

## Research Article

# Seasonal, Monthly, and Weekly Variations in Admissions, in-Hospital Mortality, and Length of Stay in Acute Ischemic Stroke in Northern Israel

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## Abstract

**Background:** The data describing the interrelation between stroke and meteorological conditions in countries with relatively uniform weather year-round are extremely limited and fragmented.

**Patients and methods:** In this retrospective cohort study we explored the seasonal, monthly, and weekly variations in admissions, in-hospital mortality, and length of stay among 2753 patients suffering from acute ischemic stroke and hospitalized in general wards of the largest tertiary hospital in northern Israel during the period from 2000 to 2008.

**Results:** Admissions due to acute ischemic stroke were found to be significantly more frequent on weekdays (2049, 74.4%) than on weekends (704, 25.6%) ( $p=0.0004$ ). January was found to be the month with the largest number of admissions (281, 10.2% of all admissions), and December and May had the lowest number of admissions relative to all other months (205, 7.4%). Regarding in-hospital mortality, 448 patients (16.3% of all patients) died during their hospitalization due to acute ischemic stroke. There was a statistically significant difference in the distribution of in-hospital deaths by seasons, with winter found to be the season with the highest in-hospital mortality ( $p=0.0008$ ) as compared with that of autumn (the season with the lowest mortality, which was used as a reference). No ethnic differences were found for seasonal, monthly, or weekly admissions or for in-hospital mortality.

**Conclusions:** An association was found between winter season and excess in-hospital mortality among patients with acute ischemic stroke hospitalized in general wards in northern Israel.

## INTRODUCTION

The issue of chronobiological variations has been the subject of numerous studies in many fields of general medicine on the whole and vascular disease and stroke in particular [1-6]. Several factors make this phenomenon especially difficult to address in patients with acute ischemic stroke. One factor is the biological heterogeneity of patients, such as age, gender, race, and ethnicity. Another factor is the different etiopathogenetic mechanisms involved in acute ischemic stroke, including cardioembolism, lacunar strokes resulting from small vessel disease, and major strokes resulting from large vessel occlusion. In addition, a variety of risk factors, such as hypertension, diabetes, smoking

and many others may play an independent role in seasonal, monthly, and weekly variations in acute ischemic stroke. Finally, the extreme variations in climate in different countries and between the Northern and Southern Hemispheres constitute another complicating factor in our understanding of seasonal and monthly variations in acute ischemic stroke. Although there is a clear trend in the literature towards a winter increase in the incidence of acute ischemic stroke in northern countries, little comparative data are available for southern countries.

This study aimed to explore the seasonal, monthly, and weekly variations in admissions, in-hospital mortality, and length of stay in patients hospitalized in general wards with acute

ischemic stroke in northern Israel (as presented by the stroke population of the largest tertiary hospital of Northern Israel, admitting patients from the ER and also from other hospitals in the area). The range of age in patients with stroke is very wide thus influencing the mortality rates. In an attempt to minimize the age differences in the study population we chose the population of patients hospitalized in general wards (where older patients with stroke are generally hospitalized).

## Patients and methods

This study is based on data for 2753 consecutive admissions of patients suffering from acute ischemic stroke and hospitalized in general wards of the largest tertiary hospital in northern Israel during the period from 2000 to 2008. The data were retrieved from the computerized system at Rambam Health Care Campus in Haifa, Israel, which contains data on demographic and risk factors, clinical status, work-up results, treatment regimens, and discharge details for all patients hospitalized since the year 1999. The data are collected by doctors and nursing personal and include detailed information on all aspects of hospitalization; chart records are not used in our hospital. Data included in the study were demographic (age, gender) and vascular risk factors, date of admission and discharge, and date of in-hospital death. Patients with in-hospital strokes were excluded from the study. Seasons were classified as followed: winter – December, January and February; spring: March, April and May; summer – June, July and August and autumn – September, October and November.

Risk factors were defined as follows: Hypertension was defined by either the record of a systolic blood pressure  $\geq 140$  mm Hg or a diastolic blood pressure  $\geq 90$  mm Hg, by the use of antihypertensive medication, or by a previously established diagnosis of hypertension. Diabetes mellitus was defined by a recorded random blood glucose level  $\geq 200$  mg/dL, by the use of insulin or an oral hypoglycemic agent, or by a previous diagnosis of diabetes mellitus. Hyperlipidemia was defined by the use of lipid-lowering medications or by a previous diagnosis of hyperlipidemia. Atrial fibrillation was defined by following the medical records or by a previously established diagnosis of atrial fibrillation. Ischemic heart disease was defined by a history of myocardial infarction or angina pectoris, or by a previous diagnosis of ischemic heart disease. Peripheral vascular disease (PVD) was defined by a history of intermittent claudication, peripheral vascular surgery, or angioplasty or by a previous diagnosis of peripheral vascular disease.

