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Time to Recovery From Diabetic Ketoacidosis and Its Predictors Among Adult Diabetic Ketoacidosis Patients in Debre Markos Referral Hospital, North West Ethiopia, 2021: A Retrospective Cohort Study

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BAHIR DAR UNIVERSITY

COLLEGE OF MEDICINE AND HEALTH SCIENCES

SCHOOL OF HEALTH SCIENCES,

DEPARTMENT OF ADULT HEALTH NURSING

TIME TO RECOVERY FROM DIABETIC KETOACIDOSIS AND ITS PREDICTORS AMONG ADULT DIABETIC KETOACIDOSIS PATIENTS IN DEBRE MARKOS REFERRAL HOSPITAL, NORTH WEST ETHIOPIA, 2021: A RETROSPECTIVE COHORT STUDY

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Study area	Debre Markos referral hospital

APPROVAL SHEET

I, the undersigned MSc student, declare that I have submitted my original work on the title of time to recovery and its predictors of DKA among adult DKA patients in Debre Markose referral hospital, North West Ethiopia, 2021: a retrospective cohort study.

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Date of Submission: 02/11/2013 E.C

Adviser’s approval sheet

I hereby certify that I have supervised, read, and evaluated this thesis titled “Time to recovery from diabetic ketoacidosis and its predictors among adult diabetic ketoacidosis patients in Debre Markos referral hospital, NorthWest Ethiopia, 2020/21: a retrospective cohort study” by Dessie Temesgen prepared under my guidance. I recommend the thesis be submitted for oral defense and final submission.

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We hereby certify that we have examined this thesis entitled “Time to recovery from diabetic ketoacidosis and its predictors among adult diabetic ketoacidosis patients in Debre Markos referral hospital, North West Ethiopia, 2020/21: a retrospective cohort study” by Dessie Temesgen”. We recommend that _____ is approved for the degree of “_____”

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Abstract

Introduction: Diabetic ketoacidosis is an acute life-threatening complication of diabetes mellitus. With appropriate treatments, diabetic ketoacidosis patients are expected to make a full recovery within 24 hours. Previous studies did not address variables such as duration of diabetic ketoacidosis symptoms, and blood glucose level. In addition, the recovery time and its predictors of diabetic ketoacidosis in adult patients are not well known in Ethiopia.

Objective: To assess time to recovery from diabetic ketoacidosis and its predictors among adult diabetic ketoacidosis patients in Debre Markos referral hospital, North West Ethiopia, 2021

Methods: A retrospective cohort study was employed among 452 records of adult diabetic ketoacidosis patients who were admitted starting from January 1, 2016 to January 1, 2021 using their medical registration number. Data were entered into Epi-data version 4.6 and analyzed using Stata version 14. A Kaplan Meier survival curve was used to estimate diabetic ketoacidosis-free survival time. In addition, a generalized log-rank test was utilized to compare diabetic ketoacidosis-free survival time between different categorical explanatory variables. Cox proportional hazards model was used to identify predictors of time to diabetic ketoacidosis recovery time. Variables with a P-value < 0.25 in the bivariable analysis were entered into a multivariable Cox proportional hazards model to identify predictors of recovery time at $p \leq 0.05$.

Result: The median time to recovery from diabetic ketoacidosis for all observations was 24 hrs. Severity of diabetic ketoacidosis (AHR=0.24, 95%CI=0.16-0.35), duration of diabetic ketoacidosis (AHR=0.46, 95%CI 0.33-0.64), diabetes duration (AHR=1.74, 95%CI 1.35-2.25), and random blood sugar level (AHR=0.64, 95%CI= (0.51-0.79) were significant predictors of recovery time.

Conclusion and recommendation: The median time to recovery from diabetic ketoacidosis was relatively prolonged. The hospital shall give special attention to patients with the identified predictors. Further study using a prospective design by including admission pH and admission serum potassium level is advised.

Keywords:-Diabetic ketoacidosis, recovery time, Debre Markose, Ethiopia

Abbreviations and Acronyms

ADA	American Diabetes Association
BG	Blood Glucose
CKD	Chronic Kidney Disease
CVD	Cardio Vascular Disorder
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
ETB	Ethiopian Birr
HTN	Hypertension
IV	Intravenous
RBS	Random Blood Sugar
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UK	United Kingdom
USA	United States of America

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1. Introduction

1.1. Background

Diabetic ketoacidosis (DKA) is the most common acute hyperglycemic emergency in people with diabetes mellitus (1). DKA occurs due to the consequence of an absolute or relative lack of insulin and concomitant elevation of counter-regulatory hormones, usually resulting in the triad of hyperglycemia, metabolic acidosis, and ketosis (2). If the initial diagnosis of type1diabetes is delayed or if type 2 DM precipitated by major surgery, severe illness such as myocardial infarction or infection usually presents with DKA (3, 4). DKA occurs mostly in young people with uncontrolled type 1 diabetes mellitus (T1DM) but can also occur in adults with poorly controlled type 2 diabetes mellitus (T2DM) (1, 2).

The American Diabetes Association(ADA) classifies DKA by severity depending on the degree of acidosis and altered sensorium as mild (Arterial pH 7.25–7.30 and Alert), moderate (Arterial pH7.00 to<7.24 and Alert/Drowsy), or severe (Arterial pH<7.00 and Stupor) (5). The diagnostic criteria for DKA accepted by most experts in the field are a blood glucose(BG) greater than 250 mg/dL, pH lower than 7.3, serum bicarbonate lower than 15 mEq/L, increased anion gap metabolic acidosis >12, and a moderate degree of ketonemia (beta-hydroxybutyrate greater than 3mmol(6, 7).

Episodes of DKA typically require an emergency department visit or hospital admission for the patient to receive insulin, intravenous (IV) fluids, and electrolyte correction (8). The individualization of treatment based on a careful clinical and laboratory assessment is needed including restoration of circulatory volume and tissue perfusion, resolution of hyperglycemia, and correction of electrolyte imbalance and acidosis(5). Most people are treated initially with intravenous insulin and a two-bag method of fluid replacement is often used intravenous fluid without dextrose initially and, upon volume correction, infusion with dextrose correction to prevent hypoglycemia caused by the insulin therapy(6). The management of DKA includes IVs administration of 1-2L of 0.9% NaCl over 1-2 h then continues 0.9% NaCl until BG level reached to 200-250 mg/dL then change to 5% dextrose in 0.45% NaCl and an IV bolus of regular human insulin of 0.1 U/kg, followed by a continuous infusion of 0.1 U/kg/h then reduce insulin rate to 0.05

U/kg/h when BG< 250 mg/dL; in addition to these if K+ level is 3.3-5 mEq/L , add 20-40 mEq potassium chloride to replacement fluid and if K+ level <3.3 mEq/L hold insulin; give 20-30 mEq/h until > 3.3 (8). It is also important to treat any correctable underlying cause of DKA such as sepsis, myocardial infarction, or stroke (5).

Timely diagnosis, comprehensive clinical and biochemical evaluation, and effective management are key to the successful resolution of DKA(9). Resolution of DKA occurs when blood glucose is < 200 mg/dL and 2 of the following have occurred: a serum bicarbonate level ≥ 15 mEq/L, a venous pH > 7.3, a calculated anion gap ≤ of 12 mEq/L, and blood ketones <0.6 mmol/L (10, 11). Previous studies show that using standardized protocols for DKA management improves DKA recovery (12, 13).

