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Sex-differences in clinical characteristics and outcome in primary intracerebral haemorrhage

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Summary. *Introduction.* Intracerebral haemorrhage (ICH) is characterised by a high risk of mortality and disability. Studies on sex differences in ICH characteristics and outcomes have been inconclusive. The aim of our observational study is to investigate the demographics, aetiology, location, stroke care, and intra-hospital mortality of ICH patients, in order to evaluate sex differences.

Methods. Consecutive patients with primary ICH admitted to the Santa Maria della Misericordia Hospital in Perugia, Italy, between 1st January 2009 and 31st March 2017 were included. All patients were classified according to SMASH-U. Intra-hospital mortality rates and their timings were recorded for each included patient.

Results. 1,441 patients were identified on the basis of the 431 ICD-9 code. A total of 727 patients were included in the study; 322 (44.3%) were females. Females were older than males (73.9 vs 70.5, p = 0.001). Hypertensive angiopathy was the most common aetiology for both sexes. Amyloid angiopathy was more frequent in females, whereas drug-induced ICH was more frequent in males. Additionally, NIHSS was slightly higher for females. No sex difference was observed for intra-hospital mortality. Multivariate analysis performed separately on the sexes suggested that hypertension-related ICH was independently associated with an increased risk of mortality in females. For both sexes, ICH severity, evaluated using the NIHSS, correlated with an increased risk of intra-hospital mortality.

Conclusions. In our study, no sex differences in intra-hospital mortality were detected. At ICH onset females tended to be older than males. Hypertension-related ICH tended to be more severe in females and correlated with a higher risk of intra-hospital mortality.

Key words. Intra-cerebral haemorrhage, outcome, mortality, sex differences.

Differenze di genere nelle caratteristiche cliniche e nell'outcome dei pazienti con emorragia cerebrale primitiva

Riassunto. *Introduzione.* L'emorragia intracerebrale è associata ad un alto rischio di mortalità e disabilità. Gli studi scientifici focalizzati sulle differenze di genere nelle caratteristiche e nella prognosi dei pazienti con emorragia hanno portato a dati discordanti. Lo scopo del nostro studio osservazionale è di indagare, nei pazienti con emorragia cerebrale, eventuali differenze di genere riguardo a caratteristiche demografiche, eziologia, localizzazione, gestione della fase acuta e prognosi in termini di mortalità.

Metodi. Sono stati inclusi nello studio pazienti con emorragia cerebrale ricoverati consecutivamente nell'Ospedale Santa Maria della Misericordia di Perugia (Italia) tra l'1 gennaio 2009 e il 31 marzo 2017. Tutte le emorragie cerebrali sono state classificate in base alla classificazione SMASH-U. Sono stati quindi registrati il tasso di mortalità intraospedaliera e la tempistica della stessa.

Risultati. Sono stati identificati 1441 pazienti in base al codice 431 ICD-9. Un totale di 727 pazienti è stato incluso nello studio, di cui 322 (44,3%) donne. L'età media delle donne era maggiore rispetto a quella degli uomini (73,9 vs 70,5; p = 0,001). L'eziologia più frequente in entrambi i sessi è stata l'angiopatia ipertensiva. L'angiopatia amiloide era più frequente nel sesso femminile mentre l'emorragia cerebrale iatrogena era più frequente nel sesso maschile. Inoltre, l'NIHSS era leggermente più alta nelle donne rispetto agli uomini. Non sono state riscontrate differenze nella mortalità intraospedaliera. L'analisi multivariata effettuata separatamente in entrambi i sessi ha mostrato che l'emorragia da angiopatia ipertensiva era associata ad un maggior rischio di mortalità nelle donne. In entrambi i sessi, la gravità dell'emorragia cerebrale, misurata con l'NIHSS era correlata ad un maggior rischio di mortalità intraospedaliera.

Conclusioni. Nel nostro studio non sono state registrate differenze di genere nei tassi di mortalità intraospedaliera. Al momento dell'emorragia cerebrale le donne avevano un'età più avanzata rispetto agli uomini. L'emorragia da angiopatia ipertensiva tende ad essere più grave nelle donne rispetto agli uomini ed è correlata ad un maggior rischio di mortalità intraospedaliera.

Parole chiave. Emorragia intracerebrale, prognosi, mortalità, differenze di genere.

