrome and acute cerebral infarction did not show significance in cumulative survival rate, regardless of gender variation and type of diabetes (Figures 8 and 9).

Table 5 The Regression Model of Independent Variables to the Change of MYO in DKA

Multilinear Regress	R	0.737	R ²	0.543	Adjusted R ²	0.500	Tolerance	VIF
	Variables	B	SE	β	t	Sig		
Constant	397.791	139.285			2.856	0.006		
CK	0.819	0.176	0.441	4.641	<0.0001	0.954	1.048	
eGFR	-3.790	0.726	-0.620	-5.224	<0.0001	0.612	1.634	
FT3	21.185	9.364	0.218	2.263	0.028	0.924	1.082	
Gender	118.550	38.014	0.304	3.119	0.003	0.905	1.104	
Age	-4.080	1.539	-0.325	-2.651	0.011	0.575	1.739	

Abbreviations: CK, creatine kinase; eGFR, estimated glomerular filtration rate; FT3, free triiodothyronine.

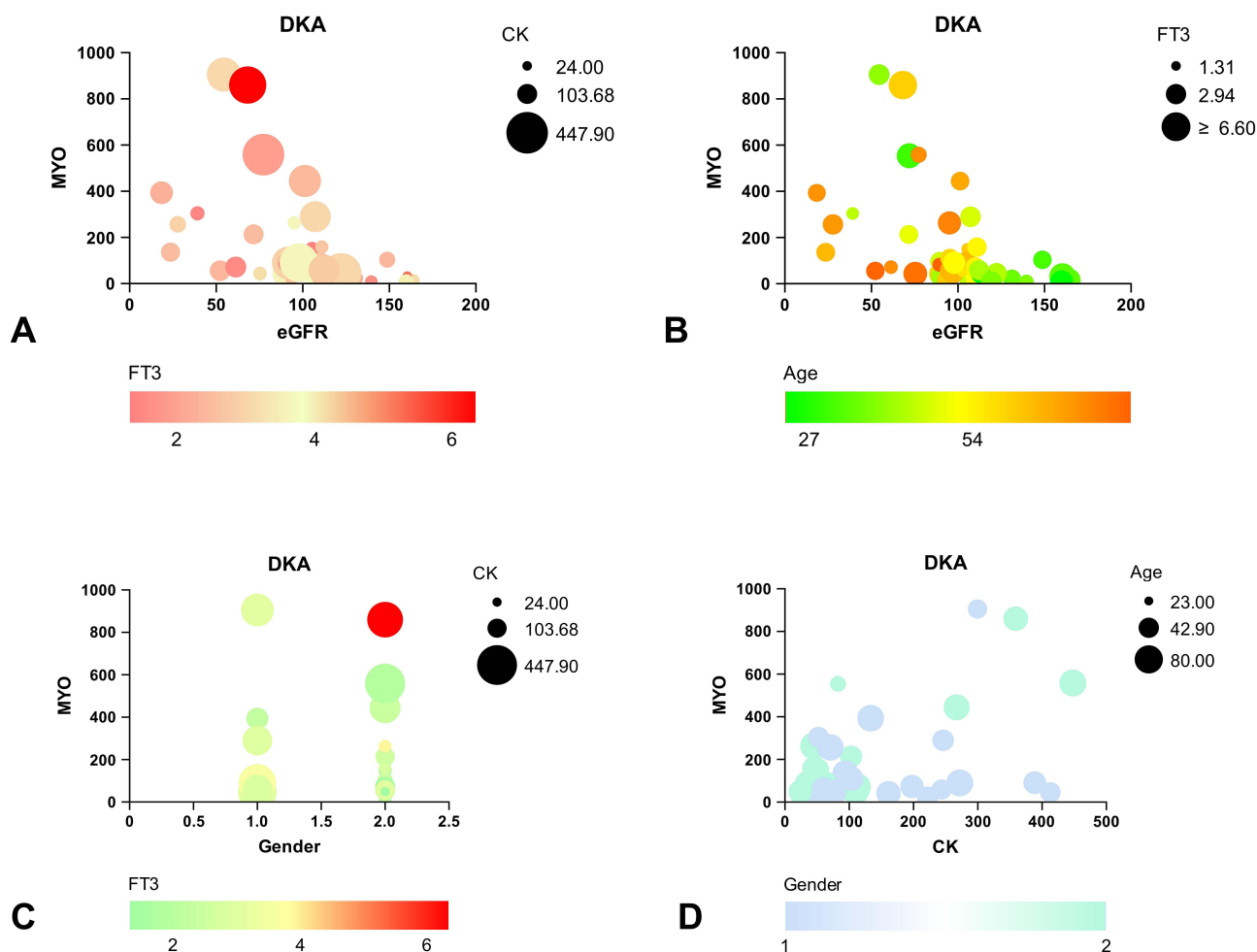


Figure 4 The independent variables including eGFR, CK, FT3, Gender, age determines the change of MYO in DKA. The presentation of bubble figure depicts the relationship between critical factors including eGFR, CK, FT3, Gender, age and MYO change. We found that as with the decrease in eGFR, CK, and status of low FT3, the MYO level will increase (A); With the age younger, and decline in eGFR, the status of low FT3, there is accompanied by MYO elevation (B); The female gender, increase in CK, the status of low FT3 were associated with the elevation in MYO (C); The younger age, female gender, and increase in CK were in line with the MYO change in HHS (D).

Abbreviations: CK, creatine kinase; eGFR, estimated glomerular filtration rate; FT3, free triiodothyronine.

Discussion

Diabetes mellitus (DM) is associated with substantial cardiovascular or cerebrovascular disease events relative to the typical populations. Diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemia state (HHS) are the severe acute complications of DM. Multiple clinical studies have revealed that DKA and HHS intensify the severity grade of the cardiovascular or cerebrovascular diseases following various episodes of DKA or HHS condition.^{10–13} The clinical

