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Risk factors and haemodynamic variables in patients with low toe-brachial index but normal ankle-brachial index

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HIGHLIGHTS

- Solitary use of ankle-brachial index (ABI) underestimated the prevalence of peripheral arterial disease (PAD).
- Patients with low ABI have increased risk of cardiovascular morbidity and mortality.
- Patients with low toe-brachial index (TBI) but normal ABI share risk factors with patients with low ABI.

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ABSTRACT

Background and aims: Classically, peripheral arterial disease (PAD) is diagnosed by a low ankle-brachial index (ABI), but the diagnosis can also be made based on toe-brachial index (TBI) measurements. The objective of this study was to characterize patients with low TBI but normal ABI, and chart potential underestimation of PAD prevalence by solitary use of ABI.

Methods: A total of 3739 consecutive patients with known or suspected PAD referred for ABI and TBI measurements in a four-year period were compared to an age- and gender matched control group (n = 17,340).

Results: In the patient cohort, 65.0% had low ABI, 20.5% had low TBI but normal ABI, and 14.5% had normal indices. When comparing the frequencies of comorbidities related to atherosclerotic disease (myocardial infarction, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic kidney failure), there were no significant differences among patients with low ABI or low TBI with normal ABI in any of the variables (all $p > 0.06$). Of the patients with low TBI and normal ABI, 18.7% were diagnosed with diabetes mellitus type I or II, and 8.2% with chronic kidney disease.

Conclusions: Patients with low TBI but normal ABI represented 20.5% of patients referred with the suspicion of PAD. Furthermore, patients with low TBI but normal ABI presented similar comorbid characteristics to patients with low ABI, who have a well-described increased risk of cardiovascular morbidity and mortality. The solitary use of ABI underestimated the prevalence of PAD in the population, and PAD screening could potentially be improved by routine application of TBI.

1. Introduction

In the lower limbs, systemic atherosclerosis leads to vessel stenosis and manifests as peripheral arterial disease (PAD). According to inter-society consensus guidelines, PAD can be diagnosed non-invasively by measuring an ankle-brachial index (ABI) or a toe-brachial index (TBI) [1]. Hand-held Doppler-derived ABI is often included in primary testing for PAD and has been validated as an atherosclerotic risk marker in various large scale screening trials [2]. Having an ABI ≤0.90 is considered diagnostic for PAD and has been shown to be a strong predictor for cardiovascular morbidity and mortality. However, current screening algorithms may underestimate the prevalence of PAD in the population, particularly during the early phase of atherosclerotic development. Additionally, conditions associated with media calcinosis such as diabetes and chronic kidney disease can lead to falsely normal or even falsely elevated pressures due to vessel stiffness. Toe vessels, on the other hand, are less susceptible to media calcinosis, which makes the TBI useful for PAD screening [3]. The use of TBI is often restricted to

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vascular laboratories due to methodological requirements in order to achieve reliable measurements. However, in recent years, promising methods have been introduced that allow easy access to bedside measurement of the TBI [4]. The patient demographics and cardiovascular risk factor profiles of patients with reduced TBI in the absence of reduced ABI, potentially patients with early atherosclerosis, remain to be described. The aim of the current study is to characterize the patients with low TBI without low ABI using a population where primary PAD testing consists of both ABI and TBI assessment in a standardized vascular laboratory.

2. Materials and methods

2.1. Design

Case control study.

2.2. Study population

All patients with known or suspected PAD referred for distal pressure assessment from 1 July, 2007–1 July, 2011 at the Department of Clinical Physiology, Viborg Regional Hospital, were eligible for this retrospective study. The Department is a regional centre for vascular diagnostics that performs distal pressure assessments for a background population of approximately 310,000 inhabitants. Inclusion criteria consisted of complete tests where ankle and toe pressures were assessed in both limbs (thus excluding limb amputees or incomplete tests). If the patient was referred more than once in the inclusion period, data from the primary investigation were used. The study was approved by the Danish Data Protection Agency (2007580010), and a waiver for access to patient files without informed consent was provided by the Danish Health and Medicines Authority (3-3013-63/1/EHE).

