Original Article

The Association between Low-Density Lipoprotein Cholesterol Goal Attainment, Physician and Patient Attitudes and Perceptions, and Healthcare Policy

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Aim: Withholding effective treatment is clinically prevalent. The CEntralized Pan-Asian survey on tHE Under-treatment of hypercholeSterolemia (CEPHEUS-PA) indicated suboptimal low-density lipoprotein cholesterol (LDL-C) goal attainment in Taiwan, which may be attributable to clinical inertia. We herein analyzed the Taiwanese cohort in the CEPHEUS-PA to identify key elements regarding clinical inertia and unsatisfactory LDL-C control.

Methods: A questionnaire regarding the attitudes and perceptions for each physician and patient was included in the CEPHEUS-PA. Physicians completed the physician questionnaire before enrolling patients, who completed the patient questionnaire before the assessment.

Results: The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline was used by 81.8% of physicians to establish the individual therapeutic targets; 50.2% of patients failed to take medications persistently. Regarding perceptions to hypercholesterolemia management, 75.9% of physicians were confident of having a sufficient number of patients at cholesterol targets; 80.2% and 65.9% of patients felt satisfied and motivated, respectively, but 46.0% had no strong feeling. The healthcare reimbursement policy used for treatment guidance was a significant determinant for LDL-C goal attainment (OR=0.32, 95% CI: 0.15-0.69, $P=0.006$) in addition to patient compliance. Low patient involvement indexed by having no strong feeling was associated with poor LDL-C control (OR=0.73, 95% CI: 0.56-0.95, $P=0.020$).

Conclusions: The referenced healthcare reimbursement policy, poor patient compliance, and low patient involvement with hypercholesterolemia management were associated with failure of LDL-C control. Our findings highlight the need to overcome those barriers to improve the under-treatment of hypercholesterolemia.

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Key words: Low-density lipoprotein cholesterol goal attainment, Treatment compliance, Guideline, Statins

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Introduction

Hypercholesterolemia is one of the major risk factors for coronary heart disease (CHD) and other atherosclerotic complications¹. Lowering the low-

density lipoprotein cholesterol (LDL-C) reduces both cardiovascular morbidity and mortality across a wide range of patients^{2, 3}. Despite the treatment benefits demonstrated by clinical trials and therapeutic targets advocated by academic societies, the majority of patients fail to achieve the LDL-C targets recommended by the practicing guidelines, particularly in the high-risk patients⁴⁻⁶. Suboptimal control is directly related to the risk level of individual patients, including the target set accordingly and the baseline LDL-C level^{6, 7}, and inadequate pharmacological treatment, including under-prescription⁸, inappropriate dosing and potency⁹, and non-compliance of both patients and physicians⁵⁻⁷. In addition to patient characteristics and compliance to lipid-lowering medications, physician characteristics and the administration policy were also associated with under-treatment and non-treatment¹⁰⁻¹².

Withholding effective treatment both from the patient and physician perspectives, referred to clinical inertia, is common in the management of chronic medical conditions^{13, 14}. Clinical inertia is attributed to concerns about the cost and side effects of therapies, inadequate follow-up, and a lack of awareness^{15, 16}. The National Health Insurance (NHI), as the backbone of the healthcare system in Taiwan, provides universal medical coverage for beneficiaries (>99% of the population) with a small portion paid by the users; therefore, financial concerns may not be a major issue. However, the under-treatment of hypercholesterolemia in Taiwan was more prevalent compared with other Asian countries^{4, 6, 7}. Because enhanced prescription coverage has been shown to improve medication persistence and to reduce vascular events¹⁷, such discrepancy occurring in a population that is well covered by the healthcare insurance program may largely reflect a lack of awareness and poor compliance. Meanwhile, little information of clinical inertia in hypercholesterolemia management is available in Asian populations. This study assessed the attitudes and perceptions of both physicians and patients and their associations with LDL-C goal attainment and statin therapy by using the information from the Taiwanese cohort of the CEntralized Pan-Asian survey on the Under-treatment of hypercholesterolemia (CEPHEUS-PA).