Table 6 The Regression Model of Independent Variables to the Change of MYO in HHS

Multilinear Regress	R	0.499	R ²	0.249	Adjusted R ²	0.217	Tolerance	VIF
	Variables	B	SE	β	t	Sig		
Constant		-104.284	160.220		-0.651	0.517		
Osmolar		0.297	0.129	0.260	2.309	0.024	0.846	1.182
UA		0.674	0.311	0.244	2.169	0.033	0.847	1.177
cTNI		97.339	44.602	0.228	2.182	0.032	0.987	1.013

Abbreviations: UA, uric acid; cTNI, cardiac troponin I.

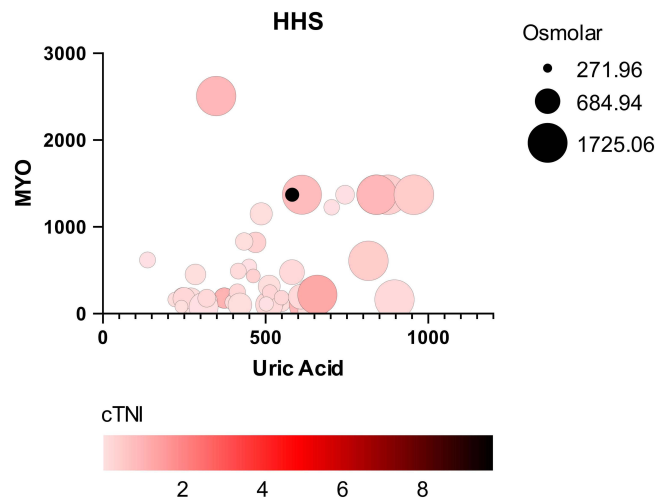


Figure 5 The independent variables including Uric acid, cTNI, osmolar determine the change of MYO in HHS. The presentation of bubble figure depicts the relationship between critical factors including Uric acid, cTNI, osmolar and MYO change. With the increase in UA, cTNI and osmolar, there is accompanied by elevation in MYO change in HHS.

Abbreviations: UA, uric acid; cTNI, cardiac troponin.

observations also have indicated during DKA and HHS, there is an increased risk for acute cardiovascular events such as acute coronary syndrome (ACS) or acute cerebral infarction or coma, especially in elderly individuals.^{14,15} Therefore, it is compulsory to recognize the onset of these complications in their early phases. However, to ensure therapeutic safety during the treatment of DKA or HHS, we should re-assess or distinguish the source of these early abnormal examinations, such as elevation of myoglobin (MYO), one indicator of the injury of striated muscle including cardiac muscle, skeleton muscle, for we have observed exaggerated elevation in most HHS. In the present study, we retrospectively analyzed the consequences of MYO elevation in both DKA and HHS and found there are distinct sources or determinants or risk factors for respective condition (Figure 10). The significance of our study identified the critical parameters to the change of MYO and linked its dynamic with the outcome of the patients with HHS through comparison and analyses of the profile of DKA and HHS, which will assist the recognition the condition and progress of these severe patients, and prediction of the prognosis and outcome of the therapy.