DKA patients with appropriate treatment are expected to make a full recovery within 24 hours (9, 11, 14, 15). Prolonged recovery of DKA leads to hypoglycemia and hypokalemia (9), renal failure, coma, cerebral edema, cardiac arrhythmia(16, 17), lung edema with respiratory failure, and thromboembolic complications(18), and leads to death (19, 20).

Timely diagnosis and initiation of management of DKA is associated with the recovery and prevents hypoglycemia and hypokalemia (9); renal failure, coma, cerebral edema, and cardiac arrhythmia (16, 18), hyperchloremia metabolic acidosis, hypophosphatemia, and thromboembolic complications (18). This in turn decrease bed occupancy in the hospital, length of hospital stay and reduce the amount of human and material resource needed to control it as well as its complications.

1.2. Statement of the problem

As DM prevalence has reached alarming levels, DKA and its complication are also increasing (4). Globally the incidence of DKA among T1DM adult patients ranges from 0–56 per 1000 person-years (PYs) and eleven studies reported prevalence with a range of 0–128 per 1000 people (21). In Ethiopia, a meta-analysis study reported there was a history of DKA in 19.9% of cases (both T1DM and T2DM) at Dessie Hospital, and in 62.0% of cases (for T1DM) at the Black Lion Hospital in Addis Ababa (22). Another study conducted in Dilla University Referral Hospital on the magnitude of DKA in newly diagnosed patients with T1DM was found to be 38% (23) and in Hawassa university comprehensive specialized hospital was 40%; among them, 28.2% and 11.8% were with T1DM and T2DM respectively(24).

DKA is the main reason for the hospitalization of patients with DM (25) and its treatment represents a substantial economic burden in terms of health care costs, both directly and indirectly, ranging from individual to national economy. For example in United Kingdom (UK), the average cost for an episode of diabetic ketoacidosis was £2064 per patient(26) and in the United States of America (USA), the total charges among DKA patients in 2017 were $6,757,748,178, with a mean of $30,836.19(27).

Even though DKA patients with appropriate treatment are expected to make a full recovery within 24 hours (9, 11, 14, 15) the resolution time of DKA is longer in African countries. For example in South Africa the average time to resolution of DKA was 21 hours; excluding severe DKA, mild and moderate DKA had an average time to resolution of 20 hours (28) and in Kenya, the median time to resolution was 59 hours(29).

The study conducted in Australia reveals that independent predictors of a slower time to resolution of DKA are lower admission pH levels and higher admission potassium levels (30). The previous study recommends that regular review of patients' biochemical parameters and strict implementation of hospital protocols may reduce complications and shortens the recovery time of DKA (30).

The previous study did not address the rates and quantity of potassium supplementation prescribed, rates of other adverse events such as hypoglycemia, the duration of DKA,

blood and glucose level. In addition, as far as my literature search, there was no study in Ethiopia reporting the estimated survival period of recovery from DKA. Therefore, this study will estimate the median time to recovery from DKA and its predictors among adult patients admitted to the Debre Markos referral hospital in Ethiopia.

1.3. Significance of the study

Studying the recovery time and predictors of DKA is important in developing preventive guidelines and treatment protocols to reduce the impact of its complication.

Additionally, this study will tell health professionals about the median recovery time and predictors of DKA recovery and then, important for the event of interventions to reduce recovery time of DKA and to shorten the treatments.

The findings of this study additionally used as baseline data for people who have an interest in carrying out further investigation. It will even be useful for health policymakers as input to document gaps and in designing attainable interventions to shorten the time to get out from DKA and related consequences.

2. Literature Review

2.1. Recovery time of DKA

The recovery time from DKA varies in studies conducted in different countries. In Australia, a retrospective study from 2010 to 2014 done on 71 DKA patients reported that the median time to resolution of DKA was 11 hr. (6.5–16.5 hr) (30). In another retrospective study done in Thailand, a total of 94 DKA episodes admitted over 14 years (2005–2018) shows that the median time to resolution of DKA was 8.5 hours(31). Multicenter retrospective study conducted at five adult intermediate and intensive care units in Paris and its suburbs, France of 122 patients admitted for DKA between 2013 and 2014 reported that the resolution times for type 1 diabetes: 16 hr., type 2 or secondary diabetes: 14 hr. and patients with newly diagnosed diabetes is 16 h(32).

In South of Iran, from 2009 to 2013 concerning the resolution time of patients with DKA, the most frequent time was less than 12 hours (66.6%), 13-24 hours (28.6%), 25-36 hours (2.34%), 37-48 hours (1.87%), and more than 48 hours (0.47%), respectively. A retrospective cross-sectional study performed in Saudi Arabia among admitted DKA adult cases from September 2017 to August 2019 revealed that more than half of the patients (53.81%) got out of DKA within 24-72 hours and 34.08% and 12.11% got out of DKA within 24 hr. and longer than 72hrs respectively (33).

In South Africa a study interviewing 69 DKA patients from 1 September to 31 December 2017 reported an average time to resolution of DKA was 21 hours(13.5- 29); excluding severe DKA, mild and moderate DKA had an average time to resolution of 20 hours (28). In 2018, prospective descriptive analysis in Kenya found that the median resolution time was 59 hours(29). A prospective observational analysis at Jimma university specialized hospital in Ethiopia from March to June 2015 reveals that for patients admitted with DKA, the meantime to be urine ketone free was 31.3±38 hours (25).

2.2. Factors of DKA recovery

2.2.1. Socio-demographic characteristics

A study conducted in India indicated that males were 7.93 times more likely to recover compared with female DKA patients(3).

2.2.2. Clinical characteristics

A study done in Australia has shown that patients presenting with mild DKA had rapid resolution of acidosis within 2.5 h (30). Another study conducted in South Africa identifies severe DKA was correlated with a longer time to resolution with an odds ratio of 4.89 (28). A study in Australia showed that patients with DKA not precipitated by infection are 44% less likely to have slower DKA resolution (30). A study carried out in Saudi Arabia revealed that patients with chronic kidney disease(CKD) had a likelihood to get out of DKA in more than 72 hours by more than four times as compared with those who did not have and also patients who had a duration of one to five years of DM were almost five times more likely to get out of DKA in more than 72 hours when compared with those who had a duration of more than five years (33). A study conducted in India reported that patients with a history of T1DM had better recovery compared with a history of T2DM (3).

2.2.3. Biochemical profile

A study done in Australia has shown that slower resolution from DKA is 1.77 times in patients with lower admission PH and 1.53 times in those with higher admission serum potassium levels (30). A retrospective study in India reports low hemoglobin was an independent predictor of a longer stay of DKA patients (34**).** Another study in India identifies serum phosphate 4.38mmol/l at presentation may lead to 2.71-fold recovery compared with serum phosphate 6.04mmol/l (3). A retrospective cohort study of adult patients admitted with incident DKA in the USA shows patients with hyperchloremia had longer times to final DKA resolution (35) and another retrospective study conducted from August 1st, 2015 – May 15th, 2016 among adults reports that initial blood glucose and beta-hydroxybutyrate were significant predictors of rapid DKA recovery(36).

2.2.4. Treatment-related factors

Randomized Clinical Trials conducted between January 2016 and March 2017 in an academic medical center in the US revealed the shorter time to DKA resolution in those

given balanced crystalloids with a median time to resolution 13.0 hours than the saline with a median of 16.9 hours(37). A retrospective study in the USA identifies that plasma glucose levels improved to <250 mg/dL earlier with two-bag protocol 7.82 hours compared with the standard one-bag system 9.14hours(38). A review in Australia shows that Ketoacidosis with sodium-glucose transport protein 2 inhibitor medications may be prolonged and recur after initial resolution(39).

