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ORIGINAL RESEARCH

Predictive Value of HbA1c-levels with Regard to In-hospital Mortality, Length of Hospital Stay and Intensive Care Utilisation versus Different Emergency Risk Scores and the Manchester Triage System in Unselected Medical Emergency Admissions

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Abstract

Objectives: To evaluate the predictive value of HbA1c levels in medical patients admitted to the emergency department (ED) regarding in-hospital-mortality, length of stay (LOS) and transferral to intensive care unit (ICU) and to compare them with different physiologically based emergency scoring systems and the Manchester Triage System (MTS). **Methods:** In a prospective cohort-study, 1117 consecutive patients presenting to the medical ED were assessed. Data collected included age, sex, vital signs, temperature, oxygen saturation, respiratory rate, AVPU (Alert; Verbal response; response to Pain; Unresponsive)-score, MTS, different emergency scores and HbA1c. The data were correlated with LOS, hospital mortality and intensive care utilisation. **Results:** HbA1c had similar accuracy in predicting LOS as most physiologically based scores (AUC = 0.568, p = 0.688 to 0.714) and ICU utilisation (AUC = 0.525, p = 0.001 compared with MTS, for all others p = 0.077 to 0.830). HbA1c was positively correlated with LOS and ICU-transferral but correlated poorly with mortality, resulting in low predictive power (AUC = 0.501, p = 0.033 to 0.845). The subgroups with HbA1c below the median and below 6.5% had a shorter LOS (p = 0.012 and p = 0.004). The differences for other subgroups were not significant. **Conclusions:** HbA1c was positively correlated with LOS and ICU-referral, reflecting higher health-care utilisation, indicating that it may be a useful parameter in evaluating severity of illness in emergency patients.

Keywords

Glycated haemoglobin, Emergency score, Manchester Triage System, Mortality, Length of stay, ICU referral

1. Introduction

In order to provide assistance in efficiently allocating resources in the emergency department (ED), a large variety of risk assessment systems have been proposed for triaging patients [1, 9]. One of the most widely used protocols is the Manchester Triage System (MTS) which is based on major symptoms/complaints. Additionally, several scoring systems based on measurable physiological values have been developed. The most common systems are variations of the Early Warning Score System. These scores differ in the composition and weighting of the measured vital signs and other parameters. Most incorporate a combination of respiratory rate, heart rate, temperature, blood pressure, oxygen saturation and the AVPU(Alert; Verbal response; response to Pain; Unresponsive)-score. Some exclude one or more of these variables, others add additional variables like urine output, age, sex, respiratory support, a pain

TABLE 1. Scoring systems.

CART

Vital sign	value	score
RR	<21	0
	21-23	8
	24-25	12
	26-29	15
>29	22	
HR	<110	0
	110-139	
	>139	13
DBP	>49	0
	40-49	4
	35-39	6
	<35	13
Age	<55	0
	55-69	4
	>69	9

