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Individual and joint effects of borderline ankle-brachial index and high plasma total homocysteine on all-cause death in hypertensive adults

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ABSTRACT

BACKGROUND The cardiovascular hazards of total homocysteine (tHcy) are long known. In addition, despite the acknowledgment on the importance of low ankle-brachial index (ABI) (< 0.9), borderline ABI (0.91-0.99) was once commonly overlooked. This study aims to explore the independent and joint effect of tHcy level and borderline ABI on all-cause death in hypertensive population.

METHODS This study included 10,538 participants from China H-type Hypertension Registry Study. ABI was described into two groups: normal ABI (1.00-1.40) and borderline ABI. tHcy level was also divided into two groups: < 15.02 and ≥ 15.02 μmo/L. Four groups were analyzed, using COX proportional hazard regression model, separately and pairwise to observe the independent and joint effect on all-cause death.

RESULTS A total of 126 (1.2%) deaths were observed in the 1.7 years follow-up time. Borderline ABI has a higher predicted risk of death than normal ABI (HR = 1.87, 95%CI: 1.17-3.00) after adjusting for potential covariates. Compare with tHcy level < 15.02 μmo/L (low tHcy), those with tHcy ≥ 15.02 μmo/L (high tHcy) had higher risk to event outcome (HR = 1.99, 95% CI: 1.30-3.05). According to the cumulative hazard curve, group with borderline ABI and high tHcy level has significantly higher altitude and larger increasing rate over follow-up period compare to other groups. Among those with borderline ABI, participants with high tHcy had higher death risk than those with low tHcy, nevertheless, no significant different between borderline and normal ABI among those with low tHcy levels.

CONCLUSIONS Borderline ABI and tHcy level both have independent predictive value on all-cause death. The combined group of borderline ABI and high tHcy has highest risk factor of outcomes, which suggested the mutual additive value of borderline ABI and tHcy. More attention should be given to the importance of borderline ABI in hypertensive population, especially with elevated tHcy level.

Homocysteine (Hcy) is a sulfur-containing, non-proteinogenic amino acid synthesized through the transmethylation of amino acid methionine from one-carbon metabolism. Elevated plasma total homocysteine (tHcy) level is associated with endothelial dysfunction, increased blood coagulation, and metabolic disturbance, promoting cardiovascular diseases, stroke, and coronary artery disease.[1,2] Notably, patients with high Hcy levels and concomitant hypertension were suggested to be at particularly higher risk.[3] Moreover, increasing studies have explored a

positive association between advanced Hcy level with all-cause mortality. According to a recent dose-response meta-analysis, for each 5-μmol/L increment of tHcy levels, the risk for all-cause mortality increased by 33.6%.[4]

The ankle-brachial index (ABI) is an effective, well-established measure that is commonly used in the diagnosis of peripheral artery disease (PAD),[5] meanwhile was well studied as an important indicator of atherosclerosis and CVD events.[6] Although ankle-brachial index (ABI) ≤ 0.90 has been recognized as the threshold value for abnormal/low ABI, which was proven to increase the risk of all-cause mortality,[7] a study from the American Heart Association has suggested ABI between 0.91 and 1.00 should be considered as "borderline area" in terms of cardiovascular risks,[8] considering of prior probability and sensitivity of ABI calculation. Emerging studies have aimed to explore the predictive value of borderline ABI,[9–11] however, controversy remains because of limited and inconsistent data.

The current study aimed to explore the individual and joint effect of borderline ABI and tHcy on all-cause mortality among hypertensive adults. Although ABI level ≤ 0.90 has been and is going to remain significant in clinical practice, we believe broader concern should be placed on borderline ABI, especially for its value in risk differentiation and identification. To the best of our knowledge, there are no similar previous studies.

METHODS

All data were obtained from the China H-type Hypertension Registry Study (Registration number: ChiCTR1800017274), which have been thoroughly reported before.[12] Briefly, current cohort study was conducted from March 2018 in Wuyuan, Jiangxi, China, where livelihoods were mostly depend on agriculture.[13] With the primary target of establishing a national registry for hypertensive population, the China H-type Hypertension Registry Study investigated and assessed hypertension treatment and related risk factors. This study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Institute of Biomedicine, Anhui Medical University. Written informed consent were provided by all participants.

