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# Blood Pressure Variability and Mortality in Patients Admitted with Acute Stroke in a Tertiary Care Stroke Center

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

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2	Tertiary Care Stroke Center
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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

# 26 Abstract:

Background and Purpose: Elevated blood pressure (BP) in stroke correlates with unfavorable
outcomes. However, the influence of short-term variations in BP on clinical outcomes remains
uncertain.

**Methods:** This retrospective cohort study included patients admitted with acute stroke between 31 May 2016 to June 2019. 18 BP readings over three days were measured, with its variability 32 categorized into five (L1-L5) and four (L1-L4) levels for systolic and diastolic BPs 33 respectively. We then evaluated their association with mortality.

Results: 2,572 patients (82.4% male, median age  $53 \pm 9$  years) were included, 137 and 36 died during admission and by one year follow-up respectively. 83.6% had ischemic stroke/ TIA. There was increased odds of in-hospital mortality (L2, OR 2.64, 95%CI 1.44 to 4.84; L3, OR 4.20 95%CI 2.14 to 8.24; L4, OR 10.14, 95%CI 4.93 to 20.85; L5, OR 23.18, 95%CI 10.88 to 49.37), (P = 0.002 to <0.001) and (L2, OR 1.61, 95%CI 0.96 to 2.69; L3, OR 2.95 95%CI 1.70 to 5.12; L4, OR 8.00, 95%CI 4.49 to 14.25), (P= 0.071 to <0.001), respectively. This was consistent with one year mortality for systolic and diastolic BPs.

41 Conclusion: In a retrospective cohort of ethnically diverse acute stroke patient population,
42 blood pressure variability was significantly associated with both in-hospital and one year
43 mortality.

45 Keywords: Casual measurement of BP, Blood pressure variability, stroke, hypertension,
46 mortality

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**Strengths and limitations:** 

52	•	Our study included 2,572 patients which is a large cohort that adds to the validity and
53		generalizability of the results.
54	•	A minimum of ten blood pressure readings over 72 hours was required for inclusion,
55		giving a solid view of the impact of blood pressure variability on the outcomes of
56		stroke.
57	•	The follow-up period of one year with inverse probability weighted logistic regression
58		provides a robust insight to the long-term consequences of blood pressure variability
59		on the outcomes of stroke.
60	٠	Our study is limited by its retrospective design, missing values, and absence of
61		consistent synchrony in the timing of blood pressure measurements by nursing
62		personnel.
63	•	The stability of point estimates of our study outcomes meant that these limitations did
64		not significantly confound our findings.
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76 Introduction

High blood pressure (BP) is independently associated with poor outcomes in acute stroke [1,2]. Additional hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure and heart rate have been associated with poor outcomes following stroke [3]. Evidence investigating acute blood pressure variability (BPV) as a determinant of stroke outcomes is increasing [4–9]. Systolic blood pressure variability (SBPV) is being recognized as an important triggering factor for vascular events including stroke and cardiovascular events [10]. Likewise, some authors suggest that diastolic blood pressure variability (DBPV) may be as important as SBPV [11,12]. It is, however, unclear whether the control of acute SBPV and DBPV after acute stroke would provide a potentially modifiable therapeutic target and improved clinical outcomes in patients with acute stroke.

Evidence on the effect of BPV after acute stroke on the clinical outcomes remains limited. A post hoc analysis of the Intensive BP Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) dataset reported significant associations between SBPV in the hyperacute (first 24 hours) and acute (days 2–7) periods, and death and disability at 90 days, in 2,839 participants with acute intracerebral hemorrhage (ICH) (<6 hours of symptom onset), and elevated SBP (SBP>150 mmHg) [5]. Other studies have mostly assessed BPV during a period of >24 hours; the majority found significant associations between SBPV or DBPV and poor long-term functional outcome ( $\geq 3$  months) [13–17], or adverse findings on repeat neuroimaging [14,18], although not all [19,20]. Two small studies have examined the effect of short-term BPV on outcomes in acute ischemic stroke using beat-to-beat BP monitoring. Dawson et al evaluated the effect of BPV in patients with ischemic stroke and reported that DBPV and mean arterial pressure (MAP) variability predict poor 30-day outcome [21], but Graff et al found no BPV difference between good and poor outcome groups at 90 days [22].

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3 4	101	To date, no study has assessed the effect of short-term SBPV and DBPV derived from
5 6	102	casual cuff BP measures -the most commonly used BP monitoring index for patients with acute
7 8 9	103	stroke. The recommendations on this method of BP measurement are provided by the American
10 11	104	Heart Association [23]. BP measurement is done by trained nurses mostly and it is done with
12 13 14	105	the patient in supine position using a standard mercury sphygmomanometer and the appropriate
15 16	106	cuff size based on the arm circumferences. Knowledge on how best to measure and define BPV
17 18	107	has not been explored. Additionally, available evidence on the effect of BPV on outcome after
19 20 21	108	acute stroke in our region is scarce.
22 23	109	Our observational study explores the relationship between BPV, measured every four
24 25	110	hours over three days with a total of 18 readings from stroke admission and derived from
26 27 28	111	multiple closely spaced casual BP measures, and in-hospital and one year mortality.
20 29 30	112	
30 31 32	113	Methods
33 34	114	Study design and participants:
35 36 37	115	This is a retrospective cohort study of patients presenting with acute cerebrovascular accidents
38 39	116	(ischemic stroke/ transient ischemic attack (TIA) or hemorrhagic stroke) to Hamad General
40 41	117	Hospital (HGH) between 1st May 2016 and 30th June 2019. HGH, a member of Hamad Medical
42 43 44	118	Corporation (HMC) is regarded as the central hub for acute stroke care in Oatar. Over 80% of
45 46		corporation (Thyle), is regarded as the central hab for acute shoke care in Quan. Over 6070 or
	119	stroke cases are admitted or referred to HGH, thereby potentially reflecting acute stroke care
47 48	119 120	stroke cases are admitted or referred to HGH, thereby potentially reflecting acute stroke care in the whole of Qatar [24]. A multi-ethnic stroke database was established at HGH in January
47 48 49 50	119 120 121	stroke cases are admitted or referred to HGH, thereby potentially reflecting acute stroke care in the whole of Qatar [24]. A multi-ethnic stroke database was established at HGH in January 2014, where clinical details were systematically recorded by trained individuals, including the
47 48 49 50 51 52 53	<ol> <li>119</li> <li>120</li> <li>121</li> <li>122</li> </ol>	stroke cases are admitted or referred to HGH, thereby potentially reflecting acute stroke care in the whole of Qatar [24]. A multi-ethnic stroke database was established at HGH in January 2014, where clinical details were systematically recorded by trained individuals, including the clinical presentation, severity of deficits and NIHSS, TOAST classification, risk factors,
47 48 49 50 51 52 53 54 55	<ol> <li>119</li> <li>120</li> <li>121</li> <li>122</li> <li>123</li> </ol>	stroke cases are admitted or referred to HGH, thereby potentially reflecting acute stroke care in the whole of Qatar [24]. A multi-ethnic stroke database was established at HGH in January 2014, where clinical details were systematically recorded by trained individuals, including the clinical presentation, severity of deficits and NIHSS, TOAST classification, risk factors, complications, and outcome of all patients admitted with stroke, among other variables. All
47 48 49 50 51 52 53 54 55 56 57 50	<ol> <li>119</li> <li>120</li> <li>121</li> <li>122</li> <li>123</li> <li>124</li> </ol>	stroke cases are admitted or referred to HGH, thereby potentially reflecting acute stroke care in the whole of Qatar [24]. A multi-ethnic stroke database was established at HGH in January 2014, where clinical details were systematically recorded by trained individuals, including the clinical presentation, severity of deficits and NIHSS, TOAST classification, risk factors, complications, and outcome of all patients admitted with stroke, among other variables. All eligible individuals during the pre-determined timeframe were recruited from the database for

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Eligible participants were all adult patients above the age of 18 years who presented to HGH with an acute ischemic stroke, TIA, or hemorrhagic stroke. Excluded individuals were those younger than 18 years, had incomplete data regarding the diagnosis or outcomes, had severe hypoglycemia on admission (<3.3mmol/L), and patients with history of CKD.