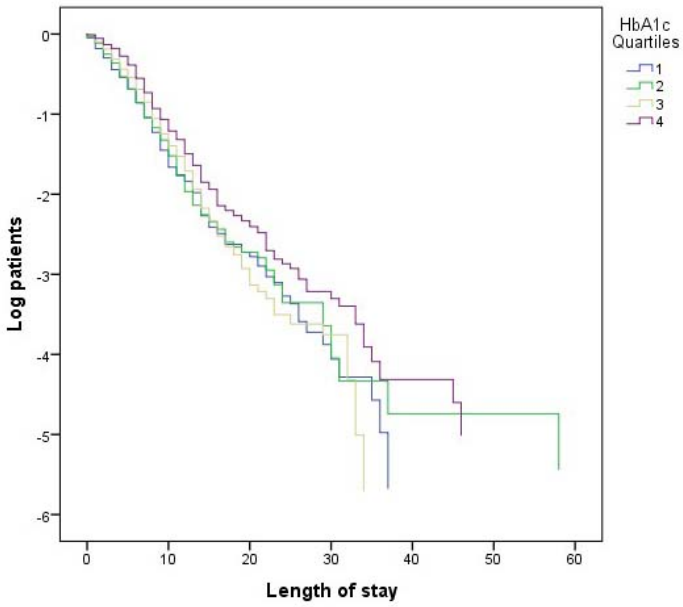

FIGURE 1. Logarithmic Kaplan Maier curve of length of stay. *1: HbA1c ≤ 5.4%; 2: HbA1c > 5.4% to < 5.8%; 3: HbA1c 5.8% to < 6.3% ; 4: HbA1c ≥ 6.3%, *:p = 0.010. The mean length of stay was significantly prolonged in the fourth quartile.*

scale or substitute the Glasgow Coma Scale for AVPU. However, there is uncertainty regarding the most adequate tool for prediction of severity of illness and the demand for available resources [1].

As one of the primary problems is the correct implementation of well-established systems, ease of use is of great importance. An ideal parameter should be easily and quickly obtainable.

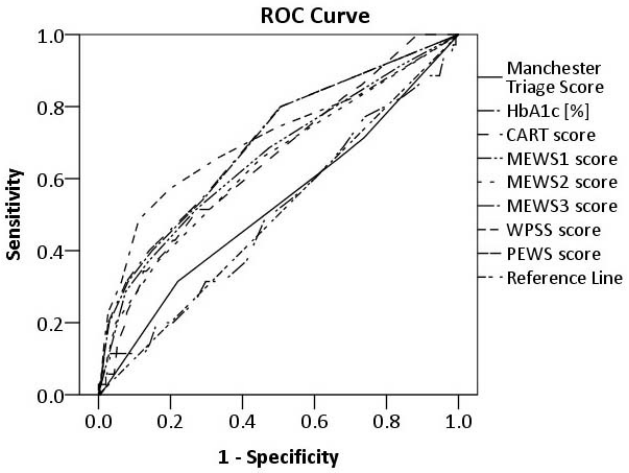

FIGURE 2. Prediction of mortality. *ROC curves for the examined systems regarding mortality.Graphic depiction of AUCs for the prediction of mortality.*

Cardiovascular events and metabolic derangements are the most common reasons for rapid, unexpected clinical deterioration and unfavorable course of the disease. Specifically, glycated hemoglobin (HbA1c) has been shown to be linked to adverse cardiovascular outcomes [10], adverse outcomes for sepsis in diabetic patients [11], increased mortality in cerebrovascular disease [12] and increased all-cause mortality [13]. Point-of-care assays that allow quick and reliable HbA1c measurements have been developed recently and are increasingly utilised in EDs [14]. Considering the high numbers of undetected cases of diabetes mellitus [15] and its rapidly increasing incidence [16], we hypothesized that HbA1c could be useful for estimation of clinical outcomes in unselected emergency room patients. Accordingly, we compared the predictive value of HbA1c to established measures for triage in the ED.

2. Methods

This study was approved by the ethical review committee of the University of Regensburg (No 14-101-0008). The research is in accordance with the Helsinki Declaration of 1975, as revised in 2010.

Data collection was in accordance with Bavarian law (BayKrG, Art. 27).

2.1 Study population

Within a prospective observational design, we enrolled consecutive patients who presented to the ED of the RoMed Hospital of Rosenheim, Germany, between June 5, 2014 and August 15, 2014. RoMed Klinikum Rosenheim is a major regional secondary care hospital in southern Bavaria with 640 beds, where approximately 27,000 inpatients and 35,000 outpatients are treated annually.

TABLE 1. Continued.

