Association Of The LH/FSH Ratio With Electrocardiogram Abnormalities In Polycystic Ovarian Syndrome

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Research Article

Keywords: Polycystic Ovarian Syndrome (PCOS), Electrocardiogram (ECG), Luteinizing/Follicle-stimulating hormone (LH/FSH) ratio

Posted Date: October 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2141531/v1

Association Of The LH/FSH Ratio With Electrocardiogram Abnormalities In Polycystic Ovarian Syndrome

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Abstract

Objective: This study aimed to investigate the association of the Luteinizing/Follicle-stimulating hormone (LH/FSH) ratio with Electrocardiogram (ECG) features in Polycystic Ovarian Syndrome (PCOS). **Methods:**Consecutive PCOS patients' record were recruited from the database of the hospital for the cross-sectional study. Serum concentrations of testosterone, pituitary, prolactin, progesterone, estradiol, LH, and FSH were measure and 12-lead ECG was performed for each subject. According to LH/FSH ratio, subjects were divided into High Group (LH/FSH Ratio $\geq$ 2, n=24), and Low Group (LH/FSH Ratio $<$ 2, n=52). 180 ECG features were automatically extracted by an ECG management system. The relationship between LH/FSH ratio and ECG variables was assessed by univariate and multivariate linear regression models.**Results:**76 patients with PCOS were enrolled. The mean values of LH in High Group were significantly higher than that in Low Group ($P < 0.0001$). P wave changes, QRS duration and ST segment changes had significantly difference between the two groups. The beginning of P wave was lower in Lead I, aVL, V2, V5, V6 in High group. Compared to Low Group, QRS duration, R-Q interval and R-S interval was narrow in High Group. There were ST depression in High Group, especially in left precordial leads such as Lead I, aVL, V5 and V6.In PCOS patients, P wave, QRS duration and ST segment changes were the most abnormalities in ECG of High LH/FSH ratio Group. **Conclusions:**The associations between LH/FSH ratio and ECG abnormalities were enhanced by the increased risk stratification of PCOS patients.

Keywords: Polycystic Ovarian Syndrome (PCOS), Electrocardiogram (ECG), Luteinizing/Follicle-stimulating hormone (LH/FSH) ratio

1 Introduction

Polycystic Ovarian Syndrome (PCOS) is considered a common endocrine system disorder affecting women of reproductive age. It is characterized by irregular menstrual cycles, chronic ovulatory dysfunction and hyperandrogenism, and it is associated with various metabolic disorders [1].

The polycystic ovary syndrome is associated with a high prevalence of metabolic disorders and cardiovascular risk factors [2]. PCOS is associated with insulin resistance, obesity, dyslipidemia, hypertension, and impaired glucose tolerance [3, 4]. PCOS also increases the risk of type 2 diabetes mellitus and metabolic syndrome. These cardiovascular risk factors in PCOS increases the risk of cardiovascular disease[5].

In PCOS, many factors, including hormones and metabolism, increase cardiovascular risk (CVR) [6]. Hormones, which include androgens, estrogens, growth hormones (GH), especially the Luteinizing/Follicle-stimulating hormone (LH/FSH) ratio play an important role in PCOS women. Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) secreted from the

anterior pituitary gland, and they are gonadotropin synthesized that stimulate ovulation [7, 8].

Generally, in healthy women, the LH/FSH ratio is usually between 1 and 2. In women with polycystic ovary disease, this ratio might reach as high as 2 or 3, namely an elevated LH/FSH ratio[9]. This change in LH/FSH ratio will lead to hyperandrogenemia, which could probably result in dyslipidemia. Dyslipidemia is one of the most common cardiometabolic complications of PCOS. It is generally recognized that hyperandrogenemia affects the occurrence of dyslipidemia. Macut et al. showed that androgen excess might alter LDL-C early in life and lead to a more atherogenic lipid metabolism [10]. In addition, it reported that hyperandrogenemia in young women with PCOS was associated with hypertension [11]. Therefore, the LH/FSH ratio in PCOS is considered to be related to accelerated cardiovascular disease.

ECG is a noninvasive, low-cost, reproducible test used to detect cardiovascular disease. Gonadal steroid hormone disorders can affect ECG abnormality, but the effects of PCOS on ECGs are still unclear. The QRS duration was wider in PCOS patients[12]. QTc interval duration is short in PCOS patients[13], which is negative related with testosterone. Francesco Orio et al. found that there was no difference in ECG pattern, expecially QT dispersion between PCOS and healthy control[14]. To date, some controversial data are available in previous research in ECG pattern in PCOS. In order to accurately measure ECG data and comprehensively describe ECG pattern, we automatically obtain 180 ECG features from each ECG peak, vallery and interval[15]. However, little is known regarding the role of the LH/FSH Ratio in evaluating the development of ECG abnormalities in PCOS. Therefore, it is very interesting to verify the relationship between LH/FSH Ratio and ECG abnormalities in patients with PCOS.

