



8-31-2024

Section: Internal Medicine

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Hassan, Mohammed Essam Eldeen Mohammed Mohammed; Abohassan, Ahmed Mohamed; Ibrahim, Atef Aboelfetouh; and Hashish, Mahmud Abdellatif (2024) "Glycated Hemoglobin as Predictor of Organ Dysfunction in Patients with Sepsis," *Al-Azhar International Medical Journal*: Vol. 5: Iss. 8, Article 24.  
DOI: <https://doi.org/10.58675/2682-339X.2600>

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# Glycated Hemoglobin as Predictor of Organ Dysfunction in Patients with Sepsis

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## Abstract

**Background:** *Diagnosis of Sequential Organ Failure Assessment (SOFA) and also quick SOFA (qSOFA) scores, moving away from the SIRS criteria. Lastly, glycated hemoglobin (HbA1c) levels serve as a measure of average blood glucose above the previous three months and are not influenced by acute illness, making it a stable marker for assessing pre-existing hyperglycemia.*

**Methods:** *An observational research that was conducted retrospectively on a group of patients whose HbA1c level was determined upon ICU admission was conducted. At the Sahel Teaching Hospital, 100 patients were involved in the research. Patients were separated into two groups: a control group of 20 healthy individuals and a case group of 100 patients. Every patient underwent a thorough history taking, including clinical and laboratory assessments and SOFA and APACHE scores were calculated.*

**Results:** *A significant positive connection was observed between HbA1c and HR, blood glucose, serum creatinine, urea, CRP, APACHE II, SOFA score at admission, length of hospital stay, level of organ dysfunction, and ICU stay. There was a significant negative connection between HbA1c and PLT and WBCs. HbA1c can significantly anticipate organ failure in sepsis patients at AUC of 0.978, P value of <0.001, and at cut off value >6 %, with 100 % sensitivity, 94.94 % specificity, 91.1 % PPV and 100 %NPV. HbA1c was the only significant predictor of the severity of organ malfunction in sepsis patients.*

**Conclusion:** *Glycated hemoglobin (HbA1c) levels at ICU admission are a significant predictor of death and the evolution of organ malfunction in sepsis patients.*

**Keywords:** Glycated Hemoglobin; Organ Dysfunction; Sepsis

## 1. Introduction

The majority of sepsis patients have increasing organ dysfunction, and multi-organ failure can be fatal. Therefore, reducing the possibility of sepsis-related in-hospital mortality requires anticipating and avoiding organ dysfunction.<sup>1,2</sup> According to international recommendations, excess lactic acid concentrations ought to be brought down to normal within three hours after hospital admission, and mean arterial blood pressure ought to be kept at 65 mmHg or above with the use of fluid resuscitation and vasopressors if necessary.<sup>3</sup> Through the correction of an aberrant macrocirculation, these recommendations aim to stop the progression of organ dysfunction. However, because organ dysfunction advancement brought on by sepsis

is tightly tied to microcirculation, new research suggests that rectifying an aberrant macrocirculation may not totally prevent organ dysfunction progression.<sup>4</sup>

An indication of the mean plasma glucose level over the previous three months is glycated haemoglobin (HbA1c) (e.g., 6% equates to 126 mg/dL; 7% to 154 mg/dL; and 8% to 183 mg/dL).<sup>5</sup> Furthermore, the HbA1c level is a valid indicator of premorbid hyperglycemia because it remains unchanged when a critical illness manifests.<sup>6</sup> Continuous hyperglycemia damages the endothelium glycocalyx, as evidenced by sepsis patients.<sup>7</sup> Thus, the degree of baseline glycocalyx degradation is correlated with an elevated HbA1c level, a marker of persistent hyperglycemia, which may subsequently promote the development of organ failure in sepsis patients.<sup>8</sup>

Accepted 21 August 2024.

