The Potential Diagnostic and Predictive Role of HbA1c in Diabetic, Septic Patients - a Retrospective Single Center Study

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Abstract

Background: Diabetes mellitus is a major risk factor of sepsis. The potential role of hemoglobin A1c (HbA1c) in diabetic, septic patients has not yet been studied.

Results: In our retrospective study we included diabetic, septic patients - in whom the diagnosis of sepsis was based on the Systemic Inflammatory Response Syndrome (SIRS) criteria (112 patients, SIRS group) - who had HbA1c levels measured either in the previous 30 days (SIRS 30d subgroup – 39 patients) or within 24 hours after their Emergency Department admission (SIRS 24h subgroup – 73 patients). We later selected those patients from the SIRS group, whose Sequential Organ Failure Assessment (SOFA) score was ≥ 2 (55 patients, SOFA group) and these patients were also divided based on the time of HbA1c measurement (SOFA 30d subgroup – 21 patients and SOFA 24h subgroup – 34 patients). We analyzed the relationship between laboratory parameters, length of hospital stay and HbA1c. We found a significant positive correlation between glucose and HbA1c, significant negative correlations between white blood cell count (WBC) and glucose, WBC and HbA1c levels in the SIRS 24h and SOFA 24h subgroups. Furthermore there was a significant positive correlation between length of hospital stay and HbA1c in the SOFA 24h subgroup. No significant correlations were found in the SIRS 30d and SOFA 30d subgroups.

Conclusions: Based on our results normal WBC with elevated HbA1c might be considered a positive SIRS criterium in diabetic, SIRS 24h patients. Besides this potential diagnostic role, HbA1c might also be an additional prognostic biomarker in diabetic, SOFA 24h patients.

Background

Sepsis is a potentially life-threatening condition. Its definition keeps on changing as we learn more and more about the underlying pathomechanism of the disease. Before 2016 the Systemic Inflammatory Response Syndrome (SIRS) criteria was used for the diagnosis of sepsis: if at least 2 out of 4 clinical findings were present in a patient with a likely infection the diagnosis of sepsis was confirmed. The SIRS criteria are the following: tachycardia (heart rate > 90), hypothermia/fever (temperature $< 36^{\circ}\text{C}$ or $> 38^{\circ}\text{C}$), hyperventilation/hypocapnia (respiratory rate > 20 or $\text{PaCO}_2 < 32$ mmHg), leukopenia/leukocytosis (white blood cell count $< 4,000/\text{mm}^3$ or $> 12,000/\text{mm}^3$ or $> 10\%$ bands). The definition distinguished sepsis, severe sepsis and septic shock (1–4). In 2016 the definition of sepsis changed once again: the SIRS criteria as well as the definition of severe sepsis were no longer recommended. According to the new definition sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The Sequential Organ Failure Assessment (SOFA) and the quick SOFA (qSOFA) scores have been introduced (4). The diagnostic algorithm of sepsis has changed: in a patient with a likely infection the use of the quick SOFA score is recommended (it consists of 3 components: systolic blood pressure ≤ 100 mmHg, altered mental status, respiratory rate ≥ 22). According to the new recommendations a positive qSOFA Score (≥ 2 points) should prompt the calculation of the SOFA score to confirm the diagnosis of sepsis. If the qSOFA score is negative (< 2 points) but sepsis is still likely, we should also calculate the SOFA score. In a patient with a negative qSOFA score (< 2 points) and an unlikely infection, sepsis can be excluded. If a patient's SOFA score is ≥ 2 the diagnosis of sepsis is confirmed. The SOFA score consists of the following: platelet count, bilirubin and creatinine levels, mean arterial pressure (MAP) or administration of vasoactive agents, altered mental status (based on the Glasgow Coma Scale) and $\text{PaO}_2/\text{FiO}_2$. Septic shock is a form of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by vasopressor requirement to maintain a MAP of 65 mmHg or greater and serum lactate levels greater than 2 mmol/L in the absence of hypovolemia (4). Lots of studies have been published since 2016 in which the SIRS, qSOFA and SOFA criteria have been compared and data are controversial (5). Some results have shown inferior sensitivity of the qSOFA score compared to the previously favored SIRS criteria in the diagnosis of sepsis (6–9). Partly due to this, the 2016 recommendations are not universally accepted, and many countries still favor the previous diagnostic criteria and therefore the SIRS criteria.

