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The classification of hospitalized patients with hyperglycemia and its implication on outcome: results from a prospective observational study in Internal Medicine

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Abstract The relevance of classifying hyperglycemic hospitalized subjects (HS) as known diabetes (D), newly discovered diabetes (ND), and stress hyperglycemia (SH) is unclear. The aim of this study was to determine the prevalence, in-hospital mortality, and length of stay (LOS) of three different phenotypes of HS. Fasting glucose ≥126 mg/dL (7 mmol/L) or random blood glucose ≥200 mg/dL (11.1 mmol/L) defined HS who were categorized into three groups: D; ND (no history of diabetes and HbA1c ≥48 mmol/mol); SH (no history of diabetes and HbA1c <48 mmol/mol). The end points of the study were in-hospital mortality and LOS. Of 1447 consecutive enrolled subjects, the prevalence of HS was 28.6 % (415/1447), of these 71.6 % had D, 21.2 % SH, and 7.2 % ND, respectively. In-hospital death was 3.9 % in normoglycemic and 6.0 % in hyperglycemic subjects. Individuals with SH had an increased risk of in-hospital death (7.9 %) (HR 2.17, 95 % CI 1.18–4.9; $p = 0.039$), while this was not observed for D and ND patients. The mean LOS was greater in ND and SH subjects. Hyperglycemia is common, and is associated with an increased risk of in-hospital mortality and extension of hospital stay. HbA1c along with clinical history is a useful tool to identify subgroups of hyperglycemic hospitalized subjects. Individuals with SH have a longer LOS, and a double risk of in-hospital mortality. Additionally, identifying previously unknown diabetes represents a remarkable opportunity for prevention of diabetes-related acute and chronic complications.

Keywords Hyperglycemia · Glycated hemoglobin · Diabetes mellitus · Stress hyperglycemia

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Introduction

Hyperglycemia is a condition frequently encountered in daily practice with hospitalized patients. It is estimated that nearly 25–35 % of admitted patients are hyperglycemic [1, 2]. Several studies have shown that hyperglycemia is associated with poor outcomes and extended hospital stay in patients hospitalized for various conditions and in different settings (i.e. coronary care and intensive care units, post-operatively) [3–9]. Moreover, these observations are not confined to diabetic patients, but are extended to individuals without a known history of diabetes [10–12]. Even though most prospective trials investigating the impact of hyperglycemia on clinical outcomes have been carried out in critically ill patients, there are data supporting the importance of hyperglycemia among non-critically ill hospitalized patients. In such cases, hyperglycemia is associated with prolonged hospital stay, increased incidence of infections, further disability after hospital discharge and increased death rate [2, 13–18]. Umpierrez and co-workers in a large retrospective cohort report that newly discovered hyperglycemia (i.e. patients without a history of diabetes) is a strong, independent predictor of in-hospital mortality [2]. Nevertheless, data are lacking regarding the prevalence and significance of hyperglycemia in unselected patients admitted to Internal Medicine units. In addition, the three proposed categories

of hospital hyperglycemia based on the history of diabetes and values of glycated hemoglobin (HbA1c), known diabetes, newly discovered diabetes, and stress hyperglycemia have not been studied in that setting, and their relevance to in-hospital outcome has not been addressed. Thus, the aim of this study was to determine the prevalence, in-hospital mortality, and length of stay in a cohort of hyperglycemic patients according to different classifications in three Internal Medicine units of a large community hospital.

