Characteristics of Wake-Up Stroke: An Experience from an Arab Cohort

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Abstract

Background:

Wake-up Stroke (WUS) doesn't have distinctive clinical characteristics. Physiological changes in circadian rhythm (cerebral autoregulation, vascular tone, blood pressure, coagulation profile) are thought to predispose to WUS.

Aim:

Our objective is to identify the characteristics WUS amongst the Arab population.

Methods:

We retrospectively assessed consecutive stroke patients of the Acute Stroke Unit of King Fahad Medical City; Riyadh, Kingdom of Saudi Arabia, presenting within five days of symptom onset from November 2010 to August 2012. The patient's demographics, risk factors, stroke volumes (ABC/2 method), location, etiology (TOAST criteria), and functional status (NIHSS, BI, GOS score) were assessed. WUS was grouped into Group A (0:00-06:00), B (06:01-12:00), C (12:01-23:59) based on the "wake up" time. Statistical analysis was done using SAS version 9.2.

Results:

Of 236 patients fulfilling the criteria 219 had an ischemic stroke. Of those, 65(29.7%) had WUS that showed more male (78% vs 62%), AF (13% vs 7%; p-0.11), cardioembolic (21% vs 16%; p -0.41), bihemispheric stroke (12% vs 7%; p-0.21) and insular stroke (23% vs 11%; p-0.039). WUS Group A (n=28) had more obese (26% vs 10%, 20%); AF (17% vs 9%, 3.8%; p-0.715); left sided (p-0.0280), subcortical, brainstem stroke; higher BI (61 vs 58 and 51; p-0.4) and GOS (4.3 vs 4.1 and 4; p-0.6). Group B (n=10) had older age (65.6 vs 60,6 years; p-0.9572), smallest volume (15 vs 26,45 cumm) of stroke. Group C WUS (n=27) had bilateral (p-0.0016), parietal lobe (p-0.0379), insular stroke (27% vs 26%, 17%; p-0.5457); large artery atherosclerosis(15% vs 12%, 6%; p-0.7262) with symptomatic stroke (20% vs 16%, 7%; p-0.7499), cardioembolic stroke (12% vs 7%, 9%, p-0.3573),largest volume of stroke (46 vs26, 14cumm), higher admission(p-0.1285) and discharge (p-0.248) NIHSS.

Conclusions:

The clinical characteristics of WUS in our Arab population were not significantly different from non WUS. However, this study revealed a significantly higher rate of involvement of insular cortex in WUS, the rationale behind this occurrence is yet to be unraveled.

INTRODUCTION

Wake-up stroke (WUS) is defined as the occurrence of new symptoms suggestive of stroke detected upon waking up from sleep. The precise time of onset is unknown. For purposes of simplicity and safety, the time of stroke is frequently standardized to the time the patient was last seen normal. In WUS, this time is commonly assigned to when the patient had slept. However, stroke may have occurred as the patient jolted awake. As no confirmatory marker exists for the time of stroke onset, these patients are excluded from acute reperfusion therapy (ART) which results in an increase

of the disabled population in society.

The origin of WUS is yet unknown. Many researchers have postulated that the circadian rhythm plays a crucial role in generating stroke at different times of the day. This hypothesis was further confirmed by a meta-analysis of stroke papers conducted by William J. Elliott et al. which showed a diurnal variation in stroke onset [1]. They showed that ischemic stroke occurs at a greater frequency (49%) from 6 am to noon. Our biological clock is dependent on environmental influences, specifically light intensity. Furthermore, He Meng et al. using pineal gland microdialysis in mice ascertained the biological clock by measuring melatonin level at different times of the day [2]. Numerous studies affirmed the role of circadian rhythm in causing a morning reduction of varied factors involved in coagulation, fibrinolytic pathway, cerebral autoregulation, cerebrovascular reactivity to changes in CO (CRCO2), endothelial function (EF), and cerebral blood flow (CBF)[3,4,5]. Circadian rhythm also exerts a surge in blood pressure (BP), platelet aggregation, and sympathetic tone in the early hours of morning [6,7,8]. Together, these factors may incite the formation of thrombus or predispose to the rupture of a preexisting fragile atherosclerotic plaque in a large artery thus towards stroke [9].

