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Relationship between adherence to the Mediterranean Diet, intracerebral hemorrhage, and its location

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Abstract *Introduction:* Although some authors evaluated the relationship between adherence to the Mediterranean Diet (MeDi) and both ischemic and hemorrhagic stroke, hemorrhagic stroke alone is not yet examined.
Aims: We conducted a retrospective study to evaluate the relationship between adherence to MeDi and intracerebral hemorrhage (ICH) and different locations of ICH (ganglionic/internal capsule, *brainstem/cerebellum*, *or lobar*).
Methods: We analyzed charts and collected data of all consecutive patients with ICH admitted to our Internal Medicine Ward from 2005 to 2014. A scale indicating the degree of adherence to the traditional MeDi Score was constructed.
Results: When compared with 100 subjects without ICH, 103 subjects with ICH had significantly higher mean values of LDL (91.1 ± 38.7 mg/dl vs. 79.2 ± 34.4 mg/dl; $p = 0.031$), triglycerides (118.9 ± 62.9 mg/dl vs. 101.6 ± 47.6 mg/dl; $p = 0.026$), and proteinuria (32.6 ± 50.0 mg/dl vs. 18.1 ± 39.6 mg/dl; $p = 0.024$) and a significantly lower mean MeDi Score (3.9 ± 1.0 vs. 7.0 ± 1.4; $p < 0.0001$). In a multiple regression analysis, smoking, diastolic blood pressure (DBP), and the MeDi Score remained significantly associated with ICH. We also observed a significantly lower mean MeDi Score in the lobar location group when compared with the ganglionic/internal capsule group (4.3 ± 1.0 vs. 3.5 ± 0.9; $p < 0.0005$).
Discussion: Our findings regarding the higher prevalence of ICH in patients with lower adherence to MeDi may be related to the fact that patients with lower MeDi Score exhibit a worse cardiovascular risk profile with increased risk factors such as hypertension and dyslipidemia.

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Introduction

Spontaneous, nontraumatic, intracerebral hemorrhage (ICH) is the second most prevalent subtype of stroke, and it is associated with high mortality and morbidity worldwide [1–8].

Adherence to the Mediterranean Diet (MeDi) is perceived to reduce the risk of cardiovascular diseases, cancer, Alzheimer's, and Parkinson's, as well as prevent premature death associated with these diseases [9,10].

A recent, multicenter Spanish study [12] reported that the MeDi supplemented with extra-virgin olive oil or mixed nuts is associated with a lower incidence of stroke.

Various evidences suggest the benefits of healthy food habits, such as consumption of adequate quantities of fruits, vegetables, legumes, unrefined cereals, and fish. Reduced intake of animal source foods is recommended to prevent stroke, at least partially, because of their favorable action on the main risk factors [10–12].

There are only a few studies on the relationship between ICH and MeDi [12,13,15], whereas no study has yet analyzed the relationship between adherence to the MeDi and localization of ICH.

Misirli et al. [13] analyzed the association of the traditional MeDi and major food groups with the incidence of and mortality rates from cerebrovascular diseases, such as ischemic and hemorrhagic stroke, among the Mediterranean population. They reported that increased adherence to the MeDi, as measured by 2-point increments in the score, was inversely associated with the incidence of cerebrovascular diseases.

Furthermore, Gardener et al. [14] reported that a higher adherence to the MeDi was inversely associated with risk of the composite outcome of ischemic stroke, myocardial infarction, or vascular death. Although they claimed that the inclusion of both ischemic and hemorrhagic stroke did not alter the study results for ischemic stroke in this cohort, hemorrhagic stroke alone was not examined.

The relationship between the MeDi and spontaneous ICH is elusive. Based on this, we conducted a retrospective study to evaluate the relationship between MeDi adherence and spontaneous ICH using the MeDi Score and determining the frequency and location of ICH.

Methods

We analyzed charts and collected data of all consecutive patients with ICH admitted to our Internal Medicine Ward from 2005 to 2014.