# **Patient involvement:**

Considering the retrospective design of the study and the use of the aforementioned stroke
database as the source of our data, patients' involvement in the conduction of this research was
not possible.

# **Data collection and variables:**

Data collection on the included participants was obtained from the stroke database and
supplemented with the patients' electronic medical records. Collected data was then entered
into a standardized data collection sheet on Microsoft Excel.

Data was obtained on 1) baseline demographics including age, sex, nationality, and medical comorbidities; 2) stroke type, whether ischemic/ TIA or hemorrhagic, and the TOAST classification; 3) severity of stroke based on NIHSS scale; 4) blood pressure readings on presentation and during the following 72 hours recorded every four hours with six readings per day, obtained using standard Dinamap which is utilized across the hospital; and 5) mortality, including in-hospital and mortality after one year post stroke.

<sup>49</sup> 146 Systolic and diastolic BP readings post-admission first three days at six regular time points
<sup>51</sup> 147 on each day were recorded. The standard deviation of SBPV were then categorized for each
<sup>53</sup> 148 person into five levels; (L1, <11mmHg; L2, 12-16mmHg; L3, 17-21mmHg; L4, 22-26mmHg;</li>
<sup>54</sup> 149 L5, >27mmHg). For DBPV, patients were grouped into four levels as follows: (L1, <8mmHg;</li>
<sup>58</sup> 150 L2, 9-11mmHg; L3, 12-15mmHg; L4, >16mmHg). Patients with eight or more missing values

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out of 18 were excluded and the standard deviations were computed for those who had 10 or more readings over three days. These levels of standard deviation were utilized as the measure of SBPV or DBPV over the first three days of admission. These two variables were used as categories in lieu of the continuous measure to avoid problems with non-linearity. Additionally, we calculated the flux of patients (the difference between the highest and the lowest BP readings) for both systolic and diastolic BPs as a clinical representation of variability. It was then tabulated by the standard deviation categories and the median values (p50) were reported. For the purpose of this study, ischemic stroke, TIAs and intracranial hemorrhage (ICH) were diagnosed according to the WHO criteria. Mortality was confirmed by reviewing the death note in patients' medical records for both in-hospital and one year post stroke mortality.

# 162 Statistical analysis:

Descriptive statistics of the cohort data were presented as medians and interquartile ranges
(IQR). Wilcoxon Rank Sum test was employed to compare the differences between groups.
For categorical variables, frequencies and percentages were reported and compared using
Pearson's Chi-square test.

167 To investigate the association of BPV with in-hospital mortality, we used multivariable 168 regression. Adjustments were made for variables that were either potentially confounding or 169 prognostic for the outcome based on a directed acyclic graph (DAG). These covariates included 170 type of stroke (ischemic vs. hemorrhagic), age, hypertension (history or newly diagnosed), and 171 history of cardiac disease. The analysis was repeated for assessment of the impact of BPV on 172 one year mortality.

54173As we had significant losses to complete follow-up within the one-year regression5556174model, we adjusted for the drop-outs from the model by running an appropriately weighted5758175regression. We first computed the probability to remain in the study at one year by regressing

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(using logistic regression) an indicator variable on several baseline explanatory variables. The fitted model gave a predicted probability for each person that someone with those characteristics would be in the model at one year. Each person was then given weight equal to 1/p, where p is their fitted probability of being in the final logistic regression model. The weighted analysis was reported, although it was not substantially different from the unweighted analysis. An inverse probability weighted logistic regression with a robust error variance was fitted to the data, using a logit-link function and a binary response variable for mortality. By applying this model, the odds ratios (ORs) and 95% confidence intervals (95% CIs) were obtained.

We used a P-value threshold of 0.05 to decide on rejection or not of the null hypothesis.
The null hypothesis was defined as the mortality difference between groups defined by BPV
was zero. Exact p-values and 95% CIs were reported for inference and to quantify precision
respectively. All statistical analyses were carried out using Stata 18.

# 190 Results

Figure 1 shows the flow chart of the study. After exclusion of ineligible subjects, 2,572 patients
were available for analysis. 2,435 (94.7%) patients survived while 137 (5.3%) died during
admission. 36 additional patients died by one year follow-up, raising the total mortality at one
year to 173/2,572 (6.7%).

Table 1 shows the baseline characteristics. The median age for all participants was 53 years (44-62); 2,120 (82.4%) were males, and 452 (17.57%) were females. 897 (34.88%) were from the Middle East and North Africa (MENA), as defined by the International Monetary Fund [25]. 1,312 (51.01%) were from South Asia, 261 (10.15%) from Southeast Asia, nine (0.35%) were from East Asia, and 93 (3.62%) were from other regions as defined by the The United Nation's geoscheme which divides Asia into East, South, and Southeast Asia [26].

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE 201 2,151 (83.6%) were diagnosed with ischemic stroke/ TIA while 421 (16.4%) had ICH. Patients 202 who died were more likely to be males and older in age. Detailed baseline characteristics

including NIHSS score on admission, comorbidities, and laboratory investigations' results on
admission are presented in table 1.

# 206 Association between SBPV and in-hospital mortality

An adjusted multivariable logistic regression model (Table 2) showed an increase in mortality odds as SBPV level increased over level 1 (L2, OR 2.64, 95%CI 1.44 to 4.84; L3, OR 4.20 95%CI 2.14 to 8.24; L4, OR 10.14, 95%CI 4.93 to 20.85; L5, OR 23.18, 95%CI 10.88 to 49.37). The P values for these odds ratios suggested that the null effect model was unlikely to have generated the study data (P=0.002 to <0.001). The model had adequate goodness of fit (AUC = 0.80) and goodness of link as determined by a linktest in Stata.

# 214 Association between DBPV and in-hospital mortality

An adjusted multivariable logistic regression model (Table 3) showed an increase in mortality odds as DBPV level increased over level 1 (L2, OR 1.61, 95%CI 0.96 to 2.69; L3, OR 2.95 95%CI 1.70 to 5.12; L4, OR 8.00, 95%CI 4.49 to 14.25). The P values for these odds ratios suggested that the null effect model was unlikely to have generated the study data (P=0.071 to <0.001). The model had adequate goodness of fit (AUC = 0.79) and goodness of link as determined by a linktest in Stata.

50 221

# 222 Association between SBPV and one year mortality

An inverse probability weighted logistic regression model (Table 4) showed an increase in
mortality odds as SBPV level increased over level 1 (L2, OR 2.30, 95%CI 1.31 to 4.02; L3,
OR 3.51 95%CI 1.86 to 6.61; L4, OR 8.60, 95%CI 4.33 to 17.08; L5, OR 19.27, 95%CI 9.25

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to 40.15). The P values for these odds ratios suggested that the null effect model was unlikely

to have generated the study data (P=0.004 to <0.001).

# 231 Association between DBPV and one year mortality

An inverse probability weighted logistic regression model (Table 5) showed an increase in mortality odds as DBPV level increased over level 1 (L2, OR 1.49, 95%CI 0.91 to 2.41; L3, OR 2.20 95%CI 1.26 to 3.84; L4, OR 6.33, 95%CI 3.55 to 11.28). The P values for these odds ratios suggested that the null effect model was unlikely to have generated the study data (P= 0.11 to <0.001).

29 237 

# 238 Discussion

Our study consistently demonstrated a strong relationship, indicating that elevated BPV is linked to in-hospital mortality and cumulative all-cause mortality at one year. This association holds true for both systolic and diastolic blood pressure, as observed through early casual in-hospital BP measurements in a multiethnic population mainly from Middle East, North Africa, and South Asia. These findings are at variance with what is currently reported in literature. Additionally, even where limited data is available, there is paucity of this with regards to DBPV on stroke outcomes. Thus far there is paucity of robust evidence to objectively guide recommendation on the frequency of BP measurements to achieve the best prognostic value of BP readings in terms of stroke related in-hospital mortality and combined all-cause mortality. Therefore, our examination of this large cohort of patients admitted with acute stroke has provided the first tranche of clinical association between BPV and mortality.