Another notable factor in the pathophysiology of WUS is the normal physiology of sleep and its effect on the cerebral metabolic rate and CBF. Although, sleep may play a prominent role in the genesis of WUS, there are likely many other contributing demographic variables.

AIM

Numerous studies attempted to identify distinctive clinical features of WUS with little success. To understand WUS among Arabs, we opted for analyzing the clinical characteristics of this cohort registered at the Acute Stroke Unit (ASU) of King Fahad Medical City (KFMC), KSA. Thus, the aim of this study was to determine the prevalence of WUS in this Arab cohort; to discern any gender, age, or risk factor predilection for WUS; to assess the immediate functional outcome; to identify specific brain regions with higher propensity to be involved in WUS and, to correlate these findings to the possible mechanism of WUS.

DESIGN/METHODS

This was a retrospective data analysis of all consecutive stroke patients admitted to ASU of KFMC, KSA from November 2010 to August 2012. The ASU of KFMC is the only JCI accredited stroke unit in the country. Here patients are admitted with clinical suspicion of acute stroke. The study included patients confirmed to have a stroke after thorough evaluation. The inclusion criteria were: age>18 years, admission to ASU within 5 days of symptoms, known activity at the time of symptom detection (sleep/awake), available vital signs upon admission, functional status upon admission and discharge, brain images, and Ultra Sonogram/Magnetic Resonance Angiographic report of neck vessel integrity. Data was collected from ASU database. CT and MRI scans were accessible through PACS.

Our study was approved by Institutional Review Board-Registration Number with OHRP/NIH,USA; IRB00008644.

In this study, we defined two groups:“Awake” group, with a known time of stroke onset, and “WUS” group, patients waking from sleep with symptoms of stroke. The exact detection time of stroke symptoms were obtained from the patient’s recollection or from an observer’s report.

We divided the WUS group into Group A (06:01-12:00),B (12:01-23:59),C (0:00-06:00), depending on the time of the day the patient awoke with symptoms of a stroke.

The variables compared were: co-existing Diabetes Mellitus (DM), hypertension (HTN), Dyslipidemia, Ischemic Heart Disease (IHD), Atrial Fibrillation (AF), stroke, and obesity. BMI>26 was regarded obese. Stroke was lateralized to left, right or bilateral. Location was categorized by anatomic region. Insular involvement was considered when it was affected solely or as part of a greater area of stroke. Functional status was assessed through standard stroke scales- National Institute of Health Stroke Scale (NIHSS), Glasgow Outcome Score (GOS), and Barthel Index (BI).

The NIHSS is a 15-item validated tool utilized in clinical trials to estimate stroke severity. It encompasses testing of level of consciousness; selective cranial nerves; motor, sensory, cerebellar functions; language; and inattention [10]. The total scores range from 0-42, with higher values indicate severity of impairments. The BI- a 10 item scale, used to measure performance in the activities of daily living [11,12,13]. The maximum score (100) suggests independence. The minimum score (0) implies complete dependence for the ADL. The GOS is a scale of disability based on a single-item with following categories: no or minimal disability/handicap; moderate disability; severe disability; persistent vegetative state; death. The GOS has shown an inter-rater reliability of 67% (k= 0.52)[14]. NIHSS

was recorded on admission and discharge day, whereas BI and GOS on the discharge day. The average duration of patients stay at ASU was 8 days.

Volume of stroke was calculated using the ABC/2 formula by viewing DWI/MRI or CT images. In ABC/2,"A"-the maximum diameter (cm) of the lesion (acute stroke area),"B"-the length (cm) of a line running perpendicular to"A", and "C"-the number of slices bearing that particular lesion multiplied by the thickness of the slice (which was uniformly 5mm)[15]. For cases with more than one acute lesion volume of each lesion were added together.

