Title Page

Title: Association of telomere length in peripheral blood leukocytes with the presence of atrial fibrillation in elderly male

Brief title: Association of telomere length with the presence of atrial fibrillation

Author's full name, highest academic degree and affiliations:

Author 1, Chuanbin Liu,MD[1],

Author 2, Jing Bai,MD[1],

Author 3, Qing Dan,MD[2],

Author 4, Xue Yang,MD[3],

Author 5, Zihao Fu,MD[1],

Author 6, Xu Lu,MD[1],

Author 7, Xiaoye Xie,BD[3],

Author 8, Li Fan,MD[3],

Author 9, Feng Cao,MD,PhD[3]*,

Author 10, Yang Li,PhD[2]*

Other members of the Study Group/Consortium, Jianwei Liu,BD[3].

[1] Medical School of Chinese PLA & National Clinical Research Center for Geriatric Disease, Beijing 100853, China.

[2] Department of Cardiology, the First Medical Center, Chinese PLA General Hospital, Beijing 100853, China;

[3]The Second Medical Center, Chinese PLA General Hospital, National Clinical Research Center for Geriatric Disease, Beijing 100853, China.

Financial support

This work was supported by the National Key R&D Program of China (2016YFC1300300 and 2016YFA0100903), the National Nature Science Foundation of China (81870249 and 81530058), the Key Project of Chinese Military Health Care Projects (17BJZ41, 18BJZ32 and

19BJZ25), and the Science Foundation of the PLA General Hospital (2018XXFC-9).

Conflicts of interests

None.

Correspondence:

Feng Cao, The Second Medical Center, Chinese PLA General Hospital, National Clinical Research Center for Geriatric Disease, No. 28 Fuxing Road, Beijing, 100853, China ; E-mail: fengcao8828@163.com

Yang Li, Department of Cardiology, the First Medical Center, Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing, 100853, China ; E-mail: liyangbsh@163.com

Association of telomere length in peripheral blood leukocytes with the presence of atrial fibrillation in elderly male

Chuanbin Liu[1], Jing Bai[1], Qing Dan[2], Xue Yang[3], Zihao Fu[1], Xu Lu[1], Xiaoye Xie[3], Jianwei Liu[3], Li Fan[3], Feng Cao[3*], Yang Li[2*]

[1] Medical School of Chinese PLA & National Clinical Research Center for Geriatric Disease, Beijing 100853, China.

[2] Department of Cardiology, the First Medical Center, Chinese PLA General Hospital, Beijing 100853, China;

[3]The Second Medical Center, Chinese PLA General Hospital, National Clinical Research Center for Geriatric Disease, Beijing 100853, China.

Correspondence:

Feng Cao, The Second Medical Center, Chinese PLA General Hospital, National Clinical Research Center for Geriatric Disease, No. 28 Fuxing Road, Beijing, 100853, China ; E-mail: fengcao8828@163.com

Yang Li, Department of Cardiology, the First Medical Center, Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing, 100853, China ; E-mail: liyangbsh@163.com

Abstract

Objective: Telomeres gradually shorten and the incidence of atrial fibrillation (AF) gradually increases with age. However, the association of telomere length with AF is still controversial. This study aims to determine the correlation between the leukocyte telomere length (LTL) and the presence of AF.

Methods: This study recruited 96 AF male patients and 97 healthy male controls (aged ≥60 years) Anthropometric, clinical and laboratory analysis were performed on all subjects. Blood LTL was detected by quantitative real-time PCR assay. PGC-1α concentration was evaluated by ELISA method. The association between LTL and AF was analyzed by simple and multivariate logistic regression.

Results: LTL in AF patients was significantly shorter than controls ($P < 0.001$). Logistic regression analysis confirmed that LTL was inversely associated with the presence of AF (OR 0.428, 95% confidence interval [CI]: 0.268-0.684; $P < 0.001$). Furthermore, we conducted a subgroup analysis of different ages and different types of AF and found that LTL was negatively correlated with age (r = -0.148, $P = 0.040$), and there was no statistical difference among different types of AF. We found that the telomere-associated molecule serum PGC-1α concentration was also negatively related to AF (OR 0.991, 95% CI: 0.985-0.997; $P = 0.004$) .

Conclusion: LTL and serum PGC-1α concentration are inversely correlated with the presence of AF in elderly male.

Key words: telomere length; leukocyte; atrial fibrillation; PGC-1α; elderly.

1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, and contributes to a high prevalence of mortality and morbidity, especially in the elderly. Studies have shown that the prevalence of AF increases with advancing age，which was 5% between 60 and 70 years old, and as high as 8% over 80 years old.[1] Thus the advancing age is one of the major risk factors for AF. However, the exact mechanism behind the influence of age on AF is still unclear.