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We found that an increase in SBPV above 11 mmHg (level 1) as well as an increase in DBPV above 8 mmHg (level 1) were significantly associated with increased in-hospital and one year mortality in patients presenting with acute ischemic or hemorrhagic stroke. Our results are consistent with recent reports from diverse patient populations which assessed the impact of blood pressure variation on stroke outcomes. In an observational study that utilized data on patients previously enrolled in CATIS trial and exclusively carried out Chinese patient cohorts [27,28], He et al., reported that 25.20% of patients died or had major disability due to BPV within a follow-up period of three months; with patients with highest systolic fluctuations having the highest risk for such outcomes [31,32]. A similar result was also found for the association of DBP fluctuations with study outcomes [28]. Another study done in 2021 in Japan concluded that increases in the coefficient of variance of SBP and DBP were significantly associated with an increased risk of recurrent stroke. Additionally, the coefficient of variance of SBP and DBP were significantly associated with an increased risk of all-cause death [29]. With respect to ICH, an abstract investigating patients who survived ICH in a period between 60-120 days after discharge was supportive that BPV is an important determinant of mortality and functional outcome in ICH survivors [30]. 

Our results, in addition to the results reported in the literature can be explained through multiple proposed pathophysiological mechanisms that can lead to the deterioration of neurological status and worsening of stroke outcomes. To begin with, the potential of reverse causality between BPV and stroke outcome must be taken into consideration, as BPV may be an outcome of worsening neurological condition. During the acute phase of stroke, BP control is affected due to involvement of autonomic nervous system [31], with baroreceptor reflex dysregulation being proposed as one of the mechanisms leading to blood pressure variability (BPV) due to alterations in control of vasomotor tone and a reduction in cardiac baroreceptor sensitivity, although the exact mechanism remains unclear [32]. 

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On the other hand, BPV exacerbates the condition of the tissue affected by stroke, leading to poorer neurological outcomes. The frequent rise in BP in hemorrhagic stroke can lead to growth of the hematoma and an increase in the arterial bleeding, while the sudden drop in BP may be a promoting factor for perihematomal ischemia. Blood-brain barrier can also be disrupted because of this variability, causing vasogenic edema [33]. As for ischemic stroke, the cerebral blood flow in the tissue affected becomes dependent on the systemic BP since the cerebral autoregulation mechanisms are impaired. This means an increase in the BP may lead to cerebral edema or hemorrhagic transformation in the focus of infarct. Additionally, the drop of systemic pressure reduces flow to the penumbra worsening its ischemia and increasing the infarct size [32]. Overall, dynamic cerebral autoregulation impairment can explain why increased BPV is connected to poor prognosis in terms of death and disability in acute stroke [32]. Causes of death can be due to these changes in a tight pressure-sensitive compartment like the skull which can lead to neurological death due to acute rise intracranial pressure and herniation or from complications due to immobility such as infections [34]

On the other hand, despite that our results were strongly supportive of the association between the increase in SBVP and DBPV and worsening stroke outcomes, other studies have dismissed these results [35–39]. A study investigated the influence of BPV on functional outcomes and the occurrence of ICH within the population enrolled in the BP TARGET trial. Their analysis revealed no significant association between BPV and either functional outcomes or the incidence of ICH. Another interesting finding is that BPV in this population was more likely in the group with strict SBP target and control [35]. Another study conducted in 2020 found that although increased early SBPV was related to worse functional outcome when patients have been treated by endovascular therapy, there was no association found in patients treated by intravenous thrombolysis [36]. In a paper published in 2018, even though they concluded that beat-to-beat BPV was a predictor for stroke recurrence, they found that short-

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term BPV on ambulatory BP monitoring was not associated with stroke recurrence or cardiovascular events in patients after a TIA or a nondisabling stroke [37]. A way to improve BPV was suggested in a 2017 study in Russia which showed that anxiety-related BPV may be improved by use of an anxiolytic within the medications given to improve BP control [38]. In the GOLIATH trial which included patients who had endovascular therapy with general anesthesia after an acute ischemic stroke, no association was found between any BP parameter including BPV and neurological outcome [39].

Based on the meta-analysis done in 2023, there is still not enough consensus in the literature that provides recommendations on the required number of readings to predict the presence of variability [9]. In our study, we believe that a minimum of 10 readings over the course of the first three days of stroke onset can be a good predictor of variability. Hence, our study shows that additional research is necessary to find parameters that may help indicate patients in greater risk for a higher BPV following a cerebrovascular accident. Furthermore, since our study focuses mainly on one outcome measure, which is mortality, more well-controlled studies need to be initiated to meticulously investigate BPV effects on other outcomes, including functional and neurologic outcomes. Lastly, finding potential effective therapy for increases in SBPV and DBPV is crucial to optimize the therapeutic approach in stroke patients to minimize the negative effects of BPV. There are several emerging studies comparing the effect of different pharmacological agents on BPV after an ischemic stroke. Drugs like fimasartan has shown these effects in a study conducted by Shin *et al.* [40]. 

Our study has several points of strength. It is noteworthy that we included a cohort of 2,572 patients who represent a relatively young population with a male sex majority due to the make-up of the country which has been reported previously and is multiethnic with majority from MENA and South Asia. This makes the dataset robust and allows for generalizability of our results. The results also show strong evidence against the null hypothesis, giving us a 

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valuable insight that is clinically relevant to the association between different BPV parameters and stroke-related mortality. The statistical analysis techniques employed showed robust good results with ROC curves which helps us assess the predictability of mortality based on parameters like SBPV and DBPV. Additionally, baseline characteristics and confounders were well-controlled and reported. Lastly, we have also had a prolonged follow-up period of up to one year after stroke onset in which mortality has been reported. In addition, we assessed the causal impact of BPV on mortality by adjusting for potential confounders determined through a DAG. In addition, we were able to demonstrate a dose-response relationship between level of BPV and mortality further strengthening the causal evidence of our results.

# 334 Limitations

Our study is limited by the inevitable consequences associated usually associated with its retrospective design, including dealing with missing values, and absence of consistent synchrony in the timing of blood pressure measurements by nursing personnel. Despite this however, the stability of point estimates of our study outcomes meant that these limitations did not significantly confound our findings.

# 38 340

# 40 341 **Conclusion**

In a retrospective cohort of ethnically diverse acute stroke patient population, blood pressure variability was significantly associated with both in-hospital and one year mortality. Clinical outcomes beyond one year remains uncertain. There is need to explore these findings further through a prospective examination of large patient cohorts to both ascertain the validity of these findings, as well as provide a prescriptive direction on blood pressure management in acute stroke management.

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# 349 Contributorship

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE



# Table 1. Baseline characteristics of the patients. 580

Variable	Level	Total	Alive	Dead	P-Valu	
v anabie		(n=2,572)	(n=2,435)	(n=137)	1 - v alu	
Age, years	Median (IQR)	53 (44-62)	53 (44-62)	55 (42,68)	0.19	
Sex						
Female	n (%)	452 (17.6%)	419 (17.2%)	33 (24.1%)	0.04	
Male		2,120 (82.4%)	2,016 (82.8%)	104 (75.9%)		
Ethnicity		0		1		
MENA	-	897 (34.88%)	848 (34.8%)	49 (35.8%)	0.34	
South Asia	n (%)	1,312 (51.0%)	1,250 (51.3%)	62 (45.3%)		
Southeast Asia		261 (10.2%)	241 (9.9%)	20 (14.7%)		
East Asia		9 (0.4%)	9 (0.4%)	0 (0.0%)		
Others		93 (3.6%)	87 (3.6%)	6 (4.4%)		
BMI	Median (IQR)	27.1 (24.4-30.3)	27.18 (24.4-30.3)	26.3 (24.2-30)	0.40	
Admission NIHSS	Median (IQR)	3 (2-8)	3 (2-7)	18 (7-25)	< 0.001	
Diagnosis						
ICH	n (%)	421 (16.4%)	355 (14.6%)	66 (48.2%)	< 0.001	
Ischemic Stroke	1	2,151 (83.6%)	2,080 (85.4%)	71 (51.8%)		
<b>Smoking Status</b>	n (%)			1	< 0.001	