In the study done in Saudi Arabia patients who had a treatment regimen of both oral medication and insulin were likely four times to get free of DKA in more than 72 hours as compared with those who only were on insulin (33). A study performed in Kenya revealed that delays in initiation of management, insufficient administration of fluids, insulin, and potassium, and inadequate monitoring have contributed to the prolonged DKA resolution times (29). A study in Ethiopia reported that diabetic ketoacidosis patients treated with more than six liters of fluid replacement, got more than sixty international unit insulin doses in the 1st 24 hours and who got supplemental potassium had recovered (40). A case report in USA Galveston identifies glucocorticoid administration delay the resolution of non-severe diabetic ketoacidosis (41).

2.3. Conceptual framework

The following conceptual framework shows the association between independent variables with a dependent variable that is developed after reviewing the literature (3, 28, 30, 33, 35, 40, 42, 43). The recovery time of DKA is affected by socio-demographic characteristics; clinical characteristics; biochemical and treatment factors of the adults which are described in figure 1 below.

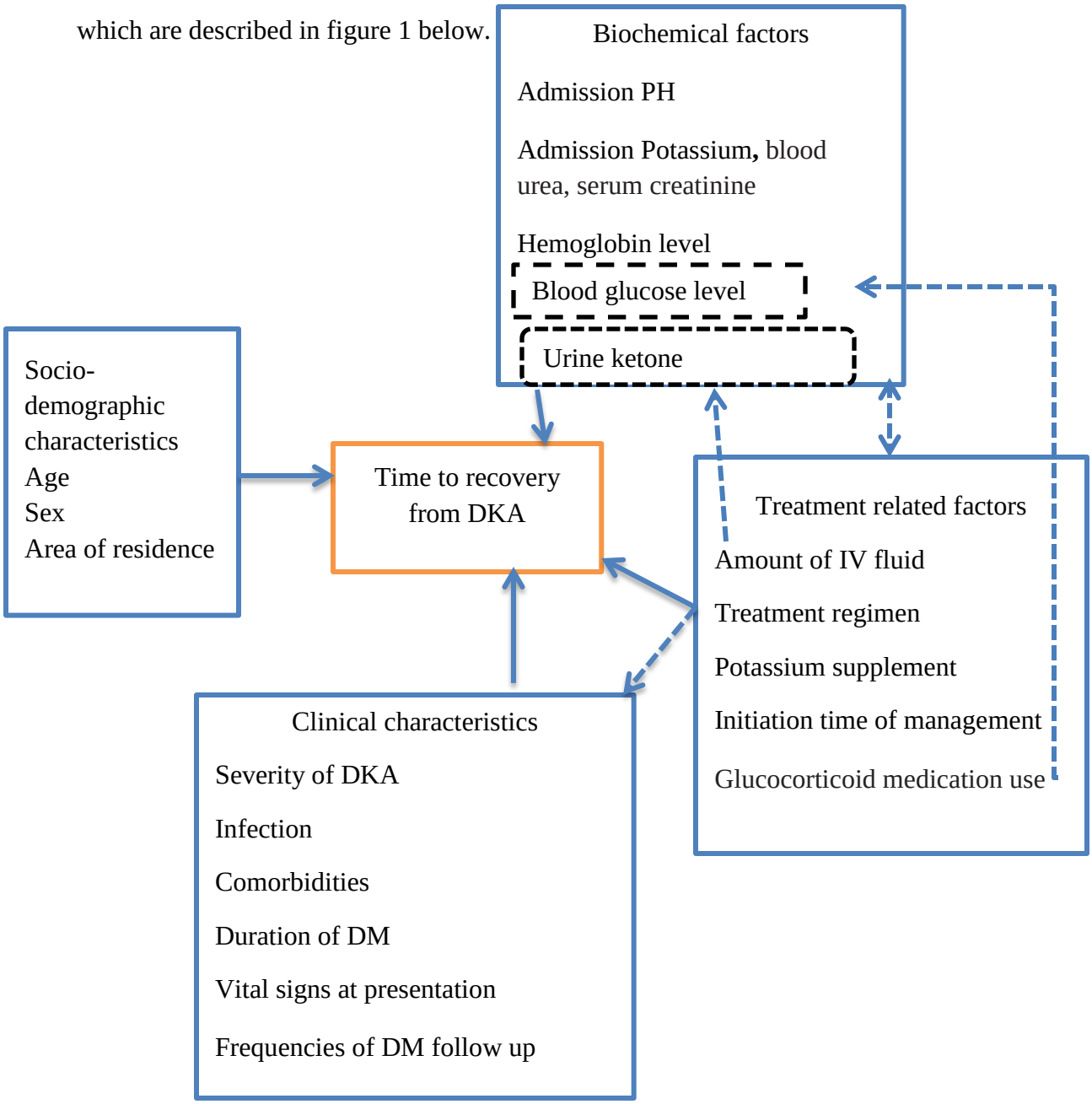

Figure 1**:** Conceptual framework showing the association between time to recovery from DKA and independent variables in Debre Markose referral hospital, 2021

3. Objectives

3.1. General Objective

- To assess time to recovery from diabetic ketoacidosis and its predictors among adult diabetic ketoacidosis patients admitted in Debre Markose Referral Hospital in Amhara Regional State, North West Ethiopia,2021

3.2. Specific Objectives

- ✓ To determine the time to recovery from diabetic ketoacidosis among adult diabetic ketoacidosis patients admitted to Debre Markose Referral Hospital
- ✓ To identify predictors of recovery time from diabetic ketoacidosis among adult diabetic ketoacidosis patients admitted to Debre Markose Referral Hospital

4. Methods and Materials

4.1. Study design

An institution-based retrospective cohort study design was employed to assess time to recovery from DKA.

4.2. Study area and period

This study was conducted at Debre Markos referral hospital which is located in the city of Debre Markos 265 Km from Bahir-Dar and 300 kilometers from Addis Ababa. The hospital is the only referral hospital in the East Gojjam zone and serves around 3.5 million people and 100 health centers and 9 district hospitals are available in the catchment area of the referral hospital (44). According to information obtained from the administrative office of the hospital, around 348 DKA patients are admitted per year. The study was conducted from January 1, 2016, to January 1, 2021, among adults who were admitted with DKA, and registration charts were retrieved from March 18- April 18, 2021.

4.3. Population

4.3.1. Source population

All adult DKA patients admitted to Debre Markos referral hospital

4.3.2. Study population

Adult DKA patient admitted to Debre Markos referral hospital during the study period and whose charts were available

4.4. Eligibility criteria

4.4.1. Inclusion criteria

Adult DKA patients above 15 years old and admitted to the hospital with DKA

4.4.2. Exclusion criteria

Adult DKA patients who were admitted to the hospital with incomplete and unavailable medical records

4.5. Sample size determination and procedure

4.5.1. Sample size determination

To determine sample size predictors significantly associated with the outcome variable were considered. Accordingly, the sample size was determined using a double population proportion formula by considering the duration of DM and presence of CKD as predictor variables of DKA recovery based on a study done in Saudi Arabia (33) by using Epi - info version 7 statistical package. It is calculated by taking a two-sided significant level (α) of 5 %, 95% confidence level, power 80 %, and 1:1 ratio of non-exposed to exposed.

Table1: Sample size calculation for predictors of recovery of DKA among adults in Deber Markose Referral Hospital, North West Ethiopia 2021

Variable	P1% and p2%	HR	Sample size	Total sample size by adding 10%
Duration of DM	P1%=15.9% P2%=7.2%	2.21	422	464
CKD	P1%=41.6% P2%=10.4%	4	60	66

P1: the proportion of outcome in exposed, P2: the proportion of outcome in non-exposed

By adding 10% missing data then finally, the largest sample size (N= 464) will be selected as the final sample size for the study.

