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A non-invasive harmonic analysis to assess risk of retinopathy in type 2 diabetes mellitus

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ABSTRACT

Aims: Assessing the hemodynamic changes of diabetic retinopathy (DR) using harmonic analysis of both non-invasively measured radial pulse and photoplethysmography (PPG) signals to propose a DR risk indicator.
Methods: A total of 1879 patients with diabetes were followed on average of 3.5 years. The radial pulse and PPG signals were measured at the beginning of the trial. Kaplan-Meier curves of the DR risk indicator was analyzed. In addition, the correlation between the measurements of the radial pulse and PPG was evaluated.
Results: In comparison of the patients' clinical characteristics, years of diabetes, systolic blood pressure, HbA1C, ACR, urinary albumin and fourth harmonic (C4) were higher in the DR group, and eGFR and third harmonic (C3) were lower. Patients in the high-DR risk group had a 1.8-fold higher risk of developing retinopathy than those in the low-risk group (log-rank test, $p < 0.001$). The correlation coefficient between radial pulse and PPG measurements for C3 and C4 were 0.727 and 0.628, respectively.
Conclusions: The harmonic analysis of radial pulse and PPG signals may be used to reflect the effect of DR in hemodynamics and the derived harmonic components may predict the risk of DR of patients with type 2 diabetes.

1. Introduction

Diabetic retinopathy (DR) is a common and serious microvascular complication among patients with diabetes. DR is one of the leading causes of blindness in the 20- to 70-year-old age group.[1] It is generally believed that the main cause of retinopathy is the destruction of retinal vascular endothelial cells due to the glycation of proteins in the retinal vasculature caused by the long-term exposure of retinal vascular cells to a hyperglycemic environment, and therefore changes in the retinal vasculature are an important basis for the clinical diagnosis of retinopathy.[2] DR is a continuous disease process with ischemia as the core problem.[3] As shown in Fig. 1, it is clinically divided into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) according to the process. Patients with NPDR often present with hemorrhages of various sizes, microaneurysms, hard exudates, soft exudates (cotton wool spots), intraretinal microvascular abnormalities, and venous looping or beading. Patients with PDR exhibit either neovascularization of the disc/elsewhere or vitreous/preretinal hemorrhage. In addition, diabetic maculopathy may be present at any stage of the disease, and these lesions can impair vision.[4] However, DR is related to the duration of diabetes. As the prevalence of diabetes is increasing, the incidence of complications such as DR is also increasing. More than 1/3 of people with diabetes will develop different forms of DR during their lifetime.[5] Diabetic retinopathy can cause permanent retinal damage or even blindness. But if detected and intervened in early stages of non-proliferative diabetic retinopathy, the loss of vision can be avoided. Therefore, regular eye examinations are essential.[6] Past research results indicate that microalbuminuria and renal function loss can be used as predictors of retinopathy in patients with type 2 diabetes, but the conclusions are still inconsistent.[7]

Arterial pressure wave measurement combined with harmonic analysis is an emerging, non-invasive technique for observing changes in the hemodynamic characteristics of organs[8,9] and for assessing the risk of macrovascular and microvascular diseases.[10,11] It has been found that

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the harmonic of arteries changes in response to changes in organ arterial blood flow in animal models.[12,13] Based on these observations, Prof. W. K. Wang and Prof. Y.Y. Lin Wang proposed the arterial system resonance theory, which has been proven clinically in patients with hypertensive therapies, diabetes, liver damage, and at the end of life.[14] In addition, several studies have found that harmonic components, either derived from radial artery or photoplethysmography (PPG) harmonic analysis, are highly correlated with disease or treatment.[15] The PPG signal is generated by the change in blood volume as the blood enters and exits the tissues, while the pulse signal is generated by the change in pressure on the walls of the radial artery as the blood passes through it. Both signals are products of the blood circulation, and both the waveforms and the period of waveforms closely resemble to each other. In this study, both arterial signals were obtained for harmonic analyses.

Since regular eye examinations are necessary to prevent DR, harmonic frequency analysis has also been shown to be useful in predicting diabetic complications.[16] In this study, we tried to find a convenient way to assess the risk for DR. The effect of DR on hemodynamics was quantified by the harmonic analysis, and the risk of retinopathy was predicted using harmonic components. In addition, the correlation between the radial pulse and PPG signals was also evaluated.