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2						
3 Non	-Smoker		1,854 (72.1%)	1,732 (71.1%)	122 (89.1%)	
5 6 St	noker	-	588 (22.9%)	577 (23.7%)	11 (8.0%)	
8 Ex- 9	Smoker	-	128 (5%)	124 (5.1%)	4 (2.9%)	
1 <mark>0</mark> Tobaco	co Chewer		2 (0.1%)	2 (0.1%)	0 (0%)	
1 <del>2</del> 1 <sub>3</sub> History	of Cardiac					
14 15 <b>D</b> 16	isease					Protec
17	Yes	n (%)	382 (15%)	346 (14.2%)	36 (26.3%)	<0.001
19 20 Not	Known		2,190 (85.2%)	2,089 (85.8%)	101 (73.7%)	соруг
22 Hype 23	ertension					gnt, In
24 Not 25	known	n (%)	630 (24.5%)	584 (24%)	46 (33.6%)	ciuang <0.001 (ciuang
26 27 K	nown		1,469 (57.1%)	1,386 (56.9%)	83 (60.6%)	
29 Newly	Diagnosed	-	472 (18.4%)	464 (19.1%)	8 (5.8%)	ses reig
<sup>31</sup> Di	abetes		()	<u> </u>		
34 Not	Known	-	874 (34%)	808 (33.2%)	66 (48.2%)	text ar
6 K	nown	n (%)	1,047 (40.7%)	995 (40.9%)	52 (38%)	<0.001 data
8 Newly	Diagnosed	-	242 (9.4%)	233 (9.6%)	9 (6.6%)	
10 11 Pre-	diabetes	-	409 (15.9%)	399 (16.4%)	10 (7.3%)	g, Al tr
43 Hyper 44	lipidemia					
1 <del>5</del> Not 16 Not	Known	n (%)	1,314 (51.1%)	1,218 (50.0%)	96 (70.1%)	20 001 S
1/ 18 K 19	nown	н (70)	466 (18.1%)	438 (18%)	28 (20.4%)	
50 Newly	Diagnosed		792 (30.8%)	779 (32%)	13 (9.4%)	lecnno
52 53 History	y of Stroke				1	
54 55 Not	Known	n (%)	2,327 (90.5%)	2,201 (90.4%)	126 (92%)	0.01
57 K	nown		245 (9.5%)	234 (9.6%)	11 (8%)	
5 <del>9</del>						

# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

1

2						
3 4 5	History of TIA					
5 6 7	Not Known	n (%)	2,555 (99.3%)	2,419 (99.3%)	136 (99.3%)	0.92
, 8 9	Known		17 (0.7%)	16 (0.7%)	1 (0.7%)	
10 11	History of DVT					
1 <u>2</u> 13 14	Not Known	n (%)	2,563 (99.7%)	2,429 (99.8%)	134 (97.8%)	< 0.001
15 16	Known	_	9 (0.4%)	6 (0.2%)	3 (2.2%)	Protect
17 18	Admission Labs					ted by
1 <u>9</u> 20 21	HbA1C	Median (IQR)	6.2 (5.5-8.6)	6.2 (5.5-8.6)	6.7 (5.8-10.4)	0.038 <b>opy</b>
22 23	Cholesterol	Median (IQR)	4.8 (4-5.7)	4.8 (4-5.7)	4.2 (3.7-5.3)	0.090 <del>, i</del> n
24 25	Triglycerides	Median (IQR)	1.4 (1-2)	1.4 (1-2)	1.3 (1-1.6)	0.058 uding
2 <del>6</del> 27 28	HDL	Median (IQR)	1 (0.8-1.2)	1 (0.8-1.2)	1 (0.9-1.3)	0.12 or us
29 30	LDL	Median (IQR)	3 (2.3-3.8)	3 (2.3-3.8)	2.8 (2-3.7)	0.13 <b>e</b>
31 32	Platelet	Median (IQR)	255 (213-306)	255 (213-306.5)	249 (214-294)	0.36 <b>ed</b> to
33 34 35	PTT	Median (IQR)	10.4 (8.7-11.3)	10.4 (8.7-11.3)	11 (9.1-12)	<0.001 an
36 37	INR	Median (IQR)	1 (1-1.1)	1 (1-1.1)	1.1 (1-1.2)	<0.001 data
3 <del>8</del> 39 40 41 42	APTT	Median (IQR)	26.5 (24.5-29)	26.5 (24.6-29)	25.9 (23.4- 29.2)	0.21 g
43 44	581					aining
45 46	582					, and s
47 48 40	583					imilar
49 50 51	584					technc
52 53	585					ologies
54 55	586					·
56 57 58	587					
59 60	588					

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1	BL	OOD PRESSURE VARIABII	LITY AND M	ORTALITY IN STR	ROKE
∠ 3 4	589				
5 6	590				
7 8	591				
9 10 11	592				
12 13	593 Table	2. Association between SBPV	V and in-hosp	ital mortality – adju	sted multivariable logis
14 15	594 regres	sion model			
16 17	595				
18 19 20	596	Level of SBPV (p50)	OR	95% CI	P Value
20 21 22	597	<11mmHg (34mmHg)	1		
22 23 24	598	12-16mmHg (50mmHg)	2.64	1.44 to 4.84	0.002
25 26	599	17-21mmHg (68mmHg)	4.20	2.14 to 8.24	<0.001
27 28	600	22-26mmHg (89mmHg)	10.14	4.93 to 20.85	<0.001
29 30 21	601	>27mmHg (117mmHg)	23.18	10.88 to 49.37	<0.001
32 33	602	*Adjusted for type of stroke	(ischemic vs. h	emorrhagic), age, hyp	ertension (history or
34 35	002	newly diagnosed), and histor	y of cardiac dis	ease.	
86 87	603				
88 88	604				
9 10 11	605				
12 13	606				
14 15	607				
46 47	608				
18 19 50	609				
50 51 52	610				
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57 58 59	613				

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE 618 Table 3. Association between DBPV and in-hospital mortality – adjusted multivariable logistic 619 regression model Level of DBPV (p50) P Value OR 95% CI <8mmHg (25mmHg) 9-11mmHg (37mmHg) 1.61 0.96 to 2.69 0.071 12-15mmHg (50mmHg) 2.95 1.70 to 5.12 < 0.001 >16mmHg (70mmHg) 8.00 4.49 to 14.25 < 0.001 \*Adjusted for type of stroke (ischemic vs. hemorrhagic), age, hypertension (history or newly diagnosed), and history of cardiac disease. Liezoni

1		BLOOD PRESSURE VARIABI	ILITY AND MO	ORTALITY IN STR	OKE
2 3 4	639				
5 6	640				
7 8	641				
9 10 11	642				
12 13	643	Table 4. Association between S	BPV and one	year mortality – inv	erse probability weighted
14 15	644	logistic regression model			
16 17	645				
18 19		Level of SBPV (p50)	OR	95% CI	P Value
20 21 22		<11mmHg (34mmHg)	1		
22 23 24		12-16mmHg (50mmHg)	2.30	1.31 to 4.02	0.004
25 26		17-21mmHg (68mmHg)	3.51	1.86 to 6.61	< 0.001
27 28		22-26mmHg (89mmHg)	8.60	4.33 to 17.08	<0.001
29 30 31		>27mmHg (117mmHg)	19.27	9.25 to 40.15	< 0.001
32 33	646	*Adjusted for type of stroke	(ischemic vs. he	morrhagic), age, hype	ertension (history or
34 35	647	newly diagnosed), and histor	ry of cardiac disea	ase.	
36 37 38	648				
39 40	649				
41 42	650				
43 44	651				
45 46 47	652				
48 49	653				
50 51	654				
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54 55 56	656				
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59 60	658				

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE 663 Table 5. Association between DBPV and one year mortality - inverse probability weighted 664 logistic regression model Level of DBPV (p50) OR 95% CI P Value <8mmHg (25mmHg) 9-11mmHg (37mmHg) 1.49 0.91 to 2.41 0.11 12-15mmHg (50mmHg) 2.20 1.26 to 3.84 0.006 >16mmHg (70mmHg) 6.33 3.55 to 11.28 < 0.001\*Adjusted for type of stroke (ischemic vs. hemorrhagic), age, hypertension (history or newly diagnosed), and history of cardiac disease. lisc



# Blood Pressure Variability and Mortality in Patients Admitted with Acute Stroke in a Tertiary Care Stroke Center (2016-2019); A Retrospective Cohort Study

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

2 3 4	1	Blood Pressure Variability and Mortality in Patients Admitted with Acute Stroke in a
5 6	2	Tertiary Care Stroke Center (2016-2019); A Retrospective Cohort Study
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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

# 26 Abstract:

> Objectives: The influence of short-term variations in blood pressure (BP) in acute stroke on clinical outcomes remains uncertain. Our study explores the relationship between blood pressure variability (BPV) from stroke admission up to 72 hours and in-hospital and one year mortality.