A total of 10,923 hypertensive participants who received ABI measurement were recruited. Six participants were excluded due to missing tHcy data; PAD patients who with prior history of revascularization were strictly excluded in this study. Three hundred and thirty-seven were excluded with baseline ABI ≤ 0.9 or >1.4, and six were lost during the 1.7 years follow-up period. In the end, 10,538 eligible participants were included in the final analysis.

ABI Collection

ABI is defined as the ratio of systolic blood pressure of the ankle artery to the upper brachial artery. Before collection, all participants were required to rest quietly for at least 10 min in a warm and suitable environment with ankle-brachial region fully exposed. Then, ABI was collected using Omron Colin BP-203RPE III device (Omron Health Care, Kyoto, Japan) by trained technicians. Bilateral ankle and upper arm blood pressure were simultaneously measured. The build-in program in the device will calculate ABI on both sides. Lower ABI was recorded and used in the final analysis.[14]

tHcy and Covariates Collection

Fast venous blood samples were collected from all participants and were analyzed in Biaojia Biotechnology Laboratory in Shenzhen, China, using automatic clinical analyzers (Beckman Coulter, Bera, California). The whole collection process was within 30 min of time. Data including total cholesterol, triglycerides, high-density lipoprotein (HDL), serum creatinine, fasting blood glucose (FBG) and tHcy were analyzed and recorded. All laboratory examinations were blinded to participation in this study.

Epidemiological and demographic data including smoking status, alcohol consumption, labor intensity, medication and medical history were obtained through a standardized questionnaire. Diabetes mellitus was defined accordingly: (1) self-reported history of diabetes mellitus; (2) FBG ≥ 7.1 mmol/L; and (3) usage of hypoglycemic drugs. Blood pressure was measured three times after at least 10 min of resting, and calculated mean value was recorded as analysis BP.

Outcome Assessment

The primary outcome of this study is all-cause

death. Death event and its specific inducement were recognized through the local death and disease registries of the National Disease Surveillance Point System and National Health Insurance System. The cause of death was further investigated by an independent Endpoint Events Review Committee using the last hospital medical records.

Statistical Analysis

ABI was described according to different level as borderline (0.91-0.99) and normal (1.0-1.4). tHcy level was divided into two groups: < 15.02 μmol/L and ≥ 15.02 μmol/L. Categorical variables were presented as frequencies (percentage), and continuous variables were described as mean ± SD. Comparison of data characteristics was performed by the chi-square test for categorical variables and 2-tailed *t*-test for continuous variables. The effects of borderline ABI and tHcy levels on primary outcome were evaluated using Kaplan–Meier curves (log-rank test) and Cox proportional hazards models (hazards ratio [HR] and 95% confidence interval [CI]) with adjustment for major covariables including sex, age, body mass index, systolic blood pressure, diastolic blood pressure, smoking status, alcohol consumption, triglyceride, total cholesterol, HDL, serum creatinine, diabetes mellitus, self-reported stroke, self-reported coronary heart disease (CHD), use of antihypertensive drugs and antiplatelet agents.

All data were analyzed using Empower (ER) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA) and the statistical package R (http://www.r-project.org). A two-tailed $P < 0.05$ denoted statistical significance.

RESULTS

Population Characteristics

A total of 10,538 hypertensive population were analyzed, among which, 4,930 population were male (46.8%), with mean age of 63.6 ± 9.1 years. The baseline tHcy was 17.8 ± 10.8 μmol/L, and mean ABI was 1.1 ± 0.1. Population characteristics stratified by ABI and tHcy level were shown in Table 1. Compared with normal ABI (1.0-1.4), participants with borderline ABI (0.91-0.99) were more likely to be female and elderly, with higher systolic blood pressure, tHcy, total cholesterol, and lower proportion of current smoke and alcohol consumption. No significant differences were observed in body mass index, fasting glucose, triglycerides, serum creatinine, and complications (diabetes mellitus, self-reported stroke and CHD) (Table 1).