2. Materials and methods

2.1. Subjects

Patients in the Diabetes Management Program were recruited from the Taipei City Hospital Zhongxiao Branch from 2016 August to 2018 July. The cohort included 1016 men and 863 women. Patient demographics and baseline medical conditions are assessed by medical records (Table 1). The study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice Guidelines. All participants signed a written informed consent form approved by the Taipei City Hospital Institutional Review Board (IRB number: ISRCTN14306167).

2.2. Study design

The study consists of 1879 patients with type 2 diabetes who had no history of retinopathy. The medical history and physical examination reports were compiled to determine the patients' demographic data, T2DM related testing results, and other clinical variables. Harmonic analysis of radial pulse and finger PPG were performed at the beginning of the study as the baseline. These clinical characteristics were also recorded at the end of the follow-up. During the study, the patients returned annually for eye examinations until they are diagnosed with diabetic retinopathy. Diabetic retinopathy is diagnosed by inspection with a digital retinal camera (CR-2 AF, Canon, Japan) and determined by a professional ophthalmologist. Subjects were enrolled from 2016/8/9 to 2018/7/31 and followed from the date of enrollment until DR was diagnosed or 2020/12/31. The average follow-up period for patients was 3.5 years.

Each subject was required to lie down in a supine position and rest for 5 min before the measurements. The pulse pressure was then obtained on the left-hand radial artery with a pulse wave analyzer TD01C (MII-ANN Technology, Taiwan). The PPG signal was obtained by the PPG sensor (AFE4400SPO2EVM, TI, USA) on the index finger of the left hand. Then, harmonic analysis was performed on the acquired signals.

Table 1
Baseline clinical characteristics of the asymptomatic patients with type 2 diabetes.

Clinical characteristics	All patients	After follow-up period	
		Without DR	With DR
N	1879	1659	220
Male (%)	54.1	54	55
Age (year)	64.4 ± 10.2	64.3 ± 9.9	64.6 ± 12.1
Body mass index (kg/m^2)	26.6 ± 4.4	26.6 ± 4.3	26.5 ± 4.8
Waist circumference (cm)	89.9 ± 10.0	89.8 ± 9.8	90.5 ± 11.8
Smoke (%)	17.2	17.5	15.3
SBP (mmHg)	128.1 ± 11.8	127.9 ± 11.4	130.1 ± 14.0*
DBP (mmHg)	74.1 ± 7.8	74.1 ± 7.7	74.0 ± 8.1
Heat rate (beat/min)	73.2 ± 11.6	72.9 ± 11.5	75.3 ± 12.1
HbA1C (%)	7.1 ± 1.3	7.1 ± 1.3	7.3 ± 1.3*
eGFR (mL/min/1.73 m^3)	89.9 ± 31.5	90.5 ± 30.8	85.4 ± 35.9*
ACR (mg/g)	114.7 ± 441.7	96.4 ± 394.2	252.4 ± 689.4*
LDL (md/dL)	95.3 ± 31.4	94.9 ± 30.1	98.3 ± 38.9
HDL (mg/dL)	50.8 ± 15.1	50.9 ± 15.3	50.1 ± 13.8
Total cholesterol (md/dL)	161.6 ± 34.7	161.2 ± 33.9	165.0 ± 40.2
Triglyceride (mg/dL)	134.9 ± 114.4	134.7 ± 117.1	136.7 ± 92.5
Micro albumin (mg/dL)	115.7 ± 457.8	98.3 ± 380.2	247.7 ± 826.9*
Duration of diabetes (years)	9.7 ± 7.9	9.3 ± 7.8	12.8 ± 9.3*
C3_r	0.492 ± 0.122	0.496 ± 0.121	0.461 ± 0.129*
C4_r	0.588 ± 0.266	0.576 ± 0.249	0.677 ± 0.356*
C3_f	0.450 ± 0.099	0.454 ± 0.098	0.424 ± 0.108*
C4_f	0.540 ± 0.193	0.532 ± 0.183	0.600 ± 0.246*

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, eGFR = estimated glomerular filtration rate, ACR = Albumin to Creatinine Ratio, LDL = low-density lipoprotein cholesterol, HDL = high-density lipoprotein cholesterol, C3_r = the third harmonic component of radial pulse wave, C4_r = the fourth harmonic component of radial pulse wave, C3_f = the third harmonic component of finger photoplethysmography and C4_f = the fourth harmonic component of finger photoplethysmography.

