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Glycemic Disturbances on Admission as a Predictor of Inpatient Mortality

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Abstract

Introduction: Our aim was to determine the influence of glycemic disturbances on admission in the emergency department (ED) on hospital mortality.

Methods: This is a case-control retrospective analytical study. The cases were patients deceased during hospitalization and controls where those discharged in the same time period. Patients were age-matched and the final outcome of the study was hospital mortality. Rapid Emergency Medicine Score (REMS) and Charlson comorbidity index as well as blood analysis (full blood count, glucose, renal function, ions) were determined. Abnormal glucose levels (dysglycemia) were those considered to be < 70 or > 200 mg/dl. We used logistic regression, integrated discrimination improvement (IDI) index and ROC curves to determine the predictive mortality capacity.

Results: 1153 patients were included in the study. Hyperglycemia was detected in 171 (14.8%) patients whilst hypoglycemia in 19 (1.6%) patients, with a prevalence of dysglycemia at 16.4%. The best model to predict hospital mortality included REMS (OR_{1point} = 1.09; CI 95% 1.033-1.15; p = 0.001), Charlson comorbidity index (OR_{1point} = 1.42; CI 95% 1.31-1.55; p < 0.001), hemoglobin ($OR_{1gr/dl}$ = 0.89; CI 95% 0.84-0.95; p < 0.001), thrombocytopenia (OR = 2.95; CI 95% 1.71-5.11; p < 0.001), leucocytosis (OR = 1.94; CI 95% 1.47-2.56; p < 0.001), diabetes mellitus (DM) (OR = 0.5; CI 95% 0.35-0.71; p < 0.001) and presence of dysglycemia (OR = 1.8; CI 95% 1.2-2.8; p = 0.005).

There was a significant improvement in the area under the ROC curve between the best predictive model chosen versus that including only the REMS score (0.522 vs 0.7478; p < 0.0001).IDI index after inclusion of dysglycemia was 0.00678 (p = 0.009).

Conclusions: The inclusion of dysglycemia in the mortality predictive scores increases its discrimination capacity in predicting hospital mortality.

Keywords

Hyperglycemia, Hypoglycemia, Diabetes, Hospital mortality

Introduction

The ED is the first and most important gateway of gravely ill patients with the aim to predict mortality. The REMS score [1,2] is composed of clinical variables, which include age, blood pressure, heart rate, oxygen saturation, respiratory rate, and Glasgow Come Score and is an invaluable tool in predicting mortality in the ED. However, other variables such as blood analyses are not included and may improve in predicting mortality outcome. As an example, the acute physiology and chronic health evaluation (APACHE) score used in patients in intensive care unit (ICU) in our country, incorporated analytical tests and demonstrated to be superior to its predecessor APACHE II [3] in measuring severity of disease and predicting mortality.

Abnormal glucose levels (dysglycemia), both hyper [4] and hypoglycemia [5], have been associated with an increase in hospital mortality. However, it is unclear whether it is an independent risk factor for mortality or a marker for underlying severe disease, as intensive glucose control has not demonstrate to reduce hospital mortality in critically ill patients in ICU [6], as well as those in general wards [7].

The aims of our study were:

1. To determine the importance of dysglycemia on admission as a marker of hospital mortality.
2. To evaluate whether adding glucose levels on admission to mortality predictive scores improves their discrimination capacity.
3. To determine whether the best predictive model for hospital mortality includes glucose levels.

Material and Methods

Study design

Retrospective analytical case-control study.

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Table 1: Patient characteristics according to initial serum glucose level.

	ALL	GLYCEMIA 70 - 200	GLYCEMIA < 70	p (< 70 vs 70 - 200)	GLYCEMIA > 200	p (> 200 vs 70 - 200)
Sex (% men)	55.5	55.3	68.4	ns	55	ns
Age (years)	77.3 (14.3)	77 (14.6)	71.4 (15.8)	ns	79 (12.5)	0.038
REMS	10 (2.8)	9.8 (2.8)	10 (3.2)	ns	10,9 (2.8)	< 0.001
Charlson	2.3 (2.1)	2.2 (2.1)	4.3 (2.6)	< 0.001	2,4 (1.9)	ns
Diabetes (%)	26.9	19.9	42.1	0.018	64.3	< 0.001
Na^+ (mEq/L)	139 (6.3)	139 (6.1)	140 (9.1)	ns	138 (7.1)	ns
K^+ (mEq/L)	4.5 (0.8)	4.5 (0.75)	4 (1.2)	ns	4.6 (1)	ns
Hemoglobin (g/dl)	12.2 (2.5)	12,1 (2.5)	10.8 (3.1)	0.031	12.6 (2.5)	0.008
Leucocytosis (%)	50.4	47.3	26.3	ns	70.6	< 0.001
Thrombocytopenia (%)	10.1	9.8	31.6	0.002	9.5	ns
Glomerular filtrate (ml/min)	57.2 (29.6)	58.6 (29.6)	51.7 (46.3)	ns	49.9 (26.1)	< 0.001