Patient admissions in our Internal Medicine Ward occur mainly from the city of Palermo, which is the most populous city in Sicily (Italy).

Since 2001, we had administered a validated food-frequency questionnaire, adapted to the Sicilian population, to all patients (or relatives when patients were unable to answer) admitted to our ward for evaluating their nutritional profile. This analysis represents a retrospective study of charts and collected data of patients with ICH admitted from 2005 to 2014.

As controls we analyzed 100 consecutive patients without ICH admitted to our Internal Medicine ward from December 2013 to April 2014 for other reasons than acute stroke (hemorrhagic or ischemic) and without a clinical history of ischemic stroke or ICH.

- The primary outcome in this study was:
  - to evaluate differences in mean MeDi Score between patients with ICH and control subjects without ICH
- The secondary outcome was:
  - to evaluate the relationship between ICH location and adherence to the MeDi measured by the MeDi score

The diagnosis of ICH was based on the following criteria [5]:

- lobar anatomic location
- other anatomic locations (ganglionic/internal capsule or brainstem/cerebellum)
- no diagnostic evidence of small vascular malformations (intracerebral arteriovenous malformations, cavernous angiomas, or venous angiomas)
- no diagnostic evidence of brain tumors
- no history of previous treatment with pro-hemorrhagic drugs such as anticoagulants, amphetamines, and other sympathomimetic drugs

ICH has been classified based on its location within the brain parenchyma, with "ganglionic/internal capsule" as ICH being located within the basal ganglia and internal capsule, brainstem-cerebellum as ICH being located within the pons or cerebellum, lobar as hemorrhages located in cortical–subcortical areas and follows a "lobar" pattern across one or, less often, multiple lobes of the brain [5].

Cardiovascular risk factors for cases and controls were evaluated by the following criteria:

- type 2 diabetes mellitus was determined using a clinically based algorithm that included age at onset, presenting weight and symptoms, family history, onset of insulin treatment, and history of ketoacidosis [8].
- hypertension was defined according to the 1993 World Health Organization criteria (systolic blood pressure (SBP) $\geq$140 mm/Hg and/or diastolic blood pressure (DBP) $\geq$90 mm/Hg in subjects who are not taking antihypertensive medication or undergoing other antihypertensive treatment on admission) [9].
- hypercholesterolemia was defined as the total serum cholesterol $\geq$200 mg/dl and hypertriglyceridemia as total serum triglyceride $\geq$150 mg/dL by the National Cholesterol Education Program–Adult Treatment Panel III reports [10,11] to determine the optimal total serum cholesterol and triglyceride levels

On admission to hospital, the blood pressure of all patients is measured as well as the levels of serum glucose, creatinine, serum uric acid, serum cholesterol, and serum triglyceride, along with urinary albumin excretion (UAE) values, are detected. Coronary artery disease was

identified from a history of physician-diagnosed angina, myocardial infarction, or any previous revascularization procedure determined by a questionnaire. Cerebrovascular diseases (ICH and TIA/ischemic stroke) were identified by the patient history, a specific neurological examination performed by specialists, and hospital or radiological records (brain CT or brain MRI) of definite TIA or stroke. The study protocol has been approved by the Ethics Committee of the Policlinico "P. Giaccone" Hospital. All patients or their relatives gave their written informed consent to participate in the study and use the collected data for publications.

MeDi score

All patients with ICH admitted to our ward (or their relatives) completed a 137-item validated food-frequency questionnaire [10,12] adapted to the Sicilian population. A scale indicating the degree of adherence to the traditional MeDi was constructed by Trichopoulou et al. [13]. A value of 0 or 1 was assigned to each of nine indicated components using the sex-specific median as the cutoff. For beneficial components (vegetables, legumes, fruits, nuts, cereal, and fish), individuals whose consumption was below the median were assigned a value of 0, and individuals whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat, poultry, and dairy products), individuals whose consumption was below the median were assigned a value of 1, and individuals whose consumption was at or above the median were assigned a value of 0.