Symptomatic large vessel stroke is defined when stenosis in large artery is believed to be the cause. Stroke etiology was assessed through TOAST classification. The TOAST (trial of ORG 10172 in acute stroke treatment) classification denotes five subtypes of ischemic stroke: large-artery atherosclerosis (embolus/thrombosis); cardioembolism (high-risk/medium-risk); small-vessel occlusion (lacune); stroke of other determined etiology; and stroke of undetermined etiology[16]. TOAST classification has a reliable inter-observer agreement for accurately predicting stroke prognosis.

RESULTS

We identified 236 patients fulfilling the inclusion criteria. 17 had intra-cerebral hemorrhage. Thus, the study included 219 ischemic stroke patients. Among them, WUS was observed in 65 (29.6%) and Awake stroke in 154 (70%). We found WUS detected from 12am to 6am in 28 (43%), 6am-12pm in 10 (15%), and from 12pm to 12am in 27 (41%) of the patients (Figure1). WUS stroke had higher Insular cortex involvement than Awake stroke. Among WUS subgroups statistical significance was seen for left side strokes in the 12 am-6am group and for parietal lobe and bihemispheric WUS in the 12pm-12 am group.

The detailed results of different variables are illustrated in Table 1-4. Table 1 shows results of all the variables compared between Awake and WUS stroke. Table 2 shows Statistical Analysis of Continuous Variables between Awoke and WUS group. Table 3 shows results of different variables of the subgroups of WUS. Table 4 shows comparisons between the continuous variables of WUS subgroups.

STATISTICAL ANALYSIS

The statistical analysis of the values of different variables was conducted using the SAS (version 9.2) system.

The statistical analysis of the continuous variables of Awoke, WUS groups, and the WUS subgroups is illustrated in Table 1 and 3.

The statistical significance of categorical variables was obtained either by using Pearson Chi-square statistic or Fisher Exact test from PROC FREQ. The variable in WUS that illustrated significant p value was involvement of insular cortex (p value of 0.0103). All other categorical values had no significance between the 2 groups.

Among the subgroup of WUS the p-value was significant in left hemispherical stroke which was seen in Group A (p-value 0.0280). The Pearson chi-square statistic had a value of 7.1535 with 2 degree of freedom. Bilateral stroke had a significant -value of 0.0016 in Group C. Parietal lobe stroke in Group C had significant p-value of 0.0379. The other chi-square statistics had similar values and are asymptotically equivalent. The other statistics (phi coefficient, contingency coefficient, and Cramer') are measures of association derived from the Pearson chi-square. For Fisher's exact test, the two-sided-value was 0.0417 (less than 0.05), which showed statistical association between Time Group C and Parietal lobe stroke. The other categorical variables did not show any association between the different timed WUS.

The multivariate analysis of variance (MANOVA) was used to assess the combined effect of the response variables such as: AGE, SBP, DBP, PULSE, VOLUME, NIHSS, NIHSS, BI, and GOS vs. the independent variable and the different time. The results were obtained from PROC GLM (General Linear Model SAS software procedure) but none exhibited any statistical significance. Non-parametric test using SAS software PROC NPAR1WAY demonstrated volume of stroke having statistical significant association with the WUS occurring at Group C time.

DISCUSSION

Several attempts have been made by researchers to characterize WUS. To describe WUS the pathophysiology of such stroke must be comprehended. WUS occurs either during sleep or during transition from sleep to awakening. In accordance with other studies, we demonstrated a diurnal variation in the occurrence of WUS. Therefore, we postulate that WUS results either from an inherent diurnal fluctuation in various stroke-promoting factors or from the physiological influence of sleep on these factors.