Patients

All patients (n = 650) who deceased during the hospitalizationin our hospital between the 1st of July and the 31st of December 2014 were collected as cases. 647 patients who were discharged in the same period were used as controls. Patients were age-matched.

Final outcome

Hospital mortality

Predictive variables

We collected the following variables in the ED:

- Clinical characteristics: sex, age, level of consciousness, blood pressure, heart rate, respiratory rate, oxygen saturation and temperature. With this information REMS score was calculated.
- Previous illnesses, including known DM, with Charlson comorbidity index calculation.
- Blood analysis: glucose, creatinine (with glomerular filtration rate determined using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation), ions, full blood count. We defined hyperglycemia as a glucose level > 200 mg/dl, and hypoglycemia as < 70 mg/dl. Dysglycemia was defined as the presence of hyper or hypoglycemia.

Laboratory methods

Serum glucose was determined using hexokinase enzyme method. Other laboratory parameters were determined using standardized auto-analyser.

Statistical method

Mean and standard deviation were determined for describing quantitative variables and frequency distribution was determined for describing qualitative variables. We used student T-test and Chi-square test respectively to compare data.

We calculated potential mortality risk factors using univariate and multivariate logistic regression analysis. We evaluated the contribution of dysglycemia in three models with progressive adjustment:

Model 1: REMS

Model 2: Model 1 + known diabetes, sex, sodium, potassium, glomerular filtration rate, hemoglobin, thrombocytopenia and leucocytosis.

Model 3: Model 2 + Charlson comorbidity index

Using the IDI index, we calculated the improved predictive mortality capacity of each predictive model with the addition of dysglycemia. Finally we determined the best predictive hospital mortality model using sequential backward exclusion procedure. We used the ROC curve analysis to calculate the difference of predictive power between the model including only REMS and the best predictive model. Statistically significant differences were defined as $p < 0.05$. We used the programs SPSS 22.0 and R 3.2.1 to extrapolate the data.

Results

Patient characteristics according to initial glucose level

We collected data from 1297 patients (650 cases and 647 controls). 144 of these did not have available initial glucose levels in ED resulting in their elimination from the study and leaving 1153 patient data for the analysis.

The patients excluded were younger (70.1 vs 77.3 years; $p < 0.001$), more frequently men (68.1 vs 55.5%; $p = 0.004$), they had lower percentage of leucocytosis (29.6 vs 50.4%; $p = 0.033$), and lower REMS score (8.2 vs 9.3; $p < 0.001$) and Charlson comorbidity index (1.4 vs 2.3; $p < 0.001$).

The commonest causes of admission to the ED were dyspnoea (17%) and fever (5.9%). We detected hyperglycemia on admission in 171 (14.8%) patients and hypoglycemia in 19 (1.6%) patients, resulting in a total prevalence of dysglycemia of 16.4%. Table 1 shows the patient characteristics classified by initial serum glucose levels. It is shown that those patients who presented with hypoglycemia had worse Charlson score, had lower hemoglobin levels, and were more likely to be diabetic and thrombocytopenic. Patients with hyperglycemia were more likely to be diabetic and elderly, have worse REMS score, have higher levels of hemoglobin and leucocytosis and have a lower glomerular filtration rate. In table 2 the differences between cases and controls are presented along with the univariate risk associated to

Table 2: Case and control characteristics.