Setting, patients, and methods

This was a prospective, observational, non-interventional study carried out in three Internal Medicine units with a total of 97 beds, of the University and General Hospital of Careggi, Florence, Italy. All consecutive adult patients admitted to the units between November 1st 2013 and April 30th 2014 were enrolled. Individuals were hospitalized through the Emergency Department (ED) for acute medical conditions. Patient information was collected regarding demographic characteristics, medical history, blood glucose (BG) levels on admission and during hospital stay, HbA1c (Bio-rad variant II dual kit, Biorad laboratories Inc., California, USA), concurrent medical diagnoses, medical treatment for glucose control, length of stay, and in-hospital mortality. Systematic assessment of BG level by blood sample on admission was a routine procedure for patients evaluated in the ED (random sample), and on the first morning after admission (fasting glucose sample) for all admitted patients. During hospitalization four daily glucose measurements (three fasting pre-prandial blood glucose and one post-prandial 2 h after evening meal) by bedside capillary blood glucose monitoring (Accu-chek inform II, Roche diagnostics Gmbh, Mannheim, Germany) were performed on patients with hyperglycemia. The results obtained through glucometers were centralized to the core clinical chemistry laboratory and the laboratory staff performed periodical quality and accuracy control of the devices [19]. Hypoglycemia was defined as the presence of BG level <70 mg/dL, whereas severe hypoglycemia was defined by the presence of BG level <40 mg/dL or hypoglycemia with neurological manifestations or requiring medical intervention.

The modified early warning score (MEWS), that explores the body temperature, respiratory rate, cardiocirculatory functions, and neurologic systems, was recorded for each patient [20, 21].

The study protocol was approved by the local ethics committee, and all subjects gave an informed consent to participate in the study. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Definition of in-hospital hyperglycemia and its categories

According to international guidelines [22], hyperglycemia is defined as an admission or in-hospital fasting glucose ≥126 mg/dL (7 mmol/L) on two or more determinations, or a random blood glucose ≥200 mg/dL (11.1 mmol/L) [10–12]. For the purpose of the study, patients not matching the criteria of hyperglycemia were defined as normoglycemic. Notably, in all hyperglycemic patients, an HbA1c was evaluated to discriminate patients with stress hyperglycemia from those with previously undiagnosed diabetes. Categories of hyperglycemic patients were then defined as follows:

(a) diabetics (D): patients with a well-documented history or on medications for diabetes mellitus;
(b) newly discovered diabetics (ND): patients without a known history of diabetes, and with a value of HbA1c on admission ≥48 mmol/mol (≥6.5 %);
(c) stress hyperglycemia (SH): patients without a known history of diabetes, and with a value of HbA1c on admission <48 mmol/mol (<6.5 %).

End points of the study

All patients were followed during hospitalization to evaluate the occurrence of death and its causes. The primary end point of the study was in-hospital mortality; the secondary end point was length of hospital stay.

Statistical analysis

Data were expressed as mean ± standard deviation or as proportions. In general, statistical comparisons were performed using Student's *t* test and one-way ANOVA models for the comparison of continuous normally distributed variables and Mann–Whitney *U* test for continuous not normally distributed variables. The Chi-square test or Fisher's exact test was used for the comparison of categorical variables. Relative association (OR) of variables with predefined outcome measures and 95 % CI were calculated using univariate logistic regression analysis, the reference group was that of normoglycemic patients. A logistic regression analysis with LOS and mortality as dependent variables was performed including age of subjects as a proportional variable, considering age tertiles (19–70, 70–81, 82–100 years). All *p* values were two-tailed and considered significant when <0.05 (95 % CI).

All analyses were performed using 21.0 SPSS statistical software (SPSS, Chicago, Illinois).