Method

The CEPHEUS-PA (ClinicalTrials.gov Identifier: NCT00687492), a prospective, cross-sectional survey on the pharmacological treatment of hypercholesterolemia enrolled patients across 8 Asian countries

in 2008. The protocol was approved by the local Institutional Review Board of each hospital. The written informed consent was obtained from each patient before they were enrolled into the study. The design and the main findings have been previously reported in detail⁶. A questionnaire for each physician and patient was included in the CEPHEUS-PA. The physician questionnaire consisted of questions targeting the attitudes and perceptions to hypercholesterolemia management. The patient questionnaire comprised questions related to attitudes (including awareness and compliance to hypercholesterolemia management), experiences, and perceptions (including satisfaction, compliance, and involvement with hypercholesterolemia management). Each physician first completed the physician questionnaire before enrolling patients; each patient completed the patient questionnaire before the physical and biochemistry assessment.

Among 501 invited physicians, 29 were from Taiwan. Of the 7,281 patients with evaluable data, 13.7% were Taiwanese patients.

Statistics

Descriptive statistics included numbers, means and standard deviations, and frequency distributions. Factors that potentially affect LDL-C goal attainment and statin therapy allocation were investigated in the univariate analysis. For physician factors, physician characteristics and contents of the physician questionnaire were analyzed in a univariate analysis by means of generalized linear mixed model analysis with a random effect of the physician using the NLMIXED procedure of the Statistics Analysis System statistical software (Cary, North Carolina, United States). The NLMIXED procedure fits and specifies nonlinear mixed model by maximizing the approximation to the likelihood integrated over the random effects. For patient factors, contents of the patient questionnaire were analyzed in a univariate logistic model. The estimated odds ratio (OR) and 95% confidence interval (CI) were calculated. All analyses were performed on the per-protocol population. A *P* value <0.05 was considered to be statistically significant.

Result

Characteristics of Physicians and Practice

The mean age of the physicians was 46.9 ± 7.1 years; 93.1% were men. The average experience in practice was 19.8 ± 7.3 years. The majority were cardiologists (55.2%) followed by endocrinologists (24.1%). All physicians used LDL-C as the laboratory measure for the therapeutic targets; the total chole-

terol levels were also used to set the individual targets by 93.1% of the physicians. The high-density lipoprotein cholesterol (HDL-C) and triglyceride levels were referenced by 69.0% and 86.2% of the physicians. Most physicians provided lipid information to their patients; the total cholesterol, LDL-C, HDL-C, and triglyceride levels were used by 96.6%, 93.1%, 69.0% and 86.2% of the physicians, respectively. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline was the most frequently used guidance (81.8%), followed by the healthcare reimbursement policy (54.5%) and the national guideline (45.5%), to establish the individual therapeutic targets.

For hypercholesterolemia management, statin therapy was recommended to the majority of their patients (87.7%); 86.2% of the physicians reviewed their patients' cholesterol levels at least once every 6 months; 73.9% of their patients attended the hypercholesterolemia review. The mean duration of the hypercholesterolemia review once the patients achieved their targets was 4.7 ± 1.5 months. Among the patients with set cholesterol targets, 51.6% stayed at the targets persistently whereas 9.6% never attained their therapeutic goals.

Patient Attitudes and Experiences toward Hypercholesterolemia Management

Among 999 patients, 42.9% and 42.7% have heard or been told about LDL-C and HDL-C, respectively; 62.1% have been provided with their cholesterol levels but only 45.6% have been given the individual targets (**Table 1**). Most patients either identified that they failed to attain their cholesterol goals (21.2%) or were unsure about whether they had reached their cholesterol targets (43.0%). The majority of the patients were recommended for cholesterol level check-up at least every 3 months (74.2%). However, patient compliance to lipid-lowering medications was unsatisfactory as 50.2% of patients forgot to take medications, including 6.8% who forgot to take medications more than once a week or 43.3% forget to take medications less than once a week. In addition, 83.7% of the patients thought that they could miss a tablet without it affecting their cholesterol levels.

With regard to experiences toward hypercholesterolemia management, 69.3% of the patients received recommendations for lifestyle changes and concomitant lipid-lowering medications when they were first diagnosed; 65.8% of the patients stayed on the same regimen throughout the treatment.

