Epidemiology and Clinical Outcome of Metabolic Syndrome in Medical Critically Ill Patients with Hemorrhagic Stroke

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Background: Metabolic syndrome (MetS) is becoming a health risk prevalent in US, European populations, and in many countries. The aim of this study was to estimate the prevalence of MetS, its relation to age and sex and its effect on mortality of acute hemorrhagic stroke patients admitted to ICU in Zagazig university hospitals, Egypt , within a period of 10 months.
Patients and methods: Three hundred patients with acute hemorrhagic stroke, diagnosed by brain CT, were enrolled in this study. All of them were subjected to thorough history, clinical, and neurological examination, including Glasgow coma scale (GCS) and calculation of APATCHE II score and anthropometric measurements .
Results: The prevalence of MetS in patients with acute hemorrhagic stroke was 32%. It was more prevalent in females than males (39% vs 26.8%, P-value <0.001). MetS is increased in both genders up to the age of 60ys then its prevalence in females exceeded that in males. Patients with MetS had significantly higher ages compared to those without MetS . Increased number of MetS components is associated with increased mortality in patients with cerebral hemorrhage. The relative risk (RR) of mortality was increased with increasing age, female gender, hyperglycemia, elevated serum triglyceride and decreased serum HDL-C and smoking by 1.7, 1.68, 1.02, 3, 1.4 and 1.5 fold, respectively. Admission APATCHE II score ≥ 20, and GCS < 8 increased the RR of mortality by 12 and 1.8 fold, respectively while the presence of MetS increases the RR of mortality by 1.8 fold . Backward stepwise regression analysis revealed that MetS and APATCHE II score were good predictors of mortality in hemorrhagic stroke patients.
Conclusion: Metabolic syndrome is prevalent in acute hemorrhagic stroke patient's especially in elderly females and is associated with poor clinical outcome. MetS and APATCHE II may be used as independent predictors of mortality in those patients.
Keywords: Metabolic syndrome and Hemorrhagic Stroke

INTRODUCTION

The metabolic syndrome (MetS) is defined as a clustering of components that are associated with increased risk of cardiovascular disease (CVD) as well as stroke. Although there are divergent criteria for the identification of the MetS, they all tend to agree that the MetS core components include obesity, insulin resistance, dyslipidemia, and hypertension**[1].**

MetS is becoming a health risk not only prevalent among US and European populations but also in many countries. Recent studies had demonstrated the correlation between MetS and acute ischemic stroke **[3,4]**. The association between MetS and atherthrombotic or non embolic ischemic stroke and also hemorrhagic stroke was confirmed by **Ninomiya et al., [5]**. The adverse effects of MetS which enhance the development and progress of atherosclerotic lesions in arteries supplying the brain might account for the increased risk of stroke events **[6].** In micro vascular brain disease, the small penetrating arterioles of the subependymal and the pial micro vascular systems tend to become stenosed and undergo lipohyalinosis or they may dilate to form micro aneurysms **[7].** From the pathological point of view both lipohyalinosis and micro aneurisms, almost invariably, coexist in the same individual, thus making him liable to develop either the ischemic or the hemorrhagic stroke **[8].** Among components of MetS, high blood pressure(HTN) has the highest risk of hemorrhagic stroke followed by abdominal obesity **[9].**

Therefore, we performed this study to estimate the prevalence of MetS in acute hemorrhagic stroke patients admitted in the medical Intensive Care Unit (ICU) in Zagazig University Hospital within a period of 10 months and its relation to age and sex as well as to find out the relative risk of MetS with its different components together with the effect of age, sex, GCS and APACTHE II score on mortality in those patients .

PATIENTS AND METHODS

This prospective observational, descriptive and analytic study had been carried out for the subjects admitted in stoke subunit of medical ICU Zagazig University Hospitals from June 2012 to March 2013.