Results

During the study period, in which 1447 patients were enrolled, the incidence of hyperglycemia was 28.6 % (415/1447) of all admitted patients in that time frame. The main demographic and clinical characteristics of normoglycemic and hyperglycemic patients, shown in Table 1, were similar. In general, the age was advanced, both genders were similarly represented and the prevalence of comorbidities was high, with a prevalence of three or more, in roughly 74 % of the population. Hyperglycemic patients were largely represented by diabetes in 71.6 %, followed by stress hyperglycemia 21.2 % and newly discovered diabetes 7.2 %. The prevalence of 3 or more comorbidities including cardiovascular disease was significantly higher in patients of the groups D and ND with respect to group SH and to normoglycemic patients. The primary reasons for admission were community acquired pneumonia, acute or acutely de-compensated congestive heart failure, sepsis, and acute exacerbations of chronic obstructive pulmonary disease, not differing substantially among groups (Table 1). The mean MEWS calculated on admission did not differ among groups ($p = 0.181$, Table 1). Mean BG levels at different intervals were significantly higher in patients of the groups D and ND with respect to group SH (Table 2). As expected, patients with SH had significantly lower HbA1c values than the other two groups of hyperglycemic patients (Table 2). During hospitalization 383 patients (92.1 %) were on insulin therapy, of which number: 209 patients (67.9 %) were treated with a basal bolus regimen, 56 patients (18.2 %) with a sliding scale regimen, and 42 patients (10 %) with only basal or basal plus regimen. The proportions of the scheme of treatment did not differ among the three groups. Only one individual was treated with an intravenous insulin infusion.

The average capillary BG values during in-hospital stay differed among groups, being more elevated in the group D than in ND and SH, respectively (Table 2).

Total hypoglycemic events occurred in nearly 15 % of the population, present mainly in known or newly discovered diabetic patients (Table 2). Severe hypoglycemia was infrequent, occurring in roughly 2 % and was confined to diabetic patients. Only one episode of hypoglycemia occurred in the group of normoglycemic patients. It was a spontaneous, severe episode without consequences, occurring in a patient with advanced liver cirrhosis.

Overall in-hospital death occurred in 40 normoglycemic patients (3.9 %) and in 25 hyperglycemic patients (6.0 %). Of these, 17 patients (5.7 %) died in the D group, 7 (7.9 %) in the SH group, and 1 (3.3 %) in the ND group. Causes of death were mainly infectious and cardiovascular diseases (Table 3). Sepsis was the most frequent cause of death in patients with hyperglycemia with respect to normoglycemic patients (Table 3).

Among several clinical and laboratory variables shown in Tables 1 and 2, also considered for the univariate logistic regression analysis, hyperglycemia was associated with an increased risk of in-hospital death with respect to the normoglycemic population (OR 1.72, 95 % CI 1.02–2.89; $p < 0.041$). Moreover, among hyperglycemic patients only, those with stress hyperglycemia had an increased risk of in-hospital death (OR 2.17, 95 % CI 1.18–4.9; $p = 0.039$) compared to the normoglycemic subjects, while this was not observed for diabetics (D group OR 1.59, 95 % CI 0.9–2.81; $p = 0.11$).

There was no influence of age, included in the analysis as age tertiles (19–70, 71–80, 82–100 years), on mortality at univariate regression logistic analysis.

Hypoglycemia was related with an increased risk of in-hospital death (OR 3.45, 1.47–8.10; 95 % CI, $p = 0.004$). This result, however, was statistically significant only for diabetic patients (OR 3.40, 1.26–9.20 95 % CI, $p = 0.016$), and not for patients with stress hyperglycemia (OR 6.08, 0.93–39.60 95 % CI, $p = 0.06$). Causes of death in patients with hypoglycemia were mainly cardiovascular ($n = 3$) and sepsis ($n = 4$), with an additional case of advanced cancer in the D group. Sepsis and cerebral hemorrhage were the causes of death in two patients in the SH group.

The mean length of hospital stay was nearly 10 days (median 8 days), and was greater in the group of patients with ND and SH with respect to diabetics and to normoglycemics (Table 3). No influence of age on hospital stay duration was detected at univariate logistic regression analysis included in the analysis as age tertiles. In general, hyperglycemic patients did not have a greater probability of being hospitalized more than 7 days with respect to normoglycemic patients (OR 1.45, 95 % CI 0.83–1.31; $p < 0.001$). Nonetheless, patients with stress hyperglycemia had a greater probability of being hospitalized for more than 7 days (SH group OR 1.8, 1.103–2.96, $p = 0.014$), while this was not observed for the other groups of patients with hyperglycemia (D group OR 0.56, 0.26–0.87 95 % CI, $p = 0.009$; ND group OR 1.29, 0.61–2.72 95 % CI, $p = 0.50$). The occurrence of hypoglycemic events was not associated with an increased probability of hospital stay longer than 7 days (OR 0.92, 95 % CI 0.56–1.53; $p = 0.756$).