Sepsis is usually bacterial in origin (caused mainly by Gram positive bacteria), however viral and fungal causes could also be in the background (10). Its global incidence is increasing, and it can be as high as 437/100000/year (11). Major risk factors of sepsis include: advanced age (≥ 65 years), previous hospitalization (especially in the previous 90 days, intensive care unit admission, nosocomial infections, community-acquired pneumonia), immunosuppression (e.g. neoplasms, renal failure, liver failure, AIDS, splenectomy) and genetic factors (10, 12–23). Diabetes mellitus, a metabolic disorder which has become a global health burden partly due to its rising incidence, is another major risk factor for sepsis (24). Immune response is severely altered in diabetics: neutrophil chemotaxis, phagocytosis, intracellular bactericide activity, opsonization as well as cell-mediated immunity are all affected (25–29). Therefore, infections are more common in diabetics compared to non-diabetic individuals. Poor glycemic control and hyperglycemia further increases the chance of infections in diabetics (25–29).

Hemoglobin in newly formed red blood cells is minimally glycosylated. The membrane of circulating red blood cells is permeable to glucose therefore it could be irreversibly attached to hemoglobin in a non-enzymatic way. HbA1c gives us information regarding mean blood glucose concentration over the lifespan of red blood cells (120 days) and its value correlates best with mean blood sugar levels over the previous 8–12 weeks. HbA1c is widely used nowadays to diagnose diabetes and monitor carbohydrate metabolism in diabetics (30–37), however its potential role in diabetic, septic patients has not yet been studied.

Results

Diabetic, septic patients with HbA1c levels measured within 24 hours after emergency department admission

SIRS 24 h patients

SIRS 24 h patients were 72.8 ± 12.7 years old (73 patients, 47 females, 26 males). All our patients were type II diabetics. Anthropometric data, past medical history, anti-diabetic therapy, laboratory parameters of patients as well as length of hospital stay in survivors were summarized in a table (Table 1). We analyzed the relationship between laboratory parameters and HbA1c as well as the correlation between length of hospital stay and HbA1c. Additionally we examined the relationship between leukocyte count and glucose, platelet count and glucose, and length of hospital stay and glucose levels. (Fig. 1.). In these patients there was a significant positive correlation between glucose and HbA1c levels ($p < 0.001$) (Fig. 2/a). We found significant negative correlations between white blood cell count and glucose ($p = 0.01$) (Fig. 2/b), white blood cell count and HbA1c levels ($p = 0.001$) (Fig. 2/c). The same correlations were observed in most cases even if patients were divided based on gender, anti-diabetic therapy (oral anti-diabetic agents vs. insulin therapy), age (< 65 yrs vs. ≥ 65 yrs) and hospitalization in the previous 90 days (Table 2).

Table 1
Anthropometric data, anti-diabetic therapy and laboratory parameters of diabetic, SIRS 24 h and SOFA 24 h septic patients. Data are presented as mean $\pm$ standard deviation or median (lower-upper quartile).

