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High Blood Pressure Increases the Risk of Cerebral Microbleeds in Hypertensive Individuals

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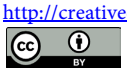

Abstract

Introduction: Hypertension is the leading preventable risk factor for major cardiovascular diseases worldwide. Recently, compelling evidence has emerged associating hypertension with cerebral microbleeds (CMBs), which are subclinical hemorrhages in the brain resulting from structural abnormalities in the small vessels that supply the brain. In addition to overall elevated blood pressure (BP), elevation in individual parameters such as systolic BP, diastolic BP, pulse pressure and mean arterial pressure could also individually be important risk factors for CMBs. This study aimed to assess the association between CMBs and blood pressure, and assess blood pressure parameters that could be possible risk factors for CMB. **Methods**: A retrospective case-control study was conducted from August 2021 to September 2022 on patients who underwent MRI due to primary complaints of limb disorders, loss of consciousness, persistent dizziness, and intermittent headaches. The patients were divided according to MRI results into 52 cases (those who had CMBs) and 52 controls (those who had no CMBs). Extracted data were analyzed in SPSS. Chi-square test, binary logistic regression, and Spearman's correlation analysis were conducted. **Results:** In total, 104 cases and control patients were assessed, with mean (±SD) age 70.6 ± 8.56 vs 68.9 ± 8.93 years respectively ($p > 0.05$). CMB patients had more cases of stroke, hyperlipidemia and diabetes than non-CMB patients. Systolic blood pressure (SBP), diastolic blood pressure, pulse pressure (PP) and mean arterial pressure (MAP) were all considerably raised in CMB patients than non-CMBs patients. Blood pressure grades were positively correlated with the severity of CMBs ($r = 0.22$; $p = 0.044$). Logistic regression analysis showed that SBP and MAP were in-

dependent risk factors for CMBs (age and sex adjusted odds ratio = 1.420; 95% CI: 1.030 - 1.851, and 1.310; 95% CI: 1.011 - 1.631 respectively). **Conclusions:** In summary, this study found that hypertension was positively correlated with CMBs severity, and that SBP and MAP are independent risk factors for CMBs in patients with hypertension.

Keywords

Hypertension, Pressure, Risk, Cerebral, Microbleeds

1. Introduction

Hypertension is the leading preventable risk factor for major cardiovascular diseases (CVD) worldwide [1]. It is defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg [2]. Due to an aging world population, the global prevalence of hypertension has risen sharply and continues to rise [3]. It is estimated that the global prevalence of elevated systolic BP (≥140 mmHg) rose by 3.2% from 17.3% in 1990 to 20.5% in 2015 [1], while in China, it ranges between 18.0% - 44.7% [4]. Hypertension is known to cause several CVDs including stroke [5]. Recently, compelling evidence has emerged associating hypertension with cerebral microbleeds (CMBs) [6] [7] [8] [9]. While insidious hypertension has long been known to induce intracranial hemorrhage (ICH) [10], and CMBs are one of the causes of ICH [11], it is until recently that links between hypertension and CMBs have been documented.

Cerebral microbleeds (CMBs) are tiny subclinical hemorrhage in the brain that occurs as a result of structural abnormalities in the small vessels that supply the brain [12]. The mechanism for the development of CMBs is still not fully understood, and patients often do not present with specific signs and symptoms [12]. They are identified when lesions made of small perivascular hemosiderin deposits are detected on MRI using susceptibility-weighted imaging [13]. CMBs occur in approximately 29.4% of patients > 65 years of age [14] and have, most recently, been increasingly seen among hospitalized Covid 19 patients ([15], p. 19).

Hypertension has emerged as a crucial risk factor for CMBs. A population based cohort study involving 344 randomly selected 70 to 87 years old hypertensive individuals in Sweden revealed that 26% of the cohort had CMBs, increasing from 19% among individuals in their 70s to 30% among those in their 80s [8]. Similarly, a study involving 218 patients without any history of cerebrovascular disease revealed that 16.1% of the participants had CMBs, and each standard deviation increase in ambulatory blood pressure increased the risk of CMBs by 1.9-fold [16]. Other studies by Lyu *et al.* [7], Yamashiro *et al.* [17] and Reddy *et al.* [6] conducted among hospital patients have all linked hypertension to the occurrence of CMBs. Evidence suggests that as a person ages, functional changes occur in the heart, such as diastolic and systolic dysfunction, and electrical dys-

function (45). These changes are insidious and, in the long term, lead to vasculopathies that eventually disproportionately triggers CMBs in the elderly patients more frequently than in the relatively young ones.

