Association Between Neck Circumference and Poor Outcome in Spontaneous Intracerebral Hemorrhage Patients: A Prospective Observational Study.

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Abstract

Background: Obesity is one of the major risk factors of intracerebral hemorrhage (ICH). Neck circumference (NC) is an indicator of obesity, and little is known about the role of NC in patients with ICH. This study aimed to assess the association between NC and functional outcome in ICH patients.

Methods: We prospectively analyzed data of ICH patients who received treatment at our institution from January 2018 to November 2019. Patients were categorized as two groups according to 180-day Modified Rankin Scale (MRS) score. Univariate and multivariate analyses were performed to assess whether NC was associated with poor outcome in ICH patients. Receiver operating characteristic (ROC) curve analysis was performed to manifest the significance of NC in predicting the functional outcome of ICH patients.

Results: A total of 312 patients were enrolled in our study. Multivariate logistic regression analysis indicated that NC was an independent predictor of 180-day poor functional outcome (odds ratio [OR] = 1.205, 95% confidence interval [CI]: 1.075-1.350, p = 0.001). ROC analysis revealed that NC could predict poor functional outcome at 6 months.

Conclusion: NC is an independent predictor of unfavorable functional outcome at 6 months in ICH patients.

Background

Spontaneous intracerebral hemorrhage (ICH) is a devastating healthcare event accounting for 10–15% of all strokes [1, 2], which has the characteristics of high mortality and morbidity and limited treatment options [3]. Obesity is one of the major risk factors of stroke [4], and is associated with increased morbidity and mortality in the general population [5, 6]. However, obesity appears to have a survival advantage in patients with certain diseases including heart failure, coronary artery disease, and chronic kidney disease [7–9]. In addition, recent studies has linked this phenomenon, known as the “obesity paradox”, to ICH [10, 11].

Body mass index (BMI) was an indicator that most commonly used to assess obesity. Whereas, previous studies have showed that neck circumference (NC) could be used as a simple, feasible and stable evaluation index because it is not easily affected by eating or body position [12, 13]. In addition, NC is related to oropharyngeal fat infiltration, narrowing the upper respiratory tract [14]. However, little is known about the role of NC in patients with ICH. The purpose of this study was to explore the relationship between the NC and the prognosis of ICH.

Methods

Study design
This is a single-centre prospective study. We identified all the patients with ICH visited to West China hospital from January 2018 to November 2019. Informed consent was obtained from all patients or family members. All procedures in the study were approved by the Ethics Committee of the West China Hospital of Sichuan University (Sichaun, China).

**Patients**

We defined inclusion criteria as follows: 1) A diagnosis of intracranial hemorrhage by computed tomography (CT); 2) Blood routine examination and laboratorial tests were conducted within 24 hours after admission; 3) ≥ 18 years. Patients who met the following criteria were excluded: 1) that ICH was attributable to aneurysm, arteriovenous malformation or moyamoya disease; 2) that ICH was attributable to acute cerebral infarction, thrombolysis of cerebral or myocardial infarction; 3) patients with prior systemic diseases such as immunological disease, neurological disease, recent infectious disease, severe hepatic, renal dysfunction and coagulation dysfunction. 4) patients with isolated intraventricular hemorrhage; 5) patients with a history of neck surgery.

**Clinical and laboratory parameters.**

Baseline clinical and demographic parameters were collected at hospital arrival, including NC, BMI, HNR (height-to-NC ratio), age, sex, medical history, Glasgow Coma Scale (GCS) score on admission, blood pressure, cigarette consumption and alcohol use, history of stroke, medical history of hypertension, diabetes mellitus, and history of endotracheal intubation and tracheotomy.

Laboratorial variables were also recorded including white blood cells (WBC), platelet, blood glucose, cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C). The NC (cm) was taken to the nearest 1 mm, using plastic tape measure. It was taken in a plane as horizontal as possible, at a point just below the larynx (thyroid cartilage) and perpendicular to the long axis of the neck (the tape line in front of the neck at the same height as the tape line in the back of the neck). Two reviewers independently estimated the values of NC. Any disagreement between the two reviewers was solved by the consensus. Height (m) and weight (kg) were measured at the bed side by trained staff on admission using a measure and a digital weight scale, respectively, and BMI (kg/m$^2$) was calculated as standard. Admission HNR was calculated as the ratio of the height to the NC.

