Predictors of In-Hospital Mortality after Acute Ischemic Stroke in Subjects with and without Diabetes Mellitus

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Abstract: *Background*: Diabetes mellitus is a well-established risk factor for ischemic stroke and is associated with increased in-hospital mortality. The aim of the present study was to determine the potential predictors of in-hospital mortality after an ischemic stroke in diabetic and nondiabetic subjects.

Methods: 159 diabetic subjects (66 males / 93 females, mean age ± SD: 77.4 ± 6.4 years) and 159 non diabetic subjects (66 males / 93 females, mean age ± SD: 77.3 ± 5.2 years) hospitalized for ischemic stroke were studied. Demographic characteristics and laboratory tests on admission as well as outcome were recorded. Brain computed tomography scan was performed in all study subjects.

Results: In-hospital death rates did not differ between the diabetic and the nondiabetic patients [36 (22.6%) vs. 27 (17.0%), respectively, P = 0.20]. In the diabetic study group multivariate analysis, after controlling for CRP, total cholesterol, LDL-C, urea and creatinine levels, demonstrated that death was related with WBC count (OR: 1.002, 95% CI: 1.001-1.004, P = 0.005), glucose levels (OR: 1.007, 95% CI: 1.002-1.012, P = 0.008), and UA levels (OR: 1.51, 95% CI: 1.003-2.260, P = 0.05). In the nondiabetic study group, after controlling for WBC count, CRP, total cholesterol and LDL-C levels, death was related only with glucose levels (OR: 1.016, 95% CI: 1.001-1.031, P = 0.03).

Conclusions: WBC count and UA levels on hospital admission are independent predictors for in-hospital mortality in diabetic subjects with ischemic stroke. Plasma glucose levels are predictor for in-hospital mortality in both diabetic and nondiabetic subjects.

INTRODUCTION

It is well established that diabetic patients suffer often from macrovascular complications [1] while cardiovascular morbidity and mortality is particularly common in this group of patients [2]. A lot of studies have shown that diabetes mellitus (DM) is a major risk factor for increased mortality after acute ischemic stroke [3, 4] as well as after intracerebral hemorrhage [5]. Interestingly, a recent study showed that unknown diabetes is a strong risk factor for in-hospital mortality in subjects with acute ischemic stroke [6].

Studies in the general population have showed the predictive significance for increased mortality after acute stroke of different factors, including increased age [7], presence of DM [8], atrial fibrillation [9], increased hematocrit, leukocytosis [10], and hyperglycemia [11]. Studies, such as above, might help to determine factors influencing the outcome in subjects hospitalized for acute stroke. Therefore, the identification of predictors for in-hospital mortality might contribute to reduce death rates after acute stroke by enhancing the application of specific therapeutic strategies to the patients. However, the existing literature data, regarding the predictive significance of different factors for in-hospital mortality, especially in diabetic subjects, are limited.

Therefore, we conducted the present study in order to evaluate the prognostic value of different variables, including medical history and laboratory tests on admission, for in-hospital mortality in diabetic and nondiabetic subjects with acute ischemic stroke.

METHODS

A total of 318 patients admitted to the Third Department of Internal Medicine (General Hospital of Nikaia, Athens, Greece) between June 2006 and December 2008 with acute ischemic stroke were included in the study. Only the patients with the onset of symptoms up to 12 hours before admission to the emergency room were recruited into the study. The ischemic stroke was confirmed in all patients by brain computed tomography (CT) scan. Stroke diagnosis was ascertained according to WHO criteria [12].

At baseline, demographic data (age, sex), history of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease (CAD), atrial fibrillation, and previous stroke, were obtained. The collection of the data was based on a history taken directly from the patients or their relatives and records from previous hospitalizations and diagnoses made during the present hospitalization. Patients were classified as having

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recognized diabetes if their medical records contained documentation of a previous history of diabetes, diagnosis of diabetes on admission, or the use of an oral antihyperglycemic agent or insulin at the time of hospital admission. Arterial hypertension as well as hyperlipidemia was recorded according to medical history and relevant drug treatment. CAD was defined as presence of angina, history of previous myocardial infarction, positive stress testing, revascularization procedures or stenosis > 50% at the coronary arteries. Atrial fibrillation was defined as the persistent replacement of consistent P waves by rapid oscillations or fibrillatory waves on the electrocardiogram. Previous stroke was defined as history of hospitalization for a syndrome of rapidly developing clinical signs of focal or global disturbance lasting for 24 hours or longer, attributed to ischemic or hemorrhagic lesions in the brain and verified with CT scan.