While linkages between hypertension and stroke or ICH are well documented globally, there are still limited studies on its association with CMBs. Moreover, there is evidence to suggest that blood pressure parameters could also individually be important risk factors for CMBs; for instance, the Framingham study revealed that knowing systolic blood pressure (SBP) alone correctly classified 99% of hypertension [18], while Tully *et al*. [19] showed that elevated SBP raised the odds of developing cerebrovascular disease 3 folds. More recently, Jiang *et al*. [20] showed that elevated pulse pressure (PP) was associated with a significant increase in cardiovascular mortality in old age. All these studies suggest that certain individual blood pressure parameters could be more associated with cardiovascular or cerebrovascular diseases than others.

In this retrospective observational study, we explored the association between hypertension and CMBs in a cohort of patients at our hospital. We further individually assessed systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and mean arterial as potential independent risk factors for CMBs. Other risk factors analyzed were age, gender and other CMB comorbidities.

2. Materials and Methods

This study was conducted in accordance with the STROBE guidelines [21]. A retrospective case-control study was conducted at the first affiliated Renmin Hospital of Wuhan University. Patients recruited were those who underwent brain MRI scan using susceptibility weighted imaging (SWI) following primary complaints of limb disorders, loss of consciousness, persistent dizziness, and intermittent headaches. Permission to conduct the study was sought from Renmin Hospital of Wuhan University Research Ethics Committee. The committee waived patient's rights to consent since it was a retrospective study. A total of 104 patients (72 males and 32 females, aged 18 - 95 years) were recruited from August 2021 to September 2022. Patients were divided according to MRI results into 52 cases (those who had CMBs) and 52 controls (those who had no CMBs). Recruited cases were those who had radiologically confirmed CMBs as seen on MAGNETOM Avanto & Prisma 3T MRI systems (Siemens, Germany) using SWI sequence, with parameters were set as: 800 ms repetition time, 20 - 50 ms echo time, 20 - 30 flip angles, 256 × 256 matrix, 240 × 100 vision, 7-mm scan slice thickness, and 2.5 mm spacing. These data were extracted from the hospital electronic medical database and the picture archiving and communication system (PACS). Cerebral microhemorrhages were defined as a loss of circular signal with a uniform diameter of 2 - 5 mm, possessing a clear margin, with no edema around the circular punctate non-sulcus area.Those excluded were subjects with no record of blood pressure measurements, those who had radiologically con-

firmed CMB but diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral amyloid angiopathy (CAA) or Moyamoya disease.

2.1. Blood Pressure Measurements and Comorbidities

For blood pressure measurements, we retrieved single recordings from the database for each patient. Hypertension was defined according to the International Society of Hypertension (ISH) [22] as blood pressure readings ≥ 140/90 mmHg. Pulse pressure (PP) was calculated Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) as the arithmetic difference between the former and the latter. Blood pressure measurements were classified according to the International Society of Hypertension (ISH) as: normal (<139/89 mmHg); grade 1 hypertension (140 - 159/90 - 99 mmHg); and grade 2 hypertension (≥160/100 mmHg) [22]. Other comorbidities collected were diabetes, hyperlipidemia, and stroke, all defined by the World Health Organization criteria for diagnosing hypertension, diabetes, and hyperlipidemia. Furthermore, smoking history, and history of alcohol intake were also extracted. Stroke diagnosis was conformed based on definitive diagnosis and treatment from Renmin Hospital of Wuhan University, and image findings of obsolete cerebral lesions. Other important data collected were: subject demographic information, clinical and medical characteristics, and treatment details. Cardiovascular risk factors assessed were systolic and diastolic blood pressure, pulse pressure, mean arterial pressure, gender, age, cholesterol levels, diabetes, and smoking and alcohol consumption [23].

2.2. Brain MRI Scan Results

All brain MRI results retrieved were conducted and interpreted by highly qualified radiologists. When viewed on MAGNETOM Avanto & Prisma 3T MRI systems (Siemens, Germany) using SWI sequence, CMBs were seen as small homogenous, and round foci with low signal intensity, having a diameter < 10 mm and without peripheral edema. Similar structures such as vascular gap, cavernous hemangioma, calcified plaque of atherosclerosis, hemosiderin deposition on the pia mater, and calcification of the globus pallidus were excluded. Location of CMBs were categorized into; lobar (cortical gray and subcortical or periventricular white matter), deep (deep gray matter: basal ganglia and thalamus; and the white matter of the corpus callosum, internal, external, and extreme capsule), and infratentorial (brain stem and cerebellum. CMBs were defined as: non-CMB (0), mild (1 - 2), moderate (3 - 10) and severe (>10) and patients grouped accordingly.