Firstly, for this is a real-world investigation, in our demographic data of diabetic patients, we found significant disparity regarding the normal data such as age, duration of diabetes, type of diabetes distribution, and glucose metabolic profile such as diabetic antibodies, FPG, C-peptide, HbA1c, glycated albumin, and electrolyte status on the admission of

Table 7 The Dynamic of MYO with Variation Range in HHS

MYO				
Range				
Day	Mean	SD	Lower Limit	Upper Limit
1	576.800	818.567	23.10	4000.00
2	649.241	773.365	16.30	4000.00
3	520.780	563.780	13.50	1991.40
4	628.183	677.621	12.00	2728.60
5	898.019	1248.250	22.60	4000.00
6	273.564	326.882	16.00	1369.86

Abbreviations: Mean, mean levels of variables; SD, standard deviation;

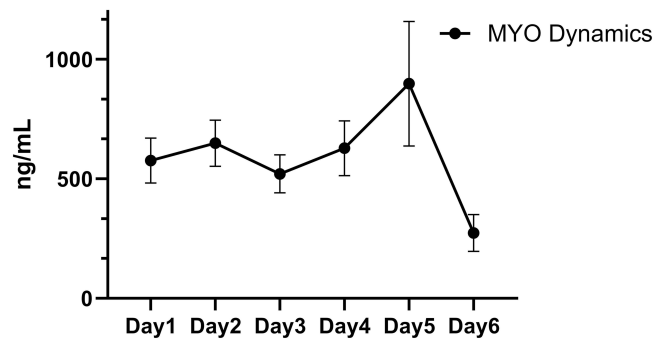


Figure 6 The dynamic of MYO in HHS during treatment. **Abbreviation:** MYO, myoglobin.

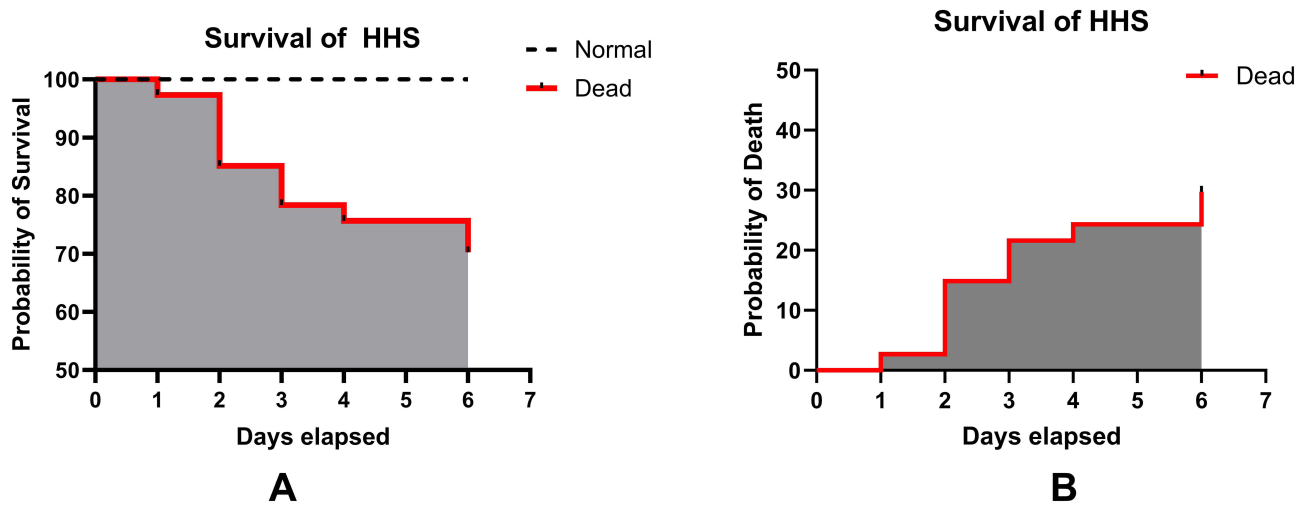


Figure 7 The probability of survival (A) and death (B) of HHS undergoing treatment. We found increased percentage of un-recovery in this study. With the decline in estimated survival rate, the death rate increased to 29.73%, in corresponding to the estimated survival rate of 70.27%.

ward including osmolar pressure, as well as serum lipid profiles. These data were largely in line with our observation in clinics that DKA patients may be younger. HHS frequently onset in aged patients and both conditions result from poor control of blood glucose triggered by multiple inducers such as infection and nonconformity of hypoglycemic treatment, thus manifested with extreme hyperglycemia, dyslipidemia, lower pancreatic islet function displayed by impaired C-peptide relative to normal T2DM patients.¹⁶ Comparing the levels of autoantibodies (GAD, ICA, and ICA) among the three groups revealed that patients with type 1 diabetes mellitus (T1DM) were more prone to developing DKA. In

Table 8 The Cox Regression Analysis of HHS Reveals the Risk Factors Associated with the Survival During Treatment

						95% Exp(B) CI	
Variables	B	SE	Wald	Sig.	Exp(B)	Lower Limit	Upper Limit
Age	0.066	0.023	8.049	0.005	1.068	1.021	1.118
Pct	0.097	0.031	9.446	0.002	1.101	1.036	1.171

Notes: The Exp(B) shows the relative risks of variables including age and Pct to the un-recovery outcome in this study.