Available online 31 August 2024

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<https://doi.org/10.58675/2682-339X.2600>

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We proposed the hypothesis that the level of HbA1c would be linked to the evolution of organ malfunction and the death of patients in the intensive care unit (ICU) who have sepsis.<sup>9</sup>

The goal of this research was to determine the connection between ICU death and morbidity rate, the HbA1c level upon admission, as well as the extent of organ failure progression 72 hours following admission.

## 2. Patients and methods

This retrospective observational research was conducted from May 2021 to March 2023 on 100 patients who had their HbA1c level determined upon admission to the ICU unit at the Sahel Teaching Hospital.

All participants gave their verbal informed consent, and information confidentiality was guaranteed. Along with institutional review board approval, permission was also acquired from the faculty of the medical ethical committee.

Inclusion criteria for study cases:

Patients who were infected, older than 20 years, had an HbA1c level measurement at the time of direct entry to the ICU, and had a Sequential Organ Failure Assessment (SOFA) score of more than 2 points.

Exclusion criteria: had a serious neurological illness that would have contributed to organ failure, patient refusal, or any conditions that would have affected the HbA1c level. The duration of hospitalization in the ICU was lower than 24 hours.

Patients were classified into two groups as follows:

Group A: The control group comprised 20 patients with healthy individuals.

Group B Comprised 80 patients who were sepsis-related ICU admissions.

All cases underwent a full history with emphasis on a date and source of admission, ICU stay, vital signs, SOFA score, GCS score, complications, and comorbidities.

A full clinical examination was done, and laboratory investigations were performed (complete blood count). CBC was measured by Mindray BC-3000 plus. Reagent: M-30R Rinse, M-30D diluent, and M-30CFL Lyse, electrolyte Panel: Sodium, Potassium, Chloride, and Bicarbonate; liver and Kidney function tests, lipid profile, coagulation Profile, procalcitonin—PCT, arterial Blood Gas (ABG), C-Reactive Protein (CRP), blood Culture, HbA1C was measured on the first hospital day. Reagent: Fast-HbA1C Turbidimetry(Singel) -Biomed.)

APACHE II and Sequential organ failure assessment (SOFA) scores were computed upon admission for every patient. Each organ system receives a value between 0 and 4 in the SOFA

score, depending on how dysfunctional it is, and the total SOFA score serves as an indicator of overall morbidity. A higher SOFA score correlates with increased mortality risk, making it a valuable prognostic tool in intensive care settings. For five systems, the evolution of organ dysfunction brought on by sepsis was assessed 72 hours after ICU admission (heart, lungs, liver, coagulation, and kidney).

Statistical analysis:

The collected data was analyzed using SPSS 28.0. (IBM Inc., Armonk, NY, USA). Statistically significant was considered if p-value <0.05.

## 3. Results

The variation between the two groups was insignificant concerning the baseline characteristics. Other comorbidities, clinical examination, laboratory investigations, organ dysfunction and Outcome of the studied groups according is shwed in details in [Table 1](#)

*Table 1. Baseline characteristics, comorbidities, clinical examination, laboratory investigations, organ dysfunction and Outcome of the studied groups according to HbA1c level*