Physician and Patient Perceptions to Hypercholesterolemia Management

Most of the physicians did not feel frustrated (75.9%), stressful (65.5%), or pressured (62.1%) to effectively treat their patients for achieving cholesterol targets (**Fig. 1A**). In addition, 75.9% of the physicians were confident of having a sufficient number of patients at their cholesterol targets. Regarding lipid-lowering medications, 24.5% of the physicians were frustrated that the guideline indicated lifestyle changes alone as the first-line therapy in all patients whereas 44.8% were not, and 69.0% of the physicians prescribed lipid-lowering medications regardless of the patient compliance to lifestyle changes. As for concerns about lipid-lowering medications, 55.2% of the physicians agreed that the efficacy was associated with patient compliance, and only 27.6% and 20.7% disagreed that patients would be concerned about their conditions if medications were increased or frequently changed, respectively.

Most patients were satisfied with the level of information available to them about high cholesterol (64.0%) and were not frustrated that they were unsure whether lipid-lowering medications are effective enough (62.3%) (**Fig. 1B**). Furthermore, most patients identified the importance of compliance (90.5%) and 57.8% disagreed with discontinuation of medications once the patient achieved the cholesterol targets. However, 46.2% forgot to take the medications sometimes. With regard to patient involvement in hypercholesterolemia management, the majority of the patients were either satisfied (80.2%) or motivated (65.9%), and a few were either concerned (13.7%) or confused (9.0%). However, 46.0% of the patients had no strong feeling toward cholesterol management.

Determinants of LDL-C Goal Attainment

The significant non-patient related factors were the reference guidelines used (OR=0.32, 95% CI: 0.15-0.69, healthcare reimbursement policy vs. others, $P=0.006$), and the proportion of patients treated with statins (OR=1.73, 95% CI: 1.14-2.62, $P=0.012$), fibrates (OR=0.59, 95% CI: 0.37-0.94, $P=0.029$), or other lipid-lowering medications (including ezetimibe, nicotinic acid, and omega-3 acid ethyl) (OR=0.13, 95% CI: 0.03-0.54, $P=0.007$) (**Table 2**). Furthermore, less frequent cholesterol reviews and better patient compliance to lipid-lowering medications were associated with LDL-C goal attainment. The compliance to lipid-lowering medications at the patient level was closely related to LDL-C goal attainment (**Fig. 2**). Furthermore, low patient involvement indexed by having no strong feeling toward cholesterol manage-

Table 1. Hypercholesterolemia management according to the patient questionnaire

Variable	Number
Patient awareness	
Heard or has been told about LDL-C	
Yes	429
No	382
Cannot remember	186
Heard or has been told about HDL-C	
Yes	427
No	383
Cannot remember	185
Has been informed about the cholesterol level	
Yes	620
No	378
Has been given a target cholesterol level	
Yes	456
No	248
Current situation according to the patient	
Not been given a cholesterol target	136
Not reached the cholesterol target	212
Unsure whether reaching the cholesterol target	430
Reached the cholesterol target	207
Patient compliance	
Frequency the patient was seen for check-up of cholesterol level	
More frequent than once every 3 months	216
Every 3 months	526
Every 6 to 12 months	207
Frequency of lipid-lowering medications missed	
More than once a week	68
Once a week or less	433
Frequency the patient thought that missing medications would not affect the cholesterol level	
More than once a week	180
Once a week or less	656
Patient experience	
Measures taken by the doctor when the patient was first diagnosed	
Only advised to change lifestyle	126
Only prescribed medications	157
Both advised lifestyle changes and prescribed medications	692
Neither advised lifestyle changes nor prescribed medications	13
Changes of lipid-lowering medications since first prescribed	
Still on the same tablet	657
Still on the same tablet but the dose has been increased	23
Have changed tablets	267

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

ment was associated with less LDL-C goal attainment (OR=0.73, 95% CI: 0.56-0.95, $P=0.020$).

Determinants of Statin Therapy Allocation

Significant physician characteristics for statin therapy allocation included the specialty of the physi-

cians and the proportion of their patients persistently staying at target (**Table 3**). Patient awareness of their current situation, particularly the recognition of treatment failure, was a significant predictor of being allocated to non-statin therapy. Other factors regarding patient perceptions included patients who stopped

Fig. 1. The perception section of the physician (A) and the patient (B) questionnaire

Q1=feeling frustrated of not being always able to effectively treat patients with cardiovascular disorders.