Radiological results collected from head CT within 24 h after admission to hospital included hematoma location, hematoma size, presence of Intraventricular hemorrhage (IVH). Hematoma volume was measured by ABC/2 method as described previously [15]. Two reviewers independently estimated all the head CT scans. Any disagreement between the two reviewers was solved by the consensus.

The functional outcome was assessed by 180-day MRS score by telephone or outpatient visiting. MRS score ≥ 3 was defined as unfavorable outcome including severe disability, persistent vegetative state, as well as death.

**Statistical analysis.**
All the baseline characteristics including clinical variables, laboratorial parameters and radiological data were compared between patients with poor outcome and with favorable outcome. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR) for normal distribution and non-normal distribution, respectively, whereas categorical variables were expressed as frequency and percentage. Univariate analyses were conducted by independent t test or Mann–Whitney U test or Chi-square ($\chi^2$) test or Fisher’s exact test. Independent t test or Mann–Whitney U test were applied to compare continuous variables. Chi-square ($\chi^2$) test or Fisher’s exact test were conducted to compare categorical data. Variables significant at $p < 0.20$ level in the univariate analysis were retained in the multivariate model. For interpretation purposes, some variables were classed as follows: GCS score as “13–15 points”, “9–12 points” and “3–8 points”; and hematoma location as “lobe”, “basal ganglia”, “thalamus”, “cerebellum” and “brainstem”. Receiver operating characteristic (ROC) analysis was performed to indicate the predictive value of NC for the functional outcome of ICH patients. The cut-off value of NC was decided by Youden index from the ROC curve. A value of $p < 0.05$ was considered as statistical significant. All the above-mentioned statistical analyses were performed by SPSS version 21.0 (SPSS, Chicago, IL, USA).

Results

From January 2018 to November 2019, 312 consecutive patients (229 males and 83 females) with spontaneous ICH who met the inclusive criteria were enrolled in this prospective study, the lost rate of follow up was 2% (7/367, Fig. 1).

The univariate analysis shown that patients with poor functional outcome at 6 months had higher NC (p = 0.007), higher HNR (p = 0.015), higher hematoma size (p < 0.001), higher WBC count (p < 0.001), higher blood glucose level (p = 0.005); and had lower age (p = 0.036), lower GCS score on admission (p < 0.001). On the side, the proportion of patients with IVH (31.7% versus 50.8%, $p = 0.001$), endotracheal intubation (26.8% versus 67.7%, $p < 0.001$) and tracheotomy (9.8% versus 27.0%, $p < 0.001$) were higher in the poor outcome group, as well as the patients with basal ganglia hemorrhage (40.7% versus 55.0%) and brainstem hemorrhage (13.0% versus 25.4%) [Table 1]. The multivariate analysis indicated that NC (OR = 1.205, 95% CI: 1.075–1.350, $p = 0.001$), BMI (OR = 0.829, 95% CI: 0.722–0.953, $p = 0.009$), GCS (9–12 points) [OR = 4.139, 95% CI: 1.912–8.960, $p < 0.001$], GCS (3–8 points) [OR = 57.537, 95% CI: 15.725–210.526, $p < 0.001$], hematoma size (OR = 1.062, 95% CI: 1.034–1.092, $p < 0.001$), basal ganglia hemorrhage (OR = 6.300, 95% CI: 2.285–17.375, $p < 0.001$) and brainstem hemorrhage (OR = 16.223, 95% CI: 3.226–81.572, $p = 0.001$) were significantly correlated with poor functional outcome at 6 months (Table 2). ROC curve analysis showed that NC could predict poor functional outcome with an area under the curve of 0.591 (95% CI: 0.527–0.655, $p = 0.007$, Fig. 2). The value of 39.45 cm for NC was the best cut-off in predicting function outcome of ICH patients according to Youden index and we found that the proportion of poor outcome in patients with NC $\geq$ 39.45 cm and patients with NC < 39.45 cm was 63.1% and 55.1%, respectively.
Table 1
Clinical characteristics related to 180-day outcome in patients with ICH