Introduction

Intracerebral haemorrhage (ICH) accounts for 10-15% of all strokes; it is characterised by about 50% mortality within the first month after the event, and only about 20%-25% of survivors are able to live independently at six months[1]. Gender differences relating to stroke has been reported worldwide; however, most studies focus primarily on ischemic stroke[2-4]. Indeed, they report that

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age, atrial fibrillation (AF) and high National Institute of Health Stroke Scale (NIHSS) are independently associated with contributing to an unfavourable outcome[5]. Hence, changes in guidelines and treatment approaches have been introduced to reflect these findings, leading to easier access for females to evidence-based acute ischemic stroke treatment, including thrombectomy and thrombolysis treatments[6].

Sex differences in ICH characteristics and outcomes have not been thoroughly studied, and the reported results are inconclusive. A meta-analysis in 2010[1] and a review published in 2015[7] both emphasise the conflicting results reported regarding sex differences in ICH outcomes. According to this recent review[7], reported ICH case fatalities range from 16.2% to 51.8% in females and 18.8% to 51.8% in males, with outcome data showing even less consistency. A recent comprehensive and prospective 11-year study, taking into account the covariables that could influence outcome data, reported a 3-month mortality rate amongst ICH patients of 42.5%, with no sex differences. Three-month morbidity was higher amongst females. However, this difference was not significant after adjustment for previous mRS and ICH score [OR 1.47 95% (CI 0.86-2.52), p = 0.152][8]. Based on these data, female ICH patients seem to have worse outcomes.

For this reason, our observational study investigated the demographics, aetiology, location, stroke care, and intra-hospital mortality of ICH patients in a single-centre hospital-based registry, in order to evaluate sex differences.

Methods

This retrospective, single-centre, observational study included consecutive ICH patients admitted to the internal medicine, internal and vascular medicine, neurosurgery, endocrinology and metabolic diseases, geriatrics, oncology, haematology units, as well as the stroke unit and intensive care unit at the Santa Maria della Misericordia Hospital in Perugia, Italy, between 1st January 2009 and 31st March 2017. The inclusion criterion was a ICD-9-CM diagnostic code of 431, at either admission or discharge. This diagnostic code identifies cases of haemorrhage within the brain parenchyma. Whenever re-bleeding was detected in patients, the most recent episode was used for classification purposes.

The 2010 American stroke association's definition of ICH was adopted, i.e. that ICH is "the rapid development of neurological signs and symptoms attributable to the accumulation of blood within the brain parenchyma or ventricles not caused by trauma".

Patients with primary subdural/epidural haematoma, traumatic ICH or haemorrhage due to brain cancer (non-vascular origin), as well as those with primary subarachnoid haemorrhage, with or without ICH, and haemorrhagic transformation of a cerebral infarction, with or without thrombolysis, were excluded.

All patients were classified according to SMASH-U, which classifies ICH according to the underlying cause: structural lesions (cavernomas and arteriovenous malformations), medication (anticoagulation), amyloid angiopathy, systemic diseases (liver cirrhosis, thrombocytopenia, and various rare conditions), hypertension, and undetermined causes[9]. Unlike the SMASH-U study, we also included aneurysms in the structural lesion group, along with arteriovenous malformations (AVMs) and cavernomas. Whereas the medication group included patients prescribed VKAs regardless of their INR values, NOACs or antiplatelets. The A, S, H, U groups adopted the same inclusion criteria as SMASH-U.

Risk factors

Data regarding ICH risk factors were collected for each patient including age, sex and history of: hypertension (BP >140/90 mmHg twice before the stroke or patient currently under antihypertensive treatment), myocardial infarction, ICH (year and location), diabetes mellitus (pre-prandial glycaemia ≥126 mg/dl for at least 2 examinations, post-prandial glycaemia ≥200 mg/dl, HbA1c ≥7% or currently on glucose-lowering treatment), atrial fibrillation (AF), and/or systemic diseases (thrombocytopoenia, coagulation disorders, renal failure, liver disease). Medication history was investigated for each patient focusing on oral anticoagulants (OATs), direct oral anticoagulants (NOACs), heparin and antiplatelet agents.