Telomere length shortens is found common with age in the majority of tissues and cells, thus it is often used as a marker of aging.[2] Researches have showed that leukocyte telomere length (LTL) was related to a variety of cardiovascular disease, including atherosclerosis, left ventricular hypertrophy and heart failure, but the relevance to AF was still controversial.[3-5] Roberts *et al* [6] demonstrated that there was no relationship between mean telomere length and AF, when patients with AF were compared to those without AF in the Cardiovascular Health Study. By contrast, Carlquist *et al* [7] found that the decreased telomere length was related to the presence of AF. In addition, Su *et al* [8] have shown that shortened LTL was associated with recurrence of AF and was an independent risk factor. Additionally, some researchers have put forward a concept of "Telomere-p53-PGC regulatory axis", that was, the shortening of cardiomyocytes' telomeres will activate p53 expression, thereby inhibiting peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1), causing a series of reactions such as oxydative stress, intracellular Ca^{2+} overload, eventually inducing AF.[9-12]

The aim of this study was to determine the correlation between the LTL and telomere-associated molecules and the presence of AF in elderly male.

2 Materials and methods

2.1 Patients

This study consisted of a population of 96 elderly male AF patients and 97 male non-AF healthy controls (aged ≥60 years). All the people enrolled in the group were consecutively had routine medical checkup at the the First Medical Center and the Second Medical Center of Chinese PLA General Hospital from April to October 2018. The separated leukocytes and serum samples were stored in the "Geriatric Disease Bio-Sample Bank" of the National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital. AF patients were diagnosed according to the guidelines established by the European Society of Cardiology in 2010.[13] Patients were excluded from the study if they had valvular heart disease, acute coronary syndrome, dilated or hypertrophic cardiomyopathy, congenital heart disease, previous cardiac surgery, congestive heart failure, hyperthyroidism, inflammatory diseases, systemic disease, or renal failure. Patients with incomplete data sets were also excluded. AF patients were then divided into paroxysmal AF group (n = 36), persistent AF group (n = 37), and permanent AF group (n = 23). The study protocol was approved by the Human Ethics Review Committee of our hospital and a signed consent form was obtained from each subject.

2.2 Collection of the clinical data

Anthropometric (height, weight, and blood pressure), clinical characteristics, and laboratory analysis were performed on all subjects. Transthoracic echocardiography was

performed by experienced echocardiologists on all patients to evaluate the characteristics of their left atrial diameter (LAD). Venous blood was collected after a minimum of 10 hours of fasting for further examination.

2.3 Realtime PCR for the leukocyte telomere length

Serum and leukocytes were obtained from blood samples by centrifugation and stored at -80°C until analysis.The telomere repeat and a single copy of each sample were measured with quantitative real-time PCR separately (GenePool Biotech Corporation, China). The relative LTL was calculated as the ratio of telomere repeats to single-copy gene copies (T/S ratio).[8] Primers:

p53 mRNA: forward—CCATCCTCACCATCATCACACT,

reverse— GCACAAACACGCACCTCAAA

PGC-1α mRNA: forward—TGACGACGAAGCAGACAAGAC,

reverse—GAACAAGAAGGAGACACATTGAACA

Actin mRNA: forward—ACTTAGTTGCGTTACACCCTT,

reverse—GTCACCTTCACCGTTCCA

Telomere repeat: forward—ACACTAAGGTTTGGGTTTGGGTTTGGGTTTGGGTTAGTGT,

reverse—TGTTAGGTATCCCTATCCCTATCCCTATCCCTATCCCTAACA

Single copy gene: forward—CTTCATCCACGTTCACCTTG,

reverse—GAGGAGAAGTCTGCCGTT

2.3 ELISA for the serum **PGC-1α**

An enzyme-linked immunosorbent assay kit (Jianglai Biotech Corporation, China) was utilized to evaluate serum PGC-1α concentrations. DNA and RNA were extracted from leukocytes by

TIANamp Blood DNA Kit (TIANGEN Biotech Corporation, China) and RNAprep pure Blood Kit (TIANGEN Biotech Corporation, China) guided by the protocol of the manufacture respectively. Then the p53 mRNA and PGC-1α mRNA were detected. The telomere repeat and a single copy of each sample were measured with quantitative real-time PCR separately (GenePool Biotech Corporation, China). The relative LTL was calculated as the ratio of telomere repeats to single-copy gene copies (T/S ratio).[8] All measurements were performed blinded with respect to clinical data.

2.4 Statistical analysis

The data were exhibited as means ± standard errors. The unpaired t-test, chi-square tests, or the Mann-Whitney U test were utilized to determine the parameter differences between AF patients and the controls. Simple and multiple logistic regression analysis was performed to determine the correlation of LTL with the presence of AF. Chi-square tests, one-way ANOVA, or Kruskal-Wallis test were utilized to determine the parameter differences between different age and AF subgroups. Pearson correlation analysis was used to analyze the correlation of LTL and serum PGC-1α concentration with the subtype of AF and age. The correlation between LTL and serum PGC-1α concentration and other parameters was analyzed using simple linear regression analysis. Then, a multiple stepwise linear regression analysis was used to determine the contribution of various factors to LTL and serum PGC-1α concentration. A value of *P* less than 0.05 was statistically significant.