Abbreviations: Pct, procalcitonin; sig, significance; CI, confidence interval.

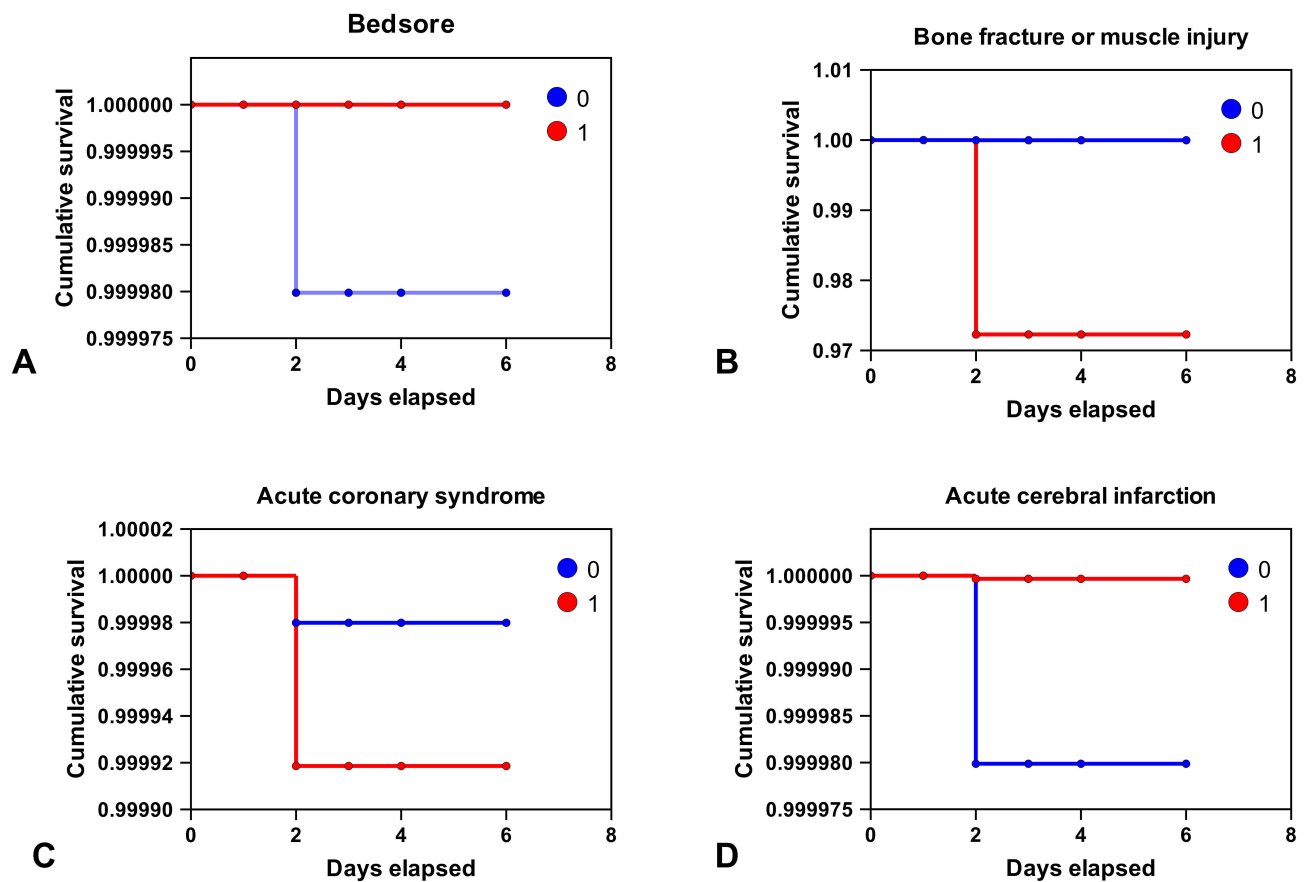


Figure 8 The comparisons of separately clinical conditions: (A) Bedsore, (B) Bone fracture or muscle injury, (C) Acute coronary syndrome, (D) Acute cerebral infarction, of the potential source of elevated MYO on the risks of un-recovery outcome of HHS. The analyses revealed that only bone fracture or muscle injury which may result in elevated MYO significant influenced the outcome of HHS.