	Controls	Cases	p	OR	IC 95%
Hypoglycemia (%)	0.8	2.4	0.032	3.16	1.04-9.6
Hyperglycemia (%)	11.9	17.3	0.01	1.56	1.1-2.2
Dysglycemia (%)	12.6	19.7	0.001	1.7	1.23-2.35
Sex (% men)	54.1	56.7	ns	1.1	0.9-1.4
Age (years)	77.9 (14.3)	76.8 (14.4)	ns	0.995	0.986-1.003
REMS	9.7 (2.7)	10.1 (2.9)	0.012	1.05	1.01-1.1
Charlson	1.54 (1.6)	2.9 (2.3)	< 0.001	1.44	1.34-1.55
Diabetes (%)	27	26.8	ns	0.99	0.76-1.3
Na^+ (mEq/L)	139 (5.1)	138 (7.1)	0.011	0.98	0.96-0.99
K^+ (mEq/L)	4.4 (0.65)	4.5 (0.91)	0.004	1.25	1.07-1.46
Hemoglobin (g/dl)	12.8 (2.2)	11.6 (2.7)	< 0.001	0.83	0.79-0.87
Leucocytosis (%)	42.9	56.6	< 0.001	1.74	1.37-.2
Thrombocytopenia (%)	4.4	14.8	< 0.001	3.7	2.3-6
Glomerular filtrate (ml/min)	60.8 (25.1)	54.3 (32.6)	< 0.001	0.992	0.989-0.996

Table 3: Prognostic influence of glycemic disturbances on admission with progressive adjustments for potencial confounding factors.

	Model 1	Model 2	Model 3
ALL			
Hyperglycemia	1.51 (1.08-2.13)	1.74 (1.14-2.67)	1.78 (1.15-2.75)
Hypoglycemia	3.37 (1.11-10.24)	2.6 (0.76-8.89)	1.88 (0.53-6.73)
Dysglycemia	1.62 (1.17-2.26)	1.83 (1.22-2.75)	1.81 (1.19-2.75)
NO DM			
Hyperglycemia	2.96 (1.6-5.5)	3.07 (1.47-6.43)	2.85 (1.36-5.97)
Hypoglycemia	9.27 (1.18-72.8)	3.57 (0.39-32.7)	2.94 (0.28-30.5)
Dysglycemia	3.38 (1.88-6.1)	3.1 (1.53-6.28)	2.83 (1.4-5.75)
Previous DM			
Hyperglycemia	1.1 (0.68-1.77)	1.1 (0.62-1.93)	1.18 (0.65-2.1)
Hypoglycemia	1.23 (0.28-5.45)	1.64 (0.34-7.96)	1.23 (0.24-6.41)
Dysglycemia	1.1 (0.69-1.76)	1.14 (0.66-1.97)	1.2 (0.68-2.1)

Model 1: dysglycemia + REMS.

Model 2: model 1 + previous DM, sex, sodium, potassium, glomerular filtrate, hemoglobin, thrombocytopenia y leucocytosis.

Model 3: model 2 + Charlson score.

Table 4: Improved IDI after addition of dysglycemia in the three models.

	Improved IDI	CI 95%	P value
ALL			
Model 1	0.00739	0.00251-0.01227	0.003
Model 2	0.00781	0.00254-0.01308	0.004
Model 3	0.00678	0.00172-0.01184	0.009
No DM			
Model 1	0.02152	0.01216-0.03088	< 0.0001
Model 2	0.01404	0.00628-0.02180	< 0.0001
Model 3	0.01080	0.00356-0.01804	0.004
Previous DM			
Model 1	0.00047	(-0.00208)-0.00302	0.718
Model 2	0.00083	(-0.00253)-0.00418	0.628
Model 3	0.00149	(-0.00296)-0.00594	0.509

Model 1: addition of dysglycemia to REMS.

Model 2: addition of dysglycemia to REMS, DM, sex, sodium, potassium, glomerular filtrate, hemoglobin, thrombocytopenia, and leucocytosis.

Model 3: addition of dysglycemia to REMS, DM, sex, sodium, potassium, glomerular filtrate, hemoglobin, thrombocytopenia, leucocytosis, and Charlson score.

each variable. Patients who died had a higher prevalence of hyper, hypo and dysglycemia, higher REMS and Charlson scores, lower glomerular filtration rate, higher potassium and lower sodium levels, and greater alterations in the full blood count.