2 Results

2.1 Clinical characteristics of the Study Population

The study included 76 women who were diagnosed with PCOS according to Rotterdam ESHRE/ASRM sponsored PCOS consensus criteria [16]. The values of LH/FSH Ratio ranged from 0.05 to 10.95 for all subjects, with a mean of 4.38 $\pm$ 1.91. According to LH/FSH Ratio, we divided the subjects into two groups: High Group (LH/FSH Ratio $\geq$ 2, n=24), and Low Group (LH/FSH Ratio $<$ 2, n=52). The clinical characteristics of all patients are summarized in Table 1. The concentrations of serum Testosterone(T), LH, estradiol (E2), and high density lipoprotein cholesterol(HDL-C), were higher in High group than those in Low group ($P = 0.049$, $P < 0.001$, P=0.014, respectively). Two groups had similar hormone levels: FSH, PRL, progesterone (P),Free thyroxine (FT4), free triiodothyronine (FT3) and thyroid stimulating hormone (TSH). No significant differences were observed in mainly biochemical markers, such as aspartate transaminase(AST), alanine transaminase(ALT), total bilirubin(TBil), direct bilirubin(DBil), indirect

bilirubin(IBil), urea nitrogen(BUN), creatinine(Cr), total cholesterol(CHOL), triglycerides(TG), low density lipoprotein cholesterol(LDL-C), fasting plasma glucose(FPG), hemoglobin A1C (HbA1c) and uric acid(UA) between the two groups.

2.2 Electrocardiographic Manifestations stratified by LH/FSH Ratio

High group had significantly lower values of the duration of QRS complex, the Q-R interval, the R-S interval, the beginning point of P wave in Lead I(I(PB)), Lead aVL(aVL(PB)), Lead V2(V2(PB)), Lead V5(V5(PB)), Lead V6(V6(PB)), the end point of P wave in Lead aVR(aVR(PE)), the R wave amplitude in Lead aVL(aVL(R)), the beginning of T wave in Lead I(I(TB)), the end of T wave in Lead I(I(TE)), the amplitude of ST segment at 20 ms from J point in Lead V5(V5(ST20)) and V6(V6(ST20))compared to Low group. In short, most of ECG features of High group manifested lower than those of Low group.

2.3 Univariate and multivariate Linear Regression Analysis

Both univariate and multivariate linear regression analysis indicated that statistically significant and negative relationships were observed between some of ECG Manifestations and LH/FSH Ratio. In model 0, the standardized β-estimates for the duration of QRS complex (QRS duration) were -0.044 (p = 0.034). Similar findings were also observed for R-Q interval, R-S interval, the beginning of P wave in Lead I (I(PB)), V2 (V2(PB)), V5(V5(PB)) and V6 (V5(PB)), the ending of P wave in Lead aVR (aVR(TE)), the beginning and ending of T wave in Lead I (I(TB), I(TE)), the amplitude of ST segment at 20 ms from J point in Lead V5 (V5(ST20)), and V6 (V6(ST20)). In model 1, the standardized β-estimates for the duration of QRS complex were -0.05 (P = 0.038). Similar findings were also observed for the R-Q interval, the beginning of P wave in Lead aVL (aVL(PB)), V2 (V2(PB)) and V5 (V5(PB)). However, positive relationships were only observed for testosterone (β=0.442, P=0.041) in model 1.

Table 1 PCOS patient's characteristics between different LH/FSH ratio [n (%)]