Compared with low tHcy (< 15.02 μmol/L), participants with high tHcy levels (≥ 15.02 μmol/L) had higher baseline total cholesterol, serum creatinine level, proportion of current smoking, alcohol consumption, the prevalence of self-reported stroke and CHD, also with lower body mass index.

After a mean time of 1.7 years follow-up, 126 cases of primary outcome happened (1.2%), which included 69 (55%) cardiovascular death. Proportion of all-cause death was significantly higher in borderline ABI groups than normal ABI (2.6% *vs.* 1.1%), and in tHcy ≥ 15μmol/L groups compared to tHcy < 15.02 μmol/L (1.8% *vs.* 0.6%).

The Individual Effect of Borderline ABI and Homocysteine

Compared with normal ABI, borderline ABI was associated with higher risk for all-cause death (HR = 1.87, 95% CI: 1.17-3.00; $P = 0.009$) (Table 2) and cardiovascular death (HR = 2.00, 95% CI: 1.09-3.66; $P = 0.025$) (Supplementary Table 1) after adjusting for sex, age, body mass index, systolic blood pressure, diastolic blood pressure, smoking status, alcohol consumption, tHcy, triglyceride, total cholesterol, HDL, serum creatinine, diabetes mellitus, self-reported stroke, usage of antihypertensive drugs and antiplatelet agents. High tHcy levels were independently associated with elevated risk of all-cause death (HR = 1.99, 95% CI: 1.30-3.05; $P = 0.002$) (Table 2) and cardiovascular death (HR = 3.05, 95% CI: 1.59-5.86; $P < 0.001$) (Supplementary Table 1) after adjusted for covariates.

The Joint Effect of Borderline ABI and Homocysteine

According to Figure 1, we can observe significant differences existed between four groups (normal ABI and low tHcy, borderline ABI and low tHcy, normal ABI and high tHcy, borderline ABI and high tHcy) (log-rank test $P < 0.0001$). Highest cumulative hazard of all-cause death were presented in the

Table 1 The baseline characteristics of stratified ankle-brachial index and total homocysteine (median) levels.