3 Results

3.1 Baseline clinical characteristics

AF patients showed higher body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), creatinine (Cr), uric acid (UA), LAD , glycated hemoglobins (GHb) and as well as reduced total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) compared with the controls (Table 1). There were no significant differences in other characteristics between the two groups.

3.2 telomere length in AF patients was significantly shorter than non-AF controls

AF patients showed significantly shorter LTL compared with non-AF controls ($P < 0.001$) (Fig 1A). Simple logistic regression analysis indicated that BMI, SBP, DBP, TC, HDL-C, Cr, UA, GHb, LAD, T/S ratio, PGC-1α mRNA and serum PGC-1α showed a trend toward an association with the presence of AF (Table 2). All these parameters were then entered into a multivariate logistic regression model. LTL (T/S ratio) (OR 0.428, 95% CI 0.268-0.684; $P < 0.001$) remained to be adversely associated with the presence of AF (Fig 2).

Pearson correlation analysis showed that LTL in eldery male was significantly negatively correlated with age (r = -0.148, $P = 0.040$) (Fig 1B). In AF patients (r = -0.091, $P = 0.377$) and control group (r = -0.111, $P = 0.278$), the LTL was also negatively correlated with age but no statistical difference. Then the elder were divided three groups according to the WHO.[14] LTL in AF patients was significantly shorter than in controls in the elderly age group (60-74 years)($P = 0.001$), and shorter when compared with controls in AF patients in the senile age group (75-89

years) and the long-living group (≥90 years) but not statistically significant (Fig 1C). In AF subgroups, there were no significant differences of LTL among the paroxysmal AF, persistent AF and permanent AF group (Fig 1D).

3.3 The expression of telomere-associated molecules in AF patients

In our research, the expression of p53 mRNA in AF patients was higher than the controls, but there was no statistical differences (Fig 3A). Interestingly, the expression of PGC-1α mRNA in leukocytes significantly reduced in AF patients ($P = 0.008$) (Fig 3B), so as the serum PGC-1α concentration ($P = 0.001$) (Fig 3C).

In AF subgroups, there were no significant differences of serum PGC-1α concentration among the paroxysmal AF, persistent AF and permanent AF group (Fig 3D). Serum PGC-1α concentration was significantly reduced in AF patients in the elderly age group(60-74 years) and the senile age group (75-89 years), and also reduced in the long-living group (≥90 years) but not statistically significant (Fig 3E). Pearson correlation analysis showed that serum PGC-1α was negatively correlated with age (r = -0.108, $P = 0.136$), also in AF patients (r = -0.105, $P = 0.308$) and controls (r = -0.176, $P = 0.085$) (Fig 3F). Simple logistic regression analysis indicated that serum PGC-1α showed a trend toward an association with the presence of AF (Table 2). Then, a multiple stepwise logistic regression analysis was confirmed that the serum PGC-1α concentrations remained to be adversely associated with the presence of AF(OR 0.991, 95% CI: 0.985-0.997; $P = 0.004$) (Fig 2).

3.4 The correlation of LTL and serum PGC-1α concentration with other clinical characteristics

Simple linear regression analyses showed that LTL was negatively correlated with age (r = -0.148, *P* = 0.040), UA (r = -0.142, *P* = 0.049), LAD (r = -0.225, *P* = 0.002) and positively correlated with HDL-C (r = -0.148, *P* =0.040) , Serum PGC-1α (r = 0.147, *P* = 0.041) and PGC-1α mRNA (r = 0.224, *P* = 0.002). Multiple stepwise regression analysis showed that age (β = -0.147, *P* = 0.034) remained to be inversely associated and PGC-1α mRNA (β = 0.187, *P* = 0.007) positively associated with LTL (Table 3).

Simple linear regression analyses showed that serum PGC-1α was negatively correlated with LAD (r= -0.198, *P* = 0.006) and positively correlated with TC (r = 0.145, *P* = 0.044) , BUN (r = 0.154, *P* = 0.033) and T/S ratio (r = 0.147, *P* = 0.041). Multiple stepwise regression analysis showed that LAD (β = -0.166, *P* = 0.024) remained to be inversely associated and BUN (β = 0.147, *P* = 0.038) positively associated with serum PGC-1α (Table 4), suggesting that the PGC-1α may be related to heart structure and kidney function.

Discussion

The present study revealed that LTL is significantly shorter in AF patients as compared with healthy control, indicating that LTL is inversely correlated with the presence of AF in elderly male. In the subgroup analysis of age, our data confirmed that LTL was negatively related to age.

However, no statistically significant differences were recorded among different types of AF. Furthermore, we found that the telomere-associated molecule PGC-1α, the serum concentration of which was also inversely correlated with AF. To the best of our knowledge, this study was the first to demonstrate the relationship between the serum PGC-1α concentration with AF in elderly, which suggesting that serum PGC-1α could be a convenient and non-invasive bio-marker for monitoring the presence and progression of AF.