Variables	Low Group (N=52)	High Group (N=24)	*p*
Age (years)	24.9±5.8	23.6±3.9	0.272
PCOS duration (month)	6(1,20)	7(1,18)	0.379
T (nmol/L)	1.64(1.3,1.99)	1.88(1.55,2.68)	0.049
FSH (mU/mL)	4.38±1.97	4.19±1.99	0.691
PRL (ng/mL)	379.5(214.22,605.58)	457.5(268.13,740.83)	0.405
P (nmol/L)	0.5(0.3,1.4)	0.6(0.38,2.32)	0.530
LH (mU/mL)	5.16(2.98,6.79)	12.82(7.35,16.63)	<0.001
E2 (pg/mL)	140(91.75,218.25)	181.5(144,373.75)	0.014
FT3 (pmol/L)	4.29(3.89,4.8)	4.08(3.76,4.57)	0.498
FT4 (pmol/L)	12.91(11.96,14.54)	12.8(12.34,14.42)	0.855
TSH (mU/mL)	1.32(0.92,2.35)	1.69(1.12,2.26)	0.654
AST (mmol/L)	19.5(16,30.75)	17(14,23)	0.138
ALT (mmol/L)	17.5(11,44)	13(9,26)	0.083
TBil (mmol/L)	7.7(4.82,9.88)	7.8(5.4,11.1)	0.584
DBil (mmol/L)	1.9(1.42,2.48)	2(1.6,2.8)	0.333
IBil (mmol/L)	5.95(3.55,7.4)	6.3(3.6,8)	0.675
BUN (mmol/L)	3.84(3.27,4.38)	3.64(3.21,4.47)	0.987
Cr (mmol/L)	54(46.5,60.5)	49.5(45.52,58.75)	0.322
FPG (mmol/L)	4.88(4.6,5.43)	4.6(4.27,5.36)	0.189
HbA1c (mmol/L)	5.7(5.3,7.27)	5.3(5.1,5.5)	0.140
CHOL (mmol/L)	4.76±0.98	4.61±0.87	0.538
TG (mmol/L)	1.21(0.87,2.05)	1.06(0.7,1.25)	0.057
HDL-C (mmol/L)	1.13(0.86,1.37)	1.32(1.15,1.53)	0.012
LDL-C (mmol/L)	2.97±0.87	2.81±0.9	0.470
UA (mmol/L)	361(298.5,481)	330.5(284,350.5)	0.058

Low Group: LH/FSH Ratio $<$ 2; High Group: LH/FSH Ratio $\geq$ 2 group; T: Testosterone; FSH: Follicle stimulating hormone; PRL: Prolactin; P: progesterone; LH: Luteinizing hormone; E2: Estradiol; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; AST: Aspartate Transaminase; ALT: Alanine aminotransferase; TBil: total bilirubin; DBil: direct bilirubin; IBil: indirect bilirubin; BUN: urea nitrogen; Cr: creatinine; FPG: Fasting plasma glucose; HbA1c: hemoglobin A1C; CHOL: total cholesterol; TG:triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; UA: uric acid.

Table 2 Difference of ECG features between different LH/FSH ratio in PCOS patient

Variables	Low Group (N=52)	High Group (N=24)	*p*
ECG normal	30(57.69)	17(70.83)	
ECG abnormal	22(42.31)	7(29.17)	
Average HR	83.0±13.6	83.2±15.2	0.944
QRS duration (ms)	100.25±7.76	95.42±7.01	0.011
R-Q interval (ms)	49.04±3.69	46.88±4.06	0.024
R-S interval (ms)	50(48,54)	48(45,50.25)	0.022
T wave duration (ms)	173.5(164.25,188)	174(163,194)	0.885
QT interval (ms)	366.13±29.84	357.96±28.18	0.262
QTc interval (ms)	426(412.75,438.5)	418.5(401,434.25)	0.142
QRS axis	62.5(43.75,77.25)	69(55.25,78.5)	0.569
R(V1)+S(V5)	0.51(0.32,0.72)	0.44(0.29,0.62)	0.421
R(V5)+S(V1)	1.87±0.63	1.91±0.52	0.764
I(PB) mV	0.06±0.02	0.04±0.02	0.000
aVL(PB) mV	0.03(0,0.04)	0(0,0)	0.020
V2(PB) mV	0.05(0.04,0.06)	0.04(0.03,0.05)	0.008
V5(PB) mV	0.05(0.04,0.06)	0.04(0.03,0.06)	0.021
V6(PB) mV	0.06(0.04,0.07)	0.05(0.04,0.05)	0.037
II(PE) mV	0(0,0)	0(0,0)	0.038
aVR(PE) mV	0.08(0.06,0.1)	0.06(0.06,0.08)	0.019
I(TB) mV	0.16(0.14,0.21)	0.14(0.11,0.18)	0.020
I(TE) mV	0.16(0.14,0.21)	0.14(0.11,0.18)	0.020
V5(ST20) mV	0.02(0.01,0.04)	0.01(0,0.02)	0.023
V6(ST20) mV	0.02(0.01,0.03)	0.01(0.01,0.02)	0.007

I(PB): the beginning point of P wave in Lead I; aVL(PB): the beginning point of P wave in Lead aVL; V2(PB): the beginning point of P wave in Lead V2; V5(PB): the beginning point of P wave in Lead V5; V6(PB): the beginning point of P wave in Lead V6; aVR(PE): the end point of P wave in Lead aVR; aVL(R): the R wave amplitude in Lead aVL; I(TB): the beginning of T wave in Lead I; I(TE): the end of T wave in Lead I; V5(ST20): the amplitude of ST segment at 20 ms from J point in Lead V5; V6(ST20): the amplitude of ST segment at 20 ms from J point in Lead V6.