Discussion

In this study we report the prevalence and outcome of in-hospital hyperglycemia and its subtypes (known diabetes, newly diagnosed diabetes, and hospital-related or stress

Table 1 Demographic and clinical characteristics of the study population

	Normoglycemic patients ($n = 1032$)	All hyperglycemic patients ($n = 415$)	Diabetes ($n = 297$)	Newly discovered diabetes ($n = 30$)	Stress hyperglycemia ($n = 88$)
Age, mean ± SD (years)	75.8 ± 11.3	76.0 ± 11.1	76.3 ± 10.3	76.6 ± 12.6	75.6 ± 13.6
Male, *n* (%)	496 (48.1 %)	201 (48.4 %)	151 (50.8 %)	15 (50.0 %)	35 (39.8 %)
European ethnicity, *n* (%)	1005 (97.4 %)	409 (98.5 %)	292 (98.3 %)	30 (100 %)	87 (98.9 %)
BMI, mean ± SD (kg/m^2)	25.4 ± 5.3	26.3 ± 4.9	26.5 ± 5.1	26.6 ± 4.4	25.3 ± 4.5
Smoking habit, *n* (%)	507 (49.1 %)	204 (49.2 %)	143 (48.1 %)	18 (60.0 %)	44 (50.0 %)
Artificial nutrition, *n* (%)	52 (5.1 %)°	55 (13.2 %)	37 (12.5 %)	3 (10 %)	15 (17.1 %)
Enteral feeding	34 (3.3 %)	37 (8.9 %)	28 (9.4 %)	2 (6.7 %)	7 (8.0 %)
Parenteral	18 (1.8 %)	18 (4.3 %)	9 (2.2 %)	1 (0.3 %)	8 (9.1 %)
Comorbidities, *n* (%)					
Diabetes	–	297 (71.6 %)	297 (100 %)	–	–
Hypertension	746 (72.3 %)	309 (74.5 %)	23 (77.8 %)	25 (83.3 %)^	53 (60.2 %)*
Dyslipidemia	284 (27.5 %)	137 (33.0 %)	115 (38.7 %)	8 (26.7 %)	14 (15.9 %)*
COPD	376 (36.4 %)	140 (33.7 %)	98 (33.0 %)	9 (30.0 %)	33 (37.5 %)
CAD	220 (21.3 %)°,¶	130 (26.3 %)	108 (36.4 %)	7 (23.3 %)	15 (17.0 %)*
Chronic heart failure	302 (29.3 %)	139 (33.5 %)	114 (38.4 %)	3 (10.0 %)*,^	22 (25.0 %)#
Chronic kidney disease	183 (17.8 %)°,¶	109 (26.3 %)	88 (29.6 %)	7 (23.3 %)	14 (15.9 %)#
Peripheral artery disease	119 (11.6 %)°,¶	81 (19.5 %)	70 (23.6 %)	4 (13.3 %)	7 (8.0 %)*
Stroke/TIA	95 (9.2 %)°,¶	72 (17.3 %)	56 (18.9 %)	6 (20.0 %)	10 (11.4 %)#
Cognitive impairment	165 (15.9 %)°,¶	84 (20.2 %)	65 (21.9 %)	4 (13.3 %)	15 (17.0 %)
Cancer (active or previous)	185 (17.9 %)	83 (20.0 %)	59 (19.9 %)	8 (26.7 %)	16 (18.2 %)
>3 comorbidities§	590 (57.2 %)°,¶	306 (73.7 %)	255 (85.9 %)	17 (56.7 %)*,^	34 (38.6 %)*
Main reasons for hospital admission, *n* (%)					
Pneumonia	203 (19.7 %)	83 (20.0 %)	53 (17.8 %)	6 (18.2 %)	24 (27.3 %)
Heart failure	188 (18.3 %)	69 (16.6 %)	58 (19.5 %)	1 (3.0 %)	10 (11.4 %)
Sepsis	101 (9.8 %)	48 (11.6 %)	37 (11.5 %)	3 (10 %)	8 (9.1 %)
AECOPD	125 (12.1 %)	41 (9.9 %)	25 (8.4 %)	6 (18.2 %)	10 (11.4 %)
Stroke/TIA	42 (4.1 %)	24 (5.8 %)	19 (6.4 %)	–	5 (5.7 %)
Active cancer	60 (5.8 %)	22 (5.3 %)	17 (5.7 %)	–	–
Urinary tract infection	33 (3.2 %)	16 (3.9 %)	12 (4.0 %)	1 (3.0 %)	3 (3.4 %)
MEWS, mean ± SD	2.7 ± 1.8	2.8 ± 1.9	2.8 ± 1.2	2.9 ± 2.1	2.3 ± 1.4