Q2=finding it stressful trying to get patients to their cholesterol targets.

Q3=feeling pressured to get patients to reach cholesterol targets.

Q4=having a sufficient number of patients reach their cholesterol targets.

Q5=being frustrated that guidelines instruct to advise lifestyle alone as the first line therapy in all patients.

Q6=tending to prescribe a lipid-lowering medication only to patients who have proved that they can adhere to diet and exercise changes.

Q7=patient compliance decreases if a lipid-lowering medication takes too long to have an effect.

Q8=patients become concerned that their condition is more severe if their lipid-lowering medication is increased.

Q9=patients become concerned that their condition is more severe if their lipid-lowering medication is frequently changed.

S1=being satisfied with the level of information available to them about high cholesterol.

S2=being frustrated that they are unsure whether tablets are effective enough.

C1=always taking tablets daily to lower cholesterol.

C2=stopping tablets when cholesterol returns to normal.

C3=sometimes forgetting tablets.

I1=being satisfied at cholesterol management.

I2=being motivated by cholesterol management.

I3=being concerned about cholesterol management.

I4=being confused with cholesterol management.

I5=having no strong feeling toward cholesterol management.

Table 2. Determinants for LDL-C goal attainment

	LDL-C goal attainment	
	OR (95% CI)	P value
Physician characteristics		
Age, per year	1.12 (0.63-1.99)	0.692
Practice experience, per year	1.02 (0.59-1.74)	0.950
Speciality		0.491
Cardiology	Reference	
Endocrinology	0.99 (0.38-2.58)	
Other	1.66 (0.68-4.04)	
Guidelines used to establish the individual target		
NCEP ATP III	0.59 (0.19-1.84)	0.340
National guideline	0.52 (0.21-1.28)	0.147
Healthcare reimbursement policy	0.32 (0.15-0.69)	0.006
Proportion of patients for which recommended treatment		
Statins, per %	1.73 (1.14-2.62)	0.012
Fibrates, per %	0.59 (0.37-0.94)	0.029
Others*, per %	0.13 (0.03-0.54)	0.007
Proportion of patients with the set cholesterol target		
Reached and stayed at the target, per %	1.15 (0.88-1.50)	0.286
Have never reached the target, per %	0.76 (0.41-1.40)	0.364
Patient characteristics		
Patient awareness		
Current situation according to the patient		
Not been given a cholesterol target	Reference	
Not reached the cholesterol target	1.06 (0.69-1.63)	0.801
Unsure whether reaching the cholesterol target	1.18 (0.08-1.74)	0.391
Reached the cholesterol target	1.66 (1.08-2.57)	0.022
Patient compliance		
Frequency the patient is seen for check-up of cholesterol level		
More frequent than once every 3 months	Reference	
Every 3 months	0.85 (0.62-1.16)	0.300
Every 6 to 12 months	1.49 (1.02-2.20)	0.041
Frequency of lipid-lowering medications missed		
More than once a week	Reference	
Once a week or less	2.43 (1.40-4.24)	0.002
Frequency the patient thought that missing medications would not affect the cholesterol level		
More than once a week	Reference	
Once a week or less	1.49 (1.07-2.07)	0.019

*Ezetimibe, nicotinic acid, and omega-3 acid ethyl

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; OR, odds ratio.

medications when their cholesterol levels returned to normal and patients with low involvement of cholesterol management were more likely to receive statins. In addition, patients with a high satisfaction to the high cholesterol information available to them were less likely to receive statins.

Discussion

Our study indicated that there was a discrepancy between patient awareness of hypercholesterolemia management, patient compliance to lipid-lowering medications, and patient perceptions to hypercholesterolemia management. Although most patients recognized the importance of high compliance, a substan-

Fig. 2. Determinants of LDL-C goal attainment from the perception section of the physician and the patient questionnaires

tial number of patients forgot to take their medications; in particular, 14.1% forgot to take their medications at least once a week. Moreover, the under-treatment of hypercholesterolemia was attributed to the guidance of the healthcare reimbursement policy in addition to the use of non-statin therapy and unsatisfactory patient compliance.