A total number of 300 patients, presented with hemorrhagic stroke, were included in this study. All patients had a CT scan of the brain showing evidence of a recent hemorrhagic stroke. Their age ranged from 40 - 70 years with mean value ±S.D 62.73 ± 5.74 years , 125 patients of them were females and remaining were males. Metabolic syndrome in these subjects was diagnosed according to IDF criteria 2006 **[2]** as central obesity (defined as waist circumference ≥ 94cm in males and ≥80cm in females for Arab population plus two of the following : triglycerides ≥ 150 mg/dl, HDL- C < 40 for men or <50 for women, Bp ≥ 130/85 mmHg and fasting plasma glucose ≥ 100 mg/dl **.**

An informed consent was signed by the patient relatives to participate in the study.

Exclusion criteria:

1. Space occupying lesion in the brain.
2. Infectious brain disease(eg;encephalitis)
3. Evidence of recent ischemic stroke.
4. Hemorrhagic infarction

METHODS:

All subjects of this study were subjected to the following:

(I) Thorough history and clinical examination and include:

A- History of the present illness and past history of any medical disorder with particular attention to HTN, DM, CVD, dyslipidemia, smoking, past history of stroke and family history of similar attack.

B- Full general examination with special attention to; BP measurement after patient admission using a mercury sphygmomanometer with the patient recumbent in bed with the arm supported and positioned at level of the heart. Mean arterial pressure (MAP) was calculated as follow:

MAP= [(2 x Diastolic blood Pressure) + Systolic blood Pressure] ÷ 3

-Waist circumference= the minimum abdominal circumference was measured mid way between the xiphoid process and umbilicus (2).

-Pulse, temperature, cardiac examination.

C- Full neurological examination.

(II) Routine investigations including complete blood picture, renal and liver function tests, bleeding profile (PT, PTT, INR), lipid profile (LDL-C, HDL-C, total cholesterol and triglycerides), fasting and 2 hours postprandial blood glucose levels, electrolytes, serum, C-reactive protein,, chest x- ray, ECG, and arterial blood gases (ABG)

(III) Neuroimaging: All patients were examined by Computed Tomography(CT) scan of the brain on admission. The presence and location of the hemorrhage, in all patients, was documented by CT scan.

(IV) Severity assessment was done using the commonly used scoring systems in ICU for critically ill patients, Glasgow coma scale. (GCS)**[10]** and Acute Physiology and Chronic Health Evaluation (APACHE II) score**[11]**. Generally, brain injury is classified as: Severe with GCS ≤8, Moderate GCS 9-12, Minor GCS ≥13

Statistical analysis:

All collected data were first assessed before taken for analysis. The normality test of Kosmogorov-Smirnov was done to assess whether the data were normally distributed or not. Unless otherwise stated, data represent the means ±SD. Differences between parameters were tested using ANOVA or student's t-test, post hoc tests (least significant of difference) were performed for multiple comparisons between groups, while X^2 tests were used for categorical variable. Correlation between variables of interest was performed using Pearson's correlation. A multiple linear regression analysis were performed using statistical package of social sciences (SPSS) for windows version 17**(13).** A P-value ≤ 0.05 was considered statistically significant.

RESULTS

We found 32% of patients with hemorrhagic stroke had metabolic syndrome according to IDF definition. Also, there was a statistically significant increase in the prevalence of MetS in female patients compared to males (39% vs 26.8% p-value<0.001). There was a statistically increase in the mean values± SD of age, MAP, FBS, LDH, TG, WC, CRP, number of smokers, APATCHE II and decrease in HDL value, and GCS scores in MetS patients compared to those without MetS(table1).

The prevalence of MetS increases significantly with age in both genders From 40 to 60 years while the prevalence was higher in female than in male patients from 60 to 70 years (table 2).

In hemorrhagic stroke patients with MetS, the mortality was significantly increased with increasing age to be 61.2% from 60 to 70 years (table 3).

As regards to the effect of stage of hypertension on the mortality of MetS patients with hemorrhagic stroke, there was a significant increase in mortality with increasing MAP. As well as increased number of MetS components increases mortality in patients with cerebral hemorrhage. Patients with 3 components had 44% increase in mortality while those having >3 components the mortality was 66.6 %(table 4).