2.3. Statistical Analysis

Statistical data analysis was conducted using SPSS version 25 software (IBM Inc. USA). Mean ± SD was used to summarize continuous variables while categorical variables were presented as counts and percentages. Independent student's t test

was used to examine the differences between means of continuous variables, while Pearson's Chi-square test was used to analyze categorical data. Spearman's rank test was used to conduct correlation analysis. Logistic regression analysis was conducted to examine risk factors associated with CMBs. Statistical significance was set at p-value < 0.05.

3. Results

3.1. Summary of Patient Characteristics

Patient characteristics are summarized in Table 1. A total of 104 patents were recruited, 52 with CMBs and 52 without, Mean (±SD) ages 70.6 ± 8.56 vs 68.9 ± 8.93 respectively (p > 0.05). No significant difference in age was observed between the two groups, but significant difference was observed in gender as presented in Table 1. Stroke, hyperlipidemia and diabetes were more common in the CMB group than the non-CMBs group, while history of smoking and alcohol consumption were more common in the non-CMBs group. Systolic blood pressure (SBP), diastolic blood pressure, pulse pressure (PP) and mean arterial pressure (MAP) were all considerably raised in the CMBs group that in the non-CMBs group (Figure 1). The prevalence of CMBs increased with increase in age. Similarly, a patient having more than one CMB also increased with age. In the age group 50 to 59 years, 33.3% had at least 1 microbleed, which increased to 50.9% after 70 years of age (Table 2).

Table 1. Characteristics of the patients.

Characteristic	Case, N = 52	Controls, N = 52	p
Gender (male), n (%)	43 (82.7)	38 (73.1)	<0.001*
Age, y (Mean± SD)	70.6 ± 8.56	68.9 ± 8.93	0.76
SBP (mmHg)	140.0 ± 20.6	133.0 ± 19.2	0.02*
DBP (mmHg)	79.2 ± 14.2	76.8 ± 11.8	0.14
PP (mmHg)	61.0 ± 17.0	56.0 ± 14.0	0.06
MAP (mmHg)	99.4 ± 14.5	95.4 ± 13.1	0.04*
Co-morbidities			
Hypertension grade			0.12
No hypertension	25 (48.1)	34 (65.3)	
Mild hypertension	17 (32.7)	14 (26.9)	
Severe hypertension	10 (19.2)	4 (7.8)	
Stroke, n (%)	4 (7.7)	2 (1.9)	0.16
Diabetes mellitus, n (%)	1 (1.9)	0 (0)	0.31
Hyperlipidemia, n (%)	4 (5.8)	3 (5.8)	0.98
Smoking, n (%)	22 (44.2)	31 (57.7)	0.18
Alcohol, n (%)	11 (21.2)	21 (40.4)	0.03*

SBP: Systolic blood pressure. DBP: diastolic blood pressure. PP: Pulse pressure. MAP: Mean arterial pressure. *represents significant results.

Table 2. Age-specific prevalence of cerebral microbleeds (10-year strata).

Age range	Patient number	CMBs, N (%)	Multiple CMBs, N (%)
40 - 49 years	1	0 (0)	0 (0)
50 - 59 years	15	5 (33.3)	3 (20)
60 - 69 years	33	19 (57.5)	15 (45.4)
≥70 years	55	28 (50.9)	23 (41.8)
Total	104	52 (50.0%)	41 (39.4%)

CMBs: Cerebral microbleeds.

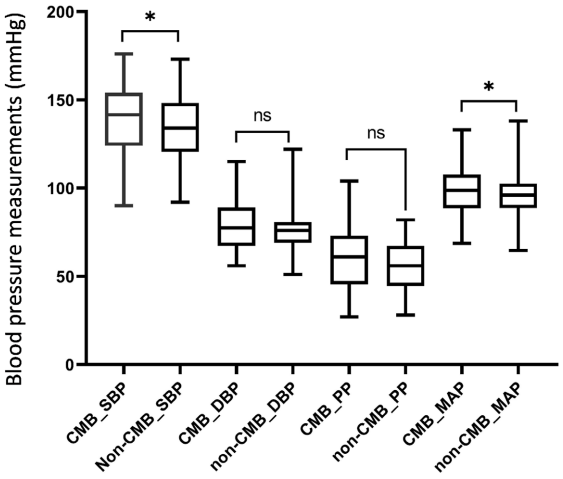

Figure 1. Comparison of blood pressure parameters between the CMB and non-CMB patients.