Location of ICH

To analyse ICH location, the first available cranial computed tomography (CT) scan was used and was evaluated by vascular neurologists blinded to clinical data. Involvement of the thalamus, basal ganglia, or internal capsule was defined as deep ICH; involvement of the cortex and cortical-subcortical junction as lobar ICH; and involvement of the cerebellum as cerebellar ICH.

Outcome

Intra-hospital mortality rates and their timings were recorded for each patient included.

Statistical analysis

The aim of the analysis was to investigate the associations between risk factors and outcome (intra-hospital mortality) in males and females. Subsequently, we

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compared these overall results between the two sexes. Continuous variables were expressed as medians and interquartile ranges (IQR 25-75). Categorical variables were expressed as percentages. Univariate analyses (c2 test or Fisher's exact test with Yate's correction when appropriate) for categorical variables and ANOVA for continuous variables, were used to carry out the sex comparisons. Multivariable logistic regression analyses were performed to identify independent predictors for mortality in the overall study population and between the sexes. The variables included in this latter analysis were: classification and location, NIHSS at admission, vascular risk factors such as hypertension, prior myocardial infarction, atrial fibrillation, age, diabetes mellitus and previous use of antiplatelets and anticoagulants. Data were analysed with the SPSS/PC Win package 25.0.

Results

Between January 2009 and July 2017, 1,441 patients were identified by ICD-9 code 431, at either admission or discharge. During data retrieval, 714/1,441 patients were excluded: 548 did not meet the data requirements, 73 had epi-subdural haemorrhages, 43 had traumatic intracerebral haemorrhages, 19 had ischemic strokes (IS), 14 had IS with haemorrhagic infarction, 7 had had bleeds in the pre-study period, 5 had bleeds associated with neurosurgical interventions and 5 had bleeding tumours (glioblastoma, metastasis, meningioma).

A total of 727 patients were included in the study; 405 (55.7%) were males, and 322 (44.3%) were females. Mean age was 72 ± 13.9 (Table 1).

Most of the patients (621/727) were admitted to the Stroke unit and neurointensive care. No sex differences were found in order to the hospitalisation setting. Patients not admitted to stroke care had usually systemic underlying pathology as cancer, haematological disorder and/or cognitive impairment. The significant differences observed with univariate analysis were that females were older than males (73.9 vs 70.5, p = 0.001) and more males than females had previous ischaemic heart disease (11.6% vs 3.4%). We did not observe any differences regarding previous antithrombotic therapy in men and women.

As regards location, no statistically significant differences were observed; however, males seemed to have deeper haemorrhages than females (44.7% vs 36.6%). As far as aetiology is concerned, hypertensive angiopathy was the most common aetiology for both sexes, and there was no significant difference between the sexes. Amyloid angiopathy was more frequent in females (5.3% vs 3.5%), whereas medication-induced ICH was more frequent in males (19.7% vs 15.5%). The severity

Table 1. Investigated univariate variables according to sex (n = 727)

	Males n = 405 (55.7%)	Females n = 322 (44.3%)	p
Age	70.5 ± 13.8	73.9 ± 13.9	0.001
SMASH-U			0.5
Structural lesion	38 (9.8%)	32 (9.9%)	
Medication	80 (19.7%)	50 (15.5%)	
Amyloid angiopathy	14 (3.5%)	17 (5.3%)	
Systemic disease	41 (10.1%)	31 (9.6%)	
Hypertensive angiopathy	138 (34.0%)	105 (32.6%)	
Undetermined	94 (23.2%)	86 (26.7%)	
ICH location			0.08
1	167 (41.2%)	156 (48.4%)	
2	181 (44.7%)	118 (36.6%)	
3	51 (12.6%)	40 (12.4%)	
Hypertension	316 (78%)	241 (74.8%)	0.3
AF	59 (14.6%)	37 (11.5%)	0.2
DM2	68 (16.8%)	42 (13%)	0.1
Obesity	14 (3.5%)	11 (3.4%)	1.0
Renal failure	10 (2.4%)	5 (1.6%)	0.4
Liver failure	14 (3.5%)	9 (2.8%)	0.7
Warfarin	51 (12.6%)	39 (12.1%)	0.9
DOACs	12 (3%)	3 (0.9%)	0.06
Antiplatelet agents	106 (26.2%)	75 (23.3%)	0.4
Previous stroke/TIA	34 (8.4%)	20 (6.2%)	0.2
Previous ischaemic heart disease	47 (11.4%)	11 (3.4%)	0.0001
Alcohol overuse	16 (4%)	1 (0.3%)	0.1
NIHSS at onset	11.36 ± 6.59	13.61 ± 7.87	0.09
Length of hospitalisation	15.25 ± 12.58	16.05 ± 12.95	0.4
Stroke care (stroke unit or neurointensive acute unit)	349 (86.2%)	272 (84.2%)	0.4
Mortality	107 (26.4%)	80 (24.8%)	0.7