3 Tables

4 Figure

5 Methods

5.1 Study Population

This is a retrospective cross-sectional study. From January 2015 to June 2021, 246 consecutive patients with PCOS who were admitted to the Third Affiliated Hospital of Sun Yat-sen University were collected in this study according

Table 3 Linear Regression Analysis: Relationship Between ECG Feature Change with Different LH/FSH Ratio in PCOS Patients

	Model 0[a]			Model 1[b]		
	β	(95%CI)	p	β	(95%CI)	p
T (nmol/L)	0.26	(-0.06,0.57)	0.111	0.44	(0.02;0.87)	0.041
E2 (pg/mL)	0	(0,0)	0.906	0	(0;0)	0.927
HDL-C (mmol/L)	0.92	(-0.17,2.00)	0.096	2.1	(-0.25;4.44)	0.079
QRS duration(ms)	-0.04	(-0.08,-0.00)	0.034	-0.05	(-0.10;-0.00)	0.038
RQ interval(ms)	-0.09	(-0.17,-0.01)	0.030	-0.11	(-0.21;-0.02)	0.022
RS interval(ms)	-0.05	(-0.12,0.01)	0.104	-0.06	(-0.13;0.02)	0.141
I(PB)mV	-14.75	(-27.60,-1.91)	0.025	-13.91	(-29.18;1.36)	0.073
aVL(PB)mV	-9.79	(-24.44,4.87)	0.188	-19.39	(-37.96;-0.81)	0.041
V2(PB)mV	-17.90	(-31.74,-4.07)	0.012	-26.90	(-41.58;-12.22)	0.001
V5(PB)mV	-16.68	(-30.67,-2.69)	0.020	-18.79	(-34.48;-3.10)	0.020
V6(PB)mV	-14.10	(-27.87,-0.32)	0.045	-15.06	(-31.37;1.25)	0.070
aVR(PE)mV	-12.25	(-22.57,-1.93)	0.021	-9.17	(-21.31;2.98)	0.136
aVL(R)mV	-1.41	(-3.33,0.52)	0.149	-0.69	(-3.32;1.95)	0.602
I(TB)mV	-5.25	(-10.37,-0.13)	0.044	-5.00	(-11.45;1.48)	0.128
I(TE)mV	-5.25	(-10.37,-0.13)	0.044	-5.00	(-11.45;1.48)	0.128
V5(ST20)mV	-15.89	(-30.63,-1.14)	0.035	-12.85	(-29.32;3.62)	0.124
V6(ST20)mV	-19.50	(-38.30,-0.87)	0.041	-14.81	(-36.13;6.51)	0.169

[a] unadjusted model.

[b] adjusted model: age, TBil, DBil, IBil, BUN, Cr, FPG, CHOL, TG, HDL-C, LDL-C, UA.

to the flow chart. The inclusion criteria were as follows: older than 18 years, final diagnosis of PCOS. PCOS patients were diagnosed based on Rotterdam ESHRE/ASRM sponsored PCOS consensus criteria. The proceedings of the conference noted that PCOS could be diagnosed, after the exclusion of related disorders, by two of the following three features: 1) oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, or 3) polycystic ovaries [16]. The exclusion criteria were as follows: patients with hypertension, diabetes mellitus, and cardiovascular disease, excessive ECG noise, and incomplete baseline data. Finally, 76 patients with PCOS were enrolled in this study. The patients were divided into two groups according to LH/FSH Ratio: High Group (LH/FSH Ratio $\geq$ 2, n=24), and Low Group (LH/FSH Ratio $<$ 2, n=52). This study was approved by the Human Ethics Boards of the Third Affiliated Hospital of Sun Yat-sen University. Given this was a retrospective study, informed consent was not required.