4.5.2. Sampling procedure

The records of adults who were admitted with DKA in the hospital from January 1 2016 to January 1 2021 were selected using MRN. The patient's charts were selected using a simple random sampling technique by a computer-generating method. Finally, data were extracted from the selected medical charts.

4.6. Variable of the study

4.6.1. Dependent variable

Time to recovery from DKA

4.6.2. Independent variables

- Socio-demographic factors

  Age, sex, residence

- Biochemical factors

  Admission PH, Admission Potassium**,** blood urea, serum creatinine and Hemoglobin level, initial blood glucose level, urine ketone

- Clinical characteristics

  The severity of DKA, Preceding infection of DKA, presence of Comorbidities, Duration of DM, vital sign at presentation, frequency of DM follow up

- Treatment factors

  Treatment regimen, Amount of IV fluid, Potassium supplement, initiation time of management, glucocorticoid medication use

4.7. Operational definition

Event: recovery from DKA during the study period

Censored: Referred, died, or discharged cases for any reason before recovery from DKA during the study period.

DKA: Adults admitted with blood glucose greater than 250 mg/dL, pH lower than 7.3, and a moderate degree of ketonemia (>3mmol)/positive urine ketone (6, 7).

DKA recovery time: the interval in hours between the first vascular filling to treat the DKA in the emergency room or the ICU to DKA resolution

DKA Resolution: the occurrence of the first blood ketone < 0.5 mmol/l, or the second negative ketonuria (1 or 2 crosses) (32).

Prolonged DKA recovery: the resolution time of DKA is longer than 24 hours (9, 11, 14,15).

Incomplete data: when the ketone negative tests and initiation time of management are not recorded.

Entry date: the time of admission with DKA diagnosis

End date: until the admitted patient recovered from DKA or discharged

4.8. Data collection procedure and tool

4.8.1. Data collection tool

A structured data extraction tool was adapted by considering study variables such as socio-demographic, biochemical, clinical, and treatment predictors from literature and also by using WHO DKA follow sheet forms. A pretest was done on 24 participants of the study in Debre Markose hospital.

4.8.2. Data collection procedure

Patient records were retrieved using their unique registration number identified in the registration books. After obtaining a permission letter from the concerned body, charts and records were reviewed and data were extracted using an English data extraction form by trained two BSC nurses and supervised by one BSC nurse. Only index cases were included and recurrent episodes of DKA were excluded to avoid selection bias.

4.9. Quality Assurance

To keep data quality the supervisor and data collectors were trained on how and what the information they should collect from the targeted data sources. Data extraction forms were checked for completeness and missing information before data collection. The completeness of the collected data were checked onsite daily during data collection and give prompt feedback by the supervisor. Besides this, the principal investigator was carefully entered and thoroughly cleans the data before the commencement of the analysis.

4.10. Data Processing and Analysis

The data were coded, cleaned, and checked for completeness and consistency. Data were entered into Epi-data version 4.6 and analyzed using Stata version 14. A Kaplan Meier

survival curve was used to estimate DKA-free survival time. In addition, a generalized log-rank test was utilized to compare DKA free survival time between different categorical explanatory variables. Pair-wise comparison tests were done to check the presence of multicollinearity between each independent variable. Bivariable and Multivariable Cox proportional hazards models were fitted to identify predictors of time to DKA recovery incidence. The necessary assumptions of the Cox proportional hazards model were verified by log minus log plot, COX-Snell residuals for the goodness of fit, and global test. Variables with P value < 0.25 in Bivariable analysis were entered into the multivariable Cox proportional hazards model to identify predictors of recovery time at $p \leq 0.05$(45). Hours were used as a time scale to calculate time to recovery. The outcome of each participant was dichotomized into censored or event (recovered).

4.11. Ethical Consideration

Ethical clearance was obtained from the institutional review board of Bahir Dar University, College of Medicine and Health Sciences (Ref. No: MD/11724/144). The formal letter was submitted to Debre-Markos referrals hospital for data collection and permission was assured. All information collected from patient cards was kept strictly confidential. Consent was not requested as it was a retrospective study.

5. Result

5.1 Socio-demographic characteristics

A total of 1281 adult DKA patients were admitted to Debre Markos referral hospital during the study period. Four hundred sixty -four (464) patients' charts were selected by computer-generated random sampling technique and 452 patient's charts were eligible among selected charts for this study and were included in the study. The median age of the participants was 25 years IQR (20-33). The majority of DKA adult patients were males and came from rural areas 295(65.27%) and 287(63.50%) respectively (Table 2).

Table 2: Socio-demographic characteristics among adult DKA patients, DMRH, North West Ethiopia, January 1, 2016 to January 1, 2021

Variable	Category	Frequency	Percent (%)
Age(years)	15-24	216	47.8
	25-34	132	29.2
	35-44	49	10.84
	45-54	39	8.63
	≥55	16	3.54
Sex	Male	295)	65.3
	Female	157	34.7
Residence	Urban	165	36.5
	Rural	287	63.5

5.2. Clinical characteristics and biochemical profile

Most DKA adult patients 296(65.49%) had previous DM history and 376 (83.19%) were T1DM. The most common clinical presentations of adult DKA patients were poly symptoms (97.35%), nausea/vomiting (64.30%), and fatigue (53.10%). The median time of duration of DKA symptoms till the treatment of the participant was 48hr IQR (96-24). Adult DKA patient's clinical presentation of the severity of DKA mild, moderate, and severe was 64.38%, 22.57%, and 13.05% respectively. One hundred ninety-six (43.36%) of the study participants had previous DKA episodes, also 72(15.93%) and 159(35.18%) had an infection before DKA and acute recent illness respectively.

Among adult DKA patients, who had a DM history 89(19.69%) had co-morbidity. The most frequent comorbidity was HTN 40 (44.94%) (Table3).

Table 3: Baseline clinical characteristics among adult DKA patients, DMRH, North West Ethiopia, January 1, 2016 to January 1, 2021

Clinical characteristics	Categories	Total No	Percent (%)
nausea/vomiting	Yes	290	64.30
	No	161	35.70
abdominal pain	Yes	53	11.73
	No	399	88.27
Fatigue	Yes	240	53.10
	No	212	46.90
poly symptoms	Yes	440	97.35
	No	12	2.65
Kussmaul respiration	Yes	90	19.91
	No	362	80.09

loss of consciousness	Yes	68	15.04
	No	384	84.96
Type of DM	T1DM	376	83.19
	T2DM	76	16.81
Type of DM Comorbidity	CVD	16	17.98
	CKD	20	22.47
	HTN	40	44.94
	Asthma	7	7.87
	others**	6	6.74

(** diabetic foot ulcer, sexual dysfunction, and chronic obstructive airway disease)

5.3. Time to recovery of adult DKA patients

The median time to recovery from DKA for all observations was 24 hrs. IQR (12-37). The median recovery time of adults from DKA was different regarding different categories of biochemical and clinical characteristics. For instance, the median recovery time of mild DKA and moderate DKA was 18hrs and 30 hrs. whereas in severe DKA was 49hrs (Table 4).