* Asterisks indicate that the mean of the variable in the DR group is significantly different from the non-DR group. ($p < 0.05$).

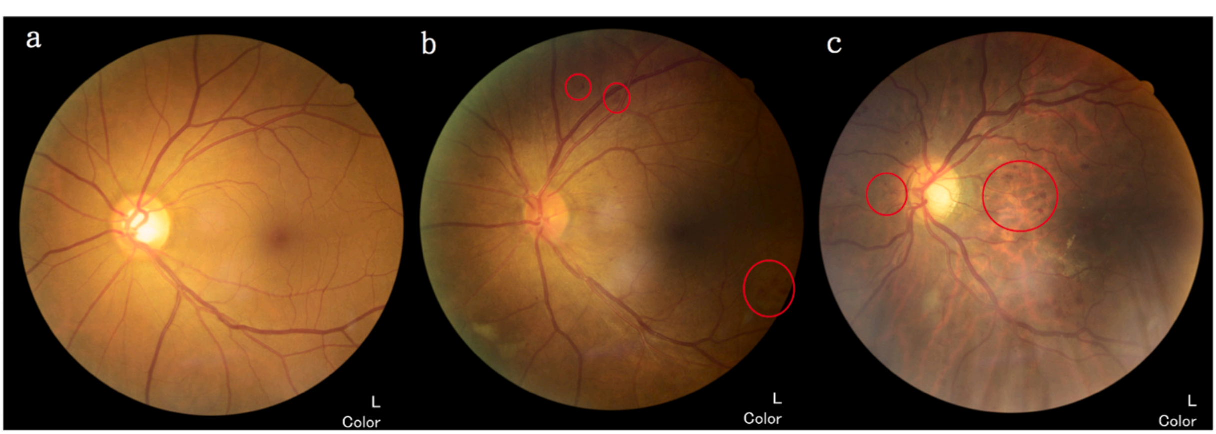

Fig. 1. Retinal images of different stages of diabetic retinopathy: (a) normal; (b) non-proliferative diabetic retinopathy with dot hemorrhage and microaneurysm shown in red circles; (c) proliferative diabetic retinopathy with small curves shown in red circles as neovascularization. (The examples are from the cases received in this study.)

The successive pulses were acquired during the 12-second period. The pulse data were recorded with a sampling rate of 400 data points per second. These data were then transformed into harmonic components and phase angle using Fourier transform. The third harmonic component (C3) and the fourth harmonic component (C4) were defined by the following equation:

$$C3 = A3/A0 \tag{1}$$

$$C4 = A4/A0 \tag{2}$$

where A0 is the mean value of pulse wave. A3 and A4 are the 3rd and 4th amplitude coefficient of Fourier series of the pulse wave. After the assessment of pulse spectrum, the blood pressure were assessed by an automatic blood pressure monitor (HBP-9020, Omron, Japan) according to the instruction manual. The assessment was performed by a well-trained operator, without the doctors and nurse present to avoid the white coat effect.

2.3. Statistical methods

Baseline values are expressed as mean ± standard deviation or prevalence rate. A *t*-test was used to understand the characteristics of the patient with and without DR after 4.4 years. To demonstrate whether the C3 and C4 were predictive of the retinopathy, the hazard ratio of retinopathy was calculated using univariate Cox regression analysis with adjusting for age, sex, smoking, body mass index, systolic blood pressure, diastolic blood pressure, duration of diabetes, estimated glomerular filtration rate (eGFR), albumin to creatinine Ratio (ACR) and glycated hemoglobin (HbA1c). The adjusted hazard ratio and its 95 % confidence intervals of retinopathy were reported.

We defined the diabetic retinopathy risk indicators (DRrisk) as high, when a patient's C3 is less than the mean of the baseline C3 and C4 is greater than the mean of the baseline C4. The DRrisk is defined as low, when a patient's C3 is greater than the mean of the baseline C3 and C4 is less than the mean of the baseline C4. The DRrisk as medium for all others. The Kaplan-Meier curves of the estimated time to the first occurrence of retinopathy according to the levels of DRrisk were plotted. The log-rank test was performed to demonstrate whether the significant influence of DRrisk on the risk of retinopathy existed. We used correlation coefficients to observe the relationship between radial arterial waves and PPG. All statistical analyses were performed using R version 1.3.1093.