SD standard deviation, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CAD* coronary artery disease, *TIA* transient ischemic attack, *HF* heart failure, *AECOPD* acute exacerbation of chronic obstructive pulmonary disease, *MEWS* modified early warning score

* $p < 0.001$ vs diabetes

° $p < 0.005$ vs hyperglycemic patients

¶ $p < 0.005$ vs diabetes

# $p < 0.05$ vs diabetes

^ $p < 0.05$ vs stress hyperglycemia

§ Including diabetes

hyperglycemia) in a cohort of patients consecutively admitted to three internal medical wards. Hyperglycemia subtypes were classified according to definite criteria with use of clinical history and HbA1c values on admission [22, 23]. All the available studies on this topic in the setting of Internal Medicine units were unable to clearly characterize patients with hospital-related hyperglycemia mainly due to the lack of HbA1c determinations [3–18]. To the best of our knowledge, this is the first study exploring the prevalence and prognostic significance of classifying hyperglycemic patients admitted to Internal Medicine units. Differentiating patients with stress hyperglycemia from those with newly discovered diabetes may have implications for the future of the patient allowing earlier diagnosis and treatment, to prevent the development of acute and chronic complications of diabetes.

Table 2 Laboratory findings, average daily blood glucose values, and hypoglycemic events during hospitalization

	All hyperglycemic patients ($n = 415$)	Diabetes patients ($n = 297$)	Newly discovered diabetes patients ($n = 30$)	Stress hyperglycemia ($n = 88$)	p
Hemoglobin A1c, mean ± SD					
(mmol/L)	53.1 ± 14.1	64.2 ± 9.6	59.2 ± 9.9	41.5 ± 4.5	<0.001*,§
(%)	7.0 ± 3.4	8.0 ± 3.0	7.6 ± 3.1	5.9 ± 1.6	
CrCl, mean ± SD (mg/dL)	64.9 ± 40.9	61.5 ± 33.7	66.4 ± 27.7	69.4 ± 37.5	0.83
Average daily blood glucose (1st day), mean ± SD (mg/dL)	160 ± 58	166 ± 61	155 ± 41	137 ± 43	<0.001*,§
Average daily blood glucose (2nd day), mean ± SD (mg/dL)	154 ± 56	162 ± 56	155 ± 64	126 ± 39	<0.001*,§
Average daily blood glucose (3rd day), mean ± SD (mg/dL)	157 ± 55	166 ± 56	150 ± 54	127 ± 43	<0.001*,§
Average daily blood glucose (4th day), mean ± SD (mg/dL)	156 ± 49	163 ± 49	146 ± 41	129 ± 40	<0.001*,§
Average daily blood glucose (discharge day), mean ± SD (mg/dL)	138 ± 50	153 ± 58	136 ± 44	113 ± 40	0.005*,§
Hypoglycemia (n, %)	63, 15.2 %	55, 18.5 %	4, 13.3 %	4, 4.5 %	0.006*
Severe hypoglycemia (n, %)	8, 1.8 %	7, 2.4 %	1, 3.3 %	0	0.312