Table 4: The median time to recovery, and comparison of DKA free time among adult DKA patients, DMRH, North West Ethiopia, January 1, 2016 to January 1, 2021

Variable	Category	Survival status of DKA		Total No (%)	Median recovery time (95%CI	Log-rank (P-value)
		Recovered No (%)	censored No (%)			
DM history	Yes	282(65.73)	14(60.87)	296(65.49)	24(23-25)	0.73
	NO	147(34.27)	9(39.13)	156(34.51)	24(22-27)	
Type of DM	T1DM	355 (82.75)	21(91.30)	376(83.19)	24(23-25)	0.62
	T2DM	74 (17.25)	2(8.70)	76(16.81)	25(20-28)	
Diabetes duration	≤ 5 years	210(48.95)	10(43.48)	219(48.67)	28(25 -30)	<0.001*
	>5 years	109(25.41)	9(39.13)	118(26.11)	16(14 -20)	
	Newly diagnosis	110(25.64)	4(17.39)	114(25.22)	24(18-25)	
Comorbidity of DM	Yes	86(20.05)	3(13.04)	89(19.69)	26(24 -30)	0.31
	NO	343(79.95)	20(86.96)	363(80.31)	24(23-25)	
history of DKA episodes	Yes	188(43.82)	8(34.78)	196(43.36)	26(24 -28)	0.04*
	NO	241(56.18)	15(65.22)	256(56.64)	24(20-24)	
Severity of DKA	Mild	278(64.80)	13(56.52)	291(64.38)	18(15-20)	<0.001*
	Moderate	96 (22.38)	6(26.09)	102(22.57)	30(26-40)	
	Severe	55(12.82)	4(17.39)	59(13.05)	49(39 -72)	
Duration of	<=24 hrs.	150 (34.97)	7(30.43)	153(33.85)	20(15-24)	<0.001*

DKA	25-48hrs	75(17.48)	5(21.74)	74(16.37)	24(19 -26)	
	49-96hrs	143(33.33)	7(30.43)	142(31.42)	26(25-29)	
	≥97hrs	61(14.22)	4(17.39)	83(18.36)	25(23-33)	
infection before DKA	Yes	71(16.55)	1(4.35)	72(15.93)	30(25-34)	0.005*
	NO	358(83.45)	22(95.65)	380(84.07)	24(22-24)	
acute recent illness	Yes	149(34.73)	10(43.48)	159(35.18)	30(26-35)	<0.001*
	NO	280(65.27)	13(56.52)	293(64.82)	22(19- 24)	
RBS in mg/dL	≤500	254(59.21)	14(60.87)	268(59.29)	20(17-23)	<0.001*
	>500	175(40.79)	9(39.13)	184(40.71)	31(27 -35)	

5.4. The incidence rate of recovery from DKA

From 452 study participants, 429 (94.9%) adults were recovered and the rest 23(5.1%) were censored observations. The lowest and the highest length of follow-up were 3.5 and 102 hours respectively, and the total person-time risk was 12546.513. The overall recovery rate from DKA was 3.42 per 100 person-hours observation (95% CI: 3.11–3.76). The recovery rate among severity of DKA in mild, moderate, and severe was 4.93 per 100 person-hours (95% CI: 4.38- 5.54), 2.61 per 100 person-hours (95% CI: 2.14 - 3.19), and 1.71 per 100 person-hours (95% CI: 1.31–2.22) respectively.

5.5. Survival estimates for time to recovery

The DKA free time of adults with DKA was estimated by the Kaplan-Meier survival curve.

The curve tends to decrease rapidly within the first 24hrs indicating that most adults recovered from DKA within this time (Fig 2). The survival estimates of DKA patients were varied among severity, duration of DM, duration of DKA, and RBS level (Figs 3-5).

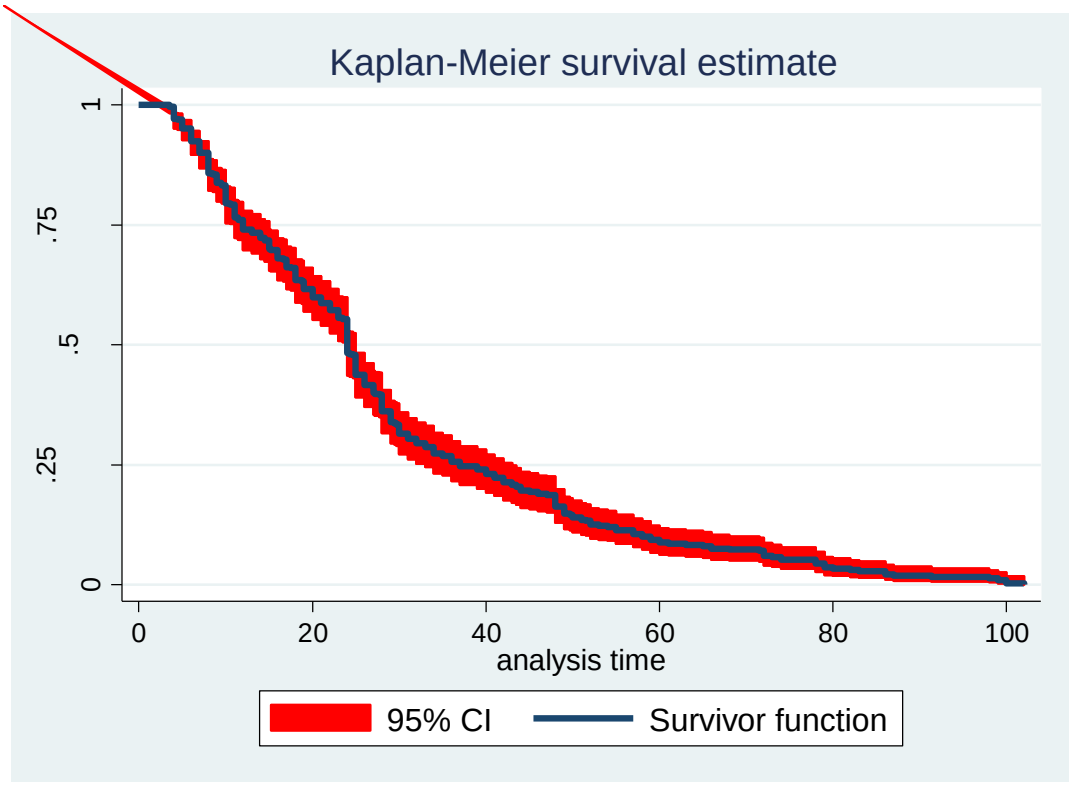

Figure 2: Overall Kaplan –Meier estimation of DKA free time functions of patients on adult DKA patients, DMRH, North West Ethiopia, January 1 2016 to January 1, 2021

5.5.1 Comparison of survival status

Log-Rank test was used to compare survival time between categories of different predictors. Based on this test, survival time among different groups of predictors such as severity, duration of DM, duration of DKA, presence of infection before DKA and acute recent illness, and RBS level were significantly different in survival time at a 5% level of significance **(**Tables 2 & 3).