Notes: 0: without respective condition; 1: with potential condition.

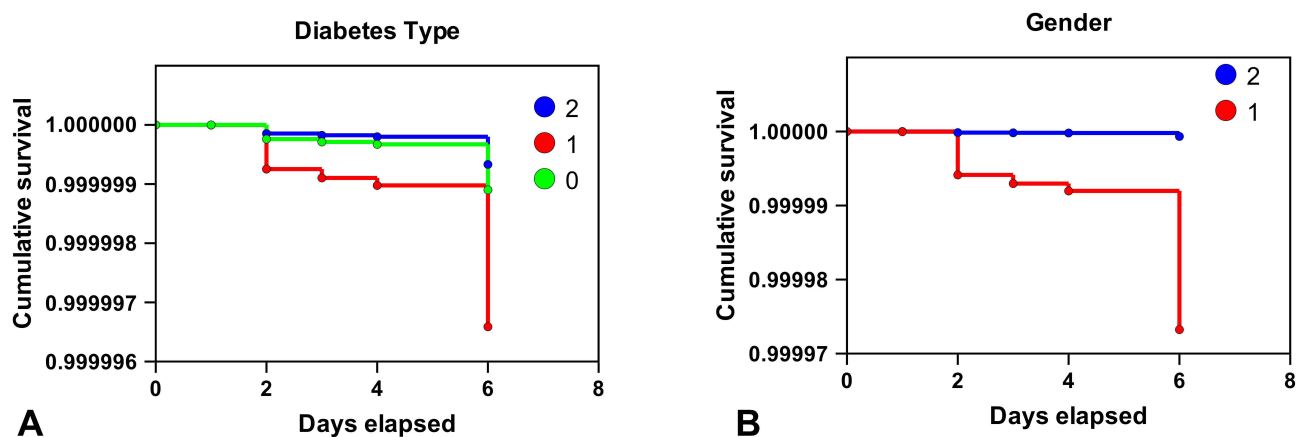


Figure 9 The effects of type of diabetes (A) and gender variation (B) on the mortality risk associated with HHS. These results demonstrated that there were no significant variations in the outcomes of HHS, irrespective of gender variation or type of diabetes.

Notes: Subfigure (A) 0: unidentified diabetes; 1: type1 diabetes; 2: type 2 diabetes; Subfigure (B) 1: male; 2: female.

contrast, those with type 2 diabetes mellitus (T2DM) were much more likely to be diagnosed after HHS, consistent with the status of China, which may be in contrast with the results from prior overseas research,^{16–18} which may be explained by the higher proportion rate of uncontrolled of blood glucose in all type diabetic Chinese patients compared with developed countries, and potential ethics variation may account for this disparity.¹⁹

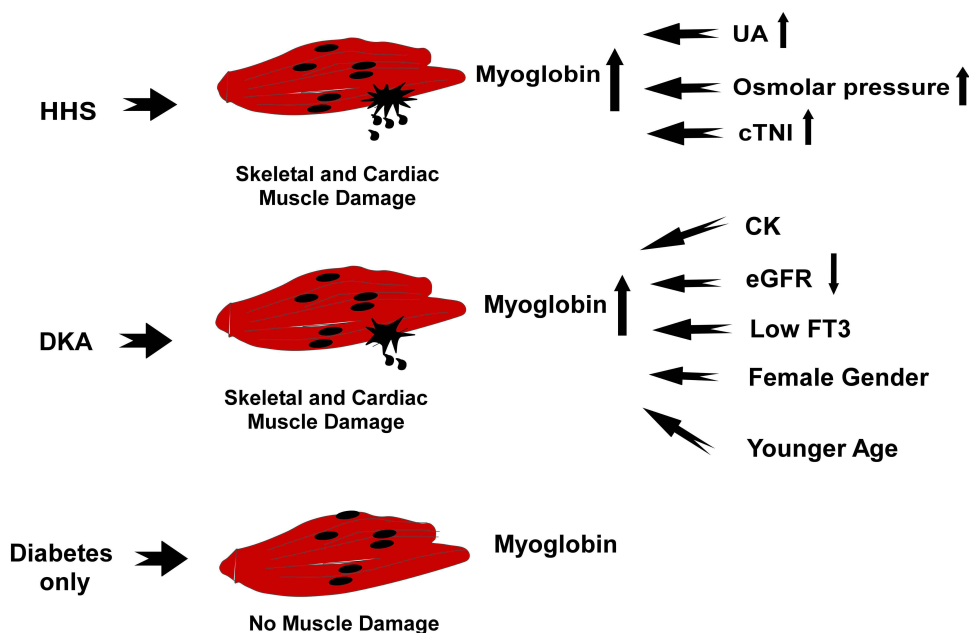


Figure 10 This illustration depicts the source of the elevated MYO in HHS and DKA relative to the normal diabetic patients. The MYO elevation in each condition could be expected from the different determinants. For HHS, the elevation of UA, osmolar, cTNI were associated with the MYO change, while in DKA, multiple indicators determined this change such as CK, eGFR, FT3, female gender, younger ages. No increased MYO in patients with diabetes only.