		TOTAL (N=120)	CASE GROUP (N=100)	CONTROL GROUP (N=20)	P VALUE
AGE (YEARS)	Mean± SD	59.8 ± 8.23	59.6 ± 8.41	61.1 ± 7.37	0.462
SEX	Range	45 - 72	45 - 72	46 - 72	0.933
	Male	73 (60.83%)	61 (61%)	12 (60%)	
	Female	47 (39.17%)	39 (39%)	8 (40%)	
BMI (KG/M <sup>2</sup> )	Mean±	28.04 ±	27.95 ±	28.5 ± 4.43	0.559
	SD	3.79	3.67		
	Range	21.2 - 35.76	21.2 - 35.76	23.31 - 35.76	
HYPERTENSION		43 (35.83%)	40 (40%)	3 (15%)	0.041*
DIABETES MELLITUS		66 (55%)	62 (62%)	4 (20%)	0.001*
DYSLIPIDEMIA		26 (21.67%)	22 (22%)	4 (20%)	1.00
ACUTE MYOCARDIAL INFARCTION		10 (8.33%)	8 (8%)	2 (10%)	0.672
CONGESTIVE HEART FAILURE		15 (12.5%)	13 (13%)	2 (10%)	1.00
ANGINA		14 (11.67%)	11 (11%)	3 (15%)	0.702
CEREBROVASCULAR ACCIDENT		16 (13.33%)	15 (15%)	1 (5%)	0.304
LIVER CIRRHOSIS		22 (18.33%)	20 (20%)	2 (10%)	0.362
HR (BEATS/MIN)	Mean±	91.2 ± 9.75	92.7 ± 9.78	83.6 ± 4.77	<0.001 *
	SD				
	Range	75 - 109	75 - 109	75 - 91	
SBP (MMHG)	Mean±	142.3 ±	143.5 ±	136.5 ±	0.041*
	SD	14.01	13.73	14.24	
	Range	120 - 170	120 - 170	120 - 160	
DBP (MMHG)	Mean±	85.3 ± 9.7	86.4 ± 9.69	79.5 ± 7.59	<0.001 *
	SD				
	Range	70 - 100	70 - 100	70 - 90	
TEMPERATURE (°C)	Mean±	37.2 ± 0.39	37.1 ± 0.38	37.2 ± 0.45	0.483
SPO <sub>2</sub> (%)	SD				0.102
	Range	36.5 - 37.8	36.5 - 37.8	36.5 - 37.8	
	Mean±	88.8 ± 10.4	88.1 ±	92.3 ± 8.54	
HB (G/DL)	SD		10.64		0.045*
	Range	70 - 100	70 - 99	71 - 100	
	Mean±	9.6 ± 1.49	9.5 ± 1.44	10.2 ± 1.63	
PLT (*10 <sup>9</sup> /L)	SD				<0.001 *
	Range	7.5 - 12.4	7.5 - 12.4	7.6 - 12.2	
	Mean±	195.01±	171.4 ±	313.1 ±	
WBCS (*10 <sup>9</sup> /L)	SD	58.2	23.03	28.77	<0.001 *
	Range	130 - 354	130 - 210	258 - 354	
	Mean±	11.7 ± 2.41	12.3 ± 1.78	8.7 ± 2.84	
HBA1C (%)	SD				<0.001 *
	Range	4.8 - 15.5	9.5 - 15.5	4.8 - 13.5	
	Mean±	7.2 ± 1.47	7.7 ± 1.06	4.8 ± 0.65	
BLOOD GLUCOSE (MG/DL)	SD				0.002*
	Range	4 - 9.5	6 - 9.5	4 - 5.8	
	Mean±	142.6 ±	149.6 ±	108 ± 44.92	
	SD	55.15	54.57		
	Range	71 - 219	71 - 219	74 - 217	