All patients underwent general and neurological examination. We recorded systolic (SBP) and diastolic blood pressures (DBP) on admission. Routine laboratory investigations were performed the day of admission to hospital, and included levels of glucose, lipid profile [total cholesterol, high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C), triglycerides], urea, creatinine, uric acid (UA) hematocrit, and white blood cell count (WBC). High sensitivity C-reactive protein (hsCRP) was determined using ADVIA 1650 (Bayer, Elkhart, IN, USA). All patients received treatment according to the current guidelines but none of them underwent thrombolysis or surgical treatment [13]. On discharge from hospital, the length of stay and the occurrence of death were recorded.

The study was approved by the local ethics committee. Informed consent form was given by patients themselves or by relatives.

STATISTICAL ANALYSIS

Statistical analysis was preformed using programs available in the SPSS statistical package (SPSS 15.0, Chicago, USA). All variables were tested for normal distribution of the data. Data are shown as mean ± SD, unless it is stated otherwise. A two sample *t*-test was used to assess differences in continuous variables, while a chi-square test was used for categorical variables. Univariate binary logistic analysis was performed to look for the relationship between death rates and the variables of interest in the sample population. Then, multivariate analysis was performed (backward stepwise method) to look for independent associations between death rates and the variables of interest. All independent variables in the multivariate analysis were tested for multicolinearity. P<0.05 was considered statistically significant.

RESULTS

Study Population Characteristics

A total of 159 diabetic subjects (66 males / 93 females, mean age ± SD: 77.4 ± 6.4 years) and equal number of non diabetic subjects (66 males / 93 females, mean age ± SD: 77.3 ± 5.2 years) were enrolled in the study. The two study groups were matched by gender and age in order to avoid confounding factors to the statistical analysis. The demographic and clinical characteristics of the study subjects according to the presence of diabetes are showed on Table **1**. The median (interquartile range) length of hospital stay was not different between the diabetic and the nondiabetic patients [6 (4-8) vs. 7 (4-8) days, respectively, P = 0.80]. In-hospital death rates did not differ between the diabetic and the nondiabetic patients [36 (22.6%) vs. 27 (17.0%), respectively, P = 0.20].

Participants with and without diabetes did not differ in terms of age, gender, presence of hypertension, atrial fibrillation, history of a previous stroke and CAD. As it was expected diabetic subjects had higher values of plasma glucose (P<0.001), and had more often hyperlipidemia (P = 0.01) than their control counterparts. Also, diabetic subjects had higher values of plasma triglycerides levels (P = 0.005), lower HDL-C levels (P = 0.001) than nondiabetic subjects. No such difference was observed regarding total cholesterol and LDL-C levels between the study groups. Furthermore, diabetic subjects had higher values of plasma urea concentrations (P<0.001), plasma UA levels (P = 0.002), WBC count (P = 0.05), and lower hematocrit level (P = 0.008) than nondiabetic subjects.

18.4% of the diabetic subjects were on insulin treatment and 81.6% on antidiabetic tablets. In the diabetic study group the most prevalent cardiovascular risk factors were hypertension (69.8%), CAD (28.9%), and history of a previous stroke (28.3%). In the nondiabetic study group the most prevalent cardiovascular risk factors were hypertension (66.7%), atrial fibrillation (27.0%), and history of a previous stroke (23.9%).

Subjects with Diabetes

In the diabetic study group univariate logistic analysis showed that death was associated with hematocrit [odds ratio (OR): 0.91, 95% Confidence Intervals (95% CI): 0.85-0.97, P = 0.005], WBC count (OR: 1.002, 95% CI: 1.001-1.004, P<0.001), hsCRP (OR: 1.009, 95% CI: 1.003-1.015, P = 0.004), total cholesterol levels (OR: 0.98, 95% CI: 0.97-0.99, P = 0.03), LDL-C levels (OR: 0.98, 95% CI: 0.96-0.99, P = 0.007), glucose (OR: 1.004, 95% CI: 1.001-1.006, P = 0.006), urea levels (OR: 1.013, 95% CI: 1.004-1.023, P = 0.006), creatinine (OR: 2.79, 95% CI: 1.46-5.32, P = 0.002), and UA levels (OR: 1.42, 95% CI: 1.14-1.79, P = 0.002). No any significant relationships were found between death and sex, age, SBP, DBP, history of hypertension, CAD, hyperlipidemia, previous stroke, atrial fibrillation, plasma HDL-C and tiglycerides levels (Table **2**).