Characteristics	Total	Ankle-brachial index		*P*-value	tHcy, μmol/L		*P*-value
		0.91-0.99	≥ 1.0, ≤ 1.4		< 15.02	≥ 15.02	
N	10,538	847	9,691		5,261	5277	
Age, yrs	63.6 ± 9.1	64.8 ± 10.2	63.5 ± 9.0	< 0.001	61.6 ± 8.7	65.6 ± 9.1	< 0.001
Male	4930 (46.8%)	324 (38.3%)	4606 (47.5%)	< 0.001	1860 (35.4%)	3070 (58.2%)	< 0.001
BMI, kg/m^2	23.6 ± 3.8	23.4 ± 3.9	23.6 ± 3.8	0.066	23.9 ± 3.6	23.4 ± 4.0	< 0.001
SBP, mmHg	148.3 ± 17.6	149.6 ± 19.6	148.2 ± 17.4	0.023	148.3 ± 16.9	148.3 ± 18.3	0.950
DBP, mmHg	89.2 ± 10.7	88.4 ± 11.6	89.2 ± 10.6	0.033	89.6 ± 10.2	88.7 ± 11.1	< 0.001
Ankle-brachial index	1.1 ± 0.1	1.0 ± 0.0	1.1 ± 0.1	< 0.001	1.1 ± 0.1	1.1 ± 0.1	0.600
Diabetes mellitus	1910 (18.1%)	161 (19.0%)	1749 (18.0%)	0.486	924 (17.6%)	986 (18.7%)	0.135
Self-reported stroke	659 (6.3%)	67 (7.9%)	592 (6.1%)	0.038	254 (4.8%)	405 (7.7%)	< 0.001
Self-reported CHD	522 (5.0%)	50 (5.9%)	472 (4.9%)	0.184	236 (4.5%)	286 (5.4%)	0.027
Smoking status				0.012			< 0.001
Never	6119 (58.1%)	529 (62.5%)	5590 (57.7%)		3531 (67.1%)	2588 (49.0%)	
Former	1695 (16.1%)	111 (13.1%)	1584 (16.3%)		653 (12.4%)	1042 (19.7%)	
Current	2723 (25.8%)	207 (24.4%)	2516 (26.0%)		1076 (20.5%)	1647 (31.2%)	
Alcohol consumption				< 0.001			< 0.001
Never	6620 (62.8%)	579 (68.4%)	6041 (62.3%)		3565 (67.8%)	3055 (57.9%)	
Former	1520 (14.4%)	134 (15.8%)	1386 (14.3%)		627 (11.9%)	893 (16.9%)	
Current	2396 (22.7%)	134 (15.8%)	2262 (23.3%)		1068 (20.3%)	1328 (25.2%)	
Laboratory results							
Total homocysteine, μmol/L	17.9 ± 10.8	18.8 ± 11.7	17.8 ± 10.7	0.011	12.5 ± 1.5	23.2 ± 13.1	< 0.001
FBG, mmol/L	6.2 ± 1.6	6.2 ± 1.6	6.2 ± 1.6	0.539	6.2 ± 1.7	6.2 ± 1.5	0.685
Total cholesterol, mmol/L	5.1 ± 1.1	5.3 ± 1.2	5.1 ± 1.1	< 0.001	5.1 ± 1.1	5.2 ± 1.1	0.014
Triglyceride, mmol/L	1.8 ± 1.3	1.8 ± 1.2	1.8 ± 1.3	0.504	1.8 ± 1.3	1.8 ± 1.3	0.008
HDL, mmol/L	1.6 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	0.010	1.6 ± 0.4	1.6 ± 0.5	< 0.001
Serum creatinine, μmol/L	71.5 ± 45.0	74.4 ± 52.6	71.2 ± 44.3	0.051	59.6 ± 22.4	83.3 ± 57.2	< 0.001
Outcome events							
All-cause death	126 (1.2%)	22 (2.6%)	104 (1.1%)	< 0.001	32 (0.6%)	94 (1.8%)	< 0.001
Cardiovascular death	69 (0.7%)	14 (1.7%)	55 (0.6%)	< 0.001	12 (0.2%)	57 (1.1%)	< 0.001

Values are *n* (%) or mean ± SD. Diabetes mellitus was defined according to three criteria: (1) self-reported history of diabetes mellitus; (2) FBG ≥ 7.1 mmol/L; and (3) the use of hypoglycemic drugs. BMI: body mass index; CHD: coronary heart disease; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL: high-density lipoprotein; SBP: systolic blood pressure; tHcy: total homocysteine.

combined group with borderline ABI and High tHcy(tHcy ≥ 15.02 μmol/L). Whereas the combined group with normal ABI and tHcy < 15.02 μmol/L has the lowest risk. Similar pattern was observed for cardiovascular death (Supplementary Figure 1).

Among those with borderline ABI, participants with high tHcy had higher death risk than those with low tHcy. However, no significant differences in the risk of all-cause death between borderline ABI and normal ABI were observed among those with low tHcy levels. Taking the combined group with normal ABI and low tHcy as reference, the combined group of borderline ABI and High tHcy has the highest risk of all-cause death (HR = 3.62, 95% CI: 1.91-6.85; $P < 0.001$) and cardiovascular death (HR = 6.07, 95% CI: 2.50-14.76; $P < 0.001$) (Table 3, Supplementary Table 2). Multivariate logistic analysis was performed in participants who without comorbidities. Participants with borderline ABI and High tHcy, borderline ABI and low tHcy, normal ABI and High tHcy were separately compared with normal ABI and low tHcy, respectively,

Table 2 The individual effect of borderline ABI and total homocysteine levels on all-cause death.