| Characteristic            | Favorable outcome (n = 123) | Poor outcome (n = 189) | p-Value |
|--------------------------|-----------------------------|------------------------|---------|
| NC(cm)                   | 41.01 ± 4.79                | 42.46 ± 4.68           | 0.007*  |
| BMI(kg/m^2)              | 25.46 ± 4.29                | 26.14 ± 3.75           | 0.142   |
| HNR                      | 4.03 ± 0.41                 | 3.92 ± 0.37            | 0.015*  |
| Age(years)               | 61(49, 70)                  | 56(46, 67)             | 0.036*  |
| Sex (male)               | 86(69.9%)                   | 143(75.7%)             | 0.262   |
| Hypertension             | 99(80.5%)                   | 164(86.8%)             | 0.136   |
| Diabetes mellitus        | 12(9.8%)                    | 9(4.8%)                | 0.085   |
| Prior stroke             | 3(2.4%)                     | 10(5.3%)               | 0.260   |
| Smoking                  | 40(32.5%)                   | 52(27.5%)              | 0.343   |
| Drinking                 | 26(21.1%)                   | 54(28.6%)              | 0.142   |
| SBP(mmHg)                | 161.70 ± 29.90              | 165.74 ± 27.98         | 0.207   |
| DBP(mmHg)                | 94.58 ± 17.96               | 98.43 ± 17.74          | 0.063   |
| GCS score on admission   | -                           | -                      | <0.001**|
| 13–15                    | 80(65.0%)                   | 27(14.3%)              | -       |
| 9–12                     | 38(30.9%)                   | 58(30.7%)              | -       |
| 3–8                      | 5(4.1%)                     | 104(55.0%)             | -       |
| ICH location             | -                           | -                      | <0.001**|
| Lobe                     | 32(26.0%)                   | 17(9.0%)               | -       |
| Basal ganglia            | 50(40.7%)                   | 104(55.0%)             | -       |
| Thalamus                 | 18(14.6%)                   | 16(8.5%)               | -       |
| Cerebellum               | 7(5.7%)                     | 4(2.1%)                | -       |
| Brainstem                | 16(13.0%)                   | 48(25.4%)              | -       |
| Hematoma size (ml)       | 15.0(6.2, 27.3)             | 31.9(15.3, 55.8)       | <0.001**|

Data are expressed as n (%), mean ± standard deviation, or median (interquartile range), as appropriate.*P < 0.05, **P < 0.001. ICH, intracerebral hemorrhage; NC, neck circumference; BMI, body mass index; HNR, height-to-NC ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage; WBC, white blood cells; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.
| Characteristic       | favorable outcome (n = 123) | poor outcome (n = 189) | p-Value  |
|----------------------|-----------------------------|------------------------|----------|
| Presence of IVH      | 39 (31.7%)                  | 96 (50.8%)             | 0.001*   |
| Endotracheal intubation | 33 (26.8%)                  | 128 (67.7%)            | < 0.001**|
| Tracheotomy          | 12 (9.8%)                   | 51 (27.0%)             | < 0.001**|
| WBC, x10^9           | 9.98 ± 3.88                 | 12.39 ± 4.09           | < 0.001* |
| Platelet, x10^9      | 173.98 ± 60.66              | 181.21 ± 69.63         | 0.347    |
| Blood glucose (mmol/L) | 7.75 ± 2.89                 | 8.68 ± 2.75            | 0.005*   |
| Cholesterol (mmol/L)  | 4.47 ± 1.08                 | 4.43 ± 1.19            | 0.758    |
| HDL-C (mmol/L)       | 1.35 ± 0.43                 | 1.32 ± 0.52            | 0.568    |
| LDL-C (mmol/L)       | 2.61 ± 0.77                 | 2.59 ± 0.98            | 0.854    |