Evaluating dysglycemia as a marker for hospital mortality

In the total sample it was shown that hyperglycemia, as well as hypoglycemia and dysglycemia, were associated with an increased risk of mortality. However, although hyperglycemia and dysglycemia were independent predictors for mortality in the adjusted analysis (Table 3), hypoglycemia lost the statistical significance after the adjustment for variables included in the models 2 and 3.

The interaction between dysglycemia and DM was significant (p = 0.006) so we undertook stratified analysis for this variable (Table 3), which showed that hyperglycemia and dysglycemia were independent predictive mortality markers for non-diabetic patients but not for known diabetics.

Discriminative analysis

We used the IDI index to determine whether dysglycemia could improve the power of discrimination in the three models described in the material and methods section. In the total sample of patients and in those without a history of DM, information about the presence of dysglycemia on admission improved the predictive capacity of hospital mortality in all three models (Table 4).

Selecting the best predictive model

From the total sample we determined that the best model for predicting hospital mortality was that including REMS (OR_{1point} = 1.09; CI 95% 1.033-1.15; p = 0.001), Charlson comorbidity index (OR_{1point} = 1.42; CI 95% 1.31-1.55; p < 0.001), hemoglobin ($OR_{1gr/dl}$ = 0.89; CI 95% 0.84-0.95; p < 0.001), thrombocytopenia (OR = 2.95; CI95% 1.71-5.11; p < 0.001), leucocytosis (OR = 1.94; CI 95% 1.47-2.56; p < 0.001), DM (OR = 0.5; CI 95% 0.35-0.71; p < 0.001) and presence of dysglycemia (OR = 1.8; CI 95% 1.2-2.8; p = 0.005).

There was a significant improvement in the area under the ROC curve between the best predictive model chosen and that including only the REMS score (0.522 vs 0.7478; p < 0.0001) as show in figure 1.

Discussion

In this study we have showed that the presence of dysglycemia (hyper or hypoglycemia) on admission in the ED is a marker for increased risk of hospital mortality. It improves the discriminative ability of a clinical validated model (REMS) and of an expanded model with clinical and analytical variables. However, this prognostic marker on arrival to the ED is most significant, clinically and statistically, in those patients without a history of DM. Additionally, we showed that a model with inclusion of clinical and analytical variables (REMS, Charlson comorbidity index, dysglycemia, full blood count, DM), improves the capacity to predict hospital mortality respect to REMS.

The first predictive mortality scales were used in medical and surgical patients within the ICU such as the APACHE [8] with its modifications over the years [9], which is based on clinical variables, age, previous general health and laboratory markers. Further on, other specific scales started to appear for trauma patients [10], for patients with sepsis (Mortality in Emergency Department Sepsis score) [11], acute coronary syndrome [12], asthma [13], and pneumonia [14]. Additionally, these tools expanded for the use in the ED such as the rapid acute physiology score (RAPS) [15] and REMS which improved the RAPS predictive capacity by incorporating oxygen saturation and age into the marking scheme [1]. For this reason we decided to use