It is well known that nature possesses a biological clock that operates in a 24hr rhythm, called the circadian rhythm. Although this cycle is endogenous, studies in the field of

chronobiology have demonstrated that light intensity is its most powerful modulator. This association has been further proven by the observation that melatonin, a sleep-promoting hormone, is released at higher levels during night [17]. A meta-analysis on numerous international reports showed an excess risk of 40% for acute myocardial infarction, 29% for sudden death and 49% for acute stroke from 6 am to noon [1].This enhanced probability is believed to reflect circadian fluctuation of stroke-promoting factors especially early morning impaired cerebral auto-regulation, CRCO2, and decreased CBF, EF with blunted flow-mediated arterial dilatation [3,4,5] coupled with heightened platelet aggregation and sympathetic activity [6,7,8]. The study on daily rhythm of CBF velocity by Deirdre A Conroy et al. demonstrated existence of 24-hour rhymicity in CBF volume in a state of limited periodic external stimulation and constant posture [5]. The morning endothelial dysfunction is thought to be caused by increased plasma levels of an L-arginine inhibitor [18]. Inadequate plasma L-arginine level contributes to the reduced availability of NO, an important messenger molecule recognized for protecting organs from ischaemic damage. The morning surge of BP and rate pressure product can rupture a fragile atherosclerotic plaque [9, 19]. Furthermore, in presence of impaired auto-regulation in early morning, high BP with decreased EF can result in stroke. Studies have also shown diurnal variation in levels of Factor VII, proteins C, S, antithrombin III, plasminogen activator inhibitor-1, prothrombin fragment, D-dimers, and tissue factor pathway inhibitor activity in healthy humans [20]. These changes can provoke a morning hypercoagulable and hypofibrinolytic state [21,22]. Collectively, these factors lead to a variation in the risk of stroke at different times of the day.

Other hypothesis on WUS pathophysiology lies with the physiology of normal sleep. Sleep comprises non-rapid eye movement (NREM) and rapid eye movement (REM) stages. REM sleep constitutes 20-25% of adult sleep duration. There are 4-5 cycles each in order of N1-N2-N3-N2-REM per sleep [23]. There is a larger proportion of deep sleep stage (N3) earlier at night. In contrast, REM stage increases in the two cycles just before natural awakening. In healthy individuals during sleep, different areas of the brain have different magnitude of activity. During sleep there is relative suspension of sensory activity and inactivity of nearly all voluntary muscles. PET and SPECT studies have shown a decrease in CBF (26%) and average cerebral metabolism during NREM (N1,N2) sleep, which reaches a nadir in deep (N3) sleep. The areas of the brain that show deactivation are insular cortex, brain stem tegmentum, thalamus, associative cortices of the frontal, and parietal lobes. During transition from NREM to REM sleep, there is a global increase in CBF [24]. REM causes activation of limbic and paralimbic structures. Rapid eye movement provokes enhanced sympathetic activation especially evident in the early morning hours before awakening. Thus, depending on the stage of sleep, the regional CBF and metabolism varies. Hence, stroke detected upon awakening relies on the stage of sleep the patient traversed and also on the time of the day the sleep occurred.

In this retrospective study on an Arab cohort, we found 65 (29.6%) out of 219 patients having WUS. This rate is higher than that published in previous papers (8-28%). In a recent population-based study by J. Mackey et al conducted in USA comprising 1,854 ischemic strokes, WUS was found to occur in 14% [25]. Moradiya Y et.al on other hand found WUS comprising 29.8% of all ischemic stroke cases in their analysis of data from the International Stroke Trial [26].

In this cohort, timing of WUS varied widely with the majority occurring from 12am-6am, and 6 am being most frequent. This finding is different from the report of a meta-analysis of 31 publications that showed highest incidence of stroke from 6am to 12pm [1]. However, their study did not separate WUS from non-WUS. Our finding is in agreement with the finding of Sükrü Torun, who examined 526 consecutive Turkish ischemic stroke patients (not classified as WUS) found stroke to occur most commonly from 4am to 6am [27]. He hypothesized that earlier wake-up time of this population due to cultural/religious reasons may explain this difference. Kocer A et al. also mentioned religious factors being a cause for the earlier timing of stroke onset in this part of the world [28].