Data are expressed as n (%), mean ± standard deviation, or median (interquartile range), as appropriate.*P < 0.05, **P < 0.001. ICH, intracerebral hemorrhage; NC, neck circumference; BMI, body mass index; HNR, height-to-NC ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage; WBC, white blood cells; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.
Table 2
Multivariate analysis of predictors for poor outcome at 6 months

| Predictors                              | OR (95% CI)         | P Value |
|-----------------------------------------|---------------------|---------|
| NC (per 1 cm increase)                  | 1.205 (1.075–1.350) | 0.001*  |
| BMI(per 1 kg/m² increase)               | 0.829 (0.722–0.953) | 0.009*  |
| GCS score on admission                  | -                   | -       |
| GCS(13–15 points)                       | Reference           | -       |
| GCS(9–12 points)                        | 4.139 (1.912–8.960) | < 0.001** |
| GCS(3–8 points)                         | 57.537 (15.725-210.526) | < 0.001** |
| ICH location                            | -                   | -       |
| Lobe                                    | Reference           | -       |
| Basal ganglia                           | 6.300 (2.285–17.375) | < 0.001** |
| Thalamus                                | 3.751 (0.856–16.444) | 0.080   |
| Cerebellum                              | 0.363 (0.045–2.893) | 0.338   |
| Brainstem                               | 16.223 (3.226–81.572) | 0.001* |
| Hematoma size (per 1 ml increase)       | 1.062 (1.034–1.092) | < 0.001** |
| Presence of IVH                         | 3.176 (1.476–6.834) | 0.003*  |

Adjustment by diastolic blood pressure, age, hypertension, diabetes mellitus, drinking, endotracheal intubation, tracheotomy, white blood cells and blood glucose. *P < 0.05, **P < 0.001. NC, neck circumference; BMI, body mass index; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; OR: odds ratio, CI: confidence interval.

Discussion

To the best of our knowledge, this is the first study that focused on the NC in patients with ICH. We found that NC was an independent risk factor for poor prognosis of ICH, and BMI was independently inversely associated with poor outcome in ICH patients. NC is an indicator of obesity that reflects human health [16–21]. Previous studies have shown that NC is associated with an increased risk of hypertension [18], diabetes [17, 21] and metabolic syndrome [19]. NC is also found to be associated with congestive heart failure incidence and coronary heart disease mortality [20]. However, researches regarding the association between NC and ICH were limited.

According to the “obesity paradox”, obese and overweight stroke patients had favorable prognosis than those with a normal or lower BMI [22–24]. Consistent with these findings, we found that BMI was independently inversely associated with poor outcome in ICH patients. Interestingly, we also found a contradictory relationship between BMI and NC in predicting the prognosis of ICH. One possible
explanation for the paradoxical phenomenon may be that the two obesity indicators are different in fat
distribution. BMI only reflects the total body obesity and NC represents an alternative method for
measuring upper body subcutaneous fat [25]. Moreover, it had been demonstrated that NC was
associated with oropharyngeal fatty infiltration, which narrows the upper airway, resulting in obstructive
sleep apnea (OSA) [14].

A retrospective study found that the larger the NC (≥ 43.2 cm in men and ≥ 36.8 cm in women), the
higher the incidence of obstructive sleep apnea was 2.52 times in men and 3.13 times in women [26].
And, it was reported that compared with BMI, NC better explained the change in apnea-hypopnea index in
morbidly obese women (n = 115) in the predictive model [27]. OSA had been reported to be associated
with ICH. The hypoxia and hemodynamic responses associated with OSA may predispose to stroke [28].
Moreover, OSA was associated with the development of perihematoma edema [29], which may cause
poor outcome after ICH [30–32]. Several mechanisms may have influence on the development of
encephalomalacia after ICH. The early stage of cerebral edema occurs in the first few hours after ICH, which
involves hydrostatic pressure induced by formation of hematoma and retraction of clot, the second
phase, caused by production of thrombin and activation of the coagulation cascade, occurs within the
first 24 hours, and the delayed stage involves in red blood cells hemolysis and hemoglobin-induced
toxicity [33, 34]. The sizes of perihematoma edema have also been related to several factors such as the
level of serum ferritin and increased matrix metalloproteinase-9 activity, which is an important enzyme for
the blood brain barrier remodeling and perihematoma edema development [35–38].