Risk factors	*N*	Events	Crude model		Adjusted model	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause death	10,538	126 (1.2%)				
Ankle-brachial index						
Continuous, per SD (0.1) decrement			1.26 (0.99-1.59)	0.057	1.26 (1.01-1.57)	0.044
Categories						
Normal: 1.0-1.4	9,691	104 (1.1%)	Ref.		Ref.	
Borderline: 0.91-0.99	847	22 (2.6%)	2.43 (1.53-3.85)	< 0.001	1.87 (1.17-3.00)	0.009
Total homocysteine, μmol/L						
Continuous			1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.03)	0.001
Categories (median)						
< 15.02	5250	32 (0.6%)	Ref.		Ref.	
≥ 15.02	5288	94 (1.8%)	2.95 (1.97-4.40)	< 0.001	1.99 (1.30-3.05)	0.002

Data are presented as *n* (%) unless other indicated. Crude model adjusts for none. Adjusted model adjusts for sex, age, body mass index, systolic and diastolic blood pressure, smoking status, alcohol consumption, triglyceride, total cholesterol, high-density lipoprotein, serum creatinine, diabetes mellitus, self-reported stroke, self-reported coronary heart disease, antihypertensive drugs, antiplatelet agents. Adjustment of tHcy were needed when analysis ABI. ABI: ankle-brachial index; HR: hazard ratio; tHcy: total homocysteine.

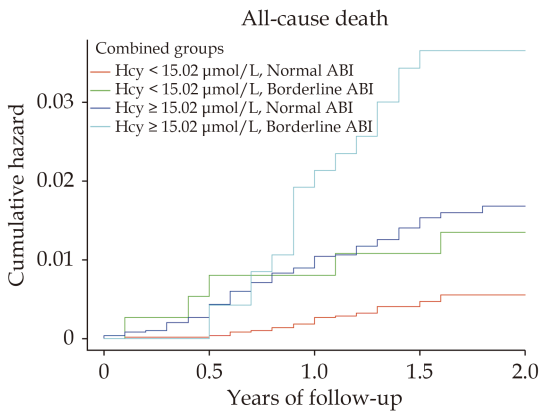

Figure 1 Kaplan–Meier curves of cumulative hazards of all-cause death by ABI (borderline ABI versus normal ABI) and total homocysteine(median) levels (< 15.02 μmo/L *vs.* ≥ 15.02 μmo/L). ABI: ankle-brachial index.

and found that the combined group of borderline ABI and high tHcy has the highest risk of all-cause death in participants who without diabetes mellitus history, stroke, or coronary heart disease (Table 4). Similar results were found for cardiovascular death (Supplementary Table 3).

DISCUSSION

This study observed that both borderline ABI and tHcy were independently and significantly associated with increased risk of all-cause mortality, and that a combination of borderline ABI with high tHcy level further differentiate risk of all-cause mortality. Current research is, to our knowledge, the first study that have explored this topic. Our findings, if further confirmed, have important clinical and public health implications.

Increasing studies have determined to explore the risk stratification ability of borderline ABI (0.91-0.99),[15–17] however, results have remained controversial. Study from the Shinken Database observed a positive co-relationship between borderline ABI and all-cause (HR = 2.27, *P* = 0.005).[9] In addition, borderline ABI instead of normal ABI (1.11-1.20) was observed to better predict risk of major coronary events, all-cause and cardiovascular death in Ankle-Brachial Index Collaboration's meta-analysis.[6] On contrary, in Hisayama Study, with 7.1 years follow-up time, borderline ABI was not found to be related with risk of cardiovascular events, nor all-cause death.[18] Our study results showed a positive association between borderline ABI and all-cause death. Compared to patients with normal ABI, borderline ABI population has an 87% increased risk for all-cause mortality in targeted rural hypertensive population, which agrees with Shingo Tanka's study result that borderline ABI is associated with worse clinical outcomes in high-risk population.[9]

This study not only further validated the inde-

Table 3 Joint effects of borderline ABI and total homocysteine (median, 15.02 μmol/L) levels on all-cause death.