**Design:** Retrospective observational cohort study.

32 Setting: Hamad General Hospital, a tertiary care stroke center in Qatar.

Participants: 2,820 were initially included. After exclusion of ineligible subjects, 2,554 patients (82.5% male, median age  $53 \pm 9$  years) were included. 893 (34.96%) were from the Middle East and North Africa (MENA), 1,302 (50.98%) were from South Asia, 258 (10.10%) from Southeast Asia, nine (0.35%) were from East Asia, and 92 (3.60%) were from other regions. Eligible participants were adult patients above 18 years of age who presented with acute ischemic or hemorrhagic stroke. Excluded individuals were those younger than 18 years, had incomplete data, had transient ischemic attack (TIA), had severe hypoglycemia on admission (<3.3mmol/L), or had history of chronic kidney disease (CKD).

Interventions: We measured the BP every four hours over three days with a total of 18 readings from stroke admission. We then categorized BPV into five (L1-L5) and four (L1-L4) levels for systolic and diastolic BPs respectively and evaluated their association with mortality. **Results:** There was increased odds of in-hospital mortality with increased systolic and diastolic variability (L2, OR 2.64, 95%CI 1.44 to 4.84; L3, OR 4.20 95%CI 2.14 to 8.24; L4, OR 10.14, 95%CI 4.93 to 20.85; L5, OR 23.18, 95%CI 10.88 to 49.37), (P = 0.002 to <0.001) and (L2, OR 1.61, 95%CI 0.96 to 2.69; L3, OR 2.95 95%CI 1.70 to 5.12; L4, OR 8.00, 95%CI 4.49 to 14.25), (P= 0.071 to <0.001), respectively. This was consistent with one year mortality for systolic and diastolic BPs.

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1 2		BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE
3 4	50	Conclusion: In a retrospective cohort of ethnically diverse acute stroke patient population,
5 6 7	51	blood pressure variability was significantly associated with both in-hospital and one year
7 8 9	52	mortality. Further prospective research is needed to define blood pressure variability and
10 11	53	establish interventions and management accordingly.
12 13	54	
14 15 16	55	Keywords: Casual measurement of BP, Blood pressure variability, stroke, hypertension,
10 17 18	56	mortality
19 20	57	
21 22	58	Strengths and limitations:
23 24 25	59	• Our study included 2,554 patients which is a large cohort that adds to the validity and
26 27	60	generalizability of the results.
28 29	61	• A minimum of ten blood pressure readings over 72 hours was required for inclusion,
30 31 32	62	giving a solid view of the impact of blood pressure variability on the outcomes of
33 34	63	stroke.
35 36	64	• The follow-up period of one year with inverse probability weighted logistic regression
37 38 39	65	provides a robust insight to the long-term consequences of blood pressure variability
40 41	66	on the outcomes of stroke.
42 43	67	• Our study is limited by its retrospective design, missing values, and absence of
44 45 46	68	consistent synchrony in the timing of blood pressure measurements by nursing
40 47 48	69	personnel.
49 50	70	• The stability of point estimates of our study outcomes meant that these limitations did
51 52	71	not significantly confound our findings.
53 54 55	72	
56 57	73	
58 59 60	74	

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

Introduction

High blood pressure (BP) is independently associated with poor outcomes in acute stroke [1,2]. Additional hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure and heart rate have been associated with poor outcomes following stroke [3]. Evidence investigating acute blood pressure variability (BPV) as a determinant of stroke outcomes is increasing [4–9]. However, no clear definition of blood pressure variability is yet defined by the guidelines. Systolic blood pressure variability (SBPV) is being recognized as an important triggering factor for vascular events including stroke and cardiovascular events [10]. Likewise, some authors suggest that diastolic blood pressure variability (DBPV) may be as important as SBPV [11,12]. It is, however, unclear whether the control of acute SBPV and DBPV after acute stroke would provide a potentially modifiable therapeutic target and improved clinical outcomes in patients with acute stroke.

Evidence on the effect of BPV after acute stroke on the clinical outcomes remains limited. A post hoc analysis of the Intensive BP Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) dataset reported significant associations between SBPV in the hyperacute (first 24 hours) and acute (days 2–7) periods, and death and disability at 90 days, in 2,839 participants with acute intracerebral hemorrhage (ICH) (<6 hours of symptom onset), and elevated SBP (SBP>150 mmHg) [5]. Other studies have mostly assessed BPV during a period of  $\geq$ 24 hours; the majority found significant associations between SBPV or DBPV and poor long-term functional outcome ( $\geq 3$  months) [13–17], or adverse findings on repeat neuroimaging [14,18], although not all [19,20]. Two small studies have examined the effect of short-term BPV on outcomes in acute ischemic stroke using beat-to-beat BP monitoring. Dawson et al evaluated the effect of BPV in patients with ischemic stroke and reported that

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

DBPV and mean arterial pressure (MAP) variability predict poor 30-day outcome [21], but Graff et al found no BPV difference between good and poor outcome groups at 90 days [22]. To date, no study has assessed the effect of short-term SBPV and DBPV derived from casual cuff BP measures - the most commonly used BP monitoring index for patients with acute stroke. The recommendations on this method of BP measurement are provided by the American Heart Association [23]. BP measurement is done by trained nurses mostly and it is done with the patient in supine position using a standard mercury sphygmomanometer and the appropriate cuff size based on the arm circumferences. Knowledge on how best to measure and define BPV has not been explored. Additionally, available evidence on the effect of BPV on outcome after acute stroke in our region is scarce. Our observational study explores the relationship between BPV, measured every four hours over three days with a total of 18 readings from stroke admission and derived from multiple closely spaced casual BP measures, and in-hospital and one year mortality. ier **Methods** Study design and participants: This is a retrospective cohort study of patients presenting with acute cerebrovascular accidents (ischemic stroke or hemorrhagic stroke) to Hamad General Hospital (HGH) between 1<sup>st</sup> May 2016 and 30<sup>th</sup> June 2019. HGH, a member of Hamad Medical Corporation (HMC), is regarded as the central hub for acute stroke care in Qatar. Over 80% of stroke cases are admitted or referred to HGH, thereby potentially reflecting acute stroke care in the whole of Qatar [24]. A multi-ethnic stroke database was established at HGH in January 2014, where clinical details were systematically recorded by trained individuals, including the clinical presentation, severity of deficits and NIHSS, TOAST classification, risk factors, complications, and outcome 

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

2 3 4	123	of all patients admitted with stroke, among other variables. All eligible individuals during the
5 6	124	pre-determined timeframe were recruited from the database for this study.
7 8 9	125	Eligible participants were all adult patients above the age of 18 years who presented to
10 11	126	HGH with an acute ischemic stroke or hemorrhagic stroke. Excluded individuals were those
12 13	127	younger than 18 years, had incomplete data regarding the diagnosis or outcomes, had TIA, had
14 15 16	128	severe hypoglycemia on admission (<3.3mmol/L), or had history of chronic kidney disease
17 18	129	(CKD).
19 20	130	
21 22	131	Patient involvement:
23 24 25	132	Considering the retrospective design of the study and the use of the aforementioned stroke
26 27	133	database as the source of our data, patients' involvement in the conduction of this research was
28 29	134	not possible.
30 31 32	135	
33 34	136	Data collection and variables:
35 36	137	Data collection on the included participants was obtained from the stroke database and
37 38 39	138	supplemented with the patients' electronic medical records. Collected data was then entered
40 41	139	into a standardized data collection sheet on Microsoft Excel.
42 43	140	Data was obtained on 1) baseline demographics including age, sex, nationality, and
44 45 46	141	medical comorbidities; 2) stroke type, whether ischemic stroke, TIA or hemorrhagic stroke,
40 47 48	142	and the TOAST classification; 3) severity of stroke based on NIHSS scale; 4) blood pressure
49 50	143	readings on presentation and during the following 72 hours recorded every four hours with six
51 52	144	readings per day, obtained using standard Dinamap which is utilized across the hospital; and
53 54 55	145	5) mortality, including in-hospital and mortality one year post stroke.
56 57	146	The standard deviation of SBPV were then categorized for each person into five levels;
58 59 60	147	(L1, <11mmHg; L2, 12-16mmHg; L3, 17-21mmHg; L4, 22-26mmHg; L5, >27mmHg). For

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

DBPV, patients were grouped into four levels as follows: (L1, <8mmHg; L2, 9-11mmHg; L3, 12-15mmHg; L4, >16mmHg). Patients with eight or more missing values out of 18 were excluded and the standard deviations were computed for those who had 10 or more readings over three days. These levels of standard deviation were utilized as the measure of SBPV or DBPV over the first three days of admission. These two variables were used as categories in lieu of the continuous measure to avoid problems with non-linearity. Additionally, we calculated the flux of patients (the difference between the highest and the lowest BP readings) for both systolic and diastolic BPs as a clinical representation of variability. It was then tabulated by the standard deviation categories and the median values (p50) were reported.