MEWS1							
Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
RR		≤8		9-14	15-20	21-29	>29
HR		≤40	41-50	51-100	101-110	111-129	>129
SBP	≤70	71-80	81-100	101-199		≥200	
Temp		≤35	35.1-36	36.1-38	38.1-38.5	≥38.6	
AVPU				A	V	P	U
MEWS2							
Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
RR				<24	≥24		
HR		≤40		40-129	≥130		
SBP		<80	80-85	>85			
Age				<80	80-89	≥90	
AVPU				A	V	P/U	
SO2		<85	85-89	≥90			
MEWS3							
Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
RR		<9		9-14	15-20	21-29	≥30
HR		≤40	41-50	51-100	101-110	111-129	≥130
SBP	≤70	71-80	81-100	100-199		≥200	
Temp	<35			35.0-38.4		≥38.5	
AVPU				A	V	P	U
WPSS							
Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
RR				≤19	20-21	≥22	
HR				≤101	≥102		
SBP		≤99		≥100			
Temp	<35.3			≥35.3			
AVPU				A			V/P/U
SO2	<92	92-93	94-95	96-100			

PEWS							
Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
RR		≤8		9-14	15-20	21-29	>30
HR		≤40	41-50	51-100	101-110	111-130	>130
SBP	≤70	71-80	81-100	100-199		>200	
Temp		≤35.0	35.1-36.0	36.1-37.9	38.0-38.9	≥39	
AVPU				A	V	P	U

Examined scoring systems and their composition Abbreviations and units: Age [years]; AVPU [Alert, Voice, Pain, Unresponsive]; CART, Cardiac Arrest Risk Triage; DBP, diastolic blood pressure [mmHg]; HR, heart rate [beats/min]; MEWS, Modified Early Warning System; PEWS, Patientrack Early Warning System; RR, respiratory rate [breaths/min]; SBP, systolic blood pressure [mmHg]; SO2, oxygen saturation [%];Temp, temperature [°C]; WPSS, Worthington Physiological Scoring System; CART, MEW, PEW (please add the meaning and order the abbreviations alphabetically).

2.2 Data collection

In addition to the standard operating procedure in the ED, the following data were collected upon presentation: age, sex, heart rate (HR), non-invasive systolic and diastolic blood pressure, respiratory frequency (as measured

TABLE 2. Patient characteristics.

Age, median (IQR), y	73 (61-81)
Male sex, No. (%)	606 (54.3%)
Heartrate, median (IQR), /min	85 (71-100)
Respiratory rate, median (IQR) , /min	18 (15-20)
Systolic blood pessure, median (IQR), mmHg	138 (120-157)
Diastolic blood pressure, median (IQR), mmHg	76 (65-88)
Temperature, median (IQR), °C	36.8 (36.5-37.3)
Oxygen saturation, median (IQR), %	96 (94-97)
HbA1c, median (IQR), mmol	39.9 (35.5-45.4)
HbA1c, median (IQR), %	5.8 (5.4-6.3)
AVPU:	
Alert, No., %	1004 (89.9%)
Voice, No., %	105 (9.4%)
Pain, No., %	0 (0%)
Unresponsive, No., %	8 (0.7%)
Manchester Triage System:	
Blue, No., %	6 (0.5%)
Green, No., %	243 (21.8%)
Yellow, No., %	497 (44.5%)
Orange, No., %	78 (7.0%)
Red, No., %	293 (26.2%)

Table 2: Characteristics of the tested population.
Abbreviations: IQR: Interquartile range; y: years.

via monitor), pulse oxygen saturation (SaO_2), body temperature, AVPU-Score [2]. The nurse in charge applied the standard examination within 20 minutes following presentation. Patients missing one or more data points were excluded.

Upon presentation at the ED, patients were stratified using the MTS [3] by specifically trained nurses according to protocol. MTS color levels were converted to an ordinal scale of 1 to 5 for statistical analysis.

Patients with complete data sets were followed until death, discharge from hospital or referral to another hospital. Additionally, we assessed length of hospital stay (LOS) and admission to the intensive care unit or intermediate care unit (summarized as ICU) at any timepoint during hospital stay.

HbA1c levels were determined by high pressure liquid chromatography (Tosoh Bioscience Inc, Japan) using EDTA venous blood samples acquired upon presentation.