Diabetic, septic patients		
Criteria	SIRS 24 h group	SOFA 24 h group
Number of patients (n)	73 (47f/26 m)	34 (21f/13 m)
Age (years)	72.8 ± 12.7	73.9 ± 12.3
Type 2 diabetes (n)	73	34
Comorbidities		
Hypertension (n; %)	67 (91.8)	31 (91.2)
Dyslipidemia (n; %)	31 (42.5)	12 (35.3)
IHD/AMI/PCI/CABG (n; %)	32 (43.8)	18 (52.9)
TIA/stroke (n; %)	15 (20.6)	6 (17.7)
Peripheral arterial disease (n; %)	42 (57.5)	18 (52.9)
Chronic kidney disease (n; %)	27 (37.0)	13 (38.2)
Anti-diabetic medications		
Metformin (n; %)	30 (41.1)	11 (32.4)
Sulphonyl urea (n; %)	24 (32.9)	10 (29.4)
DPP4 (n; %)	4 (5.5)	0
Insulin (n; %)	18 (24.7)	11 (32.4)
Laboratory parameters		
Glucose (mmol/l)	11.5 (7.7–16.3)	12.05 (8.5–19.2)
HbA1C (%)	7.47 ± 1.8	7.26 ± 1.9
Urea (mmol/l)	8.4 (6–12.3)	9.85 (6.2–19.4)
Creatinine (μ mol/l)	99 (77–137)	118 (95–172)
Glomerular filtration rate (ml/min*1.73 m ²)	52 (38–75)	42 (27–61)
C-reactive protein (mg/l)	77 (21–151.5)	108 (21.3–246.3)
AST (U/L)	21 (17–33.5)	25 (16–42)
GGT (U/L)	35 (21–69)	40 (16–124)
ALT (U/L)	21 (14–32)	21 (14–37)
Total bilirubin (μ mol/l)	10 (6.5–17.4)	11.2 (6.3–33.6)
White blood cell count (G/L)	15.8 ± 6.1	17.3 ± 7.3
Red blood cell count (T/L)	4.3 ± 0.7	4.3 ± 0.7
Hemoglobin concentration (g/l)	129.8 ± 22.3	133.8 ± 19.4
Thrombocyte (G/L)	252.6 ± 76.9	251.0 ± 92.8
Length of hospital stay (day)	8 (6–11.5)	8 (7–11.5)

Table 2

Correlations between various laboratory parameters in subgroups of diabetic, SIRS 24 h septic patients. Abbreviations: CRP, C-reactive protein; HbA1c, hemoglobin A1c; LOS, length of stay in survivors; RBC, red blood cell; THR, thrombocyte; WBC, white blood cell.

	n	glucose vs. HbA1c	urea vs. HbA1c	creatinine vs. HbA1c	CRP vs. HbA1c	bilirubin vs. HbA1c	WBC vs. glucose	WBC vs. HbA1c	RBC vs. glucose	RBC vs. HbA1c	THR vs. HbA1c	LOS vs. HbA1c	LOS vs. glucose	LOS vs. WBC
All	73	r = 0.74 p < 0.001	ns	ns	ns	ns	r = -0.29 p = 0.01	r = -0.37 p = 0.001	ns	ns	ns	ns	ns	ns
males	26	r = 0.84 p < 0.001	ns	ns	ns	r = -0.43 p = 0.05	ns	r = -0.48 p = 0.01	ns	ns	r = -0.46 p = 0.02	ns	ns	ns
females	47	r = 0.70 p < 0.001	ns	ns	ns	ns	r = -0.28 p = 0.05	r = -0.32 p = 0.02	ns	ns	ns	ns	ns	ns
non-insulin	53	r = 0.76 p < 0.001	ns	ns	ns	ns	r = -0.28 p = 0.04	r = -0.35 p = 0.01	ns	ns	ns	ns	ns	ns
insulin	18	r = 0.69 p = 0.001	ns	ns	ns	ns	ns	r = -0.52 p = 0.03	ns	ns	ns	ns	r = 0.57 p = 0.02	ns
under 65 yrs	17	r = 0.87 p < 0.001	ns	ns	ns	ns	ns	r = -0.53 p = 0.03	ns	ns	ns	ns	ns	ns
over 65 yrs	56	r = 0.70 p < 0.001	ns	ns	ns	ns	r = -0.28 p = 0.04	r = -0.33 p = 0.01	ns	ns	ns	ns	ns	ns
Not stay within 90 days	66	r = 0.77 p < 0.001	ns	ns	ns	ns	r = -0.32 p = 0.01	r = -0.38 p = 0.001	ns	ns	ns	ns	ns	ns
Stay within 90 days	7	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