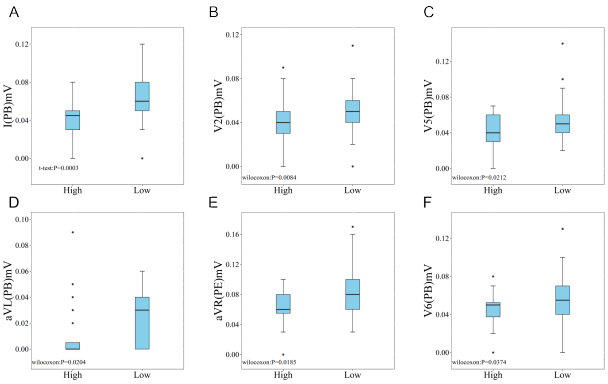

Fig. 1 **(A)** Difference of P wave beginning (PB) of Lead I between High group and Low group. **(B)** Difference of PB of Lead V2 between High group and Low group. **(C)** Difference of PB of Lead V5 between High group and Low group. **(D)** Difference of PB of Lead aVL between High group and Low group. **(E)** Difference of P ending of Lead aVR between High group and Low group. **(F)** Difference of PB of Lead V6 between High group and Low group. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

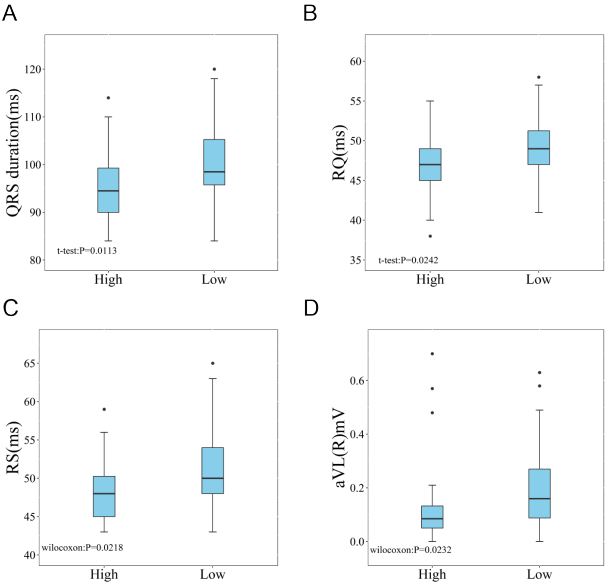

Fig. 2 **(A)** Difference of QRS duration between High group and Low group. **(B)** Difference of Q-R interval between High group and Low group. **(C)** Difference of of R-S interval between High group and Low group. **(D)** Difference of R wave amplitude in Lead aVL between High group and Low group. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

5.2 Data Collection and definitions

A standard protocol containing demographics, complications, laboratory tests, 12-lead resting ECG reports, and 180 ECG features was used to collect data.

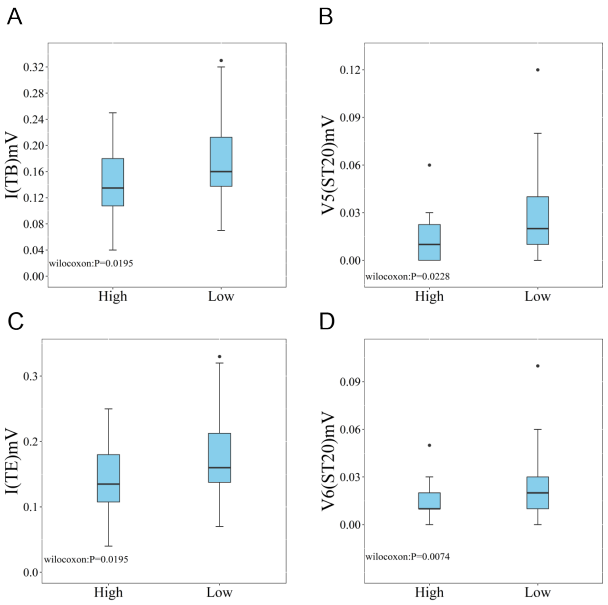

Fig. 3 **(A)** Difference of T wave beginning in Lead I between High group and Low group. **(B)** Difference of ST segment at 20ms from J point in Lead V5 between High group and Low group. **(C)** Difference of of T wave ending in Lead I between High group and Low group. **(D)** Difference of ST segment at 20ms from J point in Lead V6 between High group and Low group. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

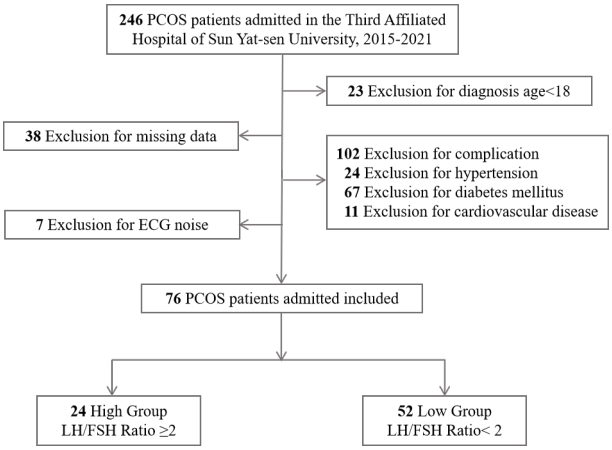

Fig. 4 A flow chart of study participant.