The estimated catchment area of our hospital includes around 200000 people. The data set was to be used in several studies. To answer questions with a confidence level of 95% and a confidence interval of 3, a sample size of 1061 patients was calculated.

Potential biases included the misapplication of the MTS protocol which we tried to address by specifically instructing the nurses.

2.3 Emergency scores

The following scores were calculated (Table 1):

Cardiac Arrest Risk Triage (CART) [4], three different versions of the Modified Early Warning Score (MEWS1-3) [5–7], Worthington Physiological Scoring System (WPSS) [8], Central Manchester University Hospitals National Health Service Foundation Trust Early Warning Score, itself a variation of the EWS, used in the Patientrack Early Warning System (PEWS) [9].

The CART-Score was initially developed to specifically asses the risk of cardiac arrest but was included as an interesting alternative as it incorporates similar and easily available parameters that have been compared to general emergency scores before [4].

2.4 Statistics

Statistical analysis was performed using SPSS Statistics Version 24 (IBM Corp. Released 2016, IBM SPSS for Windows, Version 24.0. Armonk, NY: IBM Corp), significancy in AUC differences was determined using R Version 3.3.2 (R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria. URL: www.R-project.org GNUlicense) and the R package pROC [17].

For continous parameters mean, standard deviation, median and range were calculated. For binary and categorial

TABLE 2b. Areas under the curve for the prediction of mortality Area Under the Curve.

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
MTS	0.524	0.053	0.632	0.419	0.628
HbA1c	0.501	0.051	0.99	0.4	0.601
CART	0.651	0.047	0.002	0.558	0.744
MEWS1	0.696	0.047	<0.001	0.604	0.788
MEWS2	0.64	0.052	0.005	0.539	0.741
MEWS3	0.658	0.051	0.001	0.558	0.758
WPSS	0.707	0.053	<0.001	0.603	0.812
PEWS	0.699	0.047	<0.001	0.606	0.791

2b: Numeric values of AUCs as shown in Fig. 2a.

TABLE 2c. Comparison of AUCs and corresponding p-values.

Predictor1	AUC1	Predictor2	AUC2	P-value
MTS	52.38	HbA1c	50.06	0.845
MTS	52.38	CART	65.08	0.131
MTS	52.38	MEWS1	69.6	0.07
MTS	52.38	MEWS2	64	0.191
MTS	52.38	MEWS3	65.79	0.179
MTS	52.38	WPSS	70.73	0.07
MTS	52.38	PEWS	69.88	0.07
HbA1c	50.06	CART	65.08	0.07
HbA1c	50.06	MEWS1	69.6	0.033
HbA1c	50.06	MEWS2	64	0.131
HbA1c	50.06	MEWS3	65.79	0.069
HbA1c	50.06	WPSS	70.73	0.038
HbA1c	50.06	PEWS	69.88	0.033
CART	65.08	MEWS1	69.6	0.434
CART	65.08	MEWS2	64	0.86
CART	65.08	MEWS3	65.79	0.876
CART	65.08	WPSS	70.73	0.302
CART	65.08	PEWS	69.88	0.416
MEWS1	69.6	MEWS2	64	0.333
MEWS1	69.6	MEWS3	65.79	0.07
MEWS1	69.6	WPSS	70.73	0.845
MEWS1	69.6	PEWS	69.88	0.069
MEWS2	64	MEWS3	65.79	0.845
MEWS2	64	WPSS	70.73	0.182
MEWS2	64	PEWS	69.88	0.319
MEWS3	65.79	WPSS	70.73	0.179
MEWS3	65.79	PEWS	69.88	0.069
WPSS	70.73	PEWS	69.88	0.859

2c: AUCs were tested for significant differences. Significance was assumed for p<0.05, marked by colored background. MEWS1, WPSS and PEWS were significantly better at predicting mortality in comparison to HbA1c. Abbreviations: AUC, Area under the curve; CART, Cardiac Arrest Risk Triage; MEWS, Modified Early Warning System; MTS, Manchester Triage System; PEWS, Patientrack Early Warning System; WPSS, Worthington Physiological Scoring System.