In current study, we found that LTL was significantly shorter in AF patients, and logistic regression analysis revealed that LTL was significantly related to AF. In accordance with our finding, Siland *et al* [15] followed up 7775 individuals without AF for 11.4 ± 2.9 years and found that the shortening of telomere length was significantly related to AF (P = 0.013). Besides, our findings are also supported by a previous study by Carlquist *et al* [7] which demonstrated that shortened telomere length was associated with paroxysmal AF among cardiovascular patients. Further subgroup analysis of different age groups and different types of AF found that telomere length was significantly negatively correlated with age (r = -0.148, P = 0.040), which is consistent with previous reports,[16] while there was no statistically significant difference in telomere length among different types of AF. In the subgroup analysis of age, we found that the telomere length of patients with AF in the elderly age group(60-74 years) was statistically different from that of the controls, but there was no significant difference in the senile age group (75-89 years) and the long-living group (≥90 years). We thought this may be associated with the different speed of telomere shortening at different ages, and telomere may shorten significantly in the early stages of aging. Meanwhile, we performed simple and multiple linear regression

analysis on the correlation between LTL and other clinical factors, which found that telomere length was significantly correlated with age and the expression of PGC-1α mRNA, which was consistent with the results reported in the previous literature.[9,10]

Another new finding in this article was that serum PGC-1α concentration was significantly reduced in AF patients in elder men. In this study, we not only detected the LTL, but also detected the mRNA expression of p53 and PGC-1α in leukocytes. The results showed that the AF group was significantly shorter than the controls in terms of the LTL, and the expression of PGC-1α mRNA decreased significantly, while the expression of p53 mRNA increased but there was no statistical difference. In this study, we also detected the concentration of PGC-1α in serum with the method of ELISA. We found that serum PGC-1α concentration in patients with AF was significantly lower than those in the controls, and multiple logistic regression analysis found that it was significantly related to AF. Additionally, there was no significant difference in serum PGC-1α levels in different types of AF. Meanwhile, we also found that serum PGC-1α concentration was significantly correlated with the BUN and LAD, which suggesting that it was associated with kidney function and heart size.

Studies have shown that about 70% of AF occurs between 65 and 80 years of age.[1] AF is characterized by high complications, high mortality and high recurrence rate, but its mechanism is not clear.[17-18] Our study confirmed that telomere length was negatively correlated with AF in the elderly, especially in the long-living people, and the serum concentration of the telomere downstream molecule PGC-1α was also negatively correlated with AF, suggesting that telomere length and serum PGC-1α may be a possibly predictive bio-marker for the occurrence of AF or

an important factor predicting the outcome and prognosis of AF, and even may be a possibly new target for AF intervention.[19-21]

This study has several potential limitations. Firstly, our study was of cross-sectional design and did not consider the influence of gender factors. Secondly, many AF patients accompanied with multiple diseases such as hypertension, diabetes, and coronary artery disease, etc, despite our best efforts to adjust for established and potential comorbidities, residual confounding by other unmeasured or unknown factors remains possible.

In conclusion, telomere length in peripheral blood leukocytes and serum PGC-1α concentration are negatively correlated with the presence of AF in elderly male, which may be a possibly new predictive bio-marker for the occurrence or the outcome of AF.

Funding

This work was supported by the National Key R&D Program of China (2016YFC1300300 and 2016YFA0100903), the National Nature Science Foundation of China (81870249 and 81530058), the Key Project of Chinese Military Health Care Projects (17BJZ41, 18BJZ32 and 19BJZ25), and the Science Foundation of the PLA General Hospital (2018XXFC-9).

Conflicts of interests

None.

References

1 Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol. 2011;57(11):e101-e198. doi:10.1016/j.jacc.2010.09.013

2 Milaneschi, Yuri, Penninx, et al. Telomere Length as a Marker of Cellular Aging Is Associated With Prevalence and Progression of Metabolic Syndrome[J]. Obstetrical and gynecological survey, 2015.

3 Fernández-Alvira, Juan M, Fuster V , Dorado B , et al. Short Telomere Load, Telomere Length, and Subclinical Atherosclerosis[J]. Journal of the American College of Cardiology, 2016, 67(21):2467-2476.

4 Francine Z, Marques, Scott A,et al. Telomere dynamics during aging in polygenic left ventricular hypertrophy[J]. Physiological genomics, 2016.

5 Silver E, Ras A, Cosgrove C, et al. Telomere Length as a Biomarker and Potential Contributor of Heart Failure Progression[J]. Journal of Cardiac Failure, 2015, 21(8):S28-S28.

6 Roberts J D , Dewland T A , Longoria J , et al. Telomere length and the risk of atrial fibrillation: insights into the role of biological versus chronological aging.[J]. Circulation Arrhythmia & Electrophysiology, 2014, 7(6):1026-32.