ALT (U/L)	Mean± SD	55.4 ± 22.83	57.1 ± 23.82	47 ± 14.7	0.069
AST (U/L)	Range	20 - 95	20 - 95	20 - 69	0.033*
	Mean± SD	60.2 ± 16.94	61.6 ± 16.81	52.8 ± 15.98	
	Range	30 - 101	30 - 101	31 - 81	
SERUM CREATININE (MG/DL)	Mean± SD	1.5 ± 0.42	1.6 ± 0.4	1.1 ± 0.26	<0.001*
UREA (MG/DL)	Range	0.8 - 2.3	1 - 2.3	0.8 - 2	0.046*
	Mean± SD	51.2 ± 20.45	52.8 ± 20.35	42.9 ± 19.31	
	Range	20 - 99	20 - 99	20 - 80	
CRP (MG/DL)	Mean± SD	16.4 ± 1.65	16.9 ± 1.23	13.7 ± 0.72	<0.001*
	Range	12.7 - 18.99	14.8 - 18.99	12.7 - 14.94	
	Mean± SD	26.2 ± 7.39	28.6 ± 5.16	14.2 ± 4.55	<0.001*
APACHE II	Range	8 - 37	20 - 37	8 - 20	<0.001*
	Mean± SD	8.9 ± 3.6	10.3 ± 1.95	2.0 ± 1.26	
	Range	0 - 13	7 - 13	0 - 4	
SOFA SCORE AT ADMISSION	Respirati on	63 (63%)	11 (55%)	63 (63%)	0.163
	Coagulat ion	20 (20%)	9 (45%)	20 (20%)	
	Liver	15 (15%)	4 (20%)	15 (15%)	
TOTAL SOFA SCORE	Cardiovascular	36 (36%)	6 (30%)	36 (36%)	<0.001*
	CNS	32 (32%)	3 (15%)	32 (32%)	
	Renal	28 (28%)	3 (15%)	28 (28%)	
DEGREE OF ORGAN DYSFUNCTION	Mild	79 (65.8%)	59 (59%)	20 (100%)	<0.001*
	Severe	41 (34.2%)	41 (41%)	0 (0%)	
	Mean± SD	9.98 ± 3.57	11.3 ± 2.25	3.6 ± 1	
ICU STAY (DAYS)	Range	2 - 15	8 - 15	2 - 5	<0.001*
	Mean± SD	20.1 ± 5.04	21.7 ± 3.93	12.4 ± 1.82	
	Range	10 - 28	16 - 28	10 - 15	
LENGTH OF HOSPITAL STAY (DAYS)	Mean± SD	49 (40.83%)	45 (45%)	4 (20%)	0.046*
	Range	10 - 28	16 - 28	10 - 15	
	Mean± SD	37 (30.83%)	35 (35%)	2 (10%)	
NEED FOR VENTILATION	Range	10 - 28	16 - 28	10 - 15	0.033*
	Mean± SD	49 (40.83%)	45 (45%)	4 (20%)	
	Range	10 - 28	16 - 28	10 - 15	
MORTALITY	Mean± SD	37 (30.83%)	35 (35%)	2 (10%)	0.033*
	Range	10 - 28	16 - 28	10 - 15	
	Mean± SD	49 (40.83%)	45 (45%)	4 (20%)	

LENGTH OF HOSPITAL STAY (DAYS)	0.491	<0.001*
NEED FOR VENTILATION	0.160	0.081
MORTALITY	0.088	0.339

HbA1c can significantly predict organ dysfunction in sepsis patients at AUC of 0.978, P value of <0.001, and at cut off value >6 %, with 100 % sensitivity, 94.94 % specificity, 91.1 % PPV and 100 %NPV. Table 4 and Figure 2

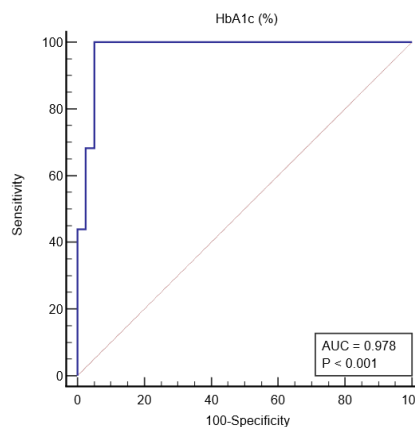


Figure 1. ROC curve analysis of HbA1c for prediction of organ dysfunction in patients with sepsis

The mean time of mortality was significantly earlier in severe group in contrast to mild group (HR= 3.2505 (95%CI) 1.1310 to 9.3418, P=0.029). Figure 2