We found the WUS group to be 1 year older. Gisele S. Silva et al. also found a slightly older age among the WUS patients in their study on neuroimaging in WUS [29].

The gender-specific risk was different in our study. In contrast to other published studies, we found males having higher incidence of WUS.

SBP, DBP and pulse rate values were higher in our WUS

group, reflecting a sympathetic drive. However, this finding cannot be correlated with certainty as most readings were taken long after the actual insult.

We found DM, hypertension, dyslipidemia, IHD, and obesity to be less frequent among WUS. But, history of old stroke and AF was frequent. These data were supported by the observation of higher frequency of cardioembolic etiology compared to small vessel occlusion in our WUS group.

To our knowledge, this is the first study that examined specific brain area's predilection for WUS. We found insular cortex to have statistically significant association with WUS as well as acute bihemispheric and left sided. Based on our understanding of function of insula we propose that as it is less active during sleep, it is incapable of exerting its influence on autonomic pathway in counteracting the sympathetic surge. Moreover, insula may be vulnerable to ischaemia due to its inherent reduced blood flow during sleep. However, whether the insula has a circadian rhythm of its own that makes it prone to stroke during sleep is unknown.

Other areas of the brain that showed higher but non-statistically significant rate of involvement are: frontal, parietal, temporal, occipital lobes, basal ganglion, IC, and midbrain.

With regard to functional status, WUS patients showed a higher mean NIHSS at presentation and discharge. However, when adjusted to the ratio of improvement, we found WUS patients having 20% improvement in mean NIHSS value upon discharge, while 13% in the Awake patients. Although trending towards a greater speed of improvement, the BI and GOS were still slightly lower. Even though these patients did not receive thrombolytic therapy, yet they demonstrated a naturally favorable prognosis. This information further emphasizes the need for intervention in this faction of stroke population as they are more likely to show greater improvement when treated with ART.

In our subgroup analysis, WUS occurred most often from 12am-6am. However, older people experienced WUS more commonly from 6am-12pm; as possibly the elders in this culture sleep during that time. Males had a slightly higher tendency of WUS from 12pm-12am. Females experienced WUS more often from 12am-6am.

Cardioembolic and symptomatic large artery atherosclerotic WUS occurred frequently from 12pm-12am. AF as more common among WUS was also seen frequently in 12am-6am group.

The 12pm-12am group showed worst immediate outcome as evidenced by highest mean NIHSS with lowest mean GOS and BI score. The mean stroke volume was the largest for the same group implying larger volume having poorer outcome. Whereas the 12am-6am group had the best outcome.

The major limitation of our study is being a retrospective chart review analysis. Secondly, it used data from a single center only. Moreover, timing of stroke detection was obtained from the patient’s or caregiver’s recollection without any objective evidence. In some cases, patient reported to ASU days after symptom onset (<5days), by which accurate time recalling might not have happened. As mentioned earlier, parameters of SBP, DBP and pulse were recorded on the day they were admitted to the ASU, which varied from few hours to 5 days post-stroke. The discharge NIHSS, GOS and BI score were also recorded at different durations of stroke.

The strength of this study lies with the comparison of different variables of stroke with different times of WUS. To the best of our knowledge, this study is the first to evaluate the location and volume of the stroke in a WUS cohort. Possibly the first ever study on WUS of Arab cohort.

This study based on a modest number of patients showed some distinctive features such as higher rate of involvement of the insular cortex and higher rates of cardioembolic etiology and AF among Arab WUS patients. Although drawing any conclusions based on this small sample size is not feasible, but this study clearly highlights the exploration of many unanswered questions. Many atherosclerotic plaques are known to exist in a silent form, but with unknown triggers, become inflamed, fissured resulting in formation of a clot. Additionally, an individual with a lifelong history of protein C deficiency or AF may suddenly develop a clot that travels to the brain. What abruptly stimulates these events? Is there an insular cortex trigger, a seizure, predetermined circadian cycle of the insula (electrical/chemical), or a procoagulant hormone that is stimulated? Future proteomic studies may discover protein(s) that contributes to WUS that is not present in non-WUS.