7 Carlquist J F , Knight S , Cawthon R M , et al. Shortened telomere length is associated with paroxysmal atrial fibrillation among cardiovascular patients enrolled in the Intermountain Heart

Collaborative Study[J]. Heart Rhythm, 2016:21-27.

8 Su C, Liu , Gao Y, et al. Study on the relationship between telomere length changes and recurrence of atrial fibrillation after radiofrequency catheter ablation[J]. Journal of Cardiovascular Electrophysiology, 2019.

9 Sahin E, Colla S, Liesa M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise.[J]. Nature, 2011, 470(7334):359-365.

10 Javid Moslehi, Ronald A. DePinho, Ergün Sahin. Telomeres and Mitochondria in the Aging Heart[J]. Circulation Research, 2012, 110(9):1226-37.

11 Summermatter S, Santos G, Perez-Schindler J, et al. Skeletal muscle PGC-1α controls whole-body lactate homeostasis through estrogen-related receptor α-dependent activation of LDH B and repression of LDH A.[J]. Pnas, 2013, 110(21):8738-8743.

12 Allison C , Mach Núria. The Crosstalk between the Gut Microbiota and Mitochondria during Exercise[J]. Frontiers in Physiology, 2017, 1(8):319.

13 Lip G YH , Halperin J L , Tse H F. The 2010 European Society of Cardiology Guidelines on the Management of Atrial Fibrillation[J]. Chest, 2011, 139(4):738-741.

14 Tatarinova O V, Nikitin I P, Neustroeva V N, et al. Arterial blood pressure in persons of elderly, senile age and long-livers of Yakutsk: population screening[J]. Uspekhi Gerontologii, 2013, 26(1):82-88.

15 Siland J E , Geelhoed B , Gelder I C V , et al. Telomere length and incident atrial fibrillation – data of the PREVEND cohort[J]. Plos One, 2017, 12(2):e0171545.

16 Zhang W , Wang Y , Hou K , et al. A correlation study of telomere length in peripheral blood

leukocytes and kidney function with age[J]. Molecular Medicine Reports, 2015:4359-4364.

17 Krupa Kansara, Souvik Sen Gupta. Chapter Fourteen–DNA Damage, Repair, and Maintenance of Telomere Length: Role of Nutritional Supplements[J]. Mutagenicity Assays & Applications, 2018:287-307.

18 Leri A, Franco S, Zacheo A, et al. Ablation of telomerase and telomere loss leads to cardiac dilatation and heart failure associated with p53 upregulation[J]. Embo Journal, 2003,22(1):131-139.

19 Allende M, Molina E, González-Porras JR, et al. Short Leukocyte Telomere Length Is Associated With Cardioembolic Stroke Risk in Patients With Atrial Fibrillation[J]. Stroke; a journal of cerebral circulation, 2016, 47(3):863.

20 Margaritis M, Patel S, Antonopoulos AS ,et al. Telomere Length Predicts Post-Operative Atrial Fibrillation in Patients Undergoing CABG Independently of Chronological Age[J]. Circulation, 2014, 130:A17369-A17369.

21 Sun D M , Yuan X , Wei H , et al. Impaired myocardium energetics associated with the risk for new-onset atrial fibrillation after isolated coronary artery bypass graft surgery[J]. Coronary artery disease, 2014, 25(3):224-229.