Demographic and clinical information, including age and PCOS duration was collected. The fasting venous blood samples were collected in the morning and analyzed shortly after sampling. Testosterone, LH, FSH, pituitary prolactin, progesterone, and estradiol, AST, ALT, TBil, DBil, IBil, FPG, BUN, Cr, UA,

TG, CHOL, LDL-C and HDL-C were measured by HITACHI 7180 automatic analyzer. HbA1C was measured by the D-10 haemolglobin testing program (Bio-Rad). HbA1c between the two groups were analyzed. FT4, FT3 and TSH were measured by chemilu-minescent inmmunoassays on Abbott i4000 automatic analyzer.

5.3 ECG Preprocessing

All subjects underwent resting surface ECG by an experienced cardiologist, with the subjects lying in the supine position (paper speed: 25 mm/s, calibration: 1mv=10 mm, ECGNET Vision 3.0, SanRui Electronic Technology, Guangdong, China). All digital 12-lead ECG data were marked with the study ID. Poor ECG data were excluded by two independent doctors. The sampling rate of ECG was 1000 Hz. Raw ECG data were stored in The Third Affiliated Hospital of Sun Yat-sen University Clinic cloud database by XML. 180 ECG features were automatically extracted by an ECG management system (ECGNET Vision 3.0, SanRui Electronic Technology, Guangdong, China) [17]. The interpretation of ECG features is shown in Supplementary Table 1. The two major components of the features are the distance between each wave and the amplitude of each wave.

5.4 Statistical Analyses

Statistical analysis was performed in R (version 3.6.2). Numerical variables which subject to the normal distribution are presented as the means ± standard deviation, and the differences between groups are compared by t-test. Continuous variables which do not subject to the normal distribution are presented as the median (upper quartile, lower quartile), and the differences between groups are compared by Wilcoxon's rank sum test. Categorical variables are expressed as numbers (percentages). Chi-square test or Fisher's exact test was applied for the comparison of Categorical variables among groups. Univariate and multivariate linear regression analysis was performed to determine potential confounding effects of LH/FSH ratio. Univariate linear regression was used to explore whether there was a significant linear relationship between each index and LH/FSH ratio; Furthermore, in order to control the influence of other covariates such as age, serum total bilirubin (TB), serum direct bilirubin (DB) and other covariates on the above relationship, we employed the multivariable linear regression model to clarify the relationship between each variable and LH/FSH, and use the stepwise regression method to exclude the collinearity between variables. Repeat the above process to study the relationship between indicators and LH/FSH. $P< 0.05$ was considered statistically significant.

Ethical approval declarations

1. Approval: This study was approved by the Human Ethics Boards of the Third Affiliated Hospital of Sun Yat-sen University

2. Accordance: The methods were carried out in accordance with the relevant guidelines and regulations.
3. Informed consent: Given this was a retrospective study, informed consent was not required.

6 Discussion

PCOS is a common hormonal disorder which is associated with an increased morbidity of cardiovascular disease. LH/FSH ratio in PCOS represents the degree of androgen disorder and may become a sensitivity biomarker of the severity of PCOS. At present, the effect of LH/FSH ratio on ECG manifestations in patients with PCOS was still rarely reported. To the best of our knowledge, the present investigation is the first study to explore the association between LH/FSH ratio and ECG manifestations. When taking 2 as the cutoff point of LH/FSH ratio. Low group is negatively associated with ST segment change, which was demonstrated as the decline of the beginning point of P wave in Lead I, Lead aVL, Lead V5, Lead 6, and the decline of ST segment in Lead 5 and Lead 6. The ST segment change is a sensitivity and reversible index for the myocardial ischemia. Another finding of this research is that High group is correlated with shorten of QRS duration. The QRS duration refers to ventricular depolarization. A prolonged QRS duration increased the risk of cardiac mortality[18].