3. Results

The baseline clinical characteristics of 1879 patients with diabetes without retinopathy were shown in Table 1. The mean age of participants was 64.4 ± 10.2 years, in which 54.1 % of the participants were male. The mean systolic, diastolic blood pressure, and the Hba1c level were 128.1 ± 11.8 mmHg, 74.1 ± 7.8 mmHg, and 7.1 ± 1.3 %, respectively. We additionally conducted a cross-sectional study of patients with and without DR after 4.4 years as shown in Table 1. In comparison of the patients' clinical characteristics, the patient cohort with DR had 37 % longer history of diabetes, 1.7 % higher systolic blood pressure, 2.8 % higher HbA1C, 162 % higher ACR, 152 % higher urinary albumin, 17 % higher C4 in radial artery, and 13 % higher C4 in finger PPG. In the other hand, the patients without DR cohort had 6 % higher eGFR 7.6 % higher C3 in radial artery, and 7.1 % higher C3 in finger PPG. Table 2 lists the clinical characteristics of patients with and without DR at the end of follow-up. Compared to the baseline in Table 1, patients with DR had lower C3 and higher C4.

By Cox regression analysis, the radial artery third harmonic component (C3_r, HR = 0.150, 95 % CI = 0.041–0.548, *P* = 0.004), fourth harmonic component (C4_r, HR = 2.252, 95 % CI = 1.412–3.592, *P* = 0.001), and finger PPG third harmonic component (C3_f, HR = 0.065, 95 % CI = 0.013–0.32, P = 0.001), and fourth harmonic component (C4_f, HR = 2.661, 95 % CI = 1.374–5.154, P = 0.004) were associated with retinopathy after correction for age, sex, smoking, body mass index, systolic blood pressure, diastolic blood pressure, duration of diabetes, ACR, eGFR, and Hba1c. Kaplan–Meier curve (Fig. 2) showed the prevalence of retinopathy by DRrisk level at 4.4 years of follow-up. There was a graded relationship between DRrisk and risk of retinopathy by both radial artery and finger PPG harmonic analyses. The cumulative incidence of DRrisk grade retinopathy increased from 9.0 % to 11.7 % to 15.8 % according to radial arterial harmonic analysis (*n* = 73, 58, 89), while the cumulative incidence of DRrisk grade retinopathy increased from 8.7 % to 11.0 % to 16.5 % according to finger PPG harmonic analysis (*n* = 58, 76, 86). Patients in the high-DR risk group had a 1.8-fold higher risk of developing retinopathy than those in the low-risk group.

The analysis of the harmonic of the radial artery and finger PPG showed the same trend, and we further analyzed the correlation between them. As shown in Fig. 3, the correlation coefficient of the third harmonic component was 0.727 (*P* < 0.001), while the correlation coefficient of the fourth harmonic component was 0.628 (P < 0.001). The correlation coefficient of heart rate between the measurement of TD01C and PPG was 0.882 (P < 0.001).

Table 2
Clinical characteristics of the patients with and without diabetic retinopathy at the end of follow-up.

Clinical characteristics	Without diabetic retinopathy	With diabetic retinopathy
N	1659	220
Male (%)	54	55
Age (year)	66.7 ± 12.1#	65.9 ± 12.1
Body mass index (kg/m^2)	26.3 ± 4.6#	26.3 ± 4.7
Waist circumference (cm)	92.1 ± 11.2#	92.7 ± 11.8
Smoke (%)	19.4	16.8
SBP (mmHg)	126.2 ± 9.9	128.1 ± 12.5*
DBP (mmHg)	74.4 ± 7.1	74.4 ± 7.3
Heat rate (beat/min)	72.6 ± 11.5	76.6 ± 12.0
HbA1C (%)	7.0 ± 1.1#	7.2 ± 1.2*
eGFR (mL/min/1.73 m^3)	79.5 ± 26.9#	78.0 ± 33.1*,#
ACR (mg/g)	96.2 ± 394.2	282.0 ± 858.3*
LDL (md/dL)	92.2 ± 29.2#	96.1 ± 37.6
HDL (mg/dL)	51.0 ± 14.9	50.4 ± 14.3
Total cholesterol (md/dL)	151.8 ± 30.3#	155.1 ± 37.0#
Triglyceride (mg/dL)	126.3 ± 84.2#	135.0 ± 96.5
Micro albumin (mg/dL)	85.8 ± 308.7	196.1 ± 511.0*
Duration of diabetes (years)	11.6 ± 7.3	13.7 ± 8.6*
C3_r	0.498 ± 0.123	0.433 ± 0.115*,#
C4_r	0.589 ± 0.287	0.733 ± 0.360*,#
C3_f	0.451 ± 0.118	0.372 ± 0.088*,#
C4_f	0.557 ± 0.390#	0.641 ± 0.266*,#