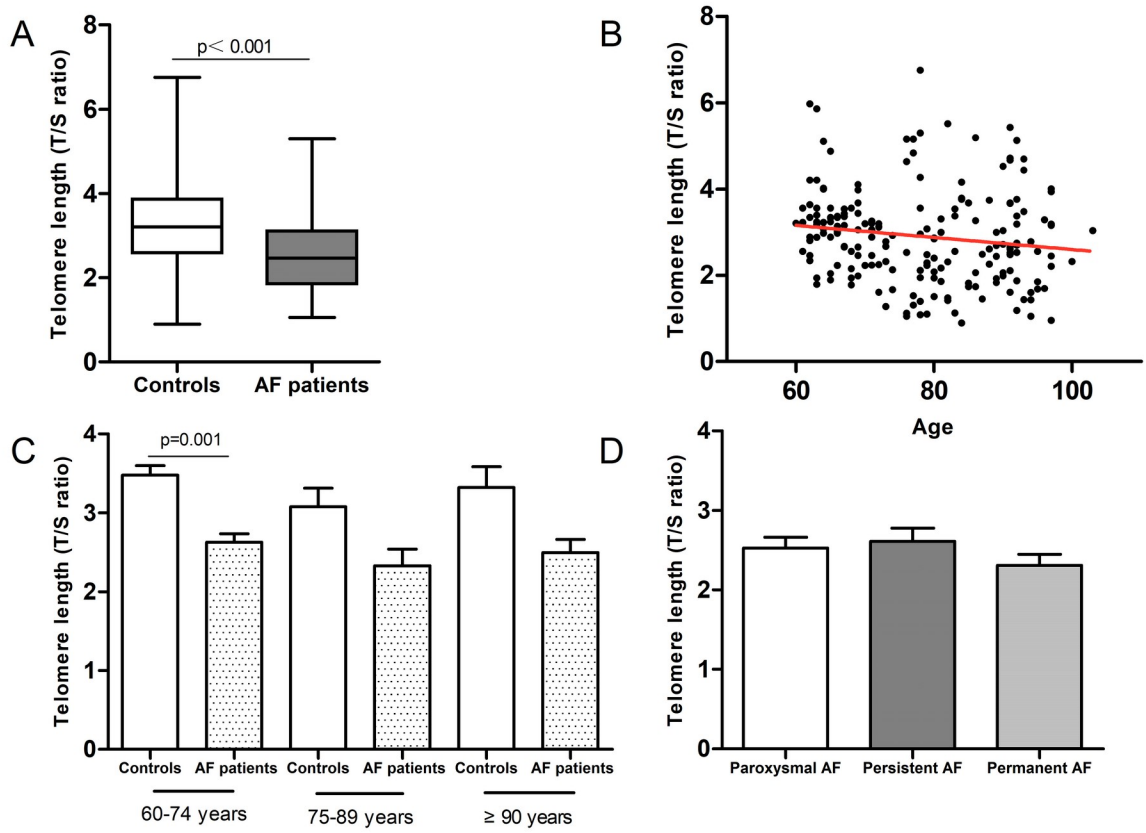

Fig 1 LTL in AF patients and the controls. (A)AF patients showed significantly shorter LTL compared with controls; (B)LTL in elderly male was significantly negatively correlated with age; (C) LTL was significantly shorter in AF patients in the elderly age group (60-74 years)(*P* =

0.001), and shorter in AF patients in the senile age group (75-89 years) and the long-living group (≥90 years) but not statistically significant; (D)There were no significant differences of LTL among the paroxysmal AF, persistent AF and permanent AF group.

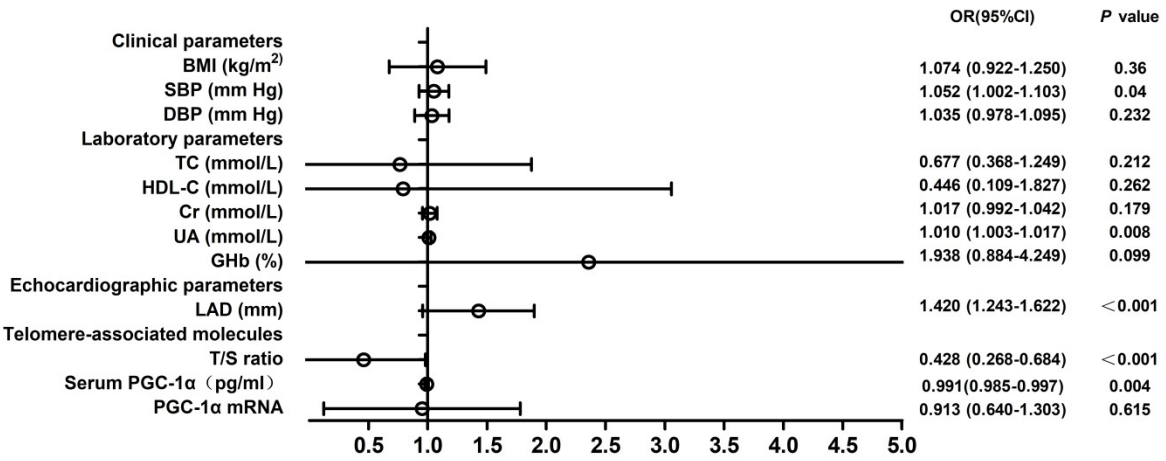

Fig 2 Multiple logistic regression analysis for the presence of AF. The OR value of LTL(T/S ratio) and serum PGC-1α are less than 1, indicating that they may be the protective factor for atrial fibrillation.