For the purpose of this study, ischemic stroke, TIAs and intracranial hemorrhage (ICH) were diagnosed according to the WHO criteria. Mortality was confirmed by reviewing the death note in patients' medical records for both in-hospital and one year post stroke mortality.

161 Statistical analysis:

Descriptive statistics of the cohort data were presented as medians and interquartile ranges
(IQR). Wilcoxon Rank Sum test was employed to compare the differences between groups.
For categorical variables, frequencies and percentages were reported and compared using
Pearson's Chi-square test.

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166To investigate the association of BPV with in-hospital mortality, we used multivariable167regression. Adjustments were made for variables that were either potentially confounding or168prognostic for the outcome based on a directed acyclic graph (DAG). These covariates included169type of stroke (ischemic vs. hemorrhagic), age, hypertension (history or newly diagnosed), and170history of cardiac disease. The analysis was repeated for assessment of the impact of BPV on171one year mortality.

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

As we had significant losses to complete follow-up within the one-year regression model, we adjusted for the dropouts from the model by running an appropriately weighted regression. We first computed the probability to remain in the study at one year by regressing (using logistic regression) an indicator variable on several baseline explanatory variables. The fitted model gave a predicted probability for each person that someone with those characteristics would be in the model at one year. Each person was then given weight equal to 1/p, where p is their fitted probability of being in the final logistic regression model. The weighted analysis was reported, although it was not substantially different from the unweighted analysis. An inverse probability weighted logistic regression with a robust error variance was fitted to the data, using a logit-link function and a binary response variable for mortality. By applying this model, the odds ratios (ORs) and 95% confidence intervals (95% CIs) were obtained.

We used a P-value threshold of 0.05 to decide on rejection or not of the null hypothesis.
The null hypothesis was defined as the mortality difference between groups defined by BPV
was zero. Exact p-values and 95% CIs were reported for inference and to quantify precision
respectively. All statistical analyses were carried out using Stata 18.

- D 188
  - **Results**

Figure 1 shows the flow chart of the study. After exclusion of ineligible subjects, 2,554 patients
were available for analysis. 2,417 (94.6%) patients survived while 137 (5.4%) died during
admission. 36 additional patients died by one year follow-up, raising the total mortality at one
year to 173/2,572 (6.7%).

54194Supplementary Table 1 shows the baseline characteristics. The median age for all5556195participants was 53 years (44-62); 2,108 (82.5%) were males, and 446 (17.5%) were females.5859196893 (34.96%) were from the Middle East and North Africa (MENA), as defined by the60

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

International Monetary Fund [25]. 1,312 (51.01%) were from South Asia, 261 (10.15%) from Southeast Asia, nine (0.35%) were from East Asia, and 93 (3.62%) were from other regions as defined by the The United Nation's geoscheme which divides Asia into East, South, and Southeast Asia [26]. 2,133 (83.5%) were diagnosed with ischemic stroke while 421 (16.5%) had ICH. Patients who died were more likely to be males and older in age. Detailed baseline characteristics including NIHSS score on admission, comorbidities, and laboratory investigations' results on admission are presented in Supplementary Table 1.

#### Association between SBPV and in-hospital mortality

An adjusted multivariable logistic regression model (Table 1) showed an increase in mortality odds as SBPV level increased over level 1 (L2, OR 2.64, 95%CI 1.44 to 4.84; L3, OR 4.20 95%CI 2.14 to 8.24; L4, OR 10.14, 95%CI 4.93 to 20.85; L5, OR 23.18, 95%CI 10.88 to 49.37). The P values for these odds ratios suggested that the null effect model was unlikely to have generated the study data (P=0.002 to <0.001). The model had adequate goodness of fit (AUC = 0.80) and goodness of link as determined by a linktest in Stata.

- Association between DBPV and in-hospital mortality

An adjusted multivariable logistic regression model (Table 2) showed an increase in mortality odds as DBPV level increased over level 1 (L2, OR 1.61, 95%CI 0.96 to 2.69; L3, OR 2.95 95%CI 1.70 to 5.12; L4, OR 8.00, 95%CI 4.49 to 14.25). The P values for these odds ratios suggested that the null effect model was unlikely to have generated the study data (P=0.071 to <0.001). The model had adequate goodness of fit (AUC = 0.79) and goodness of link as determined by a linktest in Stata. 

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# Association between SBPV and one year mortality

An inverse probability weighted logistic regression model (Table 3) showed an increase in mortality odds as SBPV level increased over level 1 (L2, OR 2.30, 95%CI 1.31 to 4.02; L3, OR 3.51 95%CI 1.86 to 6.61; L4, OR 8.60, 95%CI 4.33 to 17.08; L5, OR 19.27, 95%CI 9.25 to 40.15). The P values for these odds ratios suggested that the null effect model was unlikely to have generated the study data (P=0.004 to <0.001).

# Association between DBPV and one year mortality

An inverse probability weighted logistic regression model (Table 4) showed an increase in mortality odds as DBPV level increased over level 1 (L2, OR 1.49, 95%CI 0.91 to 2.41; L3, OR 2.20 95%CI 1.26 to 3.84; L4, OR 6.33, 95%CI 3.55 to 11.28). The P values for these odds ratios suggested that the null effect model was unlikely to have generated the study data (P= CUR. 0.11 to <0.001).

### Discussion

Our study consistently demonstrated a strong relationship, indicating that elevated BPV is linked to in-hospital mortality and cumulative all-cause mortality at one year. This association holds true for both systolic and diastolic blood pressure, as observed through early casual in-hospital BP measurements in a multiethnic population mainly from Middle East, North Africa, and South Asia. These findings are at variance with what is currently reported in literature. Additionally, even where limited data is available, there is paucity of this with regards to DBPV on stroke outcomes. Thus far there is paucity of robust evidence to objectively guide recommendation on the frequency of BP measurements to achieve the best prognostic value of BP readings in terms of stroke related in-hospital mortality and combined all-cause mortality. Furthermore, lack of definition of critical blood pressure variability further complicates the 

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situation as there is no agreement on an acceptable range of variability versus a concerning one requiring intervention that is reported in guidelines for stroke management. Therefore, our examination of this large cohort of patients admitted with acute stroke has provided the first tranche of clinical association between BPV and mortality. This could hold clinical implications on current practice resulting in proper future definition of variability.