DISCLOSURE FROM ISPUB:

This article was submitted as an abstract/poser presentation

previously and can be found here:

http://onlinelibrary.wiley.com/doi/10.1111/ijs.12367/full

We have published the article in full.

Figure 1

Showing distribution of patients in different groups

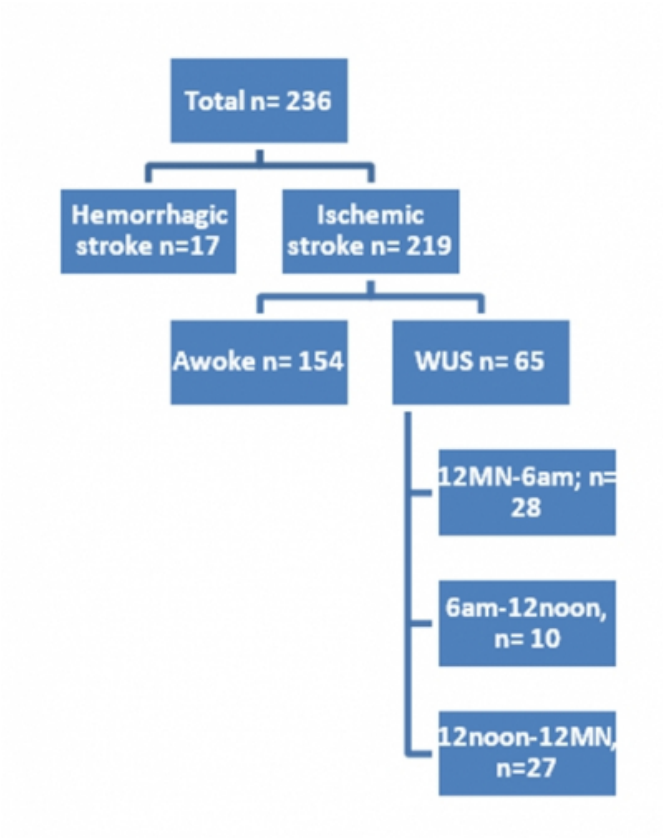

Table 1

showing results of continuous variable of Awoke stroke and WUS group.

Group	Number of patients	Variable	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Standard deviation
Awoke	154	AGE	61.02	58.53	63.51	15.65
		SBP	149.65	145.23	154.08	27.70
		DBP	78.61	76.02	81.19	16.18
		PULSE	79.22	76.69	81.74	15.76
		VOLUME	36.15	19.81	52.49	102.64
		NIHSS1	6.62	5.70	7.54	5.78
		NIHSSF	5.31	4.27	6.35	6.46
		BI	57.99	52.44	63.54	34.28
		GOS	4.34	4.16	4.51	0.96
WUS	65	AGE	62.62	58.98	66.25	14.66
		SBP	154.55	147.64	161.47	27.90
		DBP	80.00	76.95	83.05	12.29
		PULSE	77.71	74.74	80.68	12.00
		VOLUME	32.81	18.05	47.58	59.57
		NIHSS1	7.40	5.95	8.85	5.84
		NIHSSF	5.89	4.34	7.44	6.26
		BI	56.56	48.65	64.47	31.67
		GOS	4.13	3.87	4.40	0.96

Table 2a

Results of all the variables compared between Awake and WUS.