In our Study ,we found that the age over 60 years increases the relative risk (RR) of mortality by 2.5 fold , female gender increases the RR of mortality by 1.68 fold ,admission hyperglycemia increases the RR of mortality by 1.02 fold , increased serum TG increases the RR of mortality by 3 fold , decreased serum HDL-C increases the RR of mortality by 1.4 fold, smoking increases the RR of mortality by 1.5 fold, APATCHE II score ≥ 20 on admission increases the RR of mortality by 12 fold , GCS < 8 increases the RR of mortality by 1.8 fold , while the presence of MetS increases the RR of mortality by 1.8 fold (table 5) .

Using Backword stepwise regression analysis of the factor predicting survival among study group, we found that both MetS and APACHE II score are independent predictors of mortality (table 6).

Table (1): Prevalence of metabolic syndrome in the studied subjects and comparison of the mean ± SD of various variables in hemorrhagic stroke patients with and without metabolic syndrome.

VARIABLE	Met. Synd (+ve)		Met. Synd.(-ve)		P
Number of patients(%)	96 (32%)		204 (68%)		<0.001
AGE(YEARS)	64.520±5.765		58.9510±5.730		<0.001
Sex: Male/Female (%)	M=47 (48.9%)	F=49 (51.1%)	M =128 (62.7%)	F=76 (37.2%)	<0.03
Systolic blood pressure (SBP) (mmHg)	177.239±18.120		155.857±31.946		<0.024
Diastolic blood pressure(mmHg)	93.593±6.832		85.171±12.509		<0.001
Mean arterial pressure (MAP) (mmHg)	121.416±8.909		106.247±9.521		<0.001
GCS	6.156±2.163		8.078±2.790		<0.001
Fasting blood sugar mg/dl (FBS)	145.0937±40.584		113.955±37.437		<0.001
LDL-C (mg/dl)	117.517±12.488		111.274±14.874		<0.051
HDL-C (mg/dl)	41.666±8.222		44.318±7.437		<0.001
Uric acid (mg/dl)	8.510±1.835		7.970±1.666		<0.023
CRP (mg/dl)	31.760±19.988		12.495±15.311		<0.001
Triglyceride (mg/dl) (TG)	170.479±33.416		157.7646±40.50		<0.002
APACHE score	23.895±6.165		19.3515±5.418		<0.001
Waist circumference (cm)	92.437±4.144		81.276±11.155		<0.001
Smoking (%)	N=75 (78%)		N= 110 (51%)		<0.001

Table (2): Prevalence of metabolic syndrome in male and female patients with hemorrhagic stroke according to age group.

Age group	Male N %	Female N %	(χ2)	p-value
40-50 years	N=5 11.6%	N=3 6.7%	113.471	<0.001
51-60 years	N=21 44.2%	N=20 41.2%	26.629	0.05
61-70 years	N=21 44.3%	N=26 52.1%	67.411	<0.001

Table (3): Effect of age on the mortality of the patients with hemorrhagic stroke with metabolic syndrome.

Age Group	No of cases	Died	Survived	Mort rate
40-50 years	N=4	1	3	25%
51-60 years	N=41	18	25	37.5%
61-70 years	N=51	30	19	61.2%
TOTAL	N=96	49	47	52.1%

Table (4): Effect of stage of hypertension and number of component of metabolic syndrome on the mortality of MetS patients with hemorrhagic stroke.

No. of components of Met.S	**No. of cases**	**No. of Deaths**	**No. of survived**	**Mortality rate**	**(χ2)**	**p-value**
3	66	29	37	44%	103.51	<0.001
MAP (mmHg)						
<100	1	0	1	0%	88.411	<0.001
100- 112	27	7	20	26%		
113-133	30	12	18	40%		
>133	38	30	8	79%		
TOTAL	96	49	47	51%	--	--

Table (5): Relative risk of increasing age, gender, obesity, and hyperglycemia. Decreased serum HDL-C, increased serum triglycerides, smoking, decreased GCS, increased APACHE II score and MetSperce on mortality of hemorrhagic stroke patients with Met.S.