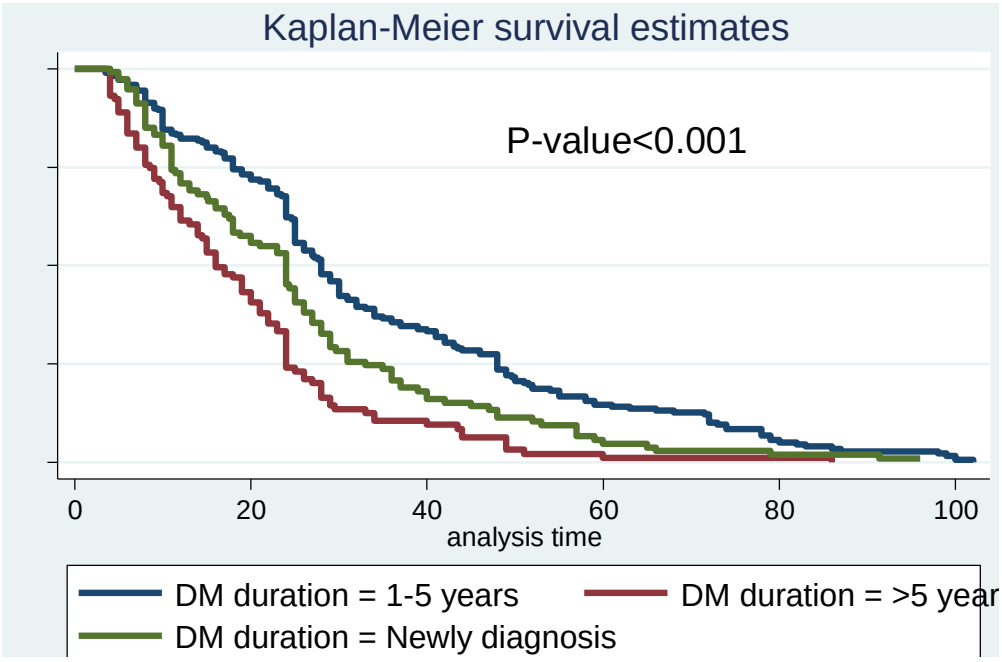

Figure 3: The Kaplan-Meier survival curves compare DKA free time of adult DKA patients between duration of DM, DMRH, North West Ethiopia, January 1 2016 to January 1 2021

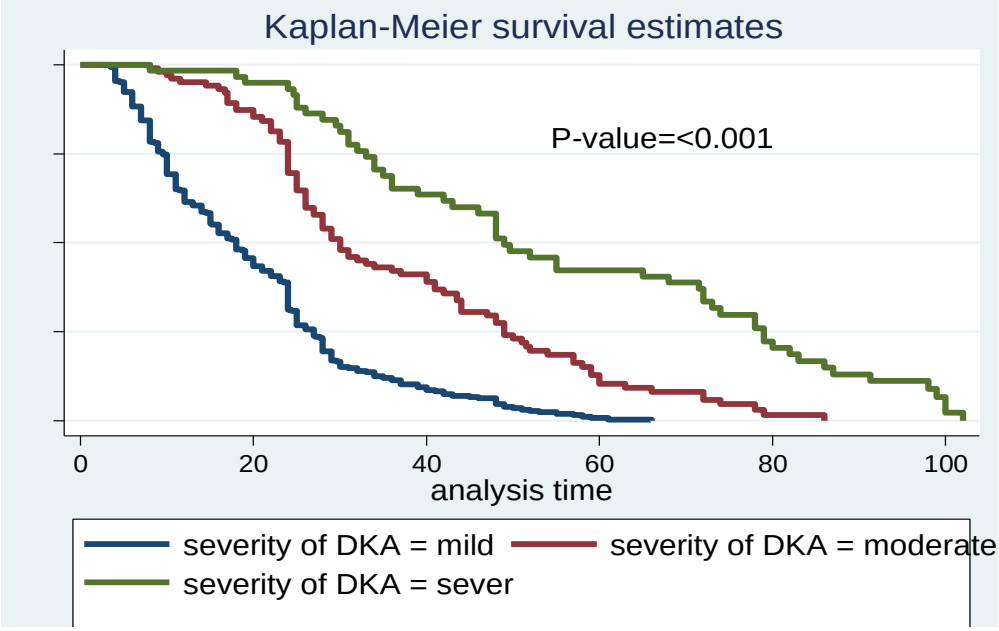

Figure 4: The Kaplan-Meier survival curves DKA free time of adult DKA patients between severity of DKA, DMRH, North West Ethiopia, January 1 2016 to January 1, 2021

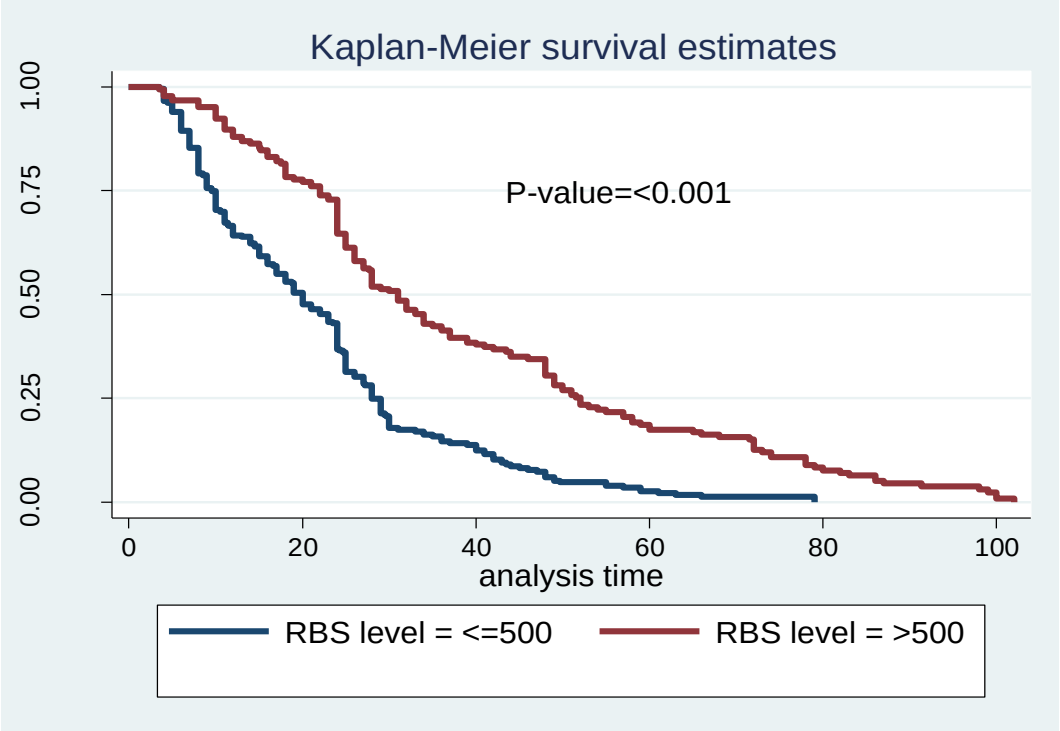

Figure 5: The Kaplan-Meier survival curves compare DKA free time of adult DKA patients between RBS level, DMRH, North West Ethiopia, January 1 2016 to January 1, 2021

5.6. Predictors of recovery time from DKA

In the Bivariable Cox, Proportional Hazards regression model; DM duration, infection before DKA, duration of DKA, acute recent illness, RBS level, and severity of DKA were all associated with DKA recovery (P <0.05). Predictors that had association at a p-value of ≤ 0.25 in bivariable Cox regression and non-collinear independent variables were included in multivariable Cox regression. In the multivariable analysis, the AHR of the severity of DKA, duration of DKA, DM duration, and RBS level was estimated as independent predictors of time to recovery with a value of p<0.05.

The recovery time was delayed by 76% (AHR=0.24, 95% CI=0.16-0.35) among severe DKA adult patients as compared with mild DKA adult patients. Also, the recovery time was delayed by 54% (AHR=0.46, 95%CI=0.35-0.59) among moderate DKA adult patients as compared with mild DKA adult patients. Adult DKA patients with RBS >500mg/dL had slower recovery as compared with those who had RBS ≤500mg/dL (AHR=0.64, 95%CI=(0.51-0.79). DKA adult patients with >5years duration of DM

follow-up had 74% faster recovery as compared with those who had a follow-up of DM duration ≤ 5 years (AHR=1.74, 95%CI 1.35-2.25).