Statistical analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items. The normal distribution of the data was assessed using the Kolmogorov–Smirnov test. Continuous data are expressed as a mean ± SD, unless otherwise specified. The basic differences between the groups were evaluated by the chi-square test or the exact Fisher test, as required for categorical variables, and by the independent Student's t-test for continuous parameters. The correlation analysis was conducted to examine the association between the MeDi Score and other clinical variables. Each categorical variable was converted into dummy variables, as appropriate. Univariate analysis of variance (ANOVA) was performed for parametric variables, and post hoc analysis using the Bonferroni method was performed to determine the intra-group differences in pairs. Multivariable logistic regression analysis was performed to examine the correlation between clinical patient characteristics, which are significant in univariate analysis (independent variables), and MeDi Score and site of ICH and severity (dependent variables). Odds ratio (OR) and its 95% confidence intervals (CIs) were also calculated and adjusted for confounding factors such as other cardiovascular risk factors (gender, diabetes, hypercholesterolemia, BMI, and atrial fibrillation). To evaluate the predictive rate of the different cutoff values of the MeDi Score in terms of the location of ICH, a characteristic operating curve of the receiver (ROC) was constructed with calculations of the area under the curve and 95% CI. The values of sensitivity and specificity were calculated. The data were analyzed by the Epi Info software (version 6.0, Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS software (version 21.0, SPSS Inc, Chicago, IL, USA). All P values were bilateral, and P values lower than 0.05 were considered statistically significant.

Results

Among patients admitted to our Internal Medicine Ward from 2005 to 2014, we have consecutively selected all patients with initial ICH. We, therefore, analyzed a total of 103 subjects with ICH and 100 control subjects without ICH. Demographic and clinical characteristics of subjects with ICH in comparison with control subjects are listed in Table 1.

The mean age of patients with ICH compared to controls was significantly higher (74.4 ± 11.1 vs. 68.9 ± 14.4; p 0.003). The proportion of current smokers in patients with ICH was higher when compared to controls (28% vs. 17%, $p < 0.0001$). Also, the values of mean SBP (140.6 ± 29.6 vs. 131.8 ± 21.2; p 0.016), DBP (79.5 ± 19.7 mm/Hg vs. 72.9 ± 13.6 mm/Hg; $p = 0.006$), and mean blood glucose levels (139.8 ± 84.5 mg/dl vs. 109.3 ± 46.5 mg/dl; $p < 0.0001$) were significantly higher. Subjects with ICH also showed significantly higher mean values of LDL-cholesterol (91.1 ± 38.7 mg/dl vs. 79.2 ± 34.4 mg/dl; $p = 0.031$), triglycerides (118.9 ± 62.9 mg/dl vs. 101.6 ± 47.6 mg/dl; p 0.026), and proteinuria (32.6 ± 50.0 mg/dl vs. 18.1 ± 39.6 mg/dl; p 0.024). Furthermore, subjects with ICH had a significantly lower mean MeDi Score (3.9 ± 1.0 vs. 7.0 ± 1.4; $p < 0.0001$).

On multiple regression analysis, confounding variables, such as smoking (OR = 4.03; 95%CI 1.15–14.2; $p = 0.030$), age (OR = 1.1; 95%CI 1.03–1.19; $p = 0.004$), DBP (OR = 1.08; 95%CI 1.01–1.15; $p = 0.024$), and the MeDi Score (OR = 0.09; 95%CI 0.04–0.23; $p < 0.0005$), was found to be significantly associated with ICH (see Table 2).