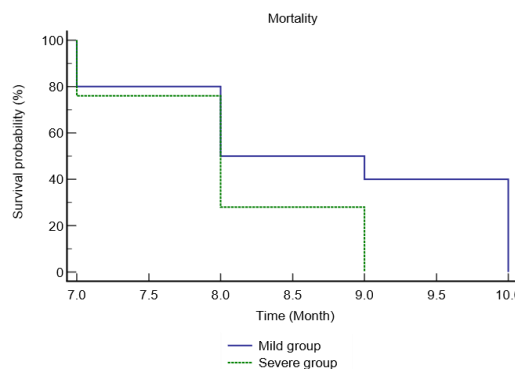


Figure 2. Moratlity for 12-months outcome in the studied groups

The multivariate logistic regression analysis exhibited that in sepsis patients, HbA1c was the sole meaningful predictor of the degree of organ failure. Table 3

Table 3. Multivariate logistic regression analysis for prediction of the severity of the organ dysfunction in patients with sepsis

	OR	95% CI	P VALUE
AGE (YEARS)	0.9819	0.9331 to 1.0332	0.482
SEX	1.646	0.6977 to 3.8833	0.142
BMI (KG/M <sup>2</sup> )	0.9952	0.9696 to 1.0216	0.625
HYPERTENSION	1.1299	0.2963 to 4.3094	0.922
DIABETES MELLITUS	0.364	0.0177 to 7.4742	0.487
DYSLIPIDEMIA	4.3683	0.4826 to 39.542	0.261
ACUTE MYOCARDIAL INFARCTION	0.6921	0.1242 to 3.8573	0.861
CONGESTIVE HEART FAILURE	0.7166	0.1342 to 3.8264	0.774
ANGINA	1.8558	0.4828 to 7.1338	0.636
CEREBROVASCULAR	0.9315	0.1277 to 6.7929	0.861

HR: heart rate, DBP: diastolic blood pressure, SPO2: oxygen saturation, Hb: hemoglobin, PLT: platelets, ALT: alanine aminotransferase, BMI: body mass index.AST: aspartate aminotransferase, WBCs: white blood cells, CPR: C-reactive protein APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, CNS: central nervous system, ICU: intensive care unit, SBP: systolic blood pressure.

A significant positive connection was observed between HbA1c and HR, blood glucose, serum creatinine, urea, CRP, APACHE II, SOFA score at admission, degree of organ dysfunction, ICU stay and length of hospital stay. The relationship between PLT and HbA1c was significantly inverse and WBCs. There was an insignificant connection between HbA1c and other parameters. Table 2 and Figure 1

Table 2. Correlation between HbA1c and other parameters

	HBA1C (%)	
	r	P
AGE (YEARS)	0.012	0.899
SEX	-0.006	0.945
BMI (KG/M <sup>2</sup> )	-0.129	0.159
HR (BEATS/MIN)	0.327	<0.001*
TEMPERATURE (°C)	-0.072	0.437
SPO <sub>2</sub> (%)	-0.121	0.189
HB (G/DL)	-0.133	0.149
PLT (*10 <sup>9</sup> /L)	-0.706	<0.001*
WBCS (*10 <sup>9</sup> /L)	-0.251	0.006*
BLOOD GLUCOSE (MG/DL)	0.221	0.015*
SERUM CREATININE (MG/DL)	0.261	0.004*
UREA (MG/DL)	0.237	0.009*
CRP (MG/DL)	0.474	<0.001*
APACHE II	0.489	<0.001*
SOFA SCORE AT ADMISSION	0.702	<0.001*
DEGREE OF ORGAN DYSFUNCTION	0.229	0.012*
ICU STAY (DAYS)	0.587	<0.001*