SOFA 24 h patients

34 type II diabetic, septic patients were in the SOFA 24 h group (21 females, 13 males, age: 74 ± 12.3 years). Anthropometric data, past medical history, anti-diabetic therapy, laboratory parameters of patients as well as length of hospital stay in survivors were summarized in a table (Table 1). We also analyzed the relationship between laboratory parameters and HbA1c as well as the correlation between length of hospital stay and HbA1c. Additionally we examined the relationship between leukocyte count and glucose, platelet count and glucose, and length of hospital stay and glucose levels. There was a significant positive correlation between glucose and HbA1c levels in the SOFA 24 h group, similarly to the one we found in SIRS 24 h patients ($p < 0.001$) (Fig. 3/a). We also found significant negative correlations between white blood cell count and glucose ($p = 0.02$) (Fig. 3/b) and white blood cell count and HbA1c levels in SOFA 24 h patients ($p = 0.02$) (Fig. 3/c). Additionally, there was a significant positive correlation between HbA1c levels and length of hospital stay in survivors ($p = 0.01$) (data not shown). The previous correlations in the SOFA 24 h group were observed in most cases even if patients were divided based on gender, anti-diabetic therapy (oral anti-diabetic agents vs. insulin therapy), age (< 65 yrs vs. ≥ 65 yrs) and hospitalization in the previous 90 days (Table 3).

Table 3

Correlations between various laboratory parameters in subgroups of diabetic, SOFA 24 h septic patients. Abbreviations: CRP, C-reactive protein; HbA1c, hemoglobin A1c; LOS, length of stay in survivors; RBC, red blood cell; THR, thrombocyte; WBC, white blood cell.

	n	glucose vs. HbA1c	urea vs. HbA1c	creatinine vs. HbA1c	CRP vs. HbA1c	bilirubin vs. HbA1c	WBC vs. glucose	WBC vs. HbA1c	RBC vs. glucose	RBC vs. HbA1c	THR vs. HbA1c	LOS vs. HbA1c	LOS vs. glucose	LOS vs. WBC
All	34	r = 0.80 p = 0.001	ns	ns	ns	ns	r = -0.39 p = 0.02	r = -0.41 p = 0.02	ns	ns	ns	r = 0.45 p = 0.01	r = 0.57 p = 0.001	ns
males	13	r = 0.95 p = 0.001	ns	ns	ns	r = -0.59 p = 0.05	ns	ns	ns	ns	r = -0.62 p = 0.02	ns	ns	ns
females	21	r = 0.73 p = 0.001	ns	ns	ns	ns	ns	ns	ns	ns	ns	r = 0.58 p = 0.01	r = 0.72 p = 0.001	ns
non-insulin	22	r = 0.82 p = 0.001	ns	ns	ns	ns	r = -0.42 p = 0.05	r = -0.44 p = 0.03	ns	ns	ns	r = 0.56 p = 0.05	r = 0.43 p = 0.01	ns
insulin	11	r = 0.79 p = 0.005	ns	ns	ns	ns	ns	ns	ns	ns	ns	r = 0.67 p = 0.04	r = 0.65 p = 0.05	ns
under 65 yrs	7	r = 0.84 p = 0.02	ns	ns	ns	ns	ns	r = -0.80 p = 0.03	ns	ns	ns	r = 0.82 p = 0.02	r = 0.91 p = 0.004	ns
over 65 yrs	27	r = 0.80 p = 0.001	ns	ns	ns	ns	ns	ns	ns	ns	ns	r = 0.45 p = 0.02	r = 0.55 p = 0.004	ns
Not stay within 90 days	29	r = 0.80 p = 0.001	ns	ns	ns	ns	r = -0.43 p = 0.02	r = -0.41 p = 0.03	ns	ns	ns	r = 0.62 p = 0.001	r = 0.73 p = 0.001	ns
Stay within 90 days	5	r = 0.96 p = 0.01	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Diabetic, septic patients with HbA1c levels measured in the previous 30 days before their emergency department admission

SIRS 30d and SOFA 30d patients

There were 39 diabetic, septic patients in the SIRS 30d group. We studied the same correlations that were previously examined in the SIRS 24 h group. We did not find any significant correlation in this population even if we later selected and examined patients whose SOFA score was positive (≥ 2) (SOFA 30d group, 21 patients) (data not shown).