On analysis of clinical and laboratory variables in terms of ICH location, we found that diabetes is more common in subjects with a lobar location than those with ganglionic/internal capsule location ($p = 0.047$); HDL values were significantly lower in the lobar group than in the brainstem/cerebellum group ($p = 0.02$). We reported a significantly lower mean MeDi Score in the lobar location group when compared with the ganglionic/internal capsule group (4.3 ± 1.0 vs. 3.5 ± 0.9; $p < 0.0005$) (see Table 3). Multinomial logistic regression analysis confirmed the association between a lower MeDi Score (OR of 2.4; IC 95% 1.4–3.9; $p = 0.001$) with lobar location compared to the ganglionic/internal capsule location and an association between a lower mean HDL value (OR = 1.06; IC 95% 1.01–1.12; $p = 0.022$) and lobar location compared to the midbrain/cerebellum location (see Table 4).

Table 1 General demographic and clinical characteristics of patients with intracerebral hemorrhage (ICH) and control subjects.

Variable	Subjects with ICH (n: 103)	Subjects without ICH (n: 100)	P
Sex (M/F) (n/%)	52/51 (50.4/49.6)	58/42 (58/42)	0.063
Age (years) (mean ± ds)	74.4 ± 11.1	68.9 ± 14.4	0.003
SBP (mean ± ds)	140.6 ± 29.6	131.8 ± 21.2	0.016
DBP (mm/Hg) (mean ± ds)	79.5 ± 19.7	72.9 ± 13.6	0.006
HR (beats/min) (mean ± ds)	84.6 ± 14.4	81.9 ± 16.1	0.235
Glucose blood levels (mg/dl) (mean ± ds)	139.8 ± 84.5	109.3 ± 46.5	**<0.0001**
Total cholesterol (mg/dl) (mean ± ds)	159.8 ± 45.4	148.0 ± 40	0.074
HDL cholesterol (mg/dl) (mean ± ds)	43.5 ± 2.9	45.4 ± 9.9	0.43
Triglicerides (mg/dl) (mean ± ds)	118.9 ± 62.9	101.6 ± 47.6	**0.026**
LDL cholesterol (mg/dl) (mean ± ds)	91.1 ± 38.7	79.2 ± 34.4	**0.031**
Creatinine (mg/dl) (mean ± ds)	1.30 ± 0.89	1.57 ± 0.88	0.196
Proteinuria (mg/dl) (mean ± ds)	32.6 ± 50.0	18.1 ± 39.6	0.024
GFR (ml/min) (mean ± ds)	62.9 ± 27.8	70.1 ± 39.1	0.15
BMI (kg/m^2)	26.4 ± 3.16	27.01 ± 5.30	0.32
Mediterranean Diet (MeDi) Score (mean ± ds)	**3.9** ± 1.0	7.0 ± 1.4	**<0.0001**
Smoking			
- non smokers	74 (71.8)	47 (47)	
- smokers	29 (28.2)	17 (17)	
- ex smokers	0 (-)	36 (36)	<0.0001
Hypertension (n/%)	80 (77.6)	45 (45)	**<0.0001**
Diabetes (n/%)	41 (39.8)	33 (33)	0.070
Hypercholesterolemia (n/%)	28 (27.18)	19 (19)	0.054
Hypertrigliceridemia (n/%)	16 (15.5)	7 (7)	**0.032**
Atrial fibrillation (n/%)	28 (27.18)	22 (22)	0.090
LVH (n/%)	49 (47.5)	28 (28)	**0.031**
Coronary artery disease (CAD) (n/%)	24 (23.3)	14 (14)	**0.024**
Previous TIA (n/%)	3 (2.9)	**3 (3)**	0.71
Previous stroke (n/%)	18 (17.4)	11 (11)	0.66
Location of ICH			
Ganglionic/internal capsula (n/%)	39 (37.8)		
Lobar (n/%)	50 (48.5)		
Brainstem/cerebellum	14 (13.5)		

Statistically significant values are indicated in bold.
ICH: intracerebral hemorrhage; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; HDL: high density lipoprotein; LDL: low density lipoprotein; GFR: glomerular filtration rate; BMI: body mass index; MeDi Score: Mediterranean Diet Score; LVH: left ventricular hypertrophy; CAD: coronary artery disease; TIA: transient ischemic attack. Statistically significant values are indicated in bold.