At the patient level, the compliance to lipid-lowering medications and the level of involvement with hypercholesterolemia management were key determinants for LDL-C control. The poor clinical outcomes and the increased medical costs have been attributed to poor compliance to the pharmacological therapies¹⁸. Meanwhile, the improvement of patient satisfaction has been closely related to increased compliance and LDL-C goal attainment^{19, 20}, and well-informed and motivated patients had a better control of risk factors and lower risk of complications²¹. Despite that most physicians (93.1%) in Taiwan gave the LDL-C information to their patients, there was a modest proportion of patients who were unaware of their cholesterol levels or targets, and 46.0% of the patients had no strong feeling toward cholesterol man-

agement in our study. Furthermore, both the CEPHEUS and the CEPHEUS-PA reported that good patient compliance to lipid-lowering medications was associated with a 49% to 77% increase in LDL-C goal attainment^{5, 6}. The pharmacy record study indicated that the medication possession ratio was closely related to the probability of LDL-C goal attainment²². Even though the majority of Taiwanese patients acknowledged the importance of taking the daily tablet and the persistence of using lipid-lowering medications, the non-compliance rate (patients forgot to take tablets more than once a week) was numerically higher in the Taiwanese cohort compared with the overall CEPHEUS-PA (18.0% vs. 15.6%).

Most of physicians were optimistic about the hypercholesterolemia management and considered that they had a sufficient number of patients at their LDL-C goals, which was in line with the result from a previous survey²³. However, the goal attainment rate was 49.5%, only 21.6% in the very high risk population, referenced by the 2004 NCEP ATP III guideline in our previous investigation. This disparity has been often reported^{23, 24}. The overestimate also occurred in

Table 3. Selected determinants for statin therapy allocation

	Statin therapy allocation	
	OR (95% CI)	P value
Physician characteristics		
Speciality		<0.001
Cardiology	Reference	
Endocrinology	0.03 (0.01-0.14)	
Other	0.65 (0.09-4.88)	
Guidelines used to establish the individual target		
NCEP ATP III	0.35 (0.02-5.67)	0.443
National guideline	0.32 (0.02-4.29)	0.373
Healthcare reimbursement policy	0.87 (0.06-12.71)	0.912
Proportion of patients with the set cholesterol target		
Reached and stayed at the target, per %	2.07 (1.43-2.99)	<0.001
Have never reached the target, per %	0.13 (0.05-0.34)	<0.001
Patient characteristics		
Patient awareness		
Current situation according to the patient		
Not been given a cholesterol target	Reference	
Not reached the cholesterol target	0.18 (0.05-0.60)	0.005
Unsure whether reaching the cholesterol target	0.38 (0.11-1.27)	0.117
Reached the cholesterol target	0.36 (0.10-1.32)	0.124
Patient compliance		
Frequency the patient is seen for check-up of cholesterol level		
More frequent than once every 3 months	Reference	
Every 3 months	0.64 (0.32-1.26)	0.194
Every 6 to 12 months	1.05 (0.43-2.52)	0.920
Frequency of lipid-lowering medications missed		
More than once a week	Reference	
Once a week or less	1.59 (0.67-3.78)	0.297
Frequency the patient thought that missing medications would not affect the cholesterol level		
More than once a week	Reference	
Once a week or less	0.59 (0.27-1.28)	0.181
Patient perceptions		
Being satisfied with the information available to them about high cholesterol	0.09 (0.01-0.69)	0.020
Stopping tablets when cholesterol returns to normal	2.28 (1.14-4.59)	0.021
Being confused about cholesterol management	7.53 (1.03-55.05)	0.047
Having no strong feeling toward cholesterol management	2.26 (1.31-3.91)	0.003

CI, confidence interval; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; OR, odds ratio.