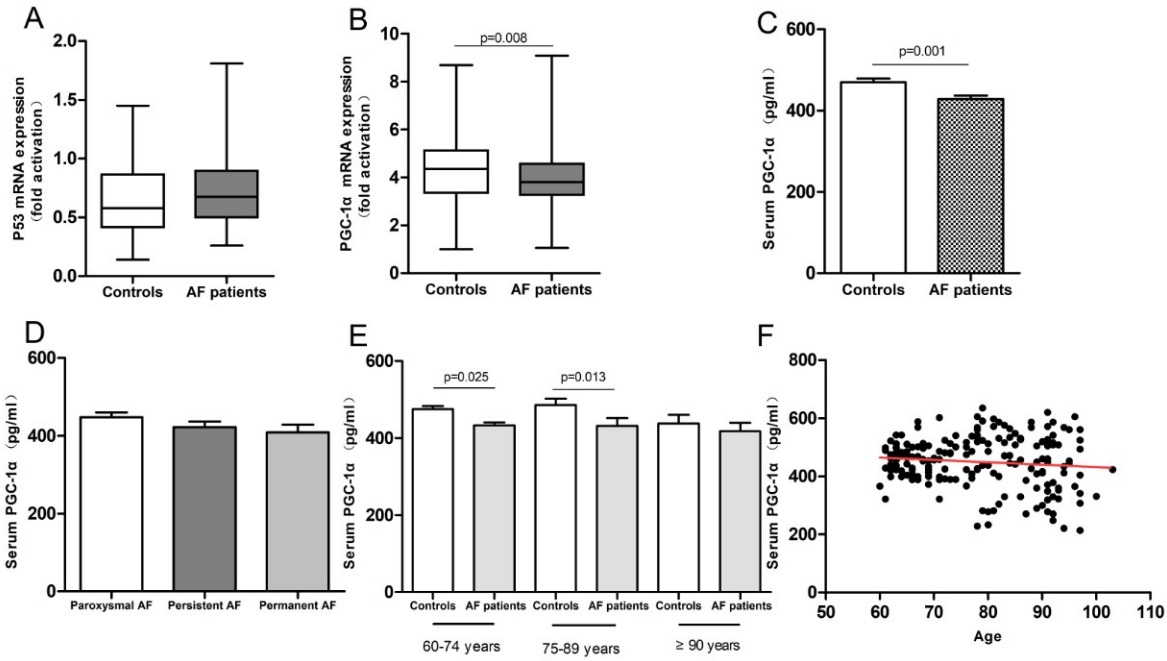

Fig 3 Telomere-associated molecules in AF patients. (A)p53 mRNA in AF patients was higher than the control, but there was no statistical differences; (B)the expression of PGC-1α mRNA in leukocytes significantly reduced in AF patients; (C)the serum PGC-1α concentration significantly reduced in AF patients; (D)there were no significant differences of serum PGC-1α concentration among the paroxysmal AF, persistent AF and permanent AF group; (E)Serum PGC-1α concentration was significantly reduced in AF patients in the elderly age group(60-74 years) and the senile age group (75-89 years), and also reduced in the long-living group (≥90 years) but not statistically significant; (F)serum PGC-1α was negatively correlated with age ($r = -0.108$, $P = 0.136$).

Table 1. Clinical and biochemical characteristics of AF patients and controls.

	The controls（n=97）	**AF patients（n=96）**	***P* value**
Clinical parameters			
Age (years)	77.69 ± 11.30	78.61 ± 11.64	0.577
BMI (kg/m^2)	23.60 ± 2.82	24.85 ± 3.16	**0.004**
SBP (mm Hg)	127.44 ± 11.08	132.00 ± 11.98	**0.007**
DBP (mm Hg)	68.35 ± 8.69	71.04 ± 8.99	**0.036**
Laboratory parameters			
TC (mmol/L)	3.93 ± 0.77	3.59 ± 0.73	**0.002**
TG (mmol/L)	1.22 ± 0.49	1.34 ± 0.58	0.108
LDL-C (mmol/L)	2.34 ± 0.76	2.21 ± 0.68	0.224
HDL-C (mmol/L)	1.42 ± 0.40	1.21 ± 0.30	**< 0.001**
Cr (mmol/L)	84.21 ± 15.89	91.32 ± 21.58	**0.010**
BUN (mmol/L)	6.31 ± 1.55	6.55 ± 1.83	0.315
UA (mmol/L)	312.22 ± 58.98	356.48 ± 79.59	**< 0.001**
FBG (mmol/L)	6.18 ± 0.95	6.15 ± 0.99	0.800
GHb (%)	6.02 ± 0.57	6.22 ± 0.67	**0.026**
Echocardiographic parameters			
LVEF (%)	60.20 ± 4.32	59.04 ± 3.92	0.053
LAD (mm)	37.08 ± 2.97	42.40 ± 4.40	**< 0.001**

Abbreviations: BMI, body mass index; SBP,systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; FBG, Fasting blood glucose; GHb, glycated hemoglobins; LVEF, left ventricular ejection fraction; LAD, left atrial diameter. *P* values with bold font mean statistically significant.