Adult DKA patients with ≥97hrs of duration DKA till treatment had slower recovery as compared with those who had ≤24hrs (AHR=0.46, 95%CI 0.33- 0.64).

Table 5:-Results of the Bivariable and Multivariable cox proportional hazards regression analysis of adult DKA patients, DMRH, North West Ethiopia, January 1 2016 to January 1 2021

Variable	Category	Recovered	Censored	Crude HR (95%:CI)	AHR (95%:CI)	P-value
Residence	Urban	158	7	1		
	Rural	271	16	0.79(0.64-0.96)	1.06 (0.86-1.30)	0.59
Severity of DKA	Mild	278	13	1		
	Moderate	96	6	0.38(0.30-0.49)	0.46(0.35-0.59)	< 0.001*
	Sever	55	4	0.16(0.11 - 0.23)	0.24(0.17-0.36)	< 0.001*
duration of DKA	<=24hrs	150	7	1		
	25-48hrs	75	5	0.77 (0.58 -1.01)	0.86(0.64-1.15)	0.30
	49-96hrs	143	7	0.64(0.51-0.81)	0.79(0.62-1.01)	0.64
	≥97hrs	61	4	0.44(0.32- 0.59)	0.46(0.33-0.64)	< 0.001*
DM duration	≤ 5 years	210	10	1		
	>5 years	109	9	2.29(1.80-2.90)	1.74(1.35-2.25)	< 0.001*
	Newly diagnosis	110	4	1.48(1.17-1.87)	1.38(1.05-1.79)	0.02*

infection before DKA	Yes	71	6	0.70(0.54-0.90)	1.06(0.79-1.43)	0.69
	NO	358	17	1		
acute recent illness	Yes	149	10	0.59(.48-0.73)	0.81(0.64-1.03)	0.08
	NO	280	13	1		
RBS in mg/dL	≤500	254	14	1		
	>500	175	9	0.44(0.36-0.54)	0.64(0.51-0.79)	< 0.001*

*p-value<0.05

5.7. Overall model fitness test

Figure (6) below shows the overall model fitness of the data in Cox Proportional hazards regression model. In the present finding, the hazard function follows the 45° line very closely. This indicates as the Cox model does fit these data to reasonable. Hence, the Cox Snell residuals test shows overall the goodness of fitness of the model (the model is a good fit).

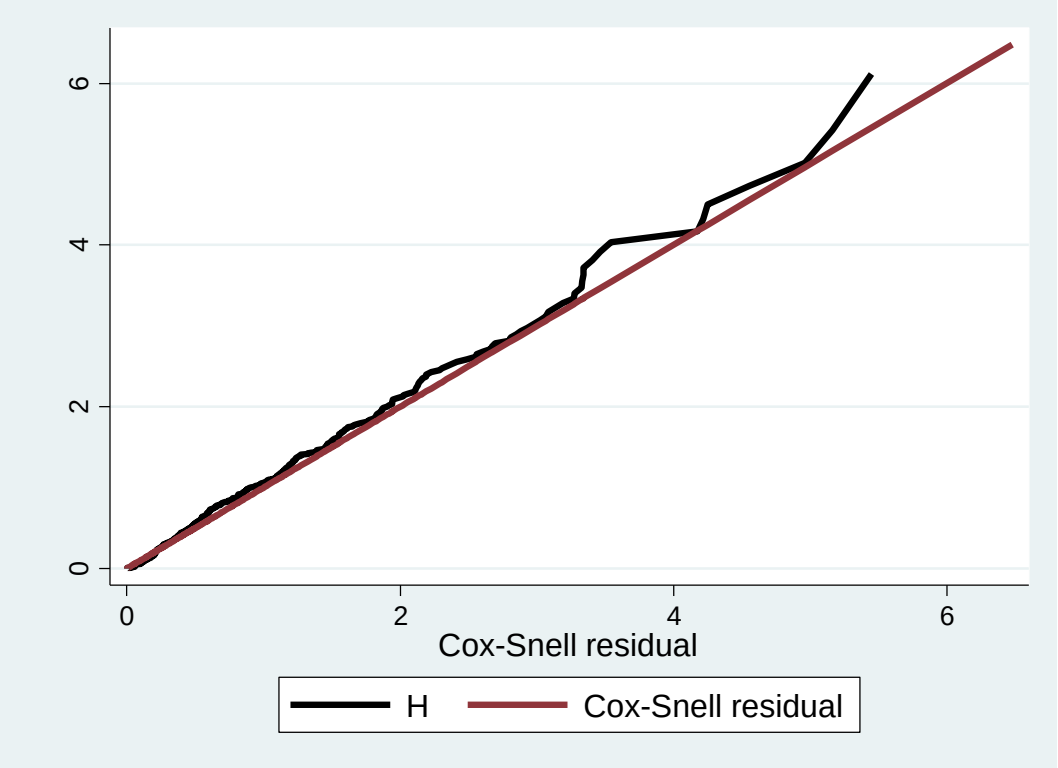

Figure 6: Cox Snell residual test showing overall goodness of fit of the Cox proportional hazards model.

5.8 Test of proportional-hazards assumption

The findings indicated that all variables included in the model satisfied PH assumptions (p value>0.05). So the model is a good fit **(**Table 6**)**.

Table 6*:*-Goodness-of-fit test is assessing proportional hazards Assumption

predictors	rho	chi2	Df	P-value
Residence	0.00077	0.00	1	0.9868
severity moderate	0.06463	1.84	1	0.1749
severity sever	-0.00474	0.01	1	0.9194
DM duration	-0.03575	0.56	1	0.4552
DM duration	-0.07950	2.64	1	0.1040
duration of DKA 25-48hrs	-0.04412	0.87	1	0.3521
duration of DKA 49-96hrs	0.07807	2.57	1	0.1086
duration of DKA ≥97hrs	0.02326	0.22	1	0.6370
Infection before DKA	0.00922	0.04	1	0.8498
Acute recent illness	0.04316	0.77	1	0.3799
RBS level	0.03597	0.59	1	0.4431
global test		12.69	11	0.3142

6. Discussion

This study was conducted to determine the time to recovery from DKA and its predictors. The median time to recovery was 24hrs (IQR 12-37). The finding of this study is almost consistent with what was observed in a study conducted in South Africa(28), and prolonged when compared with studies conducted in Australia(30) and in Thailand(31).On the contrary, it is faster than a study done in Kenya**(**29**).** The possible reason for this discrepancy could be related to the difference in the standard treatment protocol because studies show that there is an improved clinical outcome associated with insulin pump therapy compared with injection therapy(9, 46). The other possible reason may be due to low socio-economic status since low educational level increased the risk of severe DKA that leads to prolonged recovery time (47).

The severity of DKA, duration of DKA, DM duration, and RBS level were independent predictors of time to recovery. The recovery time was delayed by 76% among severe DKA adult patients as compared with mild DKA adult patients. This finding is supported by the study conducted in South Africa identifies severe DKA was correlated with a longer time to resolution (28). The possible reason in this study could be due to the disease pathophysiology, patients with severe DKA had more electrolyte abnormalities compared with the mild and moderate forms of the disease(48) which is supported with a study conducted in Australia showed that higher admission potassium levels are independent predictors of a slower time to resolution of DKA(30).

Adult DKA patients with RBS >500mg/dL had slower recovery as compared with those who had RBS ≤500mg/dL. This finding is supported by a study that revealed initial blood glucose was a significant predictor of rapid resolution of DKA patients(36). This is possibly due to extremely high blood glucose concentrations result in loss of blood volume, low blood pressure, and impaired central nervous system function (hyperglycemic coma) that prolonged DKA recovery (49).