3.2. Location and Severity of Cerebral Micro Bleeds

Of the 52 patients with CMBs, the total number of CMB lesions was 320, majority of them, 110 (34.3%) occurred in the lobar region of the brain, followed by 93 (29.1%) in deep region, and 65 (20.3%) in infratentorial region (**Figure 2**). We then graded the CMB lesions according to severity as follows; grade 0 (no lesions), grade 1 (1 - 2 lesions), grade 2 (3 - 10 lesions) and grade 3 (>10 lesions), and determined possible association with gender and age groups of the patients. Chi-square analysis showed no association between both gender and age groups and severity of CMBs (all $p > 0.05$) (**Table 3**).

3.3. Association between Blood Pressure and Cerebral Microbleeds

To assess the association between blood pressure and severity of cerebral microbleeds, blood pressure was categorized into normal, grade 1 and grade 2 according to the ISH classification [22], and Spearman's correlation analysis conducted among the blood pressure grades and severity of CMBs. The results revealed that blood pressure was correlated with CMB severity; $r = 0.22$; $p = 0.044$ (**Table 4**). Preliminary multicollinearity analysis showed no significant association among

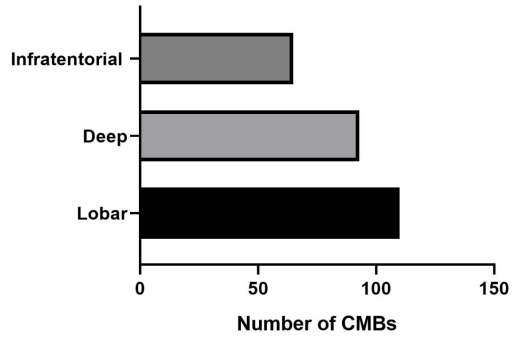

Figure 2. Distribution of CMBs in the different parts of the brain.

Table 3. Association between CMBs and age and gender.

	CMB grade					
	0 (0)	**1 (1 - 2)**	**2 (3 - 10)**	**3 (>10)**	**N**	**p**
Gender						0.08
Male	36	18	13	5	72	
Female	16	2	10	4	32	
Total	52	20	23	9	104	
Age group						0.21
40 - 49 years	1	0	0	0	1	
50 - 59 years	10	3	2	0	15	
60 - 69 years	14	10	5	4	33	
≥70 years	27	7	16	5	55	
Total	52	20	23	9	104	

Table 4. Association between CMBs and blood pressure.

	BP classification			
CMB grade	Normal	Mild	Severe	N
0 (0)	34	14	4	52
1 (1 - 2)	9	7	4	20
2 (3 - 10)	11	8	4	23
3 (>10)	5	2	2	9
Total	59	31	14	104

Spearman's r = 0.22; p-value = 0.044.

independent variables, and binary logistic regression analysis revealed that systolic blood pressure (SBP), and mean arterial pressure (MAP) were significantly associated with the presence of CMBs (all $p < 0.05$), demonstrating that SBP and MAP are independent risk factors for CMBs (age and sex adjusted odds ratio = 1.420; 95% CI: 1.030 - 1.851, and 1.310; 95% CI: 1.011 - 1.631 respectively) (Table 5).

Table 5. Univariate analysis of CMBs and blood pressure.

	B	SE	Wald	df	Sig	OR	95% CI
SBP	0.024	0.010	5.094	1	0.02*	1.420	1.030 - 1.851
DBP	0.023	0.016	2.181	1	0.14	1.024	0.992 - 1.056
PP	0.22	0.013	2.857	1	0.09	1.022	0.997 - 1.048
MAP	0.31	0.015	4.034	1	0.04*	1.310	1.011 - 1.631
Age	0.003	0.021	0.023	1	0.88	1.003	0.962 - 1.046

SBP: Systolic blood pressure. DBP: Diastolic blood pressure. PP: Pulse pressure. MAP: Mean arterial pressure. *represents significant results.