One of our aims was to estimate the influence of ethnicity on seasonal, monthly, and weekly variations in admissions, in-hospital mortality, and length of stay in patients with acute ischemic stroke. Towards this aim, Arab or Jewish ethnicity was assigned by place of birth and residence, in addition to first and family names. We examined inter-observer agreement between four observers for this method of classification of ethnicity in our population and obtained almost perfect agreement, with  $\kappa=0.96$ , as assessed by Fleiss' Kappa statistic.

## Statistical analysis

Various approaches, with different levels of sophistication,

can be applied to analysis of time-varying data. For example, a formal time-series analysis including autoregressive integrated moving average (ARIMA) modeling [7] could be employed to fully model trends and cyclic phenomena. However, we chose a simpler approach, due largely to the relatively small number of patients included in this study.

In order to examine possible differences in calendar-related effects, we assumed a probability ratio of 5:2 for weekdays vs. weekends; a 1/12 probability for each calendar month, and a 1/4 probability for each calendar season. Main analyses consisted of likelihood ratio chi-square tests of the actual vs. expected distributions of the number of cases for each weekday/weekend, month, or seasonal time period. When significant differences were detected, further subtests were performed based on reference to the time period with the smallest number of cases. (Note that the Israeli weekend is defined as Friday/Saturday). Additional analyses on length of stay employed the non-parametric Wilcoxon test, due to the non-normal distribution of the data. Basic comparisons between Jewish and Arab patients consisted of t-tests for continuous data and chi-square tests for categorical data. JMP (SAS Institute, Cary, NC, USA) was employed for statistical analysis.

## RESULTS

Table 1 presents demographic data and the distribution of risk factors profile for the patients included in the study. The mean age of patients hospitalized in general wards with acute ischemic stroke was  $75 \pm 11.7$  years. Of the 2753 patients studied, there were 1303 (47.3%) males and 1450 (52.7%) females. The seasonal, monthly, and weekly distributions of admissions are presented in Table 2. Admissions due to acute ischemic stroke were found to be significantly more frequent on weekdays (2049, 74.4%) than on weekends (704, 25.6%) ( $p=0.0004$ ). No statistical difference between seasons was found for the number of admissions. On the whole, no statistically significant differences were found for the distribution of admissions in different months. However, January was found to be the month with the

**Table 1:** Basic characteristics of patients included in the study.

Patient characteristics (number of patients in whom the information was available)	N (%)
Age (2753)	75±11.7
Male gender (2753)	1303 (47.3%)
Hypertension (2736)	2143 (78.4%)
Diabetes (2745)	1114 (40.6%)
Hyperlipidemia (2747)	779 (28.4%)
Smoking (2741)	629 (22.9%)
Ischemic heart disease (2745)	889 (32.4%)
Atrial Fibrillation (2744)	601 (21.9%)
Peripheral Vascular Disease (2750)	195 (7.1%)
Aspirin treatment before stroke (2752)	1180 (42.9%)
Clopidogrel treatment before stroke (2752)	95 (3.5%)
Warfarin treatment before stroke (2752)	248 (9%)
Previous stroke (2753)	839 (30.5%)

largest number of admissions (281, 10.2% of all admissions), and December and May had the lowest number of admissions relative to all other months (205, 7.4%).

Regarding in-hospital mortality, 448 patients (16.3% of all patients) died during their hospitalization due to acute ischemic stroke. The seasonal, monthly, and weekly distributions of in-hospital deaths are presented in Table 3. No statistically significant differences were found for the distribution of in-hospital mortality on weekdays as compared with weekends or for the distribution in different months. However, there was a statistically significant difference in the distribution of in-hospital deaths by seasons, with winter found to be the season with the highest in-hospital mortality (p=0.0008) as compared with that of autumn (the season with the lowest mortality, which was used as a reference). No significant difference was found for in-hospital mortality when spring or summer was compared with autumn. We also examined in-hospital mortality as influenced by date of admission (weekends versus weekdays) and did not find a significant relationship. No differences were found for the seasonal, monthly, or weekly distribution of length of stay in patients with acute ischemic stroke.

We also examined the influence of ethnicity (Arabs versus Jews) on seasonal, monthly, and weekly variations in admissions, in-hospital mortality, and length of stay. The comparisons between Arabs and Jews for demographic showed that the Jewish patients were older and suffered more from vascular risk factors as well as from vascular diseases. However, no differences were found for the seasonal, monthly, or weekly distribution of admissions or for in-hospital mortality. We did find a longer stay in the hospital for Jews than for Arabs suffering from acute

ischemic stroke [6 days (range 0-1840) vs. 5 days (range 1-734) median length, respectively, p =0.009]. This finding, however, was not influenced by seasonality.

**DISCUSSION**

Seasonal and monthly variations in stroke admissions have been studied in different countries and different climates. The majority of such studies have been performed in countries characterized by significant and sometimes extreme differences in seasonal characteristics, such as Japan [8-11], England [12,13], the USA [7,14,15], Scandinavian countries [16-18], and Australia [19,20], among others [21-25]. The data describing the interrelation between stroke and meteorological conditions in countries with relatively uniform conditions year-round are extremely limited and fragmented. Currently, there are almost no data on patterns of admission, in-hospital mortality, or length of stay due to ischemic stroke in Mediterranean climates, with the exception of one study from Italy [26] and one from Portugal [27] pointing to a winter excess in ischemic stroke.