ACCIDENT				
LIVER CIRRHOSIS	0.1228	0.0119 to 1.2679	0.157	
HR (BEATS/MIN)	1.021	0.9715 to 1.0729	0.413	
TEMPERATURE (OC)	0.9021	0.2631 to 3.0929	0.870	
SPO <sub>2</sub> (%)	1.0326	0.9891 to 1.0781	0.144	
HB (G/DL)	0.9415	0.6885 to 1.2877	0.706	
PLT (*10 <sup>9</sup> /L)	1.0956	0.7229 to 1.6603	0.667	
WBCS (*10 <sup>9</sup> /L)	1.0502	0.8198 to 1.3454	0.698	
HBA1C (%)	0.9792	0.9622 to 0.9964	0.018*	
BLOOD GLUCOSE (MG/DL)	1.0041	0.9957 to 1.0125	0.338	
SERUM CREATININE (MG/DL)	1.1532	0.3753 to 3.5434	0.804	
UREA (MG/DL)	0.999	0.9761 to 1.0223	0.930	
CRP (MG/DL)	0.8544	0.5867 to 1.2443	0.412	
APACHE II	0.9552	0.8738 to 1.0442	0.314	
SOFA SCORE AT ADMISSION	0.9869	0.8502 to 1.1456	0.863	

OR: odds ratio, CI: confidence interval, BMI: body mass index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, SPO<sub>2</sub>: oxygen saturation, Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, RBS: random blood sugar, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CPR: C-reactive protein, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, \*: statistically significant as p value <0.05.

Multivariate logistic regression analysis exhibited that age, SPO<sub>2</sub>, HbA1c and SOFA score at admission were the only significant mortality predictors. **Table 4**

*Table 4. Multivariate logistic regression analysis for prediction of mortality*

	OR	95% CI	P VALUE
AGE (YEARS)	7.9602	1.7628 to 35.945	0.007*
SEX	1.152	0.3884 to 3.4175	0.799
BMI (KG/M <sup>2</sup> )	0.8798	0.7586 to 1.0205	0.091
TEMPERATURE (OC)	0.4315	0.1121 to 1.6614	0.222
SPO <sub>2</sub> (%)	0.9462	0.9042 to 0.9901	0.017*
HB (G/DL)	0.9793	0.6895 to 1.3909	0.907
PLT (*10 <sup>9</sup> /L)	0.9938	0.9767 to 1.0113	0.486
WBCS (*10 <sup>9</sup> /L)	0.8116	0.6167 to 1.0681	0.136
HBA1C (%)	1.0114	1.0034 to 1.0194	0.005*
BLOOD GLUCOSE (MG/DL)	1.009	0.9997 to 1.0184	0.224
APACHE II	0.9404	0.8489 to 1.0417	0.239
SOFA SCORE AT ADMISSION	1.3859	1.0612 to 1.8101	0.017*
ICU STAY (DAYS)	0.9317	0.7430 to 1.1682	0.540
LENGTH OF HOSPITAL STAY (DAYS)	1.0795	0.9466 to 1.2311	0.254

#### 4. Discussion

In this research, the associated comorbidities, hypertension, and DM were significantly more prevalent in the case group than in the control group (P=0.041, 0.001). Also, hypertension, DM, dyslipidemia, CHF, angina, and liver cirrhosis were significantly more prevalent in the severe group in contrast to the mild group, with no significant variation between both groups concerning acute myocardial infarction and cerebrovascular accident (P <0.05).

Similarly, Guo and Shen reported that diabetes (15.9%), alcohol misuse (16.4%), and hypertension (26.4%) were the most prevalent underlying comorbidities .<sup>10</sup>

In the present study, the severe group's admission SOFA and APACHE II scores were considerably greater than those of the moderate group (P<0.001, <0.001). Regarding the outcome,

the case group's ICU stay and overall hospital stay were significantly longer than those of the control group (P<0.001, <0.001), while the case group's mortality and need for ventilation were significantly greater (P=0.046, 0.033). In terms of the result, the severe group's ICU stay and overall hospital stay were significantly longer than those of the mild group (P<0.001, <0.001), while the severe group's mortality and need for ventilation were significantly greater than those of the mild group (P<0.001, <0.001).