4. Discussion

We conducted this study to examine the association between blood pressure (BP) and the occurrence of cerebral microbleeds (CMBs) among our patients who underwent MRI examination using the 3T MRI susceptibility-weighted imaging technique. It should be noted that the MRI sequence used in detecting CMBs determines the rate of detection of microbleeds [12]. We also assessed age, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and mean arterial pressure (MAP) as independent risk factors for the occurrence of CMBs. Blood pressure parameters are non-invasive, easy to measure and economically cheap measurements that could be used to predict CMBs.

Previous studies have already shown that an association exists between CMBs and hypertension. Igase *et al.* [24] showed that SBP is positively correlated with CMBs, while Fan *et al.* [25] demonstrated that DBP is also exhibits a positive correlation with the occurrence of CMBs. More recently, Lyu *et al.* [7] showed that SBP, DBP and age are all independent risk factors for CMBs. In our study, we used Spearman's rank correlation analysis of BP grade based on CMB severity, and found that a rank correlation indeed existed between BP grade and CMB severity ($r = 0.22$, $p = 0.044$). Further assessment using a logistic regression analysis, revealed that systolic blood pressure and mean arterial pressure are independent risk factors for CMBs. However, we did not observe a statistically significant relationship between CMBs and age, diastolic blood pressure and pulse pressure, although all the three parameters appeared to be raised in CMB patients compared to non-CMB patients. Chronic hypertension leads to weakening of small vessel walls, and forces the vessel smooth muscles to be replaced by fibrous or necrotic tissues. This eventually induces atherosclerotic plaque formation, and rupture which may cause cerebral thrombosis and sometimes aneurysms [26]. In this regard, CMBs can also be considered as a type of target organ damage induced by hypertension. Presence of multiple CMB is an indication of a terminal micro-vascular lesion prone to bleeding [27].

Although our study did not find a statistically significant association between age and CMBs, we noticed that the prevalence of CMBs increased with age, and that a patient having more than one CMB also increased with age, 33.3% for pa-

tients in 50 to 59 years age group and 50.9% in patients 70 years and above (**Table 2**). This finding is consistent with Lyu *et al.* [7], who also did not find an association between age and severity of CMBs. However, unlike us, they showed that age is an independent risk factor for CMBs. We think that the difference could be in our small sample size and the slight difference in age stratification we applied compared to theirs. In addition to Lyu *et al.* [7], Imaizumi *et al.* [28], and Horita *et al.* [29] have also demonstrated that old age is indeed an independent risk factor for CMBs.

CMBs were distributed in multiple areas of the brain. Majority of them (34.3%) occurred in the lobar region consisting of the brain cortex, and sub-cortex or periventricular white matter. This was consistent with the findings by Lyu *et al.* [7] and Poels *et al.* [30] who both reported that CMBs occurred in higher frequency in the cortical and sub-cortical regions of the brain. Furthermore, majority of the patients had between 2 to 10 CMBs per patient also consistent with previous findings by Lyu *et al.* [7]. Recent evidence suggests that occurrence of CMBs could be associated with cognitive impairment in the affected individuals [31] [32], whether this is correlated with the location of the CMB lesions needs to be determined.

Our study had a few limitations. First, we did not assess medication use among the hypertensive patients. Being a chronic disease with long term medication, this could also have an effect on the blood pressure parameters, so the results should be interpreted accordingly. Second, the study sample size was small, and this could have affected the power of the study. Third, the study was retrospectively conducted and so carried all the inherent limitations of a retrospective study, and so larger scale prospective cohort studies are needed to verify these findings. Lastly, the blood pressure measurements used were single measurements extracted from the electronic database. 24 hour ambulatory blood pressure measurement could have been more reliable to use.

5. Conclusion

In summary, our study demonstrated that CMBs, as determined by the 3T MRI susceptibility weighted imaging, were associated with hypertension and that systolic blood pressure (SBP) and mean arterial pressure (MAP) were independent risk factors for CMBs. Furthermore, the CMBs were more likely to occur in the lobar region of the brain compared to the deep and infratentorial regions. In light of the limitations of the study, further studies, preferably large prospective cohorts, are needed to verify these results.

Author Contributions

(1) Concept or design: Yahya Abdullahi Ali;
(2) Acquisition of data:Yahya Abdullahi Ali and Xi Wang;
(3) Analysis or interpretation of data: Yahya Abdullahi Ali and Erick Thokerunga;
(4) Drafting of the article: Yahya Abdullahi Ali;

(5) Critical revision for important intellectual content: Erick Thokerunga, Xi Wang and Zakaria Ahmed Mohamed.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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Ethics Approval

This study was approved by the Wuhan University Renmin Hospital Research Ethics Committee.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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