Analysis of the ROC curve (see Table 5) showed that a mean MeDi Score ≤5 was significantly predictive of ICH compared to controls with sensitivity of 94% and specificity of 83%.

Furthermore, analysis of the ROC curve with regard to the lobar vs. ganglionic/internal capsule site (see Table 6) showed that a mean MeDi Score value of ≤3 was predictive for the lobar location ($p < 0.0001$), and the same value was predictive for the ganglionic/internal capsule vs. the midbrain/cerebellum location ($p = 0.017$) (see Table 7).

Table 2 Multivariable regression analysis of clinical variables associated with intracerebral hemorrhage (ICH).

GROUP[a]	OR	95% Confidence Interval	P
Smoking	**4.03**	**1.15–14.2**	**0.030**
Age	**1.11**	**1.03–1.19**	**0.004**
SBP	0.99	0.96–1.03	0.759
DBP	**1.08**	**1.01–1.15**	**0.024**
Glucose blood levels	1.01	0.99–1.02	0.102
LDL cholesterol	1.01	0.99–1.03	0.513
Triglicerides	1.00	0.99–1.01	0.901
Proteinuria	1.01	0.99–1.0	0.189
MeDi Score	**0.09**	**0.04–0.23**	**<0.0005**

Statistically significant values are indicated in bold.
[a] Reference is control group; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; MeDi Score: Mediterranean Diet Score.

Discussion

Our study reports that patients with ICH in comparison with healthy controls show a lower adherence to the MeDi (determined by the MeDi Score).

Specific dietary patterns, including the MeDi, have been associated with stroke prevention. However, only a very few data are available about the effects of MeDi on the prevention of stroke (12–16).

A recent study [16] evaluated whether the adherence to a healthy Nordic diet, including fish, apples and pears, cabbages, root vegetables, rye bread, and oatmeal, was associated with risk of stroke. During a median follow-up of 13.5 years, 2283 cases of incident stroke were verified, including 1879 ischemic strokes. Adherence to a healthy Nordic diet, as reflected by a higher Healthy Nordic Food Index score, was associated with a lower risk of stroke.

The question about the possibility of an association between the consumption of the MeDi and hemorrhagic

Table 3 General demographic and clinical characteristics of patients with intracerebral hemorrhage (ICH) with regards to hemorrhage location.