Combined groups	ABI group	*N*	All-cause death, *n* (%)	Crude model		Adjusted Model	
Total homocysteine, μmol/L				HR (95% CI)	*P* value	HR (95% CI)	*P* value
< 15.02	Normal	4888	27 (0.6%)	Ref.		Ref.	
	Borderline	373	5 (1.3%)	2.43 (0.94-6.32)	0.068	2.17 (0.83-5.66)	0.113
≥ 15.02	Normal	4803	77 (1.6%)	2.92 (1.88-4.53)	<0.001	2.03 (1.28-3.21)	0.003
	Borderline	474	17 (3.6%)	6.56 (3.58-12.03)	< 0.001	3.62 (1.91-6.85)	< 0.001

Data are presented as *n* (%) unless other indicated. Crude model adjusts for none. Adjusted model adjusts for sex, age, body mass index, systolic and diastolic blood pressure, smoking status, alcohol consumption, triglyceride, total cholesterol, high-density lipoprotein, serum creatinine, diabetes mellitus, self-reported stroke, self-reported coronary heart disease, antihypertensive drugs, antiplatelet agents. ABI: ankle-brachial index; HR: hazard ratio.

Table 4 Joint effects of borderline ABI and total homocysteine (median, 15.02 μmol/L) levels in different subgroups.

Subgroup	Combined groups	*n* (%)	HR (95% CI)	*P*-value
Without diabetes mellitus[a]	Hcy < 15.02 μmol/L, normal ABI	23 (0.6%)	Ref.	
(*n* = 8,628)	Hcy < 15.02 μmol/L, borderline ABI	4 (1.3%)	2.17 (0.75-6.32)	0.154
	Hcy ≥ 15.02 μmol/L, normal ABI	63 (1.6%)	1.87 (1.13-3.10)	0.015
	Hcy ≥ 15.02 μmol/L, borderline ABI	11 (2.9%)	2.66 (1.25-5.65)	0.011
Without stroke[b]	Hcy < 15.02 μmol/L, normal ABI	26 (0.6%)	Ref.	
(*n* = 9,879)	Hcy < 15.02 μmol/L, borderline ABI	4 (1.1%)	1.87 (0.65-5.37)	0.247
	Hcy ≥ 15.02 μmol/L, normal ABI	70 (1.6%)	1.99 (1.24-3.20)	0.004
	Hcy ≥ 15.02 μmol/L, borderline ABI	16 (3.7%)	3.66 (1.90-7.06)	<0.001
Without coronary heart disease[c]	Hcy < 15.02 μmol/L, normal ABI	25 (0.5%)	Ref.	
(*n* = 10,016)	Hcy < 15.02 μmol/L, borderline ABI	5 (1.4%)	2.47 (0.94-6.49)	0.066
	Hcy ≥ 15.02 μmol/L, normal ABI	70 (1.5%)	2.01 (1.24-3.25)	0.004
	Hcy ≥ 15.02 μmol/L, borderline ABI	15 (3.3%)	3.60 (1.84-7.03)	<0.001

[a]Adjusted for sex, age, body mass index, systolic and diastolic blood pressure, smoking status, alcohol consumption, triglyceride, total cholesterol, high-density lipoprotein, serum creatinine, self-reported stroke, self-reported coronary heart disease, antihypertensive drugs, antiplatelet agents. [b]Adjusted for sex, age, body mass index, systolic and diastolic blood pressure, smoking status, alcohol consumption, triglyceride, total cholesterol, high-density lipoprotein, serum creatinine, diabetes mellitus, self-reported coronary heart disease, antihypertensive drugs, antiplatelet agents. [c]Adjusted for sex, age, body mass index, systolic and diastolic blood pressure, smoking status, alcohol consumption, triglyceride, total cholesterol, high-density lipoprotein, serum creatinine, diabetes mellitus, self-reported stroke, antihypertensive drugs, antiplatelet agents. ABI: ankle-brachial index; Hcy: homocysteine, HR: hazard ratio.