SD standard deviation, *CrCl* creatinine clearance calculated by modification of diet in renal disease (MDRD) formula

* Diabetes vs newly discovered diabetes and stress hyperglycemia

§ Newly discovered diabetes versus stress hyperglycemia

Table 3 In-hospital death and length of hospitalization

	Normoglycemic patients ($n = 1032$)	All hyperglycemic patients ($n = 415$)	Diabetes ($n = 297$)	Newly discovered diabetes ($n = 30$)	Stress hyperglycemia ($n = 88$)
In-hospital death (n, %)	40 (3.9 %)*	25 (6.0 %)	17 (5.7 %)	1 (3.3 %)	7 (7.9 %)
Causes of death (n, %)					
Stroke	4 (0.4 %)	2 (0.5 %)	1 (0.3 %)	–	1 (1.1 %)
Cardiovascular	12 (1.2 %)	7 (1.7 %)	5 (1.7 %)	–	2 (2.3 %)
Sepsis	15 (1.4 %)	13 (3.1 %)	8 (2.7 %)	1 (3.3 %)	4 (4.5 %)
Cancer end-stage	9 (0.9 %)	3 (0.7 %)	3 (1 %)	–	–
Length of stay (days, mean ± SD)	9.1 ± 6.1#	9.9 ± 7.0	8.8 ± 6.4#	11.9 ± 9.2	10.8 ± 7.6

* $p < 0.05$ normoglycemia versus all hyperglycemic patients, diabetes or stress hyperglycemia

# $p < 0.05$ normoglycemic patients or diabetes versus newly discovered diabetes or stress hyperglycemia

In this prospective study on unselected acute medical ill patients admitted to Internal Medicine wards, we found that hyperglycemia was common; affecting nearly one out of three admitted patients. The in-hospital mortality of patients with hyperglycemia (6.0 %) was 1.5 times higher than that of patients with normoglycemia (3.9 %). Moreover, when hyperglycemia was classified according to clinical history and HbA1c values in three subtypes, diabetic patients represented the considerable majority (72 %), followed by a significant number of patients with stress hyperglycemia (21 %) and a minority with newly discovered diabetes at the time of hospitalization (7 %).

In our study population, we found that patients with stress hyperglycemia had higher in-hospital crude mortality (7.9 %) than those with diabetes (5.7 %) or those with normoglycemia (3.9 %). Nevertheless, at univariate logistic regression analysis, only patients with SH had a significant risk increase of in-hospital death and the presence of SH was related to a twofold risk increase of in-hospital mortality (HR 2.17, 95 % CI 1.18–4.9; $p = 0.039$) when compared to other hyperglycemic groups. Hospital-related hyperglycemia has been considered for many years a paraphenomenon of concurrent illness and hospitalization, and consequently has largely been neglected. In the last decade several papers address the prognostic significance of hyperglycemia in different settings and syndromes, describing a negative relationship between hyperglycemia and outcome [2–12]. Umpierrez et al. in a large

retrospective study report that total mortality in patients admitted outside the intensive care unit is fivefold higher in patients with newly discovered hyperglycemia (10 %) than in diabetic patients (1.7 %) [2]. However, because of the lack of HbA1c determinations, the authors were unable to discriminate patients with unrecognized diabetes from those with transient stress hyperglycemia among those with newly discovered hyperglycemia.