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, eGFR = estimated glomerular filtration rate, ACR = Albumin to Creatinine Ratio, LDL = low-density lipoprotein cholesterol, HDL = high-density lipoprotein cholesterol, C3_r = the third harmonic component of radial pulse wave, C4_r = the fourth harmonic component of radial pulse wave, C3_f = the third harmonic component of finger photoplethysmography and C4_f = the fourth harmonic component of finger photoplethysmography.

* Asterisks indicate that the mean of the variable in the DR group is significantly different from the non-DR group. ($p < 0.05$).

Sharp means that the mean of the variable at the end of follow-up was significantly different from baseline. ($p < 0.05$).

4. Discussion

The most frightening effects of diabetes are the accompanying complications, including microvascular and macrovascular disease. Among the microvascular complications, the most important are retinopathy and nephropathy, which are the leading causes of blindness and dialysis in adults. Therefore, measurement of microalbuminuria and

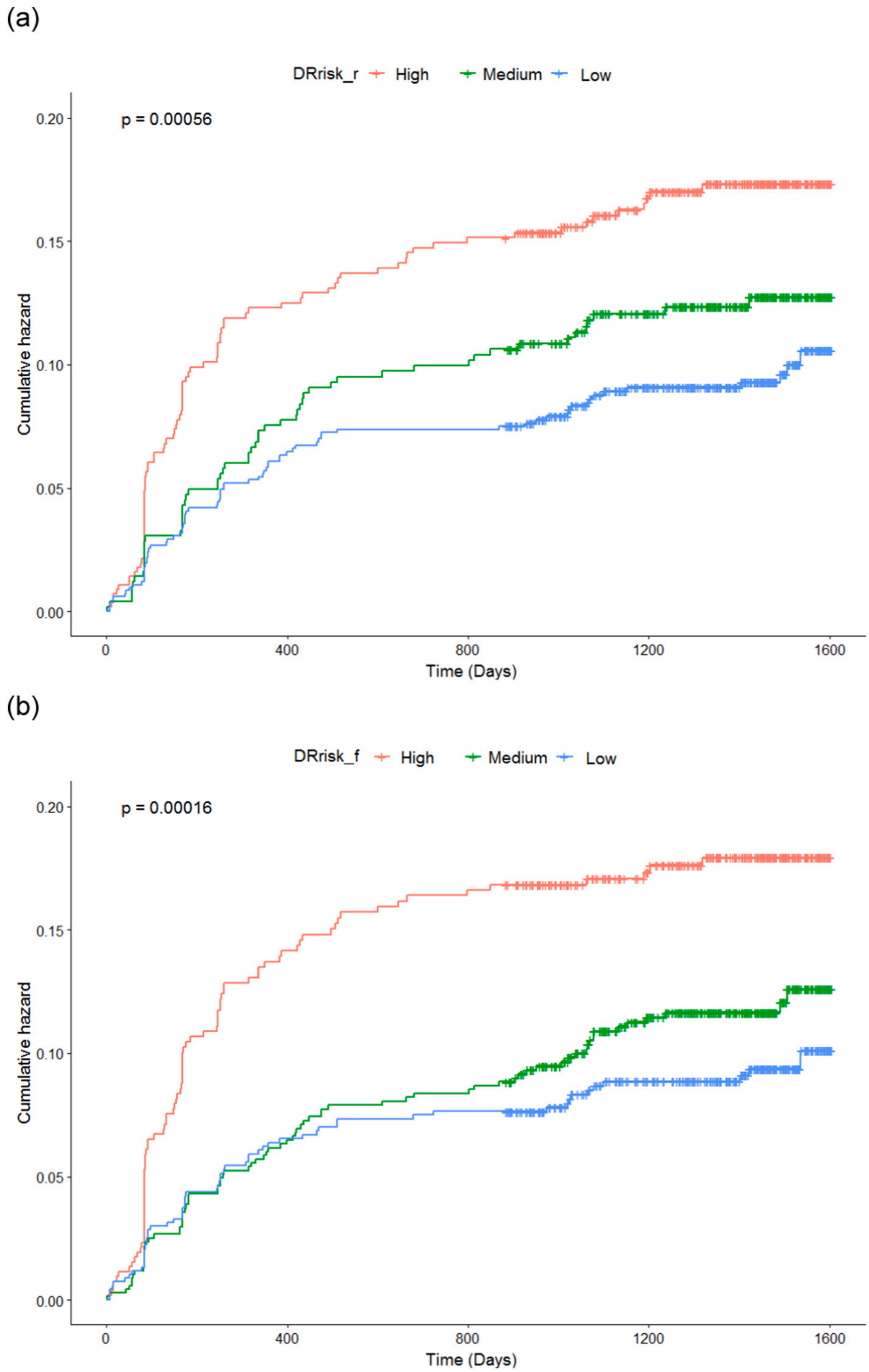

Fig. 2. Cumulative incidence of diabetic retinopathy by risk index of pulse data from (a) radial pulse and (b) finger photoplethysmography ($N = 1887$). *p* values were the result of the log-rank test.

funduscopy are very important aspects of screening for diabetic complications. However, the existence of an association between these two complications is also a topic of great interest. In some studies, microalbumin and DR have been found to be highly correlated.[17,18] The same trend was seen in this study, where patients who would have developed DR within 4.4 years had worse indicators of nephropathy (high ACR, high urinary albumin, and low eGFR) compared to patients who did not develop DR. This suggests that the progression of diabetes can lead to microvascular complications that damage the retina along with the kidneys.

In previous studies, C3 was found to be associated with diabetes, and women with lower C3 were more likely to have diabetes.[19] In this study, it was found that those with low C3 among patients with diabetes had a higher probability of developing DR within 4.4 years. This finding implies that C3 may be an important marker of diabetes. When a healthy person's C3 begins to decline, the risk of diabetes begins to increase. When a person diagnosed with diabetes C3 decrease, the risk of severe diabetes and retinopathy increases.

In some studies, C4 and the coefficient of variation of C4 have been linked to macrovascular and cardiac diseases. The patients with diabetes