Due to a momentary cessation of breathing, OSA patients with this disorder have repeated episodes of
hypoxia/reoxygenation, promoting systemic oxidative stress, clotting cascade activation, inflammation,
and damaged repair competence of the vascular endothelium [39]. Thus, through the above several
pathways, OSA may have a role in the generation of perihematoma edema. Moreover, OSA has also been
demonstrated to be associated with the enhanced activity of matrix metalloproteinase-9. Therefore, it is
reasonable to believe that the association between OSA and perihematoma edema is biologically
plausible.

Mechanical ventilation after tracheotomy or endotracheal intubation may prevent OSA-related hypoxia.
However, a previous study have reported that in acute spontaneous ICH patients, endotracheal intubation
and mechanical ventilation were associated with increased risk of hospital-acquired pneumonia and in-
hospital mortality [40]. Consistently, in the present study, we found that the proportions of patients with
tracheotomy and endotracheal intubation were higher in the poor outcome group. The reason may be that
the hematoma volume in ICH patients with tracheotomy or endotracheal intubation was larger than
patients without tracheotomy or endotracheal intubation, which suggested more severe condition and
poorer prognosis.

In addition, previous studies have shown that NC was associated with an increased risk of hypertension
[18], diabetes [17, 21] and metabolic syndrome [19], which also played a role in the occurrence and
development of ICH [41–43]. Furthermore, Pezzini et al. found that obesity, mainly through its indirect
effect on hypertension and obesity-related complication, played a role in ICH [44]. Taken together, NC should not be overlooked in evaluating ICH patients.

However, our study still has several limitations. First, this study collected data from one hospital, with a limited sample size, which may lead to selection bias. Second, NC is one of the factors causing upper respiratory tract stenosis, and the presence of other unmeasured factors will still influence our final conclusion. Third, OSA was not accurately assessed in our study. At last, all the ICH patients were only from West China Hospital, recruiting poor clinical conditions patients usually because of the medical referral system.

Conclusions

NC is an independent predictor of unfavorable functional outcome at 6 months. Further experiments are necessary to explore the specific mechanism.

Abbreviations

Body mass index (BMI); Confidence interval (CI); Computed tomography (CT); Glasgow Coma Scale (GCS); Diastolic blood pressure (DBP); High density lipoprotein cholesterol (HDL-C); HNR (height-to-NC ratio); Intracerebral hemorrhage (ICH); Interquartile range (IQR); Intraventricular hemorrhage (IVH); Low density lipoprotein cholesterol (LDL-C); Modified Rankin Scale (MRS); Neck circumference (NC); Odds ratio (OR); Receiver operating characteristic (ROC); Systolic blood pressure (SBP); White blood cells (WBC)

Declarations

Ethics approval and consent to participate

This study was permitted by the Ethics Committee of the West China Hospital of Sichuan University (Sichuan, China). Written informed consent was sought from all participants, in cases suffered severe disability and were not able to give informed consent, this was obtained from their legally authorized representatives.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors have no competing of interest to declare.

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None to report.

Authors’ contributions

YJL, HQZ and XY contributed with conception, design, analyses, interpretation and write-up of the first draft of the manuscript. JZ, MMX and FZ contributed with scientific input, analyses, interpretation and wrote sections of the manuscript. HL contributed with interpretation and scientific input. All authors read and approved the final manuscript.

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Authors’ information

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Figures

![Flow diagram of patients with spontaneous intracerebral hemorrhage.](image)

Figure 1

Flow diagram of patients with spontaneous intracerebral hemorrhage.
Figure 2

Receiver operating characteristic curve for the predictive value of NC for functional outcome in ICH patients at 6 months.