the physician self-assessment²⁵). In the current analysis, LDL-C goal attainment was not attributed to physician factors but to the referenced guidelines. All Taiwanese physicians used the treatment guidelines and LDL-C levels as references to manage hypercholesterolemia. The NCEP ATP III guideline was the most frequently used guidance. In contrast to the NCEP ATP III guideline, the use of the healthcare reimbursement policy issued by the Taiwan NHI program was associated with less likelihood of LDL-C goal attain-

ment (OR=0.32, 95% CI: 0.15-0.69, $P=0.006$). Both the national guideline (endorsed by the Taiwan health authority) and the healthcare reimbursement policy (in which the LDL-C targets were similar to the NCEP ATP III guideline published in 2002 for patients with lower to moderately high risk) have not adopted the lower LDL-C targets advocated by the updated NCEP ATP III guideline for patients with higher risk, including established recent coronary events²⁶). The CHD risk factors and CHD risk equiv-

alents identified by the international guidelines have not been completely recognized by the healthcare reimbursement policy. The discrepancy in the LDL-C targets between the guidance has resulted in the under-treatment of patients with CHD in Taiwan. The recent registry of >3000 Taiwanese patients with acute coronary syndrome indicated that statin therapy was prescribed only in 48.4% and 60.5% of the patients in the acute stage and at discharge, respectively²⁷. Similar information was repeatedly reported in Taiwan that 85.0% of the patients with acute myocardial infarction had a LDL-C level ≥ 70 mg/dL, in which 70.6% had a LDL-C reduction <40% by 3 months²⁸.

In addition to LDL-C targets, the total cholesterol level (but not non-HDL-C level, which is associated with incident CHD²⁹) is the treatment target both in the national guideline and the reimbursement policy. Furthermore, the reimbursement policy but not the national guideline mandated that patients receive regular lipid checkups at least every 3 to 6 month after the initiation of lipid-lowering medications and specifically requested that physicians lower the medications once the patient is at the therapeutic goals. The higher likelihood of attaining the LDL-C targets by patients who had less frequent checkups in our study exactly reflects the impacts of specific requirements of the reimbursement policy. Since the Taiwan NHI program balances between healthcare spending and the adoption of high-price therapeutics, there are discrepancies between the reimbursement policy and the international guidelines which generally influence medical conduct^{9, 12}. The low goal attainment rate in Taiwan, particularly in the high risk populations, was attributed to those critical factors^{4, 6, 7}. The reimbursement policy in other countries, which restrict the use of effective medications, was also associated with an increase in LDL-C levels³⁰.

Statin therapy is the cornerstone for cardiovascular risk management and LDL-C goal attainment³¹. In our previous study, some of the determinants for statin therapy allocation were inversely associated with LDL-C goal attainment (e.g., patients with CHD or an indication for secondary prevention). In this analysis, patients with a low compliance to medications and lower involvement with hypercholesterolemia management indexed in the perception section were paradoxically more likely to be given statin therapy (e.g., patients who would stop taking medications when their cholesterol levels returned to normal and who were confused or had no strong feeling toward cholesterol management). This was probably because patients with poor compliance or lower involvement

may have a higher LDL-C level, which led their physicians to start or continue statin therapy. Despite that the guidelines used by the physicians were not associated with the statin therapy allocation, the prevalent prescription of the low to medium equipotency doses under the Taiwan NHI program might still be responsible for the low LDL-C control rate observed in our study^{7, 32}.

To improve hypercholesterolemia management in Taiwan, efforts from the healthcare reimbursement system in addition to inputs from both the patients and physicians are necessary. The latest NHI reimbursement policy (effective in late 2013) has released several restrictions on pharmacological therapies but unfortunately ignored the need of very strict LDL-C control in very high risk patients. Meanwhile, patient compliance and involvement could be encouraged through the participation of academic societies and national initiatives to improve the quality of care in addition to the insurance program^{33, 34}.

Conclusion

Our findings suggested that low LDL-C goal attainment was not attributed to physician factors but to the healthcare reimbursement policy and patient compliance and involvement. Key steps must be taken to overcome those barriers and improve the under-treatment of hypercholesterolemia in Taiwan.

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Conflicts of Interest

Prof. Shing-Jong Lin was the co-principal investigator of the REALITY-Asia study.

Prof. Chern-En Chiang was the co-principal investigator of the CEPHEUS Pan-Asia survey.

The other authors declare no conflicts of interest (COI).

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