2.3. Control population

Five controls in the background population were matched by incidence density sampling to each of the cases based on age, gender, and geographic residency via the Danish National Patient Registry. Controls were excluded in case of migration, and cases could not be selected as controls. The data extraction was performed by the Department of Clinical Epidemiology, Aarhus University Hospital, in cooperation with Statistics Denmark.

2.4. Distal pressure measurements

All distal pressure tests were performed by the mercury-in-rubber strain gauge plethysmography method (Digitmatic DM2000®, Medimatic A/S, Hellerup, Denmark) according to institutional practice as described in earlier publications regarding methodology, comparison to other methods and reproducibility [5,6]. The brachial blood pressure was measured simultaneously with each toe or ankle pressure, with the side with the highest systolic pressure selected as the reference for the ABI and TBI calculations. The observers consisted of experienced laboratory technicians. The measuring protocol included a resting period of at least 15 min in supine position prior to the test in a room with stable temperature, and the mean time consumption for TBI and ABI assessment is 15 min [5]. Pre-test limb heating was ensured with heating overlays to increase reproducibility (Action Shear Smart®, Action Products Inc., Maryland, USA). A database was established based on registered entries for distal pressure measurements in Viborg Regional Hospital in the given period. The data from the pressure readings were retrieved from the patients' medical files by two observers (CH, HZ).

2.5. Covariates

Each Danish citizen receives a unique civil registration number at birth, which encodes gender and birth date and allows unambiguous linkage between health care registries. The pressure database was merged with data from the Danish National Patient Registry, which retains information on all discharges from hospitals since 1977. The information includes up to 20 discharge diagnoses coded and registered procedures according to the International Classification of Diseases [7]. The retrieved data included diagnosis of diabetes, chronic kidney failure, rheumatic arthritis, cardiac disease, and vascular disease. The database did not allow for identification of patients with prior vascular interventions. This approach to obtaining the given variables of comorbidity has previously been validated for use with the Danish National Patient Registry [8]. Based on the extracted information, a comorbidity index (the Charlton Index) was calculated [9]. The index covers 19 major disease categories weighted correspondent to their prognostic impact on survival, and it has previously been validated for use with registry-based hospital discharge diagnosis [10]. Data on dispensed prescriptive medications in the study population were retrieved from the Medical Register of the Danish Medicines Agency. The registry holds data on prescriptions filled and dispensed at all Danish pharmacies from 1995. We identified all prescriptions to the patients including anti-hypertensive drugs, lipid-lowering drugs, and glucocorticoids, up to the date of the distal blood pressure measurement.

2.6. Diagnostic criteria

PAD was diagnosed according to TASC-II criteria as ABI ≤ 0.90 or TBI < 0.70 [1]. The lowest ABI or TBI in either of the two limbs was used for the diagnosis. In cases with incompressible ankle vessels during the pressure measurement, that limb was defined as having an ABI > 1.40, and vice versa. According to age-dependent normal data, a difference between ankle and toe blood pressure of more than > 84 mmHg is abnormal for age > 60 years and of > 62 mmHg for age < 60 years [11]. A difference between the brachial pressures between the right and left arm of more than 15 mmHg was considered significant [12].

2.7. Statistics

The data are presented as the mean ± standard deviation (SD) unless stated otherwise. The differences in haemodynamic and demographic variables between the groups were analysed using an unpaired *t*-test (two groups) or one-way ANOVA (more than two groups), in the case of quantitative variables and a chi-square test (χ^2) in the case of categorical variables. With single variable comparisons a p-value < 0.05 was considered to be statistically significant, but in cases with multiple comparisons, a Bonferroni-corrected threshold was used for assessment of statistical significance. Agreement in diagnostic classification (PAD/not PAD) was analysed by Cohen's Kappa (κ) [13]. The statistical analysis was performed using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Patients

A total of 6878 distal blood pressure measurements were registered in the four year inclusion period, of which 2919 were excluded due to repeated tests, 14 for being double registrations, 37 for being cancelled exams, and 169 for being incomplete tests. There were no missing data for the distal pressures. This resulted in 3739 complete, unique patients eligible for analysis. A total of 2308 patients (62%) were referred from the department of vascular surgery, 725 (19%) from general practitioners, 318 (9%) from the department of orthopaedic surgery, 306 (8%) from the department of internal medicine, and 82 (2%) from other departments.