The first results showed that compared with DKA and T2DM only, the MYO change is significant, as is cTNI. This may be attributed to the HHS patient having minor myocardial damage or significantly impaired renal function, as indicated by a lower eGFR. Moreover, our clinical data suggested a minimal risk of primary myocardial infarction with treatment among these HHS patients.^{20,21} Furthermore, the absence of a substantial fluctuation in BNP concentration eliminated the possibility of acute or chronic heart failure. In contrast, the elevation in NT-ProBNP suggested that renal insufficiency induced by volume depletion is the main factor responsible for this change.

In the next step, we delineated the profile of hepatic and renal function among three groups; the elevated AST level may suggest the injury of striated muscle rather than the hepatic injury, which is supported by the normal level of ALT which may indicate the acute liver injury. Besides, the lower perfusion of renal glomerular and reduced kidney tubular secretion resulted in elevated plasma UA and SCr levels. In most DKA patients, due to the short duration of diabetes and possibly early impairment in glomerular function, such as diabetic kidney disease (DKD) 1 phase, an enhanced glomerular filtration rate may be represented by higher eGFR. Furthermore, when comparing the thyroid function of patients with T2DM only to that of patients with DKA and HHS, the functional changes identified in FT3, FT4, and TSH proved the presence of non-thyroid illness syndrome.²² This may provide insight into the severity stage of patients suffering from DKA or HHS.

Further, we performed multilinear regression analyses in DKA and HHS for the change in MYO and found distinct parameters determined in respective conditions. The elevation in CK, decrease in eGFR, lower FT3 status, female gender, and younger age could predict the elevation in MYO (R square: 0.543), which aligns with previous clinical observations and studies.^{23,24} However, in HHS, we found only osmolar pressure, UA level, cTNI could be critical surrogate parameters from our selected laboratory data (R square: 0.249),^{25–27} therefore, it is essential to include more potential parameters which assist the prediction of MYO change.

In our succeeded analyses, we drew the dynamic of MYO change in most HHS patients, and linked it with the outcome of patients. The results suggest that during treatment before day 5, there is a trend in the elevation of MYO, an increase accompanied by death, and an upswing to the stable plateau on Day 5, which is associated with the highest mean level of MYO. Although there is no adequate clinical data on the MYO evolution and its association with mortality in HHS, the long-term observations indicated that patients with HHS or other acute decompensated diabetic states were at increased risks for cardiovascular death or adverse macrovascular events such as major adverse cardiovascular events

(MACE).^{28,29} Multiple clinical studies have reported a significant relationship between elevated MYO and diabetic kidney disease (DKD) and further kidney injury.³⁰ A large retrospective clinical study shows that regardless of adjusting age, gender, and selected comorbidities, older age, male gender, and other factors could serve as independent mortality predictors.³¹ However, when we subsequently investigated the risk factors to the survival outcome of HHS, we only found aging and infection status represented by procalcitonin level on the admission as the continuous variables to the increased risk of death rate, which may be attributed to the lack of inclusion of MYO dynamic data. Nonetheless, we compared the potential source of MYO to the risk of death outcome. We found that MYO originating from muscle injury, such as bone or skeletal muscle injury, exclusively increased the risk of death rate relative to non-muscle injury patients. Finally, when comparing the diabetes type and gender variation, we found no apparent disparity in risks, which suggests the outcome of HHS may not be associated with gender differences and type of diabetes.

Limitations

Our study delineates the profiles and risk factors associated with the DKA and HHS, and to our knowledge, for the first time, the relationship between the MYO dynamic and the outcome and the prognosis of HHS. However, the single-center study and lack of subsequent long-term follow-up for HHS on cardiovascular or cerebrovascular events may be the weakness of the current study.