Discussion

This is the first study to evaluate the potential role of HbA1c in diabetic, septic patients. In SIRS 24 h patients we found a significant positive correlation between glucose and HbA1c levels, while significant negative correlations were observed between white blood cell count and glucose, white blood cell count and HbA1c. Correlations were observed even if patients were divided based on gender, anti-diabetic therapy (oral anti-diabetic agents vs. insulin therapy), age (< 65 yrs vs. ≥ 65 yrs) and hospitalization in the previous 90 days. One possible explanation behind the observed negative correlations between white blood cell count and glucose, white blood cell count and HbA1c is glucose toxicity, a phenomenon previously described in pancreatic beta cells (38–40). According

to previous studies, hyperglycemia in diabetic patients increases oxidative stress and induces glucose-induced apoptosis mainly in metabolically active cells (e.g. white blood cells in sepsis), resulting in cell death. There are some diabetic, septic patients - in whom sepsis is diagnosed based on the SIRS criteria - whose white blood cell count is normal, despite being septic. These diabetic, septic patients with normal white blood cell counts (WBC count between $4-12 \times 10^9/l$) have higher HbA1c levels. This observation is crucial as white blood cell count is an important part of the SIRS criteria (positive criterium: white blood cell count $< 4,000/mm^3$ or $> 12,000/mm^3$ or $> 10\%$ bands). It may occur in diabetic, septic patients - in whom diagnosis is based on the SIRS criteria - that white blood cell count is normal (between $4-12 \times 10^9/l$) and there is only one other positive SIRS criterium (heart rate > 90 , temperature $< 36^\circ C$ or $> 38^\circ C$, respiratory rate > 20 or $PaCO_2 < 32$ mmHg). According to the definition of sepsis - based on the SIRS criteria - these patients are not septic however the potential life-threatening immune processes might have already started. HbA1c - based on the negative correlation found between white blood cell count and HbA1c levels - can be a useful tool in finding these patients: in diabetic patients, normal white blood cell count ($4-12 \times 10^9/l$) with elevated HbA1c levels should be considered a positive SIRS criterium. Therefore HbA1c - measured within 24 hours after admission (preferably upon arrival) - could turn out to be an efficient way to identify these diabetic, septic patients early and initiate sepsis treatment accordingly. Further, large, multi-centric studies are needed to confirm our hypothesis.

In the SOFA 24 h group we found a significant positive correlation between glucose and HbA1c levels, significant negative correlations between white blood cell count and glucose, white blood cell count and HbA1c. We also found a significant positive correlation between length of hospital stay and HbA1c levels in survivors. A significant negative correlation was observed between white blood cell count and HbA1c in SOFA 24 h diabetic, septic patients similarly to the SIRS 24 h group. However as white blood cell count is not a SOFA criterium this correlation and therefore the possible early diagnostic potential of HbA1c is not that significant in SOFA patients. On the other hand - as there was a significant positive correlation between length of hospital and HbA1c levels in survivors - HbA1c may be a significant prognostic tool in diabetic, septic patients in whom the diagnosis is based on the SOFA criteria.

We did not find any significant correlation in SIRS 30d patients. Previous studies found no significant difference between HbA1c levels measured on admission and 30 days earlier in critically ill patients (41). Based on this the same correlations we found in SIRS 24 h patients should have been observed in SIRS 30d patients. A possible explanation for this difference is that HbA1c in our study was measured within 30 days prior to these patient's emergency department admission, and not 30 days prior exactly, and HbA1c measured on admission correlates better with glucose concentration of the previous weeks. We did not find any significant correlation in the SOFA 30d group either.

Some limitations must be noted. Despite our significant correlations, enrolment of a larger population might increase the statistical power. Additionally, HbA1c levels strongly depend on the turnover of red blood cells: slow turnover (e.g. iron, vitamin B12, or folate deficiency anemias) often results in higher, whereas fast turnover (e.g. hemolytic anemia, erythropoietin therapy) in lower HbA1c levels (30-37). Due to metabolic changes and erythropoietin treatment in patients with end-stage renal failure HbA1c levels are often altered (30, 32-37). Therefore, all patients with the above mentioned disorders have been excluded from the study. Furthermore, according to some studies HbA1c levels vary among different racial and ethnic groups (higher levels in Afro-Americans and Asians). (37). We enrolled only Caucasian patients.