PCOS is the most common endocrinological problem among women, which affect 8-13% of women of reproductive age globally. In China, the incidence of PCOS is 5.6% [19]. Patients with PCOS had increased risks of insulin resistance, visceral obesity, dyslipidemia, non-alcoholic fatty disease (NAFLD), and hypertension compared to subjects without PCOS [20, 21]. According to a retrospective cohort study, PCOS women had more hospitalizations for ischemic heart disease and cerebrovascular disease compared with the non-PCOS control subjects [22]. Due to the increased risk of cardiometabolic disease, it is crucial for clinicians to take into account in the cardiovascular risk assessment of patients with PCOS [5].

LH/FSH ratio play an important role in PCOS women. LH and FSH secreted from the anterior pituitary gland, and they are gonadotropin synthesized that stimulate ovulation. LH and FSH act on the theca cells and granulosa cells of ovarian follicles, respectively. LH acts on theca cells and promotes the biosynthesis of androstenedione. FSH acts on granulosa cells to affect the transformation of androstenedione to estradiol through aromatase activity[23]. Generally, in healthy women, the LH/FSH ratio is usually between 1 and 2. In women with polycystic ovary disease, this ratio might reach as high as 2 or 3 [9], namely an elevated LH-to-FSH ratio. Taylor et al. have reported that up to 75% of patients with PCOS have LH concentrations higher than 95% of normal values [24]. And it is reported that up to 94% of patients with PCOS have an elevated LH/FSH ratio [24]. The increase of LH pulse frequency and LH/FSH ratio impairs the development of downstream follicles and alters

the production of steroid hormones. It is thought that elevated LH in PCOS drove hyperandrogenaemia by shifting biosynthesis to androgen production as well as by stimulating theca cell hyperplasia [9, 25, 26].

Hyperandrogenemia could probably result in dyslipidemia. Dyslipidemia is one of the most common cardiometabolic complications of PCOS . Macut et al. showed that androgen excess might alter LDL-C early in life and lead to a more atherogenic lipid metabolism [27]. In addition, it reported that hyperandrogenemia in young women with PCOS was associated with hypertension [11]. Therefore, the LH/FSH ratio in PCOS is considered to be related to accelerated cardiovascular disease.

As a common characteristic of PCOS patients, LH/FSH ratio is related to lipid metabolism and glucose metabolism. And lipid metabolism and glucose metabolism are closely related to cardiovascular disease. Li Zhao et al. found that a higher LH/FSH ratio was not only significantly correlated with visceral adipose over-accumulation and dysfunction defined by lipid accumulation product (LAP), visceral adiposity index (VAI) and Chinese visceral adiposity index (CVAI), but also significantly correlated with a higher risk of visceral obesity in Chinese women over 55 years old who were postmenopausal [28].

Elevated blood glucose is a key factor in the diagnosis of metabolic diseases. Sustained high concentrations of glucose can damage blood vessels, resulting in an increased risk of heart disease. Beydoun et al. found that high glucose level and LH/FSH > 2 was negative related [29]. Consistent with their study, a significant difference in total plasma glucose between LH-dominant, normal-weight PCOS and normal-LH PCOS women was reported by Kurioka et al [30]. In addition, another study reported that the mean ratio of LH/FSH in PCOS patients with insulin resistance was significantly lower than that in PCOS patients without insulin resistance.

In our study, although no significant differences were observed in terms of FPG are HbA1c between High group and Low group, the High group showed more serious glucose metabolism disorder. Maybe it is because blood glucose is affected by many factors, such as diet, exercise and obesity.

ECG is a noninvasive, reproducible test used to detect cardiovascular disease.Previous studies have also found ECG abnormalities in PCOS patients. First, PCOS patients were prone to increased atrial conduction delay, which demonstrated prolonging P wave duration and increasing P wave dispersion[31]. Accompanied by a decline in the E/A ratio of echocardiographic examinations, abnormal atrial conduction implied impaired the left atrial in PCOS patients. It was a consistent findings that interatrial, left-sided intral-atrail, and right sided intra-atrial electromechanical interval, which was related to increased atrial fibrillation(AF) [32]. In our study, we explored the change of P wave in PCOS pateints. The beginning of P wave was lower in Lead I, aVL, V2, V5, V6 in High group. In Liner Regression Model 1, the ECG features mainly focused in the beginning of P wave in Lead aVL, V2, and V5. Lead I, aVL, V5, and V6 mainly represent the left atrial vector. Therefore, the beginning of P wave in left atrail vector may be a sensitivity marker for

impaired left atrial. In order to objective and accurate extract ECG feature, we explored an automatic system to record every digital ECG waves. PB and PE maybe a new marker for the atrial conduction dysfunction and increased risk of AF.