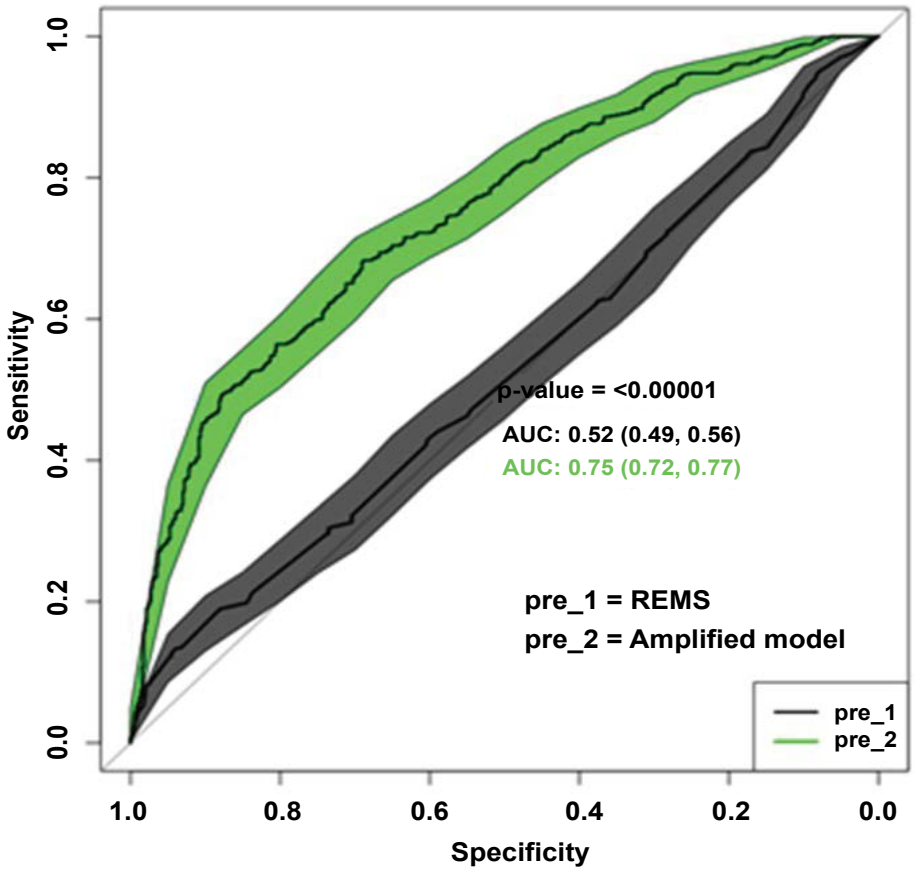

Figure 1: Curve ROC comparison predicting hospital mortality between REMS vs amplified model with REMS, Charlson comorbidity index, DM, dysglycemia, and full blood count disturbances.

the REMS scoring scheme for our sample on arrival at the ED and hypothesized that the addition of accessible and rapid analytical tests, including glucose levels, would improve its discrimination capacity as did the APACHE IV scale with its predecessor APACHEII [3].

The onset of hyperglycemia in hospitalized patients is an indicator of a bad prognosis and has been associated to increase the mortality in critically ill patients [16], patients with cardiac ischemia [17], pneumonia [18], and stroke [19]. It is believed that this is due to altered immune, endothelial, and cardiac functions with levels above 200 mg/dl [20]. However, the fact that hyperglycemia is associated with a poorer prognosis in non-diabetic patients [4] in comparison with known diabetics, and the fact that intensive glucose control does not improve the mortality outcome in hospitalized patients [6,7] may indicate that the initial hyperglycemia in the ED is a marker of disease severity rather than a direct cause of mortality. In our study patients with hyperglycemia tended to have signs of more severe disease and the effect of the hyperglycemia was only significant in non-diabetic patients, which would support it as a marker of acute stress.

Similarly, conclusions of increased hospital mortality associated with hypoglycemia [21] have been reported, and there are plausible pathophysiological mechanisms that could explain this relationship [22]. Nevertheless, this effect is less marked in insulin-induced hypoglycemia [5,23] than in spontaneous hypoglycemia, which would again indicate it as a marker of disease severity. In our study, as in others [23], patients with hypoglycemia had worse Charlson scores and an increased risk in mortality. The absence of an independent effect in multivariate analysis and the effect more marked in patients without known DM, would strengthen the role of hypoglycemia as a marker of global health.

Given the fact that both hyper and hypoglycemia have shown in other case-control studies to increase hospital mortality [24] as well as in our own, we evaluated whether this effect exists with the combined effect of dysglycemia i.e. to include both hyper and hypoglycemia. We found that the dysglycemia was included in the best predictive model made up of clinical and analytical variables, which improved significantly the discrimination capacity in predicting hospital mortality.

The strengths of our study were the inclusion of an ample sample of deceased hospital patients, age-matching patients to eliminate confounding factors, and the addition of analytical tests to predictive mortality scales. Weaknesses include the retrospective and observational nature of the study, which may limit the possibility to reach causal inferences. Additionally, the limited number of patients with hypoglycemia on admission, and the lack of other variable may have dampened the predictive importance of hyperglycemia, such as C-reactive protein. Finally, data about the influence of body mass index or previous impaired fasting glucose are not available.

In conclusion, the addition of the Charlson comorbidity index and analytical variables to the REMS score, improves the predictive capacity of hospital mortality. Among the included variables we stress the importance of glucose levels on admission in the ED due to its easy and rapid access which when incorporated into mortality prediction scales improves their discrimination capacity, especially in non-diabetic patients.

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