Conclusion

Based on our results we can conclude that even normal white blood cell count could be abnormal in diabetic, septic patients in whom the diagnosis is based on the SIRS criteria if an elevated HbA1c level is measured within 24 hours after admission (preferably upon arrival). Therefore, in these patients normal white blood cell count ($4-12 \times 10^9/l$) with elevated HbA1c levels could be considered a positive SIRS criterium.

In diabetic, septic patients, in whom the diagnosis of sepsis is based on the SOFA score and HbA1c is measured within 24 hours after admission (preferably upon arrival), HbA1c could be an important prognostic tool as there is a significant positive correlation between HbA1c levels and length of hospital stay in survivors.

Further studies focusing on the possible diagnostic and prognostic role of HbA1c in diabetic, septic patients are needed to verify our data.

Methods

We collected all cases from the Department of Emergency Medicine and later Emergency Clinic at the University of Debrecen, between 1st January 2017 and 31st December 2018 (27737 patients, 42766 cases). First, we selected patients who had their HbA1c measured in the study period (3743 patients) and later from these patients we collected those diabetic, septic patients who had HbA1c levels measured either in the previous 30 days or within 24 hours after their Emergency Department admission. Sepsis was diagnosed based on the SIRS criteria. Patients with autoimmune disease, end-stage renal failure, liver cirrhosis and active cancer were excluded from our study. As HbA1c levels highly depend on the turnover of red blood cells, patients with iron, vitamin B12, and folate deficiency anemias were also excluded. Exclusion criteria also included erythropoietin therapy and hemolytic anemia for the previous reason. This way 112 diabetic, septic patients were included in our study (SIRS group) from whom 39 had HbA1c measured in the previous 30 days (SIRS 30d subgroup) and 73 within 24 hours after their Emergency Department admission (SIRS 24 h subgroup). The past medical history (type of diabetes mellitus and date of diagnosis, hypertension, dyslipidemia, ischemic heart disease, previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting surgery, transient ischemic attack, stroke, peripheral arterial disease, chronic renal failure), anti-diabetic therapy (metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, other oral anti-diabetic agents, insulin), laboratory results (arterial blood gas results, urea and electrolytes, glucose levels, liver function tests, pancreatic enzymes, C-reactive protein - CRP, procalcitonin - PCT, albumin, full blood count), HbA1c levels and time of measurement, SIRS and SOFA scores, microbiological results, type of infection, length of hospital stay and mortality data of all patients were collected. Most laboratory parameters - with sometimes the exception of HbA1c - were measured upon arrival.

We later selected those patients from the SIRS group, whose SOFA score was ≥ 2 (55 patients, SOFA group). Patients from the SOFA group were also divided into subgroups based on the time of measurement of HbA1c (patients with HbA1c measured in the previous 30 days - SOFA 30d subgroup vs. patients with HbA1c measured within 24 hours after their Emergency Department admission - SOFA 24 h subgroup) (Fig. 1.)

The STATISTICA 13.7 (TIBCO INC. USA) software was used for data analysis. Results were either given as mean $\pm$ standard deviation or median (lower and upper quartile), respectively. We used Pearson's correlation for finding significant relationships (in case of significant correlations p was < 0.05).

Abbreviations

CRP: C-reactive protein

HbA1c: hemoglobin A1c

MAP: mean arterial pressure

PCT: procalcitonin

qSOFA: quick SOFA

SIRS: Systemic Inflammatory Response Syndrome

SOFA: Sequential Organ Failure Assessment

WBC: white blood cell count

Declarations

Ethics approval and consent to participate

The work is conform to the guiding principles of the Declaration of Helsinki, and our study subjects gave informed consent of a study that has been approved by the Institutional Committee on Human Research at our institution.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. All data generated or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors report no conflict of interest.

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Figures

Figure 1

Flowchart showing the structure of the study, enrollment and evaluation procedure, and how the patients were divided into the groups, and phases.

Figure 2

Correlations between glucose and HbA1C (%) (a), glucose and white blood cell count (b), white blood cell count and HbA1C (%) in diabetic, SIRS 24h septic patients (n=73)

Figure 3

Correlations between glucose and HbA1C (%) (a), glucose and white blood cell count (b), white blood cell and HbA1C (%) in diabetic, SOFA 24h septic patients (n=34)

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