Lee et al. discovered a substantial correlation (r = 0.320; P = 0.002) between the degree of organ malfunction progression and the HbA1c level, which is consistent with our findings. During ICU admission, 25 out of the 33 patients who had significant organ malfunction progression (75.8%) passed away .<sup>8</sup>

Furthermore, Guo and Shen found that sepsis was more common in the high HbA1c group (76.1 percent versus 35.9 percent, P<0.001) than in the low HbA1c group, while still significantly high in both groups. Furthermore, there was a greater 30-day death rate (29.7% versus 7.3%) in the high HbA1c group in contrast to the low HbA1c group (P<0.001) .<sup>10</sup>

According to the degree of organ malfunction progression, the studied patients were split up into 2 groups; mild group which comprised 79 (65.83%) patients and severe group which included 41 (34.17%) patients. The baseline characteristics (age, sex, and BMI) were insignificantly different between both groups.

Consistently, Lee et al., in their research, 33 out of 90 patients (36.7%) showed signs of severe organ malfunction progression 72 hours after ICU admission .<sup>8</sup>

SPO<sub>2</sub> was significantly decreased in the severe group as opposed to the mild group (P<0.001), with no significant variation between both groups concerning the other vital signs, including HR, SBP, DBP, and temperature. Hb concentration and platelet count were significantly reduced in the severe group in contrast to the mild group (P=0.007, <0.001). HbA1c, blood glucose, ALT, AST, serum creatinine, urea, and CRP were not substantially different between the two groups in terms of WBC count but were considerably greater in the severe group when as opposed to the mild group (P=0.05).

Lee et al. discovered, in line with our results, that patients with severe organ malfunction progression had HbA1c levels that were considerably higher than those of patients with mild organ malfunction progression (P = 0.014). In contrast to patients with mild organ malfunction progression, those with severe organ malfunction progression had greater levels of procalcitonin, liver enzymes, and lactic acid .<sup>8</sup>

Furthermore, Juhász et al. discovered a strong

positive association between HbA1c levels and glucose. Furthermore, among survivors, there was a strong positive connection between HbA1c levels and hospitalization duration. Significant negative relationships between WBC counts and HbA1c levels and glucose were discovered .<sup>11</sup>

HbA1c can significantly anticipate organ failure in sepsis patients at AUC of 0.978, P value of <0.001, and at cut off value >6 %, with 100 % sensitivity, 94.94 % specificity, 91.1 % PPV and 100 %NPV. The mean time of mortality was significantly earlier in the severe group in contrast to the mild group (HR= 3.2505 (95%CI) 1.1310 to 9.3418, P=0.029).

Guo and Shen also found that patients with a HbA1c level >6.5 % had a substantially lower survival period than those with a level <6.5 % (P < 0.001) .<sup>10</sup>

Additionally, Lee et al. stated that the log-rank test, in conjunction with the Kaplan-Meier method, showed that patients who had an HbA1c level of 6.5 % or higher had a significantly shorter survival time than patients whose HbA1c level was below 6.5 % (P < 0.001) .<sup>8</sup>

Mahmoodpoor et al. discovered that there was a doubling of the possibility of dying with each rise in HbA1c level. Without taking into account the history of diabetes, none of the survivors had significantly greater HbA1c levels than the survivors ( $7.25 \pm 1.87$  vs.  $6.05 \pm 1.22$ , respectively, P < 0.001) .<sup>12</sup>

#### 4. Conclusion

Among patients with sepsis, HbA1c was found to be the most reliable independent indicator of the severity of organ failure and mortality, even after controlling for age, SPO2, and initial SOFA score.

#### Disclosure

The authors have no financial interest to declare in relation to the content of this article.

#### Authorship

All authors have a substantial contribution to the article

#### Funding

No Funds : Yes

#### Conflicts of interest

There are no conflicts of interest.

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