Variables	Deceased (n= 49)	Survived (n= 47)	Total (n= 96)	R R
Age :				
> 60 years	48	20	68	2.5
< 60 years	8	20	28	
Gender:				
Male	33	14	47	1.68
Female	23	26	49	
Hyperglycemia:				
Present	37	26	63	1.01
Absent	19	14	33	
Serum triglyceride; (TG)				
>170 mg/dl	35	10	45	3
≤ 170 mg/dl	20	31	51	
Serum HDL-C(mg/dl)				
< 41	30	15	45	1.4
≥ 41	26	25	51	
Smoking :				
smokers = 75	51	24	75	1.5
non smokers = 21	11	10	21	
APATCHE II score :				
≥ 20	51	3	54	12.13
<20	5	37	42	
GCS				
< 8	34	15	49	1.64
≥ 8	22	25	47	
Metabolic syndrome:				
+ ve	56	40	96	1.8
- ve	57	147	204	

Table (6): Back word stepwise regression analysis of the factor predicting survival among study group.

VARIABLE	B-VALUE	St.Er	WALD	SIG.	95.0% C.I .FOR EXP	
					LOWER	UPPER
MET.S	1.023	.553	3.686	<0.03	.979	7.908
APACHE.SCORE	5.870	.648	81.991	<0.001	99.407	1261.792
CONSTANT	4.430	.628	49.843	<0.001	-----	-----

DISCUSSION

The metabolic syndrome (MetS) is becoming a health risk not only prevalent among US and European populations, but also in many countries. Recent studies demonstrated high prevalence of metabolic syndrome in ischemic stroke patients **[3&4]**.

Out of all the different proposed criteria for the definition of MetS, we used the last and most expressive definition proposed by **IDF [2].**

In this study we looked for the prevalence of MetS in subjects with cerebral hemorrhage, its relation to age and sex as well as to find out the relative risk of MetS with its different components together with the effect of age, sex, GCS and APACHE II score on mortality in those patients.

This study included 300 patients with hemorrhagic stroke. According to presence or absence of MetS criteria; we found that 32% of our patients had MetS (49 female and 47 male) . According to component distribution, we found that 30 patients had more than 3 components of MetS and 66 patients had three components (28 patients had obesity, hypertension and dyslipidemia and 38 patients had obesity, hypertension and diabetes mellitus). Also by estimating the prevalence of MetS. in male and female patients, we found that prevalence of MetS in female patients was higher than in males (39.2% vs. 26.8%) which are statistically significant (p-value < 0.001). Although in many studies there is very little difference between rates of MetS among women and men, there were some studies that had noticeably greater numbers of women that meet the MetS criteria than men [**24],**whereas others reported greater prevalence of MetS in men **[15].** The high prevalence of MetS in our female patients may be attributed to lack of physical activity and increasing weight after menopause. The difference between these reports may be due to ethnic and racial reasons.

By comparing the mean ± standard deviation of age between these patients with and without metabolic syndrome, we found that patients with MetS had significantly higher ages compared to those without MetS (64.5±5.8 vs. 58±95 respectively) in agreement with the study of **Thomas, et al in 2005 and Mokdad.et al., (2001) [16&17**] who stated that the prevalence of metabolic syndrome increased progressively with age.

This study revealed that the prevalence of MetS increased with age in both genders up to the age of 60 years. After the age of 60 years, the prevalence of MetS in females increased progressively to exceed its prevalence in men. These results coincided with **NHANES** cohorts who found that MetS prevalence continued to increase with age to the sixth decade, with prevalence in women catching up to and then exceeding that in men after the age of 60 years **[13].** These trends suggested an interaction between age and gender on the prevalence of the MetS. Also **Mokdad.et al., [18]** stated that, the MetS increase with age was related to increased obesity, particularly central obesity. Also, they stated that obesity had a relationship with age and differs according to gender. In females with ages from 40-50 years, the mean of WC is (84±7.32); while those with ages ≥50years, the mean of WC is (95±8.41) but in males the reverse occurs. In males aging from 40-60 years, the mean of WC is (87±12.4); while those aging ≥60 years, the mean of WC is (80±4.2**).**These findings indicated that central obesity, which is the cornerstone of metabolic syndrome, carries a higher risk of stroke especially of elder women**[19].**