DKA adult patients with >5years duration of DM follow-up had 74% faster recovery as compared with those who had follow-up DM duration ≤ 5 years. This finding is consistent with a study in Saudi Arabia, patients who had a duration of one to five years

of diabetes mellitus were almost five times more likely to get out of DKA in more than 72 hours when compared with those who had a duration of more than five years(33). A shorter duration of diabetes has been associated with both higher levels of HbA_{1c} and risk of all-cause hospitalizations in adults (50). In this study, a shorter duration of diabetes was predictive of slower recovery of diabetic ketoacidosis. This may be due to those DKA patients with a shorter duration of diabetes may be less knowledgeable and experienced with diabetes management, and correspondingly less adherent to insulin adjustment and diabetes management(51).

Adult DKA patients with ≥97hrs of duration DKA till treatment had slower recovery as compared with those who had ≤24 hrs. This finding is in line with a study performed in Kenya that revealed delays in initiation of management have contributed to the prolonged DKA resolution times (29). This could be due to timely diagnosis and initiation of management of DKA is associated with faster recovery(9).

7. Limitation of the study

As the study was conducted retrospectively, it failed to include all variables particularly admission pH and admission serum potassium level which could be potential predictors of the outcome variable. Since this study was conducted in one hospital, generalizability to all hospitals of the country may not be possible.

8. Conclusions

The median time to recovery from DKA was relatively prolonged. The severity of DKA, duration of DKA, DM duration, and RBS level were statistically significant predictors of time to recovery time from DKA.

9. Recommendations

Patients shall go to the health facility immediately when they become ill.

Health care providers shall closely monitor and follow particularly for those who have a shorter duration of DM follow-up and severe DKA.

Further study using a prospective design by including admission pH and admission serum potassium level is advised to fill its limitation.

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Annex

Appendix A; Information sheet

Title of the Research:-Time to recovery from diabetic ketoacidosis and its predictors among adult diabetic ketoacidosis patients in Debre Markos referral hospital, North West Ethiopia, 2020/21: a retrospective cohort study

Name of Investigator: Dessie Temesgen (BSc)

Name of the Organization: Bahir Dar University, College of Medicine and Health Sciences, Department of Adult Health Nursing.

Introduction: This information sheet was prepared for Debre Markose Referal hospital administrators, card room coordinators, and head nurses of the wards. This form aimed to make the above stakeholders clear about the purpose of this research, data collection procedures, and get permission to conduct the research.

The purpose of the Research Project was: To assess time to recovery from diabetic ketoacidosis and its predictors among adult diabetic ketoacidosis patients admitted to Debre Markose Referral Hospital in Amhara Regional State, North West Ethiopia, 2021

Procedure: to achieve the above objective first information regarding the total number of adult DKA patients and the medical registration number of each patient were obtained from the Health information and management system (HIMS) of Debre Markose Referal hospital. Then detailed information about each patient was extracted from each selected patient chart.

Risk and /or Discomfort: Since the study was conducted by taking appropriate information from the patient chart, it didn't inflict any harm on the patients. The name or any other identifying information was not recorded on the questionnaire and all information is taken from the chart was kept strictly confidential and in a safe place. The information retrieved was only used for the study purpose.

Benefits: the research has no direct benefit for one whose document/ record was included in this research. But the indirect benefit of the research for the participant and other clients in the program is clear as mentioned in the significance of the study. This is because if program planners/caregivers prepare predicted plans there will be a benefit for clients in the program of getting appropriate care and treatment services.

Of all, the research work has a paramount direct benefit for health care planners, managers, caregivers, patients, and patient families.

Confidentiality: to reassure confidentiality the data on the chart was collected by BSc holder nurses who are working out of Debre Markose Referal hospital and information was collected without the name of the clients. The information collected from this research project is kept confidential and is stored in a secured file. In addition, it is not revealed to anyone except the investigator and advisers and it is kept in a key and locked system with a computer pass ward.

Person to contact: This research project is reviewed and approved by the institutional review board of the College of Medicine and Health Science, Bahir Dar University. If anyone is wanted to know more information, he/she could contact the committee through the address below. For those who had questions, the following addresses were written for the clarity to contact us any time.

1. **Dessie Temesgen:** Bahir Dar University, College of Medicine and Health Science, Department of Adult Health Nursing: principal investigator

Cell phone: +251- 924119046

E-mail:Des52.8t@gmail.com

Appendix B: Data extraction form (Checklist)

This tool was prepared for the collection of socio-demographic characteristics of the adult, disease factors of diabetic ketoacidosis, and other related information that was important for the assessment of time to recovery and its predictors of diabetic ketoacidosis among adults diabetic ketoacidosis patients at Debre Markose referral hospital, Amhara Regional State, Ethiopia;2021. All this information was retrieved from the individual patient cards without mentioning the name of the clients. This information was collected by BSc Nurses working in Debre Markos referral hospitals.

Contact information: DESSIE TEMESGEN Cell phone+251924119046

Data collection date----------month----------Year----------

Name of data collector---------- signature----------

Name of supervisor----------signature----------

Code no----------

PART-I SOCIO-DEMOGRAPHIC CHARACTERISTICS

No.	Socio-demographic characteristics	Possible answers	
1)	Age	(--------) years	
2)	Sex	1. Male 2. Female	
3)	Residence	1. Urban 2.Rural	
PART-II Patients baseline characteristics			
4)	Previous history of diabetes mellitus	1. Yes 2. No	
5)	Type of diabetes mellitus	1. T1DM 2. T2DM 3. Others	
6)	Duration of diabetes mellitus (33)	1 ≤5 years 2 >5 years 3 Newly diagnosed	

7)	The treatment regimen for diabetes mellitus		
8)	Frequency of follow up per month		
9)	The patient had Comorbidity of diabetes mellitus up to the first diabetic ketoacidosis developed	1. Yes 2. No	**If no skip to Q 10**
10)	Comorbidity of diabetes mellitus	1. CVD 2. CKD 3. HTN 4. Asthma 5. Others(specify)	
11)	patient take corticosteroids medication	1. Yes 2. No	
12)	Admission date/Diagnosis time with DKA dd/mm/yr…….. ……time……..pm/am		
13)	Duration of DKA symptoms till the admission In hours……..		
14)	Past admission history due to DKA	1. Yes 2. No	
15)	The patient had got a preceding infection before DKA developed?	1. Yes 2. No	
16)	The patient had got acute recent illness at DKA developed?	1. Yes 2. No	

A Vital signs

Pulse	Blood Pressure	Respiration	Temperature

B Severity of DKA

Severity of DKA (Put √ Mark)		
Mild DKA	Moderate DKA	Severe DKA

Part-III Clinical characteristics of the patients at the day of admission

Clinical characteristics	Yes	No
Nausea		
Vomiting		
Abdominal pain		
Fatigue		
Polyuria± polydipsia		
Kussmaul respiration		
Other symptoms		
LOC (GCS)		

Admission laboratory tests

Date……/……/…….. with time…….

RBS	Ketone	Cr	WBC	Urea	Hgb	Na^{+}	K^{+}	HCO_3^{-}	PO_4^{-3}	Cl^{-}
			Neu Leu Eos							

Part-IV Patient's Clinical and laboratory characteristics (Flow Sheet for Monitoring DKA) and management

Date	Time	Blood glucose	IV fluid dose	K*	Ketone	PH

1 Outcome of DKA_____

2 Date and time of the second ketone-free result …….