TABLE 3. Distribution of Endpoints.

Admission to ICU, No. , %	213 (19.1%)
LOS, median (IQR), days	6 (3, 10)
LOS, mean (standard deviation), days	8.2 (7.9)
Death, No. , %	35 (3.1)
Transferral, No. , %	49 (4.4%)

Abbreviations: LOS, legth of stay; IQR, interquartile range.

parameters absolute and relative frequencies were calculated.

Mean values for LOS of different subgroups were compared using Student's t-test.

Percentages for mortality and ICU transferral were compared using the Mann-Whitney-test.

Reciever-Operator-Characteristic (ROC) curves were calculated, graphically showing the predictive power for each test regarding the endpoints. Sensitivity is plotted vertically, whilst 1-specificity (i.e. the false positive rate) is plotted horizontally. The AUC of two ROC curves were compared using Delong's test [18]. The resulting p-values of the Delong's test were adjusted using the method of Benjamini and Hochberg [19].

3. Results

During the observation period, 1202 medical patients were admitted to the ED. 85 patients were excluded from further analyses because of missing data, resulting in a final study group of 1117 patients (Table 2) which were observed until the endpoints (Table 3).

In addition to the quartiles, cut offs were chosen at HbA1c levels of 6.5% and 5.7%. Values above 6.5% indicating a poorly controlled or undiagnosed diabetes mellitus, 5.7% to 6.5%, indicating a pre-diabetic metabolic state while values below 5.7% indicate either a well-controlled diabetes or no diabetes at all.

The mean LOS for the combined lower two quartiles of HbA1c was 7.5 days while for the two higher quartiles it was 8.7 days (Table 4). This difference was statistically significant ($p = 0.012$). Mean LOS for quartile 3 (7.9 days) was significantly shorter than for quartile 4 (9.5 days, $p = 0.010$). The differences between the other quartiles did not reach significance (Fig. 1).

TABLE 4. Outcomes for HbA1c quartiles and relevant subgroups.

HbA1c-level	ICU transferral, %	LOS, median, d	LOS, mean, d	Mortality, %
First quartile (≤5.4%)	16.6	6	7.4	2.8
Second quartile (>5.4% to <5.8%)	19.7	6	7.7	3.5
Third quartile (5.8% to <6.3%)	20.7	7	7.9	3.3
Fourth quartile (≥6.3%)	19.4	7	9.5	3
<6.5%	18.6	6	7.8	3.2
≥6.5%	20.6	7	9.5	3
5.7%-≤6.5%	19.3	6	8.2	3.2
<5.7%	17.9	6	7.4	3.1

*Length of stay was prolonged in subgroups with high HbA1c levels. Patients with levels above the median (quartiles 3+4) stayed significantly longer than those with levels below (quartiles 1+2). Among those with high levels, the fourth quartile stayed significantly longer than the third. The LOS for subgroups divided by HbA1c levels of 6.5% and 5.7% also differed significantly. The rate of ICU transfers showed a trend that did not reach significance. Mortality was poorly predicted by HbA1c. Abbreviations: d, days; ICU, Intensive/intermediate care unit; LOS, Length of stay; *, p<0.05.*

Mean LOS for patients with a HbA1c below 6.5% was significantly shorter than for those with higher levels (7.8 days vs. 9.5 days, p = 0.004).

Mean LOS for patients with a HbA1c between 5.7% and 6.5% was not significantly different from those with lower levels (p = 0.143) but significantly shorter than those with values above 6.5% (p = 0.036).

While showing a trend for better outcomes for lower HbA1c values, across all subgroups neither the differences in mortality (p=0.413 to 0.971) nor in ICU transferral (p = 0.193 to 0.942) were significant (Fig. 2).

Notably, HbA1c values hardly correlated with mortality with an AUC of 0.501.

In predicting LOS, HbA1c (AUC = 0.568) provided similar results in comparison with the physiological scoring systems. The differences were not statistically significant (p = 0.688 to 0.714).