Also, the mortality was increased significantly with increasing age of patients with MetS and hemorrhagic stroke (p-value< 0.001). This was emphasized by estimating the relative risk of increasing age on mortality of patients with cerebral hemorrhage. We found that ages above 60 years had 2.5 fold ` increased risk of mortality than those with ages <60 years. These results agreed with **Thomas et al, [17],** who hypothesized that the aging process may imply changes in brain plasticity, diminishing the strength of the brain tissue that normally acts as a restriction wall to the extension of the hematoma; and this lead to hematoma expansion with worsening of condition ,and increasing mortality in old age. As regard the effect of MetS on mortality of patients with hemorrhagic stroke, we found that the relative risk of mortality was significantly increased in patients with MetS in comparison to those without MetS. by 1.8 fold. This finding was consistent with many previous studies revealed that MetS was associated with the increased mortality and morbidity of stroke patients **[20].**

The results of our study showed that the mortality of MetS patients with hemorrhagic stroke increased significantly in patients having more than three components than those with three components (66.6% vs 44% p-value < 0.001). Many previous studies found that a higher number of MetS components were associated with increased incidence of mortality in stroke patients in both genders **[21].**

By comparing mortality in relation to stages of hypertension (table 6), we found that the increase of the severity of hypertension was associated with subsequent increase in mortality to be 79% in patients with MAP > 133 mmHg in stage 4 HTN .So early identification and intervention of hypertension would be helpful to reduce stroke risk.

Also among the group of MetS , hyperglycemia carried 1.0254 fold increased risk of mortality with cerebral hemorrhage. Although this risk of mortality is low but these findings are very valuable in preventing metabolic syndrome risk as it emphasizes the cut of point of FBS from 110 to 100 mg/dl that used by IDF definition , as with good controlling of hyperglycemia, stroke risk and complication will decrease as a small change in the fasting glucose threshold may have an important impact on the associated cardiovascular risk **[22].**

As regards to the lipid profile in this study, we found that patients with MetS had statistically significant low HDL-C, and high TG serum levels in comparison to non MetS subjects (p < 0.001), and the relative risk of mortality increased by 3 and 1.4 fold with ≥ 170 and ≤ 41 mg/dl serum levels of TG and HDL-C respectively while there was no significant difference between the hemorrhagic stroke patients with and without MetS regarding serum LDL-C. Many studies were carried out to evaluate this relationship between stroke and HDL-C; as Compared with the Western populations, HDL cholesterol levels in the Asian populations were lower, especially for men. However, the incidences of stroke were higher in the Asian populations than in Western populations, suggesting that low HDL–C level might have an important role in stroke events among Asian populations. But any one could not simply identify HDL-C as a protective factor for stroke because the effects of HDL-C varied in different subtypes of stroke **[23].** The results of this work revealed that about 78% of patients with MetS were smoking while in patients without MetS the smokers were 51% which were statistically significant. Also smoking increased the relative risk of mortality by 1.5 fold than nonsmokers.

In our study, we assessed the severity of the condition using APATCHE II score and GCS. We found that APACHE II score was significantly increased in patients with MetS in comparison to non MetS patients (23.895±6.165 vs. 19.3515±5.418, p-value <0.001), and patients with scores above 20 carried 12 fold increased risk of mortality in comparison to those with scores lower than 20. These results are very important as it emphasizes the role of APACHE II score in evaluation of acute health illness **[25]**.

As regard o GCS, we found that patients with MetS had significant low GCS in comparison to non MetS patients (6.2±2.2 vs. 8.1±2.8, p-value <0.001) and the risk of mortality was increased by 1.4 fold in patients with GCS <8. This result also has importance in the value of GCS in assessing the severity of neurological condition **[10]**.

From all of the above, we had a list of factors determining or affecting the outcome of patients with cerebral hemorrhage as age, sex, MetS Perce, number of MetS components, stage of hypertension, GCS and APACHE II score. We tried to know what was the factor that carried more risk for those patients and can use it as a predictor of mortality. By using backward stepwise regression analysis of the factor predicting survival among study group, we found that MetS and APATCHE II score carried this risk and can be used as a predictor of mortality.

Finally, the finding that MetS was associated with an increased risk of stroke with its squeal of morbidity and mortality among populations reaffirmed the need to design preventive as well as treatment strategies to control the MetS as a part of the general guidelines for stroke prevention and management.

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