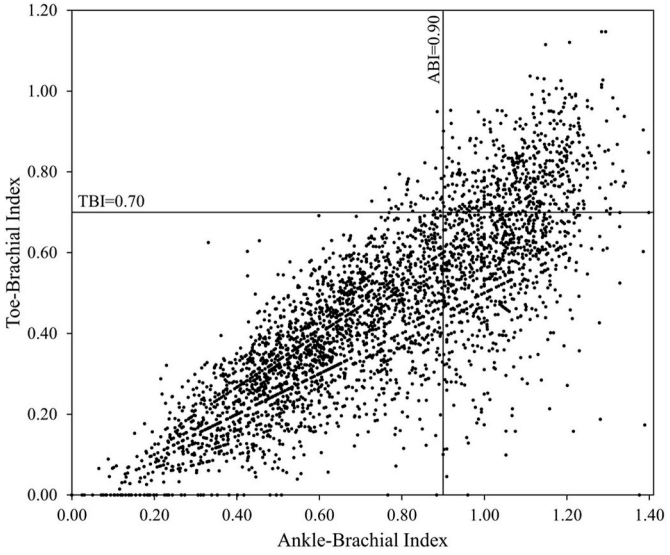

Fig. 1. Distribution of the ankle-brachial indices by toe-brachial indices among the 3739 patients, of which 65.0% had low ABI, 20.5% low TBI with normal/elevated ABI, and 14.5% normal ABI.
Patients with incompressible vessels not shown.

3.2. The prevalence of peripheral arterial disease

A total of 2433 patients (65.0%) had low ABI (irrespective of their TBI), 765 (20.5%) patients had low TBI but normal ABI, and 541 (14.5%) patients had normal ankle and toe indices (Fig. 1). The group of patients with low ABI but normal TBI was too small to allow individual analysis (n = 41). There was an overall agreement in diagnostic classification (PAD/not PAD) in 2933 of the 3739 patients (78%) between TBI and ABI with a Cohen's Kappa of 0.456 (95% CI: 0.423–0.489). The prevalence of low ABI increased with increasing age in the defined age groups ($p < 0.001$), and the prevalence of normal indices declined ($p < 0.001$), as shown in Fig. 2. In contrast, the proportion of patients with low TBI and normal ABI did not change significantly between the defined age categories (range 18–25%, $p = 0.55$). Among the 638 patients registered with diabetes, 518 (87%) had abnormal indices compared to 2640 (86%) of the 3101 patients not registered with diabetes ($p = 0.35$).

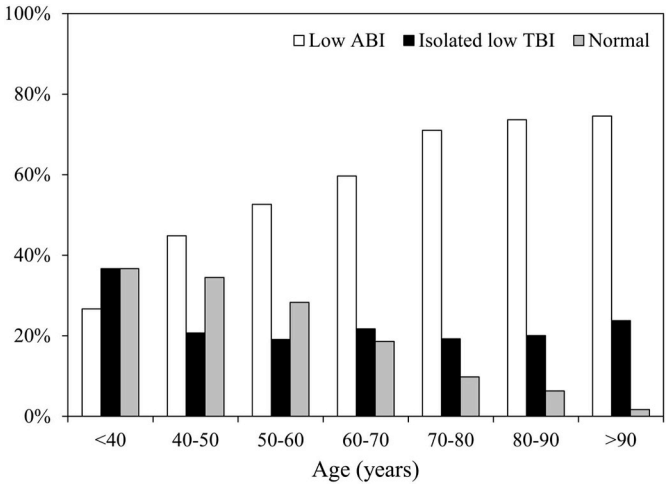

Fig. 2. Distribution of ABI and TBI categories according to age.