VARIABLES	WUS N= 65 (29.6%)	AWAKE n=154 (70%)	P value
MEAN AGE	62.62	61.012	0.2239
MALE (%)	78.4	62	
FEMALE (%)	21.5	37.6	
SBP in mmHg	154.55	149.65	0.3443
DBP in mmHg	80.15	78.6	0.8078
PULSE	77.7	79.21	0.5843
HTN	40 (61.5%)	98 (63.3%)	0.7689
DM	37 (56.9%)	98 (63.3%)	0.3506
IHD	4 (6.1%)	24 (15.5%)	0.0562
AF	9 (13.8%)	11 (7.1%)	0.1157
DYSLIPIDEMIA	16 (24.6%)	42 (27%)	0.6839
OLD STROKE	21 (32%)	45 (29%)	0.6492
OBESITY	37 (56.9%)	105 (68%)	0.1109
RT	25 (38%)	62 (40%)	0.8802
LEFT	31 (47.6%)	81 (52.6%)	0.6488
BOTH	8 (12%)	11 (7.1%)	0.2148
VOLUME in cumm	32.8148	36.1465	0.8069
FRONTAL CORTICAL (%)	35.38	29.87	0.4222
FRONTAL SUBCORTICAL (%)	13.85	18.83	0.3735
INSULA (%)	23.08	11.69	0.0103
INTERNAL CAPSULE (%)	10.77	9.74	0.8170
BASAL GANGLIA (%)	12.31	11.69	0.8970

Table 2b

THALAMUS (%)	4.62	7.14	0.4848
PARIETAL (%)	24.62	16.88	0.1842
TEMPORAL (%)	16.92	11.69	0.2964
OCCIPITAL (%)	15.38	9.09	0.1732
MID BRAIN (%)	3.08	1.95	0.6094
PONS (%)	9.23	14.94	0.2552
MEDULLA (%)	1.54	2.6	0.6317
CEREBELLUM (%)	3.08	5.84	0.3917
SMALL ARTERY OCCLUSION (%)	36.92	38.96	0.7769
LARGE ARTERY ATHEROSCLEROSIS (%)	33.85	33.12	0.9167
CARDIOEMBOLIC (%)	21.54	16.88	0.4153
STROKE OF UNDETERMINED ETIOLOGY (%)	4.62	7.79	0.3952
STROKE OF OTHER DETERMINED CAUSE (%)	3.08	2.6	0.999
SYMPTOMATIC LARGE ARTERY STENOSIS (%)	47.69	47.69	0.7423
NIHSS ON ADMISSION	7.4	6.6169	0.4345
NIHSS ON DISCHARGE	5.8923	5.3092	0.4826
BI	56.5625	57.9866	0.4907
GOS	4.1321	4.339	0.2396

Table 3

Comparisons between the Continuous variables of WUS subgroups

Time	Number of patients	Variable	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
A (0:00-06:00)	28	AGE	60.93	55.24	66.62	14.68
		SBP	153.07	141.19	164.96	30.65
		DBP	78.50	74.67	82.33	9.88
		PULSE	79.71	74.74	84.69	12.83
		VOLUME	26.72	6.52	46.93	52.11
		NIHSS1	7.11	4.96	9.26	5.55
		NIHSSF	5.32	2.91	7.74	6.22
		BI	61.11	49.21	73.01	30.07
		GOS	4.29	3.87	4.70	0.90
B (06:01-12:00)	10	AGE	65.90	53.90	77.90	16.78
		SBP	154.60	130.11	179.09	34.24
		DBP	78.20	68.89	87.51	13.01
		PULSE	70.40	62.14	78.66	11.55
		VOLUME	15.06	0.06	30.05	20.96
		NIHSS1	5.50	2.44	8.56	4.28
		NIHSSF	3.80	1.49	6.11	3.22
		BI	58.00	34.38	81.62	33.02
		GOS	4.11	3.06	5.16	1.36
C (12:01-23:59)	27	AGE	63.15	57.55	68.75	14.15
		SBP	156.07	146.97	165.18	23.02
		DBP	82.22	76.58	87.86	14.25
		PULSE	78.33	74.15	82.52	10.58
		VOLUME	45.71	16.56	74.86	73.68
		NIHSS1	8.41	5.81	11.01	6.57
		NIHSSF	7.26	4.50	10.02	6.98
		BI	51.48	38.36	64.60	33.16
		GOS	4.00	3.63	4.37	0.85