Interestingly, the mean length of hospital stay is longer in the group of patients with ND and SH with respect to diabetics and normoglycemics. However, only patients with stress hyperglycemia have a statistically significant increase in the probability of being hospitalized for more than 7 days (HR 1.40, 95 % CI 1.31–3.51; $p < 0.0001$). The 7 day cut-off was chosen because it represented the ordinary average length of hospitalization in the unselected population of patients admitted to the three units during years 2012 and 2013, and was the average length of stay for all hospitalized medical patients in Tuscany [24].

In general, patients with stress hyperglycemia have lower mean BG values during hospitalization than those with known or newly discovered diabetes (Table 2) despite a worse outcome. This seems to support the hypothesis that new hyperglycemia represents a marker of a more severe illness, and it is likely not the primary cause of increased morbidity and mortality. Although the exact reasons are not completely understood, several potential mechanisms responsible for hyperglycemia in conditions of stress have been proposed, including: insulin resistance in peripheral tissues, increased lactate availability in critical conditions, and increased gluconeogenesis and decreased glycogenolysis due to amplified secretion of cortisol, catecholamines, and glucagon, physiologically counteracting the effects of insulin [25–29, 11, 30, 31]. Even though morbidity and mortality are directly related to the disease process, hyperglycemia itself may contribute to morbidity by direct cellular toxicity [32–34]. In experimental models, severe hyperglycemia has been shown to have deleterious effects on the vascular, hemodynamic, and immune systems [35, 36]. These modifications may lead to increased morbidity, susceptibility to infections, and extension of hospital stay, effects that were also evident in this cohort.

The occurrence of hypoglycemia is associated with an increased risk of in-hospital death. The probability of dying during hospitalization is nearly 3 times higher in patients with at least one episode of hypoglycemia than in those without (HR 3.45, 1.47–8.10 95 % CI, $p = 0.004$). This finding, however, is relevant only for diabetic patients (HR 3.40, 1.26–9.20 95 % CI, $p = 0.016$), and does not reach statistical significance for patients with stress hyperglycemia or newly discovered diabetes. These findings are probably confined to known diabetics because the largest number of hypoglycemic episodes occurred in that group. Hypoglycemia is known as a poor prognostic factor associated with increased hospital mortality, and there are several mechanisms by which hypoglycemia may lead to increased mortality. These are: impairment of autonomic function, alteration of blood flow and composition, white-cell activation, the release of inflammatory mediators and cytokines, and catecholamines may induce vasoconstriction and dysrhythmias [37–39]. An alternative explanation is that hypoglycemia occurs as a result of the disease processes, representing a marker rather than a cause of increased risk of death, especially in those patients with spontaneous hypoglycemic events [40, 41].

There are some study limitations, the most relevant being that HbA1c may have some drawbacks in hospitalized patients due to the decreased sensitivity in diagnosing diabetes in patients with anemia, treated with dialysis, blood transfusions or erythropoietin therapy, even though the specificity of the test remains elevated [42]. A second limitation of the study is the lack of follow-up after hospital discharge, which may preclude the awareness of later outcome and knowledge regarding the proportion of patients with stress hyperglycemia ultimately developing diabetes.

However, this last limitation is probably less relevant since most patients identified as SH had near normalization of BG values before discharge (Table 2).

In summary, hyperglycemia is a frequent condition occurring in roughly one-third of acutely ill patients admitted to Internal Medicine units determining the increased risk of in-hospital mortality. HbA1c is a useful tool to correctly identify subgroups of hyperglycemic patients in the hospital. The identification of subgroups of hyperglycemic patients may have prognostic implications: patients with stress hyperglycemia have a longer average hospital stay and nearly a twofold risk increase of in-hospital mortality, although it remains unresolved whether stress hyperglycemia is a determinant rather than a marker of increased morbidity and mortality in acutely ill patients. Furthermore, identifying previously unknown diabetes has relevant therapeutic implications and represents a great opportunity for prevention of diabetes-related acute and chronic complications.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the

ethical standards of the institutional or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the patients for publication of the article.

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