3.3. Demographics and comorbidity

Each of the index parameters described in the Charlson comorbidity index was compared to an age- and gender-matched control group (Table 1). The mean age of the three patient groups was 69.9 ± 11.7 years *vs.* 69.0 ± 11.4 for the control group. The female proportion of the patients was 44.1% *vs.* 43.9% for the matched controls. When comparing the frequencies of comorbidities besides PAD related to atherosclerotic disease (myocardial infarction, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic kidney failure), there was no significant difference among patients with low ABI or low TBI in any of the variables (all $p > 0.06$). However, when comparing patients with normal indices to patients with low ABI, there was a significantly lower frequency in the categories of myocardial infarction, congestive heart failure, and cerebrovascular disease (all $p < 0.02$) but not in diabetes mellitus or chronic kidney failure (both $p > 0.20$).

3.4. Medication

Use of medication based on data on filled and dispensed prescriptions (Table 2), showed higher drug usage in all categories for the referred patients compared to the controls (all $p < 0.001$). There were no significant difference between patients with low ABI or isolated low TBI in terms of beta-blockers ($p = 0.36$). However, the patients with normal indices had lower usage of beta-blockers than patients with low ABI and patients with low TBI and normal ABI ($p < 0.001$). In the group with low TBI and normal ABI, 143 (18.7%) patients were diagnosed with diabetes mellitus type I or II, and 63 (8.2%) with chronic kidney disease, thus leaving at least 73.1% not diagnosed with a condition associated with vessel stiffness prior to the exam.

3.5. Hemodynamic variables

Patients with low ABI had a higher proportion of conditions related to vessel stenosis such as difference in systolic blood pressure between arms ≥15 mmHg, and increased ankle to toe blood pressure gradients, than the other two groups (all $p \leq 0.003$) (Table 3). A total of 111 patients had elevated ABI (> 1.40) in at least one limb, of which 90 (81.1%) had TBI < 0.70 and thus were diagnosed with PAD.

4. Discussion

This study shows that 20.5% of patients clinically suspected of PAD had low TBI but normal ABI, and this subgroup remain a substantial diagnostic challenge. These patients did not differ significantly from the group of patients with low ABI regarding frequency of comorbidity related to atherosclerotic disease (myocardial infarction, congestive heart failure, cerebrovascular disease, diabetes mellitus, chronic kidney failure). According to key guidelines, measurement of the TBI is reserved for patients suspected of vessel stiffness (ABI > 1.40) such as patients with diabetes or chronic kidney insufficiency [1,14]. However, more than 73% of the patients in our study have not been diagnosed with a condition related to vessel stiffness, and would thus not have been detected using conventional screening algorithms for PAD. The proportion of patients with low TBI but normal ABI and not clinically suspected of vessel stiffening are in line with findings in other studies [5,15].

The key question raised by this finding is what added diagnostic value this holds compared to solitary use of ABI. It is well described that patients with an ABI ≤0.90 have a three-to six-fold increased risk of cardiovascular mortality. However, unlike the ABI, the diagnostic limits of the TBI as a predictor of cardiovascular morbidity and mortality have not yet been thoroughly validated in large scale screening trials [16]. Nonetheless, recent studies have reported the TBI as a valid indicator of increased risk of cardiovascular mortality and morbidity [17–19].

Additionally, studies have shown better correlations with

Table 1
Demographics, and co-morbidity.