We found that an increase in SBPV above 11 mmHg (level 1) as well as an increase in DBPV above 8 mmHg (level 1) were significantly associated with increased in-hospital and one year mortality in patients presenting with acute ischemic or hemorrhagic stroke. Our results are consistent with recent reports from diverse patient populations which assessed the impact of blood pressure variation on stroke outcomes. In an observational study that utilized data on patients previously enrolled in CATIS trial and exclusively carried out Chinese patient cohorts [27,28], He et al., reported that 25.20% of patients died or had major disability due to BPV within a follow-up period of three months; with patients with highest systolic fluctuations having the highest risk for such outcomes [31,32]. A similar result was also found for the association of DBP fluctuations with study outcomes [28]. In one study which recruited patients presenting with mild stroke and large vessel occlusion undergoing best medical management (IVT, anticoagulation, antiplatelet), it was concluded that early neurological deterioration (END), defined as increase in NIHSS score of  $\geq 4$  points within 24h, was evident in the group with the highest admission SBP readings and SBPV [29]. Another study done in 2021 in Japan concluded that increases in the coefficient of variance of SBP and DBP were significantly associated with an increased risk of recurrent stroke. Additionally, the coefficient of variance of SBP and DBP were significantly associated with an increased risk of all-cause death [30]. With respect to ICH, an abstract investigating patients who survived ICH in a period between 60-120 days after discharge was supportive that BPV is an important determinant of mortality and functional outcome in ICH survivors [31]. Moreover, in one prospective study, 

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BPV in acute ischemic stroke was found to be negatively associated with favorable functional outcomes at 3 months, in addition to an increase in infarct expansion and higher risk of hemorrhagic transformation [32].

Our results, in addition to the results reported in the literature can be explained through multiple proposed pathophysiological mechanisms that can lead to the deterioration of neurological status and worsening of stroke outcomes. To begin with, the potential of reverse causality between BPV and stroke outcome must be taken into consideration, as BPV may be an outcome of worsening neurological condition. During the acute phase of stroke, BP control is affected due to involvement of autonomic nervous system [33], with baroreceptor reflex dysregulation being proposed as one of the mechanisms leading to blood pressure variability (BPV) due to alterations in control of vasomotor tone and a reduction in cardiac baroreceptor sensitivity, although the exact mechanism remains unclear [34].

On the other hand, BPV exacerbates the condition of the tissue affected by stroke, leading to poorer neurological outcomes. The frequent rise in BP in hemorrhagic stroke can lead to growth of the hematoma and an increase in the arterial bleeding, while the sudden drop in BP may be a promoting factor for perihematomal ischemia. Blood-brain barrier can also be disrupted because of this variability, causing vasogenic edema [35]. As for ischemic stroke, the cerebral blood flow in the tissue affected becomes dependent on the systemic BP since the cerebral autoregulation mechanisms are impaired. This means an increase in the BP may lead to cerebral edema or hemorrhagic transformation in the focus of infarct. Additionally, the drop of systemic pressure reduces flow to the penumbra worsening its ischemia and increasing the infarct size [34]. Overall, dynamic cerebral autoregulation impairment can explain why increased BPV is connected to poor prognosis in terms of death and disability in acute stroke [34]. Causes of death can be due to these changes in a tight pressure-sensitive compartment 

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like the skull which can lead to neurological death due to acute rise intracranial pressure andherniation or from complications due to immobility such as infections [36]

On the other hand, despite that our results were strongly supportive of the association between the increase in SBVP and DBPV and worsening stroke outcomes, other studies have dismissed these results [37-41]. A study investigated the influence of BPV on functional outcomes and the occurrence of ICH within the population enrolled in the BP TARGET trial. Their analysis revealed no significant association between BPV and either functional outcomes or the incidence of ICH. Another interesting finding is that BPV in this population was more likely in the group with strict SBP target and control [37]. Another study conducted in 2020 found that although increased early SBPV was related to worse functional outcome when patients have been treated by endovascular therapy, there was no association found in patients treated by intravenous thrombolysis [38]. In a paper published in 2018, even though they concluded that beat-to-beat BPV was a predictor for stroke recurrence, they found that short-term BPV on ambulatory BP monitoring was not associated with stroke recurrence or cardiovascular events in patients after a TIA or a nondisabling stroke [39]. A way to improve BPV was suggested in a 2017 study in Russia which showed that anxiety-related BPV may be improved by use of an anxiolytic within the medications given to improve BP control [40]. In the GOLIATH trial which included patients who had endovascular therapy with general anesthesia after an acute ischemic stroke, no association was found between any BP parameter including BPV and neurological outcome [41]. 

Based on the meta-analysis done in 2023, there is still not enough consensus in the literature that provides recommendations on the required number of readings to predict the presence of variability [9]. In our study, we believe that a minimum of 10 readings over the course of the first three days of stroke onset can be a good predictor of variability. Hence, our study shows that additional research is necessary to find parameters that may help indicate 

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patients in greater risk for a higher BPV following a cerebrovascular accident. Furthermore, since our study focuses mainly on one outcome measure, which is mortality, more well-controlled studies need to be initiated to meticulously investigate BPV effects on other outcomes, including functional and neurologic outcomes. Lastly, finding potential effective therapy for increases in SBPV and DBPV is crucial to optimize the therapeutic approach in stroke patients to minimize the negative effects of BPV. There are several emerging studies comparing the effect of different pharmacological agents on BPV after an ischemic stroke. Drugs like fimasartan has shown these effects in a study conducted by Shin et al. [42]. In recently published narrative review, they discuss that the use of antihypertensive medications like calcium channel blockers and non-loop diuretics were found to reduce BPV in outpatient visit-to-visit BP readings when used alone or in combination with other agents [43]. In contrast, beta blockers were observed to increase BPV in similar settings, which can be considered when starting inpatient antihypertensive medications for blood pressure control. Additionally, it was recommended to avoid the use of potent short acting medications as it would exacerbate the iatrogenic potential of such action on blood pressure variability [43]. 

Our study has several points of strength. It is noteworthy that we included a cohort of 2,572 patients who represent a relatively young population with a male sex majority due to the make-up of the country which has been reported previously and is multiethnic with majority from MENA and South Asia. This makes the dataset robust and allows for generalizability of our results. The results also show strong evidence against the null hypothesis, giving us a valuable insight that is clinically relevant to the association between different BPV parameters and stroke-related mortality. The statistical analysis techniques employed showed robust good results with ROC curves which helps us assess the predictability of mortality based on parameters like SBPV and DBPV. Additionally, baseline characteristics and confounders were well-controlled and reported. Lastly, we have also had a prolonged follow-up period of up to 

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one year after stroke onset in which mortality has been reported. In addition, we assessed the causal impact of BPV on mortality by adjusting for potential confounders determined through a DAG. In addition, we were able to demonstrate a dose-response relationship between level of BPV and mortality further strengthening the causal evidence of our results. 

Limitations 

Our study is limited by the inevitable consequences associated usually associated with its retrospective design, including dealing with missing values, and absence of consistent synchrony in the timing of blood pressure measurements by nursing personnel. Our results could also be affected by inability to adjust for factors that may adversely affect blood pressure like physical activity, caffeine intake, smoking, amongst others. Nevertheless, blood pressure was consistently measured while patients are supine and through arm measurement, appropriate cuff was used, and other factors like adequate rest prior to measurements were considered. Additionally, the stability of point estimates of our study outcomes meant that these limitations did not significantly confound our findings. 

> Conclusion

In a retrospective cohort of ethnically diverse acute stroke patient population, blood pressure variability was significantly associated with both in-hospital and one year mortality. Clinical outcomes beyond one year remains uncertain. There is need to explore these findings further through a prospective examination of large patient cohorts to both ascertain the validity of these findings, as well as provide a prescriptive direction on blood pressure management in acute stroke management.

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19 20	403	Competing interests
21 22	404	The authors declare that they have no conflict of interest.
23 24 25	405	
25 26 27	406	Data sharing
28 29	407	The data of this article are available upon reasonable request to the corresponding author.
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35 36	410	None.
37 38	411	
39 40 41	412	Ethics
42 43	413	This study utilized retrospectively collected data. Patients' identifiers including name
44 45	414	and healthcare numbers were removed, and subjects were anonymized by numbers. The data
46 47 48	415	was stored into an Excel sheet which was secured by a password. It was then shifted to analysis
49 50	416	which was also protected by a passcode. Given the retrospective design and the inability to
51 52	417	trace data back to individual subjects, informed consent was not required and was waived by
53 54 55	418	the Medical Research Center (MRC) at HMC. Ethical approval was provided by the MRC at
55 56 57	419	HMC, MRC-01-20-968.
58 59 60	420	

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BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

596 Table 1. Association between SBPV and in-hospital mortality – adjusted multivariable logistic 597 regression model

598				
500	Level of SBPV (p50)	OR	95% CI	P Value
399		_		
600	<11mmHg (34mmHg)	1		
	12-16mmHg (50mmHg	g) 2.64	1.44 to 4.84	0.002
601				
602	17-21mmHg (68mmHg	g) 4.20	2.14 to 8.24	< 0.001
002	22-26mmHg (89mmHg	g) 10.14	4.93 to 20.85	< 0.001
603		<i></i>		
604	>27mmHg (117mmHg	g) 23.18	10.88 to 49.37	< 0.001
001				
605	*Adjusted for type of stro newly diagnosed), and his	ke (ischemic vs. story of cardiac di	hemorrhagic), age, hyr sease.	pertension (history o
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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

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621 Table 2. Association between DBPV and in-hospital mortality - adjusted multivariable logistic

622 regression model

Level of DBPV (p50)	OR	95% CI	P Value
<8mmHg (25mmHg)	1		
9-11mmHg (37mmHg)	1.61	0.96 to 2.69	0.071
12-15mmHg (50mmHg)	2.95	1.70 to 5.12	< 0.001
>16mmHg (70mmHg)	8.00	4.49 to 14.25	< 0.001

\*Adjusted for type of stroke (ischemic vs. hemorrhagic), age, hypertension (history or newly diagnosed), and history of cardiac disease.