Table 4a

Results of different variables of the subgroups of WUS

VARIABLE in WUS	Group A (0:00-06:00)	Group B (6:01-12:00)	Group C (12:01-23:59)	P value
NUMBER OF PATIENTS	28 (43%)	10 (15%)	27 (41%)	
AGE	60.9	65.9	63	0.9572
MALE	21 (32%)	8 (12%)	22 (33.8%)	
FEMALE	7 (10.7%)	2(3%)	5 (7.6%)	
SBP	153	154	156.074	0.7450
DBP	78.50	78.2	82.2	0.8106
PULSE	79.7143	70.4	78.3	0.0828
DM	17(26.15%)	4 (6.15 %)	16(24.6%)	0.4985
HTN	18 (27.7%)	4 (6.15%)	18 (27.7%)	0.3089
IHD	0	2 (3.08%)	2 (3.08%)	0.0732
AF	5 (7.69%)	1 (1.5%)	3 (4.62%)	0.7150
DYSLIPIDEMIA	8 (12.31%)	1 (1.54%)	7 (10.7%)	0.4935
OLD STROKE	10 (15.38%)	1 (1.54%)	10 (15.38%)	0.2592
OBESITY	17 (26.15%)	7 (10.77%)	13(20.00%)	0.4254
RIGHT-SIDED STROKE	10 (15.38%)	4 (6.15%)	11 (16.92%)	0.9238
LEFT-SIDED STROKE	18 (27.69%)	6(9.23%)	8 (12.31%)	0.0280
BIHEMISPHERIC STROKE	0	0	8 (12.31%)	0.0016
FRONTAL SUBCORTICAL	3 (4.62%)	2 (3.08%)	4(6.15%)	0.7524
FRONTAL CORTICAL	9 (13.85%)	3(4.62%)	11 (16.92%)	0.7429
INSULA	5 (7.69%)	3 (4.62%)	8 (12.31%)	0.5457
INTERNAL CAPSULE	4 (6.15%)	1 (1.54%)	2 (3.08%)	0.7103

Table 4b

BASAL GANGLION	3 (4.62%)	2 (3.08%)	3 (4.62%)	0.7226
THALAMUS	2(3.08%)	0	1 (1.54%)	0.6246
PARIETAL LOBE	4 (6.15%)	1 (1.54%)	11 (16.92%)	0.0379
TEMPORAL LOBE	6 (9.23%)	1 (1.54%)	4 (6.15%)	0.6602
OCCIPITAL LOBE	2(3.08%)	1(1.54%)	7 (10.77%)	0.1361
MID BRAIN	0	0	2 (3.08%)	0.2341
PONS	3 (4.62%)	1 (1.54%)	2 (3.08%)	0.9104
MEDULLA	1 (1.54%)	0	0	0.5112
CEREBELLUM	0	0	2 (3.08%)	0.2341
SMALL ARTERY OCCLUSION	14 (21.54%)	4 (6.15%)	6 (9.23%)	0.1002
LARGE ARTERY ATHEROSCLEROSIS	8 (12.31%)	4 (6.15%)	10(15.38%)	0.7262
CARDIOEMBOLIC	5 (7.69%)	1 (1.54%)	8 (12.31%)	0.3573
STROKE OF UNDETERMINED ETIOLOGY	0	0	3 (4.62%)	0.1093
STROKE OF OTHER DETERMINED CAUSE	0	1 (10%)	0	
SYMPTOMATIC	11 (16.92%)	5 (7.69%)	13 (20.00%)	0.7499
VOLUME	26.7229	15.056	45.7096	0.1163
NIHSS ON ADMISSION	7.107	5.5	8.407	0.1285
NIHSS ON DISCHARGE	5.32	3.8	7.26	0.2481
BI	61.1	58	51.48	0.4985
GOS	4.28	4.1	4	0.6072

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