Multivariate analysis demonstrated, after controlling for hsCRP, total cholesterol, LDL-C, urea and creatinine levels, that death was related positively with WBC count (OR: 1.002, 95% CI: 1.001-1.004, P = 0.005), glucose levels (OR: 1.007, 95% CI: 1.002-1.012, P = 0.008), and UA levels (OR: 1.51, 95% CI: 1.003-2.260, P = 0.05) (Table **2**).

Subjects without Diabetes

In the nondiabetic study group univariate logistic analysis showed that death was associated with WBC count (OR: 1.004, 95% CI: 1.002-1.008, P = 0.005), hsCRP (OR: 1.008, 95% CI: 1.003-1.014, P = 0.003), total cholesterol levels (OR: 0.98, 95% CI: 0.96-0.99, P = 0.04), LDL-C levels (OR: 0.97, 95% CI: 0.96-0.99, P = 0.004), and glucose (OR: 1.018, 95% CI: 1.005-1.030, P = 0.007). No any significant

Table 1. Demographic and Clinical Characteristics of Subjects with and without Diabetes

	Diabetic Subjects	Nondiabetic Subjects	*P*
n (%)	159 (50.0)	159 (50.0)	1.00
Males/females n (%)	66 (41.5) / 93 (58.5)	66 (41.5) / 93 (58.5)	1.00
Age (years)	77.4 ± 6.4	77.3 ± 5.2	0.93
Systolic blood pressure (mm Hg)	134.6 ± 21.7	136.7 ± 24.1	0.41
Diastolic blood pressure (mm Hg)	76.6 ± 10.8	78.3 ± 10.9	0.15
Glucose (mg / dl)	207.7 ± 138.9	119.2 ± 35.2	<0.001
Total cholesterol (mg / dl)	178.3 ± 45.6	182.8 ± 43.7	0.42
HDL cholesterol (mg / dl)	40.3 ± 14.0	46.6 ± 15.9	0.001
LDL cholesterol (mg / dl)	113.1 ± 38.1	112.1 ± 37.4	0.82
Triglycerides (mg / dl)	128.8 ± 56.2	110.1 ± 49.8	0.005
Urea (mg / dl)	62.2 ± 16.4	47.6 ± 10.6	<0.001
Creatinine (mg / dl)	1.17 ± 0.6	1.06 ± 0.71	0.16
Uric acid (mg / dl)	5.8 ± 2.2	5.1 ± 1.7	0.002
WBC (10^9 / l)	9,860.6 ± 4,418.1	8,927.5 ± 4,082.7	0.05
CRP (mg / dl)	34.0 ± 18.7	35.5 ± 16.2	0.85
Hematocrit (%)	38.0 ± 5.8	39.6± 5.0	0.008
Hypertension (yes) n (%)	111 (69.8)	106 (66.7)	0.55
CAD (yes) n (%)	46 (28.9)	36 (22.6)	0.20
Atrial fibrillation (yes) n (%)	41 (25.8)	43 (27.0)	0.80
Previous stroke (yes) n (%)	45 (28.3)	38 (23.9)	0.37
Hyperlipidemia (yes) n (%)	35 (22.3)	22 (13.9)	0.01
Treatment for diabetes n (%)	-	-	-
Antidiabetic tablets	120 (81.6)	-	-
Insulin	27 (18.4)	-	-

*Median values (interquartile range). P values for the comparison between subjects with and without diabetes by independent samples t-test for continuous variables or by Pearson χ^2 for nominal variables.
HDL: high density lipoprotein; LDL: low density lipoprotein; WBC: white blood cell count; CRP: C reactive protein; CAD: coronary artery disease.

relationships were found between death and sex, age, SBP, DBP, history of hypertension, CAD, hyperlipidemia, previous stroke, atrial fibrillation, urea levels, creatinine, UA levels, plasma HDL-C and tiglycerides levels (Table **3**).

Multivariate analysis demonstrated, after controlling for WBC count, hsCRP, total cholesterol and LDL-C levels, that death was related positively only with glucose levels (OR: 1.016, 95% CI: 1.001-1.031, P = 0.03) (Table **3**).

DISCUSSION

The main finding of the present study was that WBC count, plasma glucose and UA levels on admission were independent predictors for in-hospital mortality in diabetic subjects. In the nondiabetic group plasma glucose levels was the only independent predictor for in-hospital mortality.