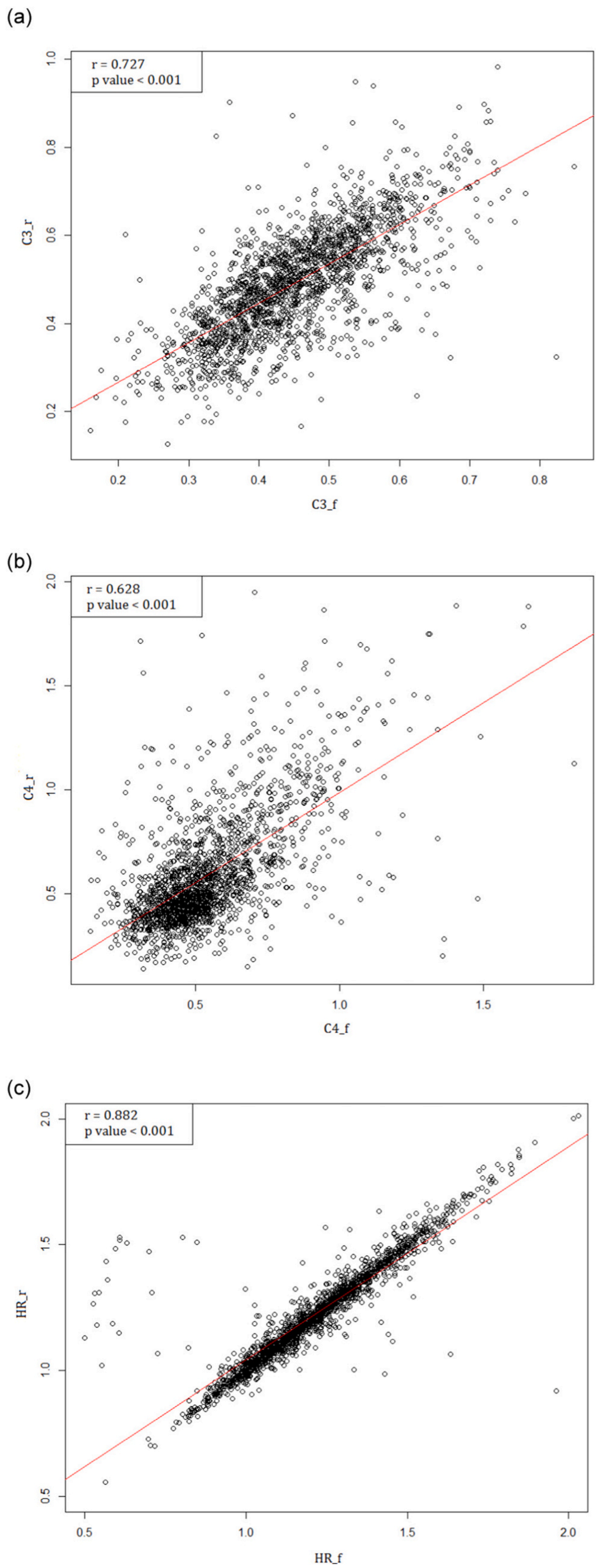

Fig. 3. Correlation of (a) the third harmonic component (C3) and (b) the fourth harmonic component (C4) (c) Heart rate (HR) between the radial pulse and finger photoplethysmography.

were divided into four groups based on the index C4, and the group with smaller C4 had a higher risk of cardiovascular complications.[11,20] In this study, a higher risk of retinopathy complications was found in the higher C4 subgroup. It is explained that there are two characteristics of the harmonic component. When the harmonic component is too high or too low, it increases the risk of disease. In addition, different combinations of high or low harmonic components may represent different types of disease risk, and changes in harmonic components can be used as indicators of disease progression.

The heart constantly pumps blood through the arterial system to transport it throughout the body. When the blood flows to the radial artery, the periodic changes in blood pressure due to the elasticity (compliance) of the blood vessels cause the amount of blood passing through the bending artery to become a periodic change in the signal waveform. A pressure sensor is used to detect the beating of the blood vessel wall, and this non-invasive method of measuring the periodic signal waveform there is called the radial pulse signal. PPG signal is a signal that is detected by the change of blood flow pulsation in the blood vessel using the principle of light absorption by the light sensor. The blood flow per unit area in the blood vessel will change with the pulsation of the heart, and the light sensor will change with the change of blood volume, making the sensing voltage also change. The amplitude of the PPG signal is therefore proportional to the amount of blood entering and exiting the tissue.[21] Both modalities are related to the blood circulation of the heart cycle beats. In this study, the heart rate calculated from pulse and PPG signals had a high correlation (RR $= 0.88$, $p < 0.01$), and the harmonic components C3 and C4 showed the same trend and positive correlation in diabetes patients with DR. The DRrisk indicators calculated by either pulse or PPG had the same predictive power for DR risk. Both measurements are