In addition, in the standard surface ECG, prolonged QRS duration are common findings in patients with PCOS. In this study, we found that the QRS duration was narrow in the High group. The QRS duration represents ventricular depolarization,which means electrical impulse propagation through the conduction system and the ventricular myocardium[18]. A prolonged QRS duration can generate ventricular dyssynchrony and is associated with worse clinical status and outcomes in heart failure patients [33]. Prolongation of QRS duration occured in 14%-47% of heart failure [34]. Previous studies showed that the QRS duration was wider in patients with PCOS than those without PCOS, which may contribute to increased cardiovascular risks [12]. Besides a recent study found that a small percentage of PCOS patients had abnormal QRS-T angles, and a large mean ovarian volume (MOV) was a powerful predictor of this abnormality [35]. In our study, QRS duration, R-Q interval and R-S interval was narrow in High group compared with Low group. But the QRS duration of two groups was within the reference value range. More clinical studies are needed to prove the clinical significance and prognosis of adverse events of this difference.

ST change is a sensitivity marker of myocardial ischemia and an independent cardiovascular risk factor [36]. Until now, there has been few study on the relationship between ST change and PCOS. There were two main reasons [12–14, 37]. First, the previous studies compared PCOS patients with healthy control, rather than different types of PCOS patients. Secondly, ST segment only measures 0.08 seconds after point J. In order to accurately measure ST segment manifestation, we innovatively split the ST segment into 5 features: TB, ST(20), ST(40), ST(60), and ST(80). In our study, we found that there were ST depression in High LH/FSH ratio group, especially in left precordial leads such as Lead I, V5 and V6. Patients with PCOS had a trend to have left ventricular hypertrophy or myocardial ischemia due to hypertension, obesity and insulin resistance [38]. ST segment change maybe an early marker to detect patients at high risk of cardiovascular events, especially in High LH/FSH ratio group of PCOS patient.

Although previous studies found out that prolonged QTc interval was closely related to PCOS [39]. In our study, there was no significant difference in the QTc interval between the two groups. Although the exact mechanisms of ECG pattern in patients with PCOS need further defining, the results of this study demonstrated the relationship between different LH/FSH ratio and ECG manifestation, especially QTc interval and ST change.

There are several limitations of our study that can impact its interpretation of clinical significance and its generalization to other populations. First, the sample size was insufficient. Second, the outcome of cardiovascular disease was lack and need further prospective cohort study. Third, the surface 12-lead

ECG is a stable, convenient and noninvasive tool with a weakness of limit information, compared with other cardiac imaging examination. Echocardiogram, cardiac magnetic resonance imaging, and radionuclide perfusion could provide more details about the cardiac lesion.

7 Conclusion

In PCOS patients, P wave, QRS duration and ST segment changes were the most abnormalities in ECG of High LH/FSH ratio Group. More subtly change of ECG might be gained to early evaluate cardiovascular risk in PCOS patients.

Acknowledgments. We thank Xu Li, Liang Yuen ,Huang Libo, Li Lidi, and Chen Hongli at The Third Affiliated Hospital, Sun Yat-sen University. We thank GUANGZHOU 3RAY Electronics Co., Ltd., and Tianpeng Technology Co., Ltd., for their contributions and assistance in terms of data extraction.

Declarations

- Funding: This study was supported by the National Natural Science Foundation of China (No. 81901447), the Science and Technology Plan Project of Guangzhou City (202007040003), the Key Area R&D Program of Guangdong Province (2019B020227003), the National Key R&D Program of China (2017YFA0105803), and the Guangdong Medical Research Foundation (A2019079).
- Conflict of interest: The authors declare no competing interests or personal relationships that could have appeared to influence the work reported in this paper.
- Ethics approval: The studies involving human participants were reviewed and approved by the Human Ethics Boards of the Third Affiliated Hospital of Sun Yat-sen University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.
- Consent to participate: Given this was a retrospective study, informed consent was not required.
- Consent for publication: Not applicable.
- Availability of data and materials: All datasets generated for this study are included in the article.
- Authors' contributions: Lin Wu, Shuhui Zheng: Conceptualization, Methodology, Original draft preparation, Writing - Review Editing, Methodology, Funding acquisition. Yanming Chen, Qian xiaoxian: Funding acquisition, Supervision. Guangyin Zhao, Yucong Sun, Borui Tian, Ying Tan, Xixiang Tang: Original draft preparation, Methodology.

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