In diabetic subjects elevated serum UA levels are related with increased risk of future stroke [14, 15]. A recent study showed that in type 2 diabetic subjects elevated plasma UA levels were associated with increased arterial stiffness, which is a well-recognised cardiovascular risk factor [16]. Several studies in the general population showed an effect of serum UA levels on prediction of stroke outcomes [17-19]. Two studies have showed that elevated levels of UA were independently associated with an increased risk of early death after acute stroke [17, 18]. In addition, in patients admitted with stroke, serum UA was an independent predictor of future cardiovascular events in the next 2 years [19]. Furthermore, a study showed that elevated UA was associated with an increased risk for acute stroke in elderly individuals [20]. A study in healthy postmenopausal women showed that serum UA levels, independently of other cardiovascular risk

Table 2. Univariate and Multivariate Logistic Analysis: The Association between Various Parameters with Death in Subjects with Diabetes

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	**95% Confidence Intervals**	**P-Value**	**Odds Ratio**	**95% Confidence Intervals**	**P-Value**
Hematocrit	0.91	0.85-0.97	0.005	-	-	-
WBC count	1.002	1.001-1.004	<0.001	1.002	1.001-1.004	0.005
CRP	1.009	1.003-1.015	0.004	-	-	-
Total cholesterol	0.98	0.97-0.99	0.03	-	-	-
LDL- cholesterol	0.98	0.96-0.99	0.007	-	-	-
Glucose	1.004	1.001-1.006	0.006	1.007	1.002-1.012	0.008
Urea levels	1.013	1.004-1.023	0.006	-	-	-
Creatinine	2.79	1.46-5.32	0.002	-	-	-
UA levels	1.42	1.14-1.79	0.002	1.51	1.003-2.260	0.05

Table 3. Univariate and Multivariate Logistic Analysis: The Association between Various Parameters with Death in Subjects without Diabetes

	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	**95% Confidence Intervals**	**P-Value**	**Odds Ratio**	**95% Confidence Intervals**	**P-Value**
WBC count	1.004	1.002-1.008	0.005	-	-	-
CRP	1.008	1.003-1.014	0.003	-	-	-
Total cholesterol	0.98	0.96-0.99	0.04	-	-	-
LDL- cholesterol	0.97	0.96-0.99	0.004	-	-	-
Glucose	1.018	1.005-1.030	0.007	1.016	1.001-1.031	0.03

factors, were associated with intima-media thickness (IMT), a well known marker of cardiovascular disease [21].

However, a study showed that in patients with ischemic stroke there was a 12% increase in the odds of good clinical outcome for each milligram per deciliter increase of UA [22]. The explanation given by the authors was that the antioxidant capacity of UA is an independent factor that ameliorates the clinical prognosis of patients with acute ischemic stroke [22].

A lot of studies have shown that WBC count measured at the time of hospital admission was associated with greater initial stroke severity [10, 23, 24] and might have a prognostic value in acute stroke survivors [10, 25]. Subjects with increased WBC count have excess risk of ischemic strokes independently of other cardiovascular risk factors [26]. Furthermore, WBC count has been shown to contribute to the initiation and further development of ischemic stroke [27, 28]. Two studies showed that WBC count measured in patients during the first 24-hours after the stroke onset was significantly elevated in comparison to healthy controls [24, 29]. However, the observed increased WBC count did not have any prognostic value for the outcome of the patients [24, 29].

It is well established that blood glucose increases after the onset of acute stroke and the increase is related to the severity of the stroke [30]. A systematically review of the existing data showed that in patients with no history of diabetes who have an ischemic stroke, even moderately elevated glucose levels are associated with both a 3-fold higher risk of short-term mortality and an increased risk of poor functional recovery compared with lower glucose levels [31]. Many studies have shown higher mean admission glucose level in nonsurvivors of stroke compared with survivors [32-34]. Furthermore, two large studies demonstrated that glucose level at hospital admission was a significant predictor of mortality [35] or poor functional recovery [36] after stroke independent of other prognostic factors. In addition, a study showed that persistent hyperglycemia was an independent determinant of infarct expansion and was associated with worse functional outcome [37].

CONCLUSION

In conclusion, WBC count, and UA levels on hospital admission are independent predictors for in-hospital mortality in diabetic subjects with ischemic stroke. Plasma glucose levels are predictor for in-hospital mortality in both diabetic and nondiabetic subjects. Therefore, early interventions aiming the above factors might have a positive result to the outcome of patients with ischemic stroke.

ABBREVIATIONS

CAD	=	Coronary artery disease
CI	=	Confidence Intervals
CT	=	Computed tomography
DBP	=	Diastolic blood pressure
DM	=	Diabetes mellitus
hsCRP	=	High sensitivity C-reactive protein
HDL-C	=	High-density lipoprotein-cholesterol
IMT	=	Intima-media thickness
LDL-C	=	Low-density lipoprotein-cholesterol
OR	=	Odds ratio
SBP	=	Systolic blood pressure
UA	=	Uric acid
WBC	=	White blood cell count

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