ICH: intracerebral haemorrhage, AF: atrial fibrillation, DM2: type 2 diabetes mellitus, DOACs: direct oral anticoagulants, TIA: transient ischaemic attack, NIHSS: National Institute of Health Stroke Scale.

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Table 2. Multivariate analysis of outcome in the two sexes

	OR	95% CI	p
SMASH-U			
Structural lesion	1	1	1
Medication	3.47	1.15-10.46	0.02
Amyloid angiopathy	1.02	0.29-3.63	0.96
Systemic disease	3.64	1.47-9.01	0.005
Hypertensive angiopathy	1.46	0.59-3.62	0.416
Undetermined	2.03	0.86-4.77	0.103
Hypertension	0.86	0.54-1.38	0.54
Antiplatelet agents	1.07	0.69-1.66	0.75
Prior AMI	1.74	0.93-3.23	0.07
Atrial fibrillation	0.96	0.51-1.81	0.91
Age	1.01	1-1.03	0.04
Anticoagulation	0.48	0.2-1.14	0.09
DM2	1.2	0.7-1.99	0.37
Sex (men)	1.04	0.72-1.41	0.84
NIHSS at admission	1.38	1.07-1.78	0.013

AMI: acute myocardial infarction, DM2: type 2 diabetes mellitus, NIHSS: National Institute of Health Stroke Scale, OR: odds ratio, 95% CI: 95% confidence interval, p: p value.

Table 3. Multivariate analysis of outcome in females

	OR	95% CI	p
SMASH-U			
Structural lesion			
Medication	0.26	0.05-1.28	0.09
Amyloid angiopathy	3.03	0.72- 2.70	0.12
Systemic disease	0.14	0.018-1.16	0.07
Hypertensive angiopathy	2.55	1.00-6.51	0.05
Undetermined	0.76	0.28-2.03	0.59
Hypertension	1.29	0.61-2.73	0.49
Antiplatelet agents	0.91	0.44-1.87	0.81
Prior AMI	0.80	0.17-3.74	0.78
Atrial fibrillation	1.16	0.42-3.18	0.77
Age	1.01	0.99-1.04	0.17
Anticoagulation	0.26	0.05-1.20	0.08
DM2	1.33	0.59-2.97	0.48
ICH location			
1			0.51
2	1.75	0.62-4.91	0.28
3	1.22	0.47-3.17	0.67
NIHSS at admission	1.35	1.06-1.72	0.014

AMI: acute myocardial infarction, DM2: type 2 diabetes mellitus, ICH: intracerebral haemorrhage, NIHSS: National Institute of Health Stroke Scale, OR: odds ratio, 95% CI: 95% confidence interval, p: p value.

of ICH was similar for both sexes, whereas the NIHSS was slightly higher for females (13.61 vs 11.36, p = 0.09). No significant difference was observed in the duration of hospitalisation (15.25 in males vs 16.05 in females, p = 0.4). No sex difference was observed with regard to intra-hospital mortality: 26.4% for males and 24.8% for females (p = 0.7).

Multivariate analysis was performed on the outcome for all patients (Table 2). Increasing age and NIHSS at admission independently correlated with higher risks of intra-hospital mortality (p = 0.04 and p = 0.013, respectively). ICH due to medication and systemic disease independently correlated with increased mortality risk (p = 0.02 and p = 0.005, respectively).

Multivariate analysis performed separately on the sexes suggested that hypertension-related ICH independently correlated with an increased risk of mortality in females (p = 0.05, Table 3). None of the aetiology types was seen to independently correlate with mortality in males, whereas a history of a previous ischemic heart attack was associated with a higher risk of mortality in this sex (Table 4). For both sexes, ICH severity, evaluated with NIHSS, was correlated with an increased risk of intra-hospital mortality.