	Low ABI (n = 2433)		Isolated low TBI (n = 765)		Normal (n = 541)		Control group (n = 17,340)		*p*
Demographics									
Age	71.4	± 10.8[a]	69.7	± 12.1	63.2	± 12.7 [a]	69.0	11.4	< 0.0001 [b]
Female	1075	44.2%	339	44.3%	236	43.6%	7622	43.9%	0.988 [c]
Comorbidity									
Myocardial infarction	282	11.6%	81	10.6%	44	8.1%	742	4.3%*	< 0.0001 [c]
Congestive heart failure	273	11.2%	87	11.4%	37	6.8% *	581	3.3%*	< 0.0001 [c]
Peripheral arterial disease	1458	59.9%	238	31.1% *	106	19.6% *	671	3.9%*	< 0.0001 [c]
Cerebrovascular disease	408	16.8%	112	14.6%	62	11.5% *	1403	8.1%*	< 0.0001 [c]
Dementia	28	1.2%	12	1.6%	3	0.6%	222	1.3%	0.385 [c]
Chronic obstructive pulmonary disease	386	15.9%	103	13.5%	60	11.1% *	1138	6.6%*	< 0.0001 [c]
Connective tissue disease	153	6.3%	67	8.8%	39	7.2%	549	3.2%*	< 0.0001 [c]
Peptic ulcer disease	199	8.2%	59	7.7%	37	6.8%	696	4.0%*	< 0.0001 [c]
Diabetes mellitus I and II	415	17.1%	143	18.7%	80	14.8%	820	4.7%*	< 0.0001 [c]
Chronic kidney disease	152	6.2%	63	8.2%	29	5.4%	250	1.4%*	< 0.0001 [c]
Hemiplegia	9	0.4%	4	0.5%	5	0.9%	34	0.2%	0.001 [c]
Leukemia	11	0.5%	3	0.4%	0	0%	39	0.2%	0.095 [c]
Malignant lymphomas	20	0.8%	6	0.8%	3	0.6%	93	0.5%	0.307 [c]
Solid tumor	28	1.2%	3	0.4%	9	1.7%	136	0.8%	0.021 [c]
Liver disease	18	0.7%	11	1.4%	8	1.5%	84	0.5%	< 0.0001 [c]
AIDS	0	0%	0	0%	0	0%	0	0%	
Mean Charlson index	**2.5**		**2.5**		**1.3**		**0.7**		

Data shown as mean (percentage) or mean (± sd). [a]$p < 0.001$ with comparison to the control group by an unpaired *t*-test; [b]*p*-value by one-way ANOVA (all three groups); *$p < 0.01$ by χ^2 test when comparing to patients with low ABI; [c]χ^2 test with comparison of all groups, degree of freedom = 3.

Table 2
Use of medication.

	Low ABI (n = 2433)		Isolated low TBI (n = 765)		Normal (n = 541)		Control group (n = 17,340)		*p* [a]
Use of medication									
ACE/AT-II	1492	61.3%	446	58.3%	259	47.9% *	5751	33.1% *	< 0.0001
Beta-blockers	1194	49.1%	390	51.0%	209	38.6% *	4986	28.7% *	< 0.0001
Calcium antagonists	1184	48.7%	343	44.8%	179	33.1% *	4391	25.3% *	< 0.0001
Diuretics	1557	64.0%	489	63.9%	291	53.8% *	6751	38.9% *	< 0.0001
Anti platelet drugs	1910	78.5%	483	63.1% *	269	49.7% *	5926	34.2% *	< 0.0001
Lipid-lowering drugs	1708	70.2%	406	53.1% *	263	48.6% *	4994	28.8% *	< 0.0001
Glukocorticoid treatment	909	37.4%	326	42.6% *	209	38.6%	4863	28.0% *	< 0.0001

Data shown as mean (percentage). *$p < 0.01$ by χ^2 test when comparing to patients with low ABI.
[a] χ^2 test with comparison of all groups, degree of freedom = 3.

angiographic findings and stronger association with a number of atherosclerotic risk factors for the TBI than the ABI [16]. Given the large population at stake with involvement of 15–20% in persons over 70 years of age, it is pivotal to chart the clinical implication of having a low TBI but normal ABI.

Among the patients with low TBI, approximately 9% had an increased ABI (> 1.40), which is associated with vessel stiffness and increased mortality, vessel stenosis, and a risk factor for major amputations [2,20,21]. Of these patients with elevated ABI, 81% had PAD according to the TBI, which is in line with findings from other studies [20]. Additionally, it has been reported that in patients with supranormal ABI, and PAD verified by angiography, approximately 92% of the patients have a TBI < 0.70 [22]. Furthermore, it has also been reported that patients with borderline abnormal index (0.90 < ABI <

Table 3
Hemodynamic parameters.