pendent predictive ability of tHcy level for all-cause mortality, which coincide with a large number of previous studies,[19–22] but also explored the value of risk stratification of tHcy level. While tHcy ≥ 10 μmol/L was believed to increases cardiovascular events and a series of pathological danger,[23] and tHcy > 15 μmol/L is the recommended standard of diagnosis. The median number 15.02 μmol/L was used as threshold value to observe the joint effect of borderline ABI and tHcy level. Highest risk for all-cause death was observed in group with borderline ABI and high tHcy levels (tHcy ≥ 15.02 μmol/L) compared to group with borderline ABI and low tHcy levels. Thus, we speculate that there might be a potential synergetic effect of borderline ABI and high tHcy levels on risk of all-cause mortality. Despite both borderline ABI and normal ABI with high tHcy levels are statistical correlated to event outcomes, the hazard ratio curve demonstrated the differences. As shown in Figure 1, the cumulative hazard of group with borderline ABI and tHcy level ≥ 15.02 μmol/L was significantly higher than other three groups with larger increasing rate over extended follow-up time. When both statistical related to all-cause death, group with normal ABI and high tHcy has much lower cumulative hazard and hazard ratio than borderline ABI and high tHcy group. Moreover, in spite of the fact that the group with borderline ABI and low tHcy level was not statistically correlated to the event outcome, this group ob-

tained very close hazards ratio and cumulative hazard with the normal ABI and High tHcy group. In this case, even with low tHcy, borderline ABI worth substantial attention since the unfavorable performance might be caused by relatively short follow-up time and small sample size. Our study's result highlighted the practical differences between borderline ABI and normal ABI, meanwhile emphasized the importance of a combination of borderline ABI and high tHcy level. Underlying mechanisms behind still requires further research.

Borderline ABI has been validated to be associated with endothelial dysfunction,[24] which is the hallmark of a variety of CVD associated pathology.[25] Studies have also shown that the elevated tHcy level is a critical initiating event of endothelial dysfunction induced diseases.[26,27] Moreover, hyperhomocycteinemia (HHcy) and ABI were suggested to be associated with mitochondrial (MT) dysfunction, vascular dysfunction, and vessel wall inflammation.[6,28–30] Furthermore, elevated of tHcy level can induce oxidant stress and subsequently increases glycation and products (AGEs), contributing to alterations of collagen contents, extracellular matrix of the vessel walls. Intravascular image in the collagen content might add on the underlying mechanisms of the efficacy of borderline ABI and advanced tHcy level in this study.[31] In the further consideration of the close correlation of ABI and tHcy level with PAD,[32–35] the association between population with borderline ABI and high tHcy level with higher risk for all-cause death is physiologically persuasive. More importantly, current study emphasized the importance of concept "borderline ABI", which was often overlooked, and observed the additive value of tHcy in borderline ABI. Broader concerns are needed for patients with borderline ABI, especially when elevated tHcy is observed.

Some potential concerns are worth mentioning. First, despite the huge sample size, this study is a single center study that conducted among only hypertensive population. Further study should be done using more diverse database. In addition, while this study provided an insight of borderline ABI and tHcy level, result might be slightly interfered consider the significantly strong indication capacity of elevated tHcy. To further explore the importance of borderline ABI, more risk factors should be considered. Last but not least, the 1.7 year of follow-up time is relatively short to observe major breakthrough but with the consideration of the positive independent and joint correlationship discovered, we have faith to carry on this study and further explore more knowledge about this field.

In conclusion, both borderline ABI and elevated tHcy levels were significantly and independently associated with advanced risk of all-cause mortality. In addition, a combination of borderline ABI and high tHcy level helps further differentiate risk of all-cause mortality among hypertensive population.

CONFLICTS OF INTEREST

None.

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AUTHORS' CONTRIBUTIONS

Study design: JPL, HHB, XH, XSC. Data collection: JPL, XYZ, YY, ZHT, ZHC, HBY, WZ, LJZ, TW, LSL, HHB, XH, XSC. Data analysis/interpretation: JPL, TYC, WZ, LSL, HHB, XH, XSC. Statistical analysis: JPL, WZ, XH, XSC. Review and revision of the article: JPL, TYC, HHB, XH, XSC.

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