All tested physiological scores showed some predictive ability regarding LOS with WPSS (AUC = 0.594) being significantly superior to the other MEWS variants (MEWS1: AUC = 0.546, p = 0.009; MEWS2: AUC = 0.550, p = 0.035; MEWS3: AUC = 0.544, p = 0.009; PEWS: AUC = 0.547, p = 0.009) and CART (AUC = 0.588) reaching significance in comparison to MEWS1 (p = 0.043), MEWS3 (p = 0.035) and PEWS (p = 0.018). The predictive power of the Manchester Triage System was on the lower end with an AUC of 0.547 but not significantly different (p = 0.180 to 0.984).

For prediction of ICU transferral, HbA1c showed a positive correlation with an AUC of 0.525. This was not significantly different from the physiological systems (p = 0.077 to 0.830).

Here, the highest AUC was reached by MTS (AUC = 0.636), reaching significance in comparison with HbA1c (p = 0.001), CART (p = 0.003) and MEWS2 (p < 0.001).

In regard to predicting ICU transfer, among the physiological scoring systems WPSS (AUC = 0.587), PEWS (AUC = 0.589), MEWS1 (AUC = 0.587), and MEWS3 (AUC = 0.583) performed significantly better than MEWS2 (AUC = 0.501, p < 0.001 for WPSS, p = 0.001 for PEWS, p = 0.001 for MEWS1 and p = 0.001 for MEWS3), and CART (AUC = 0.534, p = 0.029 for WPSS, p = 0.018 for PEWS, p = 0.021 for MEWS1 and p = 0.035 for MEWS3).

4. Discussion

In this large prospective study, we examined a number of methods of triage and evaluation of severity of illness in emergency patients. We compared HbA1c levels as a potential new parameter to the MTS and several scoring systems based on physiological parameters.

We found that HbA1c correlated with LOS and need for intensive care in unselected medical emergency patients. This is in accordance with recent studies which linked glycated hemoglobin to adverse outcomes in cardiovascular [4] and neurovascular [5] events.

The predictive power of HbA1c-levels regarding LOS was on par with the other tested methods, outperforming five of the seven competitors, underlining its potential as a possible tool in the ED.

The results regarding ICU transferral showed a positive correlation with HbA1c-levels and their predictive power was not significantly different from the six tested physiological scoring systems. Only the MTS performed significantly better here.

None of the tested methods was clearly superior in predicting all of our three endpoints. Among the (M)EWS variants, WPSS was the most useful tool in predicting negative outcomes. The MTS provided mixed results.

Considering the complexity of the physiological scoring systems which are calculated using weighted conversions of four to six parameters, we deem these results as noteworthy for a single parameter.

Interestingly, the correlation between elevated HbA1c and mortality was rather poor (AUC = 0.501). With an overall mortality of only 3.1% relatively few patients fell

into this group. A group of patients overrepresented in this group had oncological diagnoses, often suffering from advanced disease. These patients tend to receive continous medical care and are as such unlikely to suffer from uncontrolled or undetected diabetes. This group of patients suffered high mortality (40.0% of deceased versus 13.0% of the overall cohort, data not shown), which may partly explain our results regarding the correlation of mortality and HbA1c-levels.

The relatively high prevalence of oncological diagnoses in our cohort may be a limiting factor with respect to the generalisability of our findings.

5. Conclusions

Our study showed that HbA1c levels correlate with clinical outcomes of emergency patients, largely comparable with established methods of triage like MTS and (M)EWS variants.

Determination of HbA1c may provide useful additional information to identify patients at risk and may be a candidate for inclusion into early warning systems in the form of point-of-care testing.

Our data suggests that this may prove helpful in improving accuracy. In our opinion, this should be the target of further study.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. At the time of data acquisition, the authors were employed at RoMed Clinical Centre Rosenheim, Pettenkoferstr. 10, 83022 Rosenheim, Germany, where the study was conducted.

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