TABLE 2 Logistic regression analysis for the presence of AF

	Simple regression		Multiple regression	
	OR (95%CI)	***P* value**	**OR (95%CI)**	***P* value**
Clinical parameters				
Age (years)	1.007 (0.983-1.032)	0.574		
BMI (kg/m^2)	1.151 (1.043-1.269)	**0.005**	1.074 (0.922-1.250)	0.360
SBP (mm Hg)	1.035 (1.009-1.062)	**0.008**	1.052 (1.002-1.103)	**0.040**
DBP (mm Hg)	1.035 (1.002-1.070)	**0.038**	1.035 (0.978-1.095)	0.232
Laboratory parameters				
TC (mmol/L)	0.551(0.371-0.818)	**0.003**	0.677 (0.368-1.249)	0.212
TG (mmol/L)	1.560 (0.903-2.694)	0.111		
LDL-C (mmol/L)	0.672 (0.450-1.002)	0.051		
HDL-C (mmol/L)	0.173 (0.070-0.429)	**< 0.001**	0.446 (0.109-1.827)	0.262
Cr (mmol/L)	1.022 (1.005-1.039)	**0.013**	1.017 (0.992-1.042)	0.179
BUN (mmol/L)	1.091 (0.920-1.294)	0.315		
UA (mmol/L)	1.009 (1.005-1.014)	**< 0.001**	1.010 (1.003-1.017)	**0.008**
FBG (mmol/L)	0.963 (0.719-1.289)	0.799		
GHb (%)	1.705 (1.055-2.755)	**0.029**	1.938 (0.884-4.249)	0.099
Echocardiographic parameters				
LVEF (%)	0.934 (0.80-1.002)	0.055		
LAD (mm)	1.462 (1.312-1.630)	**< 0.001**	1.420 (1.243-1.622)	**< 0.001**
Telomere-associated molecules				
T/S ratio	0.444 (0.318-0.621)	**< 0.001**	0.428 (0.268-0.684)	**< 0.001**
Serum PGC-1α（pg/ml）	0.994 (0.991-0.998)	**0.001**	0.991(0.985-0.997)	**0.004**
PGC-1α mRNA	0.739 (0.582-0.937)	**0.013**	0.913 (0.640-1.303)	0.615

P53 mRNA	2.374 (0.860-6.553)	0.095

Abbreviations: CI, confidence interval; BMI, body mass index; SBP,systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; FBG, Fasting blood glucose; GHb, glycated hemoglobins; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; T/S ratio, the ratio of telomere repeats to single-copy gene copies; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α. *P* values with bold font mean statistically significant.

TABLE3 The correlation of LTL with other clinical characteristics

	Simple linear regression		Multiple linear regression	
	r	*P*	β	*P*
Clinical parameters				
Age (years)	-0.148	**0.040**	-0.147	**0.034**
BMI (kg/m2)	-0.108	0.134		
SBP (mm Hg)	0.007	0.922		
DBP (mm Hg)	-0.011	0.879		
Laboratory parameters				
TC (mmol/L)	0.079	0.276		
TG (mmol/L)	-0.060	0.406		
LDL-C (mmol/L)	0.060	0.410		
HDL-C (mmol/L)	0.167	**0.020**	0.127	0.078
Cr (mmol/L)	0.008	0.907		
BUN (mmol/L)	0.068	0.347		
UA (mmol/L)	-0.142	**0.049**	-0.102	0.158
FBG (mmol/L)	0.032	0.658		
GHb (%)	0.034	0.642		
Echocardiographic parameters				
LVEF (%)	-0.040	0.578		
LAD (mm)	-0.225	**0.002**	-0.119	0.120
Telomere-associated molecules				
Serum PGC-1α（pg/ml）	0.147	**0.041**	0.098	0.168
PGC-1α mRNA	0.224	**0.002**	0.187	**0.007**
P53 mRNA	0.092	0.204		

Abbreviations: BMI, body mass index; SBP,systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; FBG, Fasting blood glucose; GHb, glycated hemoglobins; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; T/S ratio, the ratio of telomere repeats to single-copy gene copies; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α. *P* values with bold

font mean statistically significant.

TABLE 4 The correlation of serum PGC-1α concentration with other clinical characteristics

	Simple linear regression		Multiple linear regression	
	r	*P*	β	*P*
Clinical parameters				
Age (years)	-0.108	0.136		
BMI (kg/m2)	0.047	0.516		
SBP (mm Hg)	0.091	0.209		
DBP (mm Hg)	-0.006	0.939		
Laboratory parameters				
TC (mmol/L)	0.145	**0.044**	0.095	0.187
TG (mmol/L)	0.075	0.303		
LDL-C (mmol/L)	0.131	0.069		
HDL-C (mmol/L)	0.008	0.915		
Cr (mmol/L)	0.034	0.643		
BUN (mmol/L)	0.154	**0.033**	0.147	**0.038**
UA (mmol/L)	0.069	0.344		
FBG (mmol/L)	0.055	0.447		
GHb (%)	-0.051	0.482		
Echocardiographic parameters				
LVEF (%)	-0.001	0.994		
LAD (mm)	-0.198	**0.006**	-0.166	**0.024**
Telomere-associated molecules				
T/S ratio	0.147	**0.041**	0.092	0.201
PGC-1α mRNA	0.085	0.238		
P53 mRNA	0.079	0.274		

Abbreviations: BMI, body mass index; SBP,systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; FBG, Fasting blood glucose; GHb, glycated hemoglobins; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; T/S ratio, the ratio of telomere repeats to single-copy gene

copies; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α. *P* values with bold font mean statistically significant.