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# Table 3. Association between SBPV and one year mortality – inverse probability weighted

647 logistic regression model

648				
	Level of SBPV (p50)	OR	95% CI	P Value
	<11mmHg (34mmHg)	1		
	12-16mmHg (50mmHg)	2.30	1.31 to 4.02	0.004
	17-21mmHg (68mmHg)	3.51	1.86 to 6.61	< 0.001
	22-26mmHg (89mmHg)	8.60	4.33 to 17.08	<0.001
	>27mmHg (117mmHg)	19.27	9.25 to 40.15	< 0.001
649	*Adjusted for type of stroke	(ischemic vs. I	nemorrhagic), age, hype	ertension (history or
650	newly diagnosed), and histor	ry of cardiac dis	sease.	
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# BLOOD PRESSURE VARIABILITY AND MORTALITY IN STROKE

666	Table	4.	Association	between	DBPV	and	one	year	mortality	—	inverse	probability	weighted
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667 logistic regression model

Level of DBPV (p50)	OR	95% CI	P Value
<8mmHg (25mmHg)	1		
9-11mmHg (37mmHg)	1.49	0.91 to 2.41	0.11
12-15mmHg (50mmHg)	2.20	1.26 to 3.84	0.006
>16mmHg (70mmHg)	6.33	3.55 to 11.28	< 0.001

\*Adjusted for type of stroke (ischemic vs. hemorrhagic), age, hypertension (history or newly diagnosed), and history of cardiac disease.

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n= 2,820

Total patients

n= 2,554





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1

Table 1. Baseline characteristics of the patients.

		Total	Alive	Dead	
Variable	Level	(n=2,554)	(n=2,417)	(n=137)	P-Value
Age, years	Median (IQR)	53 (44-62)	53 (44-61)	55 (42,68)	0.19
3 Sex					
5 Female	n (%)	446 (17.5%)	413 (17.1%)	33 (24.1%)	0.036
7 Male		2,108 (82.5%)	2,004 (82.9%)	104 (75.9%)	- ted by
Ethnicity	0,				copyr
2 MENA 3		893 (35%)	844 (34.9%)	49 (35.8%)	ight, in
4 South Asia	$n \left(\frac{9}{2}\right)$	1,302 (51.0%)	1,240 (51.3%)	62 (45.3%)	
6 7 Southeast Asia		258 (10.1%)	238 (9.9%)	20 (14.6%)	_ 0.33 g tor   u
9 East Asia	_	9 (0.4%)	9 (0.4%)	0 (0.0%)	ses re
1 Others	_	92 (3.6%)	86 (3.6%)	6 (4.4%)	ated to
3 4 BMI	Median (IQR)	27.1 (24.3-30.4)	27.18 (24.4-30.4)	26.3 (24.2-30)	0.39 <b>x</b>
6 Admission NIHSS	Median (IQR)	3 (2-8)	3 (2-7)	18 (7-25)	<0.001 data
<sup>8</sup> <b>Diagnosis</b>					
1 ICH	n (%)	421 (16.5%)	355 (14.7%)	66 (48.2%)	-   <0.001 <b>A</b>
<ul> <li><sup>2</sup></li> <li><sup>3</sup> Ischemic Stroke</li> <li><sup>4</sup></li> </ul>	_	2,133 (83.5%)	2,062 (85.3%)	71 (51.8%)	
5 Smoking Status					ands
7 8 Non-Smoker	-	1,839 (72.0%)	1,717 (71.0%)	122 (89.1%)	milar
0 Smoker 1	n (%)	585 (22.9%)	574 (23.8%)	11 (8.0%)	<0.001 ho
2 Ex-Smoker	-	128 (5%)	124 (5.1%)	4 (2.9%)	
4 Tobacco Chewer	-	2 (0 1%)	2 (0 1%)	0 (0%)	-
		= (0.170)	_ (0.17,0)		

History of Cardiac					
Disease					
Yes		379 (14.8%)	343 (14.2%)	36 (26.3%)	<0.00
Not Known	n (%)	2,175 (85.2%)	2,074 (85.8%)	101 (73.7%)	_ <0.00
Hypertension					
Not known	n (%)	624 (24.4%)	578 (23.9%)	46 (33.6%)	-
Known	1 (70)	1,458 (57.1%)	1,375 (56.9%)	83 (60.6%)	
Newly Diagnosed	O,	471 (18.5%)	463 (19.2%)	8 (5.8%)	-
Diabetes	~		1	1	
Not Known		867 (34%)	801 (33.1%)	66 (48.2%)	
Known	n (%)	1,039 (40.7%)	987 (40.8%)	52 (38%)	< 0.00
Newly Diagnosed		241 (9.4%)	232 (9.6%)	9 (6.6%)	-
Pre-diabetes		407 (15.9%)	397 (16.4%)	10 (7.3%)	-
Hyperlipidemia					
Not Known	n (%)	1,305 (51.1%)	1,209 (50.0%)	96 (70.1%)	< 0.00
Known		461 (18.1%)	433 (17.9%)	28 (20.4%)	
Newly Diagnosed		788 (30.9%)	775 (32%)	13 (9.5%)	
History of Stroke					0.81
Not Known	n (%)	2,310 (90.5%)	2,184 (90.4%)	126 (92%)	
Known		244 (9.6%)	233 (9.6%)	11 (8%)	-
History of TIA			1	1	
Not Known	n (%)	2,537 (99.3%)	2,401 (99.3%)	136 (99.3%)	0.92
Known		17 (0.7%)	16 (0.7%)	1 (0.7%)	1
History of DVT	n (%)		1	I	< 0.00

2						
3 4	Not Known		2,545 (99.7%)	2,411 (99.8%)	134 (97.8%)	
5	Known	_	9 (0.4%)	6 (0.3%)	3 (2.2%)	
/ 8 9	Admission Labs					
10 11	HbA1C	Median (IQR)	6.2 (5.5-8.6)	6.2 (5.5-8.6)	6.7 (5.8-10.4)	0.040
1 <del>2</del> — 13 14	Cholesterol	Median (IQR)	4.8 (4-5.7)	4.8 (4-5.7)	4.2 (3.7-5.3)	0.087
15 16	Triglycerides	Median (IQR)	1.4 (1-2)	1.4 (1-2)	1.3 (1-1.6)	0.061
17 18 10	HDL	Median (IQR)	0.97 (0.8-1.2)	0.97 (0.8-1.2)	1 (0.9-1.3)	0.12
20 21	LDL	Median (IQR)	3 (2.3-3.8)	3 (2.3-3.8)	2.8 (2-3.7)	0.13
22 23	Platelet	Median (IQR)	255 (213-306)	255 (213-306.5)	249 (214-294)	0.36
24 25 26	PTT	Median (IQR)	10.4 (8.7-11.3)	10.4 (8.7-11.3)	11 (9.1-12)	<0.001
20 27 28	INR	Median (IQR)	1 (1-1.1)	1 (1-1.1)	1.1 (1-1.2)	<0.001
29 30	APTT	Median (IQR)	26.5 (24.5-29)	26.5 (24.6-29)	25.9 (23.4-29.2)	0.21
31 32 33 34			Ľ.			

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