non-invasive, which allows the sensors design for the prevention of diabetic complications more versatile. For example, a patient with diabetes can have radial artery measurements and harmonic analysis at regular clinic visits to determine if there is an increased risk of complications. Due to the ease of use of the PPG sensor, patients can also regularly measure finger arterial signals and harmonic analysis at home. When the risk indicators of complications increase, further examination or treatment can be done as soon as possible.

However, there were weaknesses in this study, as the two measurements were performed sequentially rather than simultaneously, therefore the correlations were lower than the past research.[15,22] In addition, although strict standard procedures were followed to ensure the stability of the measurement values,[23,24] there are inevitable measurement errors,[25] with the turnover of the operators. In the future, the correlation between radial pulse and PPG can be investigated by a more rigorous experimental design such as specifying operational standard procedures for simultaneous measurements at appropriate environmental temperatures. In addition, this study was conducted on Asian populations in Taiwan, and more research is needed on the applicability of DR risk indicators to other ethnic groups.

In conclusion, the harmonic analysis of radial pulse and PPG signals may be used to evaluate the effect of DR in hemodynamics, and the harmonic component may predict the risk of DR. In the future, non-invasive and rapid measurements may be applied to the monitoring of DR and other complications with more future studies.

CRediT authorship contribution statement

Kuo-meng Liao perfotmed conceptualization, resources and writing - review & editing. Sheng-Hung Wang performed conceptualization, methodology, investigation, formal analysis and writing - original draft. Li-Ting Tsai performed conceptualization, investigation and writing - review & editing. Ying-Chun Chen performed resources and data curation. Tien-Chung Wang and Gin-Chung Wang performed conceptualization, methodology, validation and writing - review & editing.

Declaration of competing interest

None.

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