There are currently no data available on seasonal, monthly, and weekly deviations in the number of admissions, in-hospital mortality, or length of stay among patients with acute ischemic stroke in the coastal region of Israel, where the city of Haifa is located Table 4. This region is characterized by hot humid summers and relatively comfortable winters, with temperatures during the winter usually above 10°C. A significant finding of our study was higher in-hospital mortality in winter than in any other season. The vast majority of compatible data in the literature that points to an excess in mortality from acute ischemic stroke in the winter [17,22,28-32] was obtained in countries with a continental climate, characterized by a cold and relatively long

**Table 2:** Seasonal, monthly, and weekly deviations in number of admissions due to acute ischemic stroke.

	Season				Month												Day of the week	
	Fall	Winter	Spring	Summer	January	February	March	April	May	June	July	August	September	October	November	December	Weekday	Weekend
Number of admissions	691	703	648	711	281	217	228	215	205	260	238	213	227	225	239	205	2049	704
%	25.1	25.5	23.5	25.8	10.2	7.8	8.3	7.8	7.5	9.4	8.6	7.7	8.2	8.2	8.7	7.4	74.4	25.6

**Table 3:** Seasonal, monthly, and weekly deviations in in-hospital mortality in patients with acute ischemic stroke.

	Season				Month												Day of the week	
	Fall	Winter	Spring	Summer	January	February	March	April	May	June	July	August	September	October	November	December	Weekday	Weekend
Number of in-hospital deaths	91	142	112	103	57	50	42	38	32	44	30	29	23	33	35	35	332	116
%	20.3	31.7	25	23	12.7	11.2	9.4	8.5	7.1	9.8	6.7	6.5	5.1	7.4	7.8	7.8	74.1	25.9

**Table 4:** Seasonal, monthly, and weekly deviations in median length of stay (days) in patients with acute ischemic stroke.

	Season				Month												Day of the week	
	Autumn	Winter	Spring	Summer	January	February	March	April	May	June	July	August	September	October	November	December	Weekday	Weekend end
Length of stay (Median time in days)	6	6	6	6	6	7	6	6	5	6.5	6	6	6	5	6	6	6	5

winter. The mechanism involved in such winter mortality excess is speculated to be a high incidence of inter-current respiratory infections during the wintertime. If that is indeed the case, then our findings indicate that such a mechanism may be important even in countries with a relatively mild climate. Moreover, the data demonstrating an increase of respiratory infections, including high rates of influenza among hospitalized patients in winter in Israel can be found in the literature [33,34].

Another significant finding of our study was that the number of admissions was significantly lower on weekends than on weekdays. The issue of admissions on weekdays as compared with weekends was examined in several studies in terms of the probability of subsequent higher mortality among patients with acute ischemic stroke admitted on weekends. Some of these studies did demonstrate a relationship between weekend admissions and higher mortality from vascular disease, including stroke, while others did not [35-42]. No such relationship was found in our study.

We also explored possible ethnic differences in seasonal, monthly, and weekly distributions of admissions, in-hospital mortality, and length of stay in patients with acute ischemic stroke. There are extensive data in the literature about the influence of ethnicity on the appearance, development, and outcome of ischemic stroke through cultural, social, economic, and genetic mechanisms [43-47]. Our data about incidence of acute ischemic stroke in Arabs and Jews were compatible with very limited data in the literature [48]. However, there are currently no data available on a possible ethnic influence in meteorobiology. Although, we did not find any correlation between the ethnicity of patients and meteorologic parameters in the present study, this issue should be the subject of future research.

Our study has some limitations. First, we compared crude mortality rates, not adjusted for likely confounders of in-hospital mortality (demographic parameters, clinical characteristics of stroke, co-morbidities, etc). This is explained mainly by the actually unlimited number of possible cofounders which make such analysis very difficult to perform. Second, we did not include information about infections in this study. This is because it's very difficult to differentiate between seasonal environmental infections (such as seasonal flu) and in-hospital infections such as UTIs, cellulites and others). Thus, we have decided not to include this information as well as information about patients treated with antibiotics and antipyretics in this study. However, this problem will be addressed in the future. Another point was that we addressed to the admission time and not to the onset time.

Unfortunately in many cases the precise onset time of stroke is unavailable. For example in so called wake up strokes, in severe strokes or strokes with aphasia when patient is unable to report the precise time of stroke onset. We also have no data about those patients who postponed their arrival to the hospital. Thus we chose to rely on precise and documented time of admission to the hospital. Also, note that the Arab ethnicity in Israel is of two different religions - Muslims and Christians. The weekend period (Friday and Saturday) normally practiced in Israel does not include the same free day (Sunday) of the Christian population. Because we had no adequate data, further sub analysis for this population was not done. The other interesting point which will be the subject of a separate study is the influence of external factors, such as periods of military conflicts on the variations of admission because of acute ischemic stroke.

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