Conclusion

Longstanding hyperglycemia increases the possibility of acquisition of cardiovascular or cerebrovascular diseases and associated adverse events; however, in the situation of acute complications such as diabetic ketoacidosis, hyperosmolar hyperglycemia state, the incident of acute cardiovascular events may be lethal to the patients. Our study results suggest in the DKA and HHS, the determinants of the change in MYO may be different; through these critical variables, we could predict the MYO change in respective conditions. The dynamic of MYO is an essential indicator that conforms to the progress of conditions of HHS where the aging and infection status on the admission could predict the outcome of these patients, and the risk increases in the patients whose condition is closely related to the MYO change originated from the bone or muscle injury.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethical Statement

The study, including sampling, examinations, and access or utilization of the raw data for this study, obtained ethical approval from the Shanghai Pudong Hospital (WZ-010.). Study participants provided informed consent before the study. The guidelines and procedures were outlined in accordance with the Declaration of Helsinki. All the data used in this study were anonymized before their use.

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Author Contributions

All authors have made significant contributions to this work, including the conception of the study, study design, execution, data acquisition, analysis, and interpretation of the data. They have actively participated in drafting, revising, and critically reviewing the article. The final version to be published has received approval from all authors. They have collectively agreed on the journal to which the article has been submitted and are willing to take full responsibility for all aspects of the work.

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Disclosure

The authors declare that there are no potential conflicts of interest in this work.

References

- Gyldenkerne C, Mortensen MB, Kahlert J, et al. 10-year cardiovascular risk in patients with newly diagnosed Type 2 diabetes mellitus. *J Am Coll Cardiol.* 2023;82(16):1583–1594. doi:10.1016/j.jacc.2023.08.015
- Dal Canto E, Ceriello A, Rydén L, et al. Diabetes as a cardiovascular risk factor: an overview of global trends of macro and micro vascular complications. *Eur J Prev Cardiol.* 2019;26(2_suppl):25–32. doi:10.1177/2047487319878371
- Li Y, Liu Y, Liu S, et al. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. *Signal Transduct Target Ther.* 2023;8(1):152. doi:10.1038/s41392-023-01400-z
- ElSayed NA, Aleppo G, Bannuru RR, et al. 9. Pharmacologic approaches to glyemic treatment: standards of care in diabetes-2024. *Diabetes Care.* 2024;47(Suppl 1):S158–s178.
- Pasquel FJ, Tsegka K, Wang H, et al. Clinical outcomes in patients with isolated or combined diabetic ketoacidosis and hyperosmolar hyperglycemic state: a retrospective, hospital-based cohort study. *Diabetes Care.* 2020;43(2):349–357. doi:10.2337/dc19-1168
- Kitabchi AE, Umpierrez GE, Fisher JN, et al. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *J Clin Endocrinol Metab.* 2008;93(5):1541–1552. doi:10.1210/jc.2007-2577
- Fayfman M, Pasquel FJ, Umpierrez GE. Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Med Clin North Am.* 2017;101(3):587–606. doi:10.1016/j.mcna.2016.12.011
- Eubanks A, Raza F, Alkhouli M, et al. Clinical significance of troponin elevations in acute decompensated diabetes without clinical acute coronary syndrome. *Cardiovasc Diabetol.* 2012;11:154. doi:10.1186/1475-2840-11-154
- ElSayed NA, Aleppo G, Bannuru RR. 2. Diagnosis and classification of diabetes: standards of care in Diabetes—2024. *Diabetes Care.* 2024;47(Suppl 1):S20–s42. doi:10.2337/dc24-S002
- Gibb FW, Teoh WL, Graham J, et al. Risk of death following admission to a UK hospital with diabetic ketoacidosis. *Diabetologia.* 2016;59(10):2082–2087. doi:10.1007/s00125-016-4034-0
- Santos SS, Ramaldes LAL, Dualib PM, et al. Increased risk of death following recurrent ketoacidosis admissions: a Brazilian cohort study of young adults with type 1 diabetes. *Diabetol Metab Syndr.* 2023;15(1):85. doi:10.1186/s13098-023-01054-5
- Au A, Toolis M. Hyperosmolar Hyperglycaemic State (HHS) complicated by life-threatening large vessel occlusive arterial thrombosis - A mini case series and important reminder for clinicians. *Diabetes Metab Syndr.* 2022;16(6):102515. doi:10.1016/j.dsx.2022.102515
- Marren SM, Beale A, Yiin GS. Hyperosmolar hyperglycaemic state as a stroke cause or stroke mimic: an illustrative case and review of literature. *Clin Med Lond.* 2022;22(1):83–86. doi:10.7861/clinmed.2021-0734
- Wang JY, Wang C-Y, Huang Y-S, et al. Increased risk of ischemic stroke after hyperosmolar hyperglycemic state: a population-based follow-up study. *PLoS One.* 2014;9(4):e94155. doi:10.1371/journal.pone.0094155
- Huang CC, Weng S-F, Tsai K-T, et al. Long-term mortality risk after hyperglycemic crisis episodes in geriatric patients with diabetes: a national population-based cohort study. *Diabetes Care.* 2015;38(5):746–751. doi:10.2337/dc14-1840
- Tittel SR, Sondern KM, Weyer M, et al. Multicentre analysis of hyperglycaemic hyperosmolar state and diabetic ketoacidosis in type 1 and type 2 diabetes. *Acta Diabetol.* 2020;57(10):1245–1253. doi:10.1007/s00592-020-01538-0
- Rosager EV, Heltø AL, Fox Maule CU, et al. Incidence and characteristics of the hyperosmolar hyperglycemic state: a Danish cohort study. *Diabetes Care.* 2023.
- McCoy RG, Galindo RJ, Swarna KS, et al. Sociodemographic, clinical, and treatment-related factors associated with hyperglycemic crises among adults with Type 1 or Type 2 diabetes in the US from 2014 to 2020. *JAMA Network Open.* 2021;4(9):e2123471. doi:10.1001/jamanetworkopen.2021.23471
- Nishikawa T, Kinoshita H, Ono K, et al. Clinical profiles of hyperglycemic crises: a single-center retrospective study from Japan. *J Diabetes Investig.* 2021;12(8):1359–1366. doi:10.1111/jdi.13475
- Berk J, Wade R, Baser HD, et al. Case report: severe reversible cardiomyopathy associated with systemic inflammatory response syndrome in the setting of diabetic hyperosmolar hyperglycemic non-ketotic syndrome. *BMC Cardiovasc Disord.* 2015;15(1):123. doi:10.1186/s12872-015-0112-3
- Issa M, Alqahtani F, Ziada KM, et al. Incidence and outcomes of non-ST elevation myocardial infarction in patients hospitalized with decompensated diabetes. *Am J Cardiol.* 2018;122(8):1297–1302. doi:10.1016/j.amjcard.2018.07.004