Variable	Ganglionic/internal capsula (n: 39)	Lobar (n: 50)	Brainstem/cerebellar (14)	P
Sex (M/F) (n/%)	17/22 (43.5/56.4)	27/23 (54/46)	7/7 (50/50)	0.29
Age (years) (mean ± ds)	75.6 ± 11.0	73.7 ± 11.3	73.7 ± 10.8	0.70
SBP (mean ± ds)	139.0 ± 27.7	139.6 ± 28.9	148.7 ± 37.2	0.54
DBP (mm/Hg) (mean ± ds)	78.6 ± 19.3	80.5 ± 18.8	78.3 ± 25.0	0.87
HR (beats/min) (mean ± ds)	84.3 ± 16.4	85.8 ± 15.8	80.8 ± 10.6	0.56
Glucose blood levels (mg/dl) (mean ± ds)	148.3 ± 77.2	173.9 ± 94.3	141.7 ± 59.7	0.25
Total cholesterol (mg/dl) (mean ± ds)	161.1 ± 53.0	155.0 ± 39.1	167.7 ± 45.1	0.61
HDL cholesterol (mg/dl) (mean ± ds)	44.8 ± 12.5	40.3 ± 11.5	50.7 ± 15.8	**0.02**
Triglicerides (mg/dl) (mean ± ds)	119.1 ± 70.3	124.8 ± 58.9	97.7 ± 54.2	0.36
LDL cholesterol (mg/dl) (mean ± ds)	91.3 ± 44.0	89.5 ± 35.2	96.0 ± 37.7	0.85
Creatinine (mg/dl) (mean ± ds)	1.2 ± 0.6	1.4 ± 1.1	0.9 ± 0.2	0.18
GFR (ml/min) (mean ± ds)	62.9 ± 28.1	59.4 ± 29.7	75.5 ± 14.6	0.16
BMI (kg/m^2)	27.1 ± 3.3	26.1 ± 2.8	25.3 ± 3.4	0.11
MeDi Score (mean ± ds)	4.3 ± 1.0	3.5 ± 0.9	4.0 ± 0.7	**0.001**
Smoking				
- non smokers	26 (66.6)	37 (74)	11 (78.5)	
- smokers	13 (33.4)	13 (26)	3 (21.4)	0.21
Hypertension (n/%)	29 (74.3)	41 (82)	10 (71.42)	0.51
Diabetes (n/%)	11 (28.2)	26 (52)	4 (28.5)	**0.047**
Hypercholesterolemia (n/%)	12 (30.7)	11 (22)	5 (35.7)	0.54
Hypertrigliceridemia (n/%)	7 (17.9)	7 (14)	2 (15.2)	0.40
Atrial fibrillation (n/%)	9 (23.07)	13 (26)	6 (42.8)	0.14
LVH (n/%)	19 (48.7)	26 (52)	4 (28.5)	0.22
CAD (n/%)	6 (15.3)	8 (16)	0 (0)	0.18
Previous TIA (n/%)	0 (0)	3 (6)	0 (0)	0.41
Previous stroke (n/%)	6 (15.3)	13 (26)	5 (35.7)	**0.031**

Statistically significant values are indicated in bold.
ICH: intracerebral hemorrhage; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; HDL: high density lipoprotein; LDL: low density lipoprotein; GFR: glomerular filtration rate; BMI: body mass index; MeDi Score: Mediterranean Diet Score; LVH: left ventricular hypertrophy; CAD: coronary artery disease; TIA: transient ischemic attack. Statistically significant values are indicated in bold.

Table 4 Multiple regression analysis of hemorrhage location.

ICH location		OR	95% Confidence Interval	P
Ganglionic/internal capsula	HDL-cholesterol	0.97	0.94–1.01	0.21
	MeDi Score	**0.39**	**0.23–0.66**	**0.001**
Brainstem/cerebellum	HDL-cholesterol	1.04	0.98–1.09	0.12
	MeDi Score	0.69	0.37–1.33	0.25
Reference category: *Lobar*				
ICH location				
Lobar	HDL-cholesterol	**2.37**	**1.42–3.96**	**0.001**
	MeDi Score	1.02	0.98–1.06	0.17
Brainstem/cerebellum	HDL-cholesterol	**1.06**	**1.01–1.12**	**0.022**
	MeDi Score	1.46	0.78–2.73	0.22
Reference category: *ganglionic/internal capsula*				

Statistically significant values are indicated in bold.

stroke is still understudied. Garderner et al. in a multiethnic population-based cohort, the Northern Manhattan Study (NOMAS) [14], examined the association between the MeDi and myocardial infarction and stroke in a multiethnic urban sample. Nevertheless, more studies are needed to compare the relative associations of the MeDi with stroke subtypes because this study had no sufficient statistical power to examine the association between MeDi and hemorrhagic stroke. Authors observed that with high MeDi Score, with every 1-point increase, the HR of hemorrhagic stroke over a mean of 10 years of follow-up was 0. Therefore, the effect of MeDi on hemorrhagic stroke risk was more protective than that for ischemic stroke, although neither was statistically significant.

In the present study, our patients with ICH showed a higher prevalence of hypertension and hypertriglyceridemia and higher mean value of SBP and DBP and glucose blood levels.