	Low ABI (n = 2433)		Isolated low TBI (n = 765)		Normal (n = 541)		*p*-value
Regional pressures							
ABI	0.58	± 0.19	1.04	± 0.09 *	1.11	± 0.10 *	< 0.0001 [b]
0.91 ≤ ABI < 1.00 (n)	0	0%	261	32.7% [a]	79	14.4% [a]	< 0.0001 [c]
ABI > 1.40 (n)	19	0.8%	72	9.4% [a]	20	3.7% [a]	< 0.0001 [c]
TBI	0.35	± 0.17	0.54	± 0.13 *	0.81	± 0.09 *	< 0.0001 [b]
Ankle pressures [mmHg]	83	± 30	146	± 24 *	151	± 23 *	< 0.0001 [b]
Toe pressures [mmHg]	50	± 25	76	± 22 *	111	± 19 *	< 0.0001 [b]
Ankle-toe gradient [mmHg]	47	± 22	74	± 22 *	46	± 16	< 0.0001 [b]
Brachial blood pressure							
Systolic [mmHg]	144	± 23	141	± 22	137	± 19 *	< 0.0001 [b]
Diastolic [mmHg]	75	± 12	78	± 11 *	80	± 11 *	< 0.0001 [b]
Difference |right-left arm| [mmHg]	8	± 9	7	± 7*	7	± 6*	< 0.0001 [b]
Difference |right-left arm| > 15 mmHg (n)	308	12.9%	74	10.0% [a]	44	8.3% [a]	0.003 [c]

Data shown as mean (percentage) or mean (± sd). *$p < 0.001$ with comparison to patients with low ABI by an unpaired *t*-test; [a]$p < 0.05$ by χ^2 test when comparing to patients with low ABI; [b]*p*-value by one-way ANOVA (all three groups); [c]*p*-value by χ^2 test (all three groups).

1.00) have an increased mortality compared with patients with normal index (1.00 < ABI < 1.30) [2]. In the present study, approximately one-third of the patients with low TBI had borderline reduced ABI.

Regarding medication, patients with low TBI and normal or elevated ABI had a higher percentage of beta-blocker than patients with normal indices. This finding can partially be explained by a higher percentage of registered cases with concomitant cardiac disease. Nonetheless, it could be speculated that, for instance, medication that induces peripheral vasoconstriction, such as beta-blockers, would influence measurements and lead to low peripheral pressure not caused by vessel stenosis [23].

The group of patients with low TBI and normal ABI is likely a mixture of different subgroups. A proportion of the patients would have masked large-vessel disease due to false elevated or even normal ABI due to e.g. media calcinosis [24,25]. Another subgroup of the patients would have stenosis below the ankle level, or small vessel disease [26]. This study supports this concept, as approximately 36% of the patients with low TBI and normal/elevated ABI had abnormal ankle-toe blood pressure gradients, which is associated with below ankle vessel stenosis, in contrast to < 7% in the other groups. Additionally, the group with isolated low TBI has a higher proportion of patients with connective tissue disease (e.g. vasculitis) and a higher percentage of patients registered with glucocorticoid usage than the other groups. One additional subgroup would be patients with normal vessels falsely categorized as having low TBI due to peripheral vasoconstriction, possibly caused by medication, inadequate pretest limb heating, leading to an increased test variability, or the use of inappropriate diagnostic limits.

Given the increasing availability of low cost, feasible methods for PAD screening based on the TBI, and the modest agreement with ABI in diagnostic classification of the patients, this calls for a reevaluation of the ABI as the primary tool for PAD screening, such as recommended in the TASC-II guideline. However, large scale trials are needed to verify the role of the TBI as a first line diagnostic tool. We have planned to further explore the TBI as a prognostic indicator of risk of amputation, cardiovascular mortality and morbidity in a 10-years follow up for the current patient cohort.

4.1. Conclusion

This study shows that patients with low TBI but normal ABI shared many comorbidities and risk factors with patients with low ABI, who have a well-described increased risk of cardiovascular morbidity and mortality. Patients with a low TBI but normal ABI constituted 20.5% of patients referred with the suspicion of PAD. We propose that TBI measurements should be included in a comprehensive evaluation of patients with suspected PAD and not reserved for patients registered with a condition related to vessel stiffness, such as diabetes or chronic kidney failure.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Conception and design: CH, AH, JS, HZ, LP.
Analysis and interpretation: CH, AH, JS, HZ, LP.
Data collection: CH, HZ.
Writing the article: CH, AH, JS, HZ, LP.
Critical revision of the article: CH, AH, JS, HZ, LP.
Final approval of the article: CH, AH, JS, HZ, LP.
Statistical analysis: CH, AH, JS, HZ, LP.

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