22. Xu C, Gong M, Wen S, et al. The comparative study on the status of bone metabolism and thyroid function in diabetic patients with or without ketosis or ketoacidosis. *Diabetes Metab Syndr Obes.* 2022;15:779–797. doi:10.2147/DMSO.S349769
23. Agarwal A, Yadav A, Gutch M, et al. Prognostic factors in patients hospitalized with diabetic ketoacidosis. *Endocrinol Metab.* 2016;31(3):424–432. doi:10.3803/EnM.2016.31.3.424
24. Al-Azzawi OFN, Razak MKA, Al Hammady SJ. Rhabdomyolysis; is it an overlooked DKA complication. *Diabetes Metab Syndr.* 2019;13(5):3047–3052. doi:10.1016/j.dsx.2018.07.005
25. Wu XY, She D-M, Wang F, et al. Clinical profiles, outcomes and risk factors among type 2 diabetic inpatients with diabetic ketoacidosis and hyperglycemic hyperosmolar state: a hospital-based analysis over a 6-year period. *BMC Endocr Disord.* 2020;20(1):182. doi:10.1186/s12902-020-00659-5
26. Rimailho A, Riou B, Dadez E, et al. Prognostic factors in hyperglycemic hyperosmolar nonketotic syndrome. *Crit Care Med.* 1986;14(6):552–554. doi:10.1097/00003246-198606000-00007
27. Cozzolino D, Salvatore T, Torella R. Diabetic non ketotic hyperosmolar state: a special care in aged patients. *Arch Gerontol Geriatr.* 1996;22(Suppl 1):245–253. doi:10.1016/0167-4943(96)86945-7
28. Odum EP, Young EE. Elevated cardiac troponin I, creatine kinase and myoglobin and their relationship with cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Metab Syndr.* 2018;12(2):141–145. doi:10.1016/j.dsx.2017.12.001
29. Hritani AW, Jan MF, Schleis G, et al. Clinical features and prognosis of Type 2 myocardial infarction in acutely decompensated diabetic patients. *Am J Med.* 2018;131(7):820–828. doi:10.1016/j.amjmed.2018.02.007
30. Yang L, Shen Y, Li W, et al. Elevated plasma myoglobin level is closely associated with type 2 diabetic kidney disease. *J Diabetes.* 2024;16(3):e13508. doi:10.1111/1753-0407.13508
31. Kao Y, Hsu -C-C, Weng S-F, et al. Subsequent mortality after hyperglycemic crisis episode in the non-elderly: a national population-based cohort study. *Endocrine.* 2016;51(1):72–82. doi:10.1007/s12020-015-0669-8

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