Thus, our findings concerning a lower mean MeDi Score in ICH patients compared to controls can be related to a different cerebrovascular risk profile linked to low adherence to the MeDi. Our findings regarding the lower degree of SBP and DBP values and the lower frequency of hypertension in subjects with higher adherence to the MeDi seem worthy of interest. The biological plausibility explaining the causality of such findings has been supported by several studies demonstrating a protective role of the MeDi on decreased insulin resistance [17], glycemic

Table 5 ROC curve analysis of association between Mediterranean Diet Score and ICH diagnosis.

Variable	Mediterranean Diet Score
Sample size	**203**
Area under the ROC curve (AUC)	0.948
Standard Error	0.0148
95% Confidence interval	0.919 to 0.977
Significance level P	<**0.0001**
Associated criterion	<**5**
Sensitivity	94.2
Specificity	83.0

Statistically significant values are indicated in bold.

Table 6 ROC curve analysis of association between Mediterranean Diet Score and ICH location (ganglionic/internal capsula vs. lobar).

Variable	Mediterranean Diet Score
Sample size	**89**
Positive group	**50**
Negative group	**39**
ganglionic/internal capsula	
lobar	
Classification variable	ICH location
Area under the ROC curve (AUC)	0.73
Standard Error	0.0544
95% Confidence interval	0.2266 to 0.5805
Significance level P	<**0.0001**
Associated criterion	≤**3**
Sensitivity	94.2
Specificity	83.0

Statistically significant values are indicated in bold.

index [18], lower plasma concentrations of inflammatory markers, and markers of endothelial dysfunction [19].

Our results of a higher prevalence of ICH in patients with lower adherence to MeDi may be related to the fact that patients with lower MeDi Score exhibit a worse cardiovascular risk profile. These patients showed a higher prevalence of atherogenic cardiovascular risk factors such as hypertension and dyslipidemia. In addition, they had higher mean values of systolic and diastolic arterial pressure and glucose blood levels. This is because adherence to the MeDi, although exhibit worse cardiovascular risk profile, can also be independent of nutritional pathways and linked to ethnic and genetic factors.

Table 7 ROC curve analysis of association between Mediterranean Diet Score and ICH location (ganglionic vs. brainstem/cerebellum location).

Variable	Mediterranean Diet Score
Sample size	**64**
Positive group	**50**
Negative group	**14**
ganglionic/internal capsula	
brainstem/cerebellum	
Classification variable	ICH location
Area under the ROC curve (AUC)	0.690
Standard Error	0.079
95% Confidence interval	0.53 to 0.84
Significance level P	0.017
Associated criterion	**≤3**
Sensitivity	68.00
Specificity	71.43

Statistically significant values are indicated in bold.

Several randomized controlled trials (RCTs) [20–23] showed the positive effects of the MeDi diet on several cardiovascular (CVD) risk factors such as body mass index, waist circumference, blood lipids, blood pressure, inflammatory markers, and adhesion molecules and diabetes [21].

In the ATTICA study of 3042 adult men and women from Greece [24], investigators reported that participants with high blood pressure were less likely to consume the traditional MeDi compared with normotensives. A substudy [25] of the same study showed that in overweight and obese people, a greater adherence to MeDi was only modestly associated with higher insulin sensitivity, better lipid profile, and lower blood pressure levels.

Thus, according to our findings, subjects with ICH having a lower MeDi Score are more prone to risk factors for ICH such as hypertension.

On performing multiple regression analysis, age, DBP, and the mean MeDi Score were significantly associated with ICH. Furthermore, we reported that MeDi adherence is negatively associated with ICH based on multivariable analysis.

The pathogenetic explanations of this relationship are consistent with previous studies, reporting the effects of MeDi on several biological pathways.

The most studied mechanisms can mediate the positive effects of the traditional MeDi, which include lipid-lowering effects, action against oxidative stress, anti-inflammatory effects, and effects on platelet aggregation, inhibition of nutrient sensing pathways by specific amino acid restriction, and gut microbiota-mediated production of metabolites influencing metabolic health [19,23–25].