Discussion

Based on our data from a large hospital database, no sex differences were observed in the intra-hospital mortality rate of ICH patients. This is in line with a recent meta-analysis[1] and other prospective studies[8,10].

In our database, age and stroke severity independently correlated with an increased risk of intra-hospital mortality for both sexes. However, females had slightly higher average NIHSS and were on average 3 years older than males, as reported in previous studies[1,8,11].

Considering classification according to SMASH-U, ICH due to medication and to systemic disease independently correlated with an increased risk of mortality (p = 0.02 and p = 0.005 respectively) in both sexes. Indeed, anticoagulant medication has been reported as a predictive factor for haematoma expansion leading to higher mortality[12,13], whereas the underlying condition may influence the higher mortality in systemic disease-related ICH.

The multivariate analysis, exploring the variable associated with an increased risk of mortality separately in the two sexes, revealed that hypertension-related ICH was associated with intra-hospital mortality in females,

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Table 4. Multivariate analysis of outcome in males

	OR	95% CI	p
SMASH-U			
Structural lesion			0.79
Medication	0.68	0.23-1.96	0.47
Amyloid angiopathy	1.15	0.38-3.47	0.79
Systemic disease	1.22	0.34-4.43	0.75
Hypertensive angiopathy	1.33	0.57-3.12	0.50
Undetermined	0.74	0.32-1.72	0.48
Hypertension	0.59	0.32-1.10	0.09
Antiplatelet agents	1.17	0.66-2.08	0.58
Prior AMI	2.22	1.09-4.53	0.02
Atrial fibrillation	0.88	0.38-2.01	0.76
Age	1.01	0.99-1.03	0.14
Anticoagulation	0.74	0.24-2.23	0.59
DM2	1.24	0.67-2.30	0.48
ICH location			
1			0.76
2	0.82	0.36-1.87	0.64
3	1.04	0.48-2.22	0.91
NIHSS at admission	1.13	1.00-1.26	0.037

AMI: acute myocardial infarction, DM2: type 2 diabetes mellitus, ICH: intracerebral haemorrhage, NIHSS: National Institute of Health Stroke Scale, OR: odds ratio, 95% CI: 95% confidence interval, p: p value.

whereas in males no specific aetiology correlated with an increased mortality risk. This may be because the development of subclinical organ damage with ageing is more rapid in postmenopausal women with hypertension and carries a high risk of incident cardiovascular events[13,14]. These data confirm the impact of cardiovascular disease on female mortality and the need to enhance clinicians' and women's awareness of the impact of cardiovascular disease on women's health.

Hypertension-related ICH shares the same risk factors and aetiology (small vessel disease) as lacunar stroke[15] and therefore might be considered the counterpart of lacunar stroke. Furthermore, previous studies reported that lacunar stroke in females is associated with higher risk of prolonged hospitalisation due to older age and a higher incidence of obesity in females compared to males, conditions that worsen the prognosis of stroke patients[16].

Our study has some limitations: this is a retrospective, single-centre study and does not consider long-term outcomes. Furthermore, information on ICH haematoma volume was not available for all patients included in our study; therefore, it was not possible to correlate haematoma volume with outcome. Additionally, we excluded a large number of patients due to missing data. The strengths of our study are the large sample size considered (727 patients) and the inclusion of all patients admitted to our hospital in the analysis.

Conclusions

In our large single-centre study no sex differences in intra-hospital mortality were detected. At ICH onset, females tended to be older than males. Hypertension-related ICH tended to be more severe in women and correlated with a higher risk of intra-hospital mortality.

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Key messages

- Intracerebral haemorrhage (ICH) is characterised by a high risk of mortality and disability.
- Studies on sex differences in ICH characteristics and outcomes have been inconclusive.
- The aim of our observational study, which included consecutive ICH patients admitted to the the Santa Maria della Misericordia Hospital in Perugia, Italy, between 1st January 2009 and 31st March 2017 was to investigate the demographics, aetiology, location, stroke care, and intra-hospital mortality of ICH patients, in order to evaluate sex differences.
- In our study, no sex differences in intra-hospital mortality were detected. At ICH onset females tended to be older than males. Hypertension-related ICH tended to be more severe in females and correlated with a higher risk of intra-hospital mortality.

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