Among these putative positive effects, antioxidant and anti-inflammatory ones could be directly involved in the observed protective role of MeDi toward ICH incidence, whereas inhibition of nutrient sensing pathways and microbiota-mediated effects could have an indirect effect on the risk of brain hemorrhage.

A study by Esposito et al. [19] showed that patients consuming control diet had significantly lower serum concentrations of hs-CRP, IL-6, and IL-18 as well as decreased insulin resistance ($P < 0.001$) when compared with patients consuming MeDi. Furthermore, it was observed that the endothelial function score improved in the intervention group but remained stable in the control group.

On analysis of clinical and laboratory variables with regards to ICH location, we found that some cardiovascular risk factor such as diabetes and low HDL were more common in subjects with a lobar location than in those with ganglionic/internal capsule location. We also observed a significantly lower mean MeDi Score in the lobar location group than in the ganglionic/internal capsule and the brainstem/cerebellum groups.

These are original findings of our study that are not easily explainable.

Nontraumatic bleeding into the brain parenchyma is caused due to a rupture of small penetrating arteries. In deep hematomas, this has been attributed to degenerative changes in the vessel wall associated with advancing age, hypertension, diabetes, and other vascular risk factors. In addition, Charcot-Bouchard microaneurysms and lipohyalinosis of small arterioles have been suggested as possible direct pathogenetic mechanisms [26].

In lobar hematomas related to cerebral amyloid angiopathy (CAA), the underlying mechanism is a combination of vascular amyloid deposition and vessel wall breakdown, involving capillaries, arterioles, and small-sized arteries, primarily in the cerebral cortex [27].

Our findings concerning the higher frequency of diabetes and low serum levels of HDL cholesterol in our subjects with lobar ICH corroborate the role of atherosclerotic risk factors in pathogenetic mechanisms of spontaneous brain bleeding. These findings seem to be consistent with recent studies that reported several risk factors such as hyperlipidemia and diabetes in adjunction to hypertension can cause nontraumatic brain hemorrhage [28,29].

Our findings of a lower mean MeDi Score in subjects with lobar ICH are consistent with the possible pathogenetic role of vascular risk factors when compared to other possible locations (ganglionic/internal capsule and brainstem/cerebellum).

Cerebral amyloid angiopathy (CAA) is characterized histopathologically by amyloid fibrils in the small to middle-sized blood vessels, mainly the arteries, of the brain that usually manifests as lobar ICH. In about 10% of all cases of primary ICH, CAA is regarded as a possible cause [6]. Nevertheless, in case of lobar bleeding, the probability rises to 30%–70% [32].

Thus, most of our observed lobar ICH may be due to CAA.

Diabetes and cholesterol serum levels also seem to be associated with CAA. Recent studies [27–29] underlined the causal relationship between hypercholesterolemia, development of type 2 diabetes, oxidative stress consequences for cerebral amyloid angiopathy, and neurodegenerative diseases. Furthermore, another study demonstrated a flux of another oxygenated product of cholesterol, 27-hydroxycholesterol, in the opposite direction. The latter flux may be important for neurodegeneration and may be the link between hypercholesterolemia, hypocholesterolemia HDL, and CAA [29–31].

Previous data collected to determine the state of health and food consumption in patients with ICH in Sicily are lacking. Thus, our study provides the sample of subjects recruited. However, our study has some limitations, such as its retrospective nature, the small sample size, and the fact that it was conducted in a single institution. The data could also be affected by recall bias. Another limitation relies on differences between the two groups in terms of age and gender. The study reported that the higher prevalence of diabetes and hypertension are associated with cardiovascular risk factors and brain hemorrhages.

In summary, the results of our study showed that patients with ICH have a lower MeDi Score compared with control subjects without ICH and, hence, they are more likely to have a lobar location of ICH.

Conflicts of interest

None declared.

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