ORIGINAL RESEARCH

Association Between High-sensitivity C-reactive Protein and Predicted Cardiovascular Risks in Schizophrenia

Yukun Xie, MM; Yangshun Wang, MM; Peng Xu, MM; Yanhui Zheng, BSM

ABSTRACT

Context • Cardiovascular disease (CVD) is one of the main causes of premature death in patients with schizophrenia. High-sensitivity C-reactive protein (hs-CRP) is closely related to various risk factors of CVD in the general population and is a sensitive marker of subclinical inflammation.

Objectives • The study intended to evaluate the predictive value of hs-CRP for high cardiovascular risk in patients with schizophrenia.

Design • The research team designed a cross-sectional retrospective study.

Setting • The study took place at the Affiliated Brain Hospital of Guangzhou Medical University in Guangzhou, Guangdong Province, China.

Participants • Participants were 387 patients with schizophrenia who had been admitted to the inpatient clinic at the hospital between January 1, 2018 and December 30, 2019.

Outcome Measures • The research team: (1) measured participants' hs-CRP and calculated the 10-year general cardiovascular risk, with a risk of >20% being defined as a high risk; (2) compared participants' demographics and traditional cardiovascular risk factors, and the prevalence of high cardiovascular risk according to the hs-CRP quartile; (3) used the receiver operating characteristic (ROC) curves to determine the optimal cutoff value for hs-CRP to predict high cardiovascular risk; and (4) used multivariate logistic regression analysis to assess the association between hs-CRP and high cardiovascular risk.

Results • Of the 387 participants, 23 had a high cardiovascular risk (5.9%). The prevalence of high cardiovascular risk in quartiles Q1, Q2, Q3, and Q4 groups was 0%, 2.0%, 12.5%, and 9.4%, respectively, with a *P* trend < .001. The ROC analysis showed that an hs-CRP cutoff value of 2.13mg/L was a fair discriminator for high cardiovascular risk, with a C statistic of 0.74. After adjusting confounding factors by multivariate logistic regression analysis, an hs-CRP of ≥2.13 mg/L was significantly associated with high cardiovascular risk (OR = 7.81, 95% CI: 1.73 - 35.39, *P* = .008).

Conclusions • An hs-CRP of ≥2.13 mg/L can be an independent predictor of high cardiovascular risk in patients with schizophrenia. Detection of hs-CRP may be beneficial in identifying patients at high risk of cardiovascular events in this population. Further prospective studies are needed to determine the hs-CRP threshold for evaluating cardiovascular risk in schizophrenia. (*Altern Ther Health Med.* 2023;29(2):180-185)

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Cardiovascular disease (CVD) is one of the main causes of premature death in patients with schizophrenia, and their risk of death from CVD is about twice that of people without mental diseases.[1] People with mental illness often have bad lifestyle habits and environmental factors that affect them.[2-4] Also, schizophrenia patients have an increased prevalence of diseases such as obesity, diabetes, metabolic syndrome, and CVD, and low levels of inflammation often accompany those diseases.

Casper et al found that high-sensitivity C-reactive protein (hs-CRP) is closely related to various risk factors of CVD in the general population.[5] Such factors as bad eating habits and smoking, common among patients with

schizophrenia, can lead to increased hs-CRP through cytokines and related signaling pathways.[6]

An acute-stage protein, hs-CRP is a protein that liver cells produce and is a sensitive marker of subclinical inflammation. Schizophrenia is also a disease that involves inflammation.[7] Lestra et al, in an inflammatory hypothesis, speculated that elevated levels of hs-CRP may be one of the mechanisms of schizophrenia.[8]

Medical practitioners can use hs-CRP to screen patients with atherosclerosis and their associated clinical syndromes, and Casper et al have advocated measurement of hs-CRP to assess the risk of CVD.[5]

The distribution of hs-CRP levels in Asian populations differs from that in Western populations,[9] but the current normal range of hs-CRP values comes from the studies with Western populations.[10] Whether medical practitioners can use hs-CRP as a screening tool for cardiovascular risk in Chinese patients with schizophrenia is unclear. As a result, before screening patients with schizophrenia for cardiovascular risk, researchers should first assess the association between hs-CRP and risk of cardiovascular disease.

The current study intended to evaluate the predictive value of hs-CRP for high cardiovascular risk in patients with schizophrenia.

METHODS

Participants

The research team designed a cross-sectional retrospective study. Potential participants were patients with schizophrenia who had been admitted to the inpatient clinic at the Affiliated Brain Hospital of Guangzhou Medical University between January 1, 2018 and December 30, 2019.

Potential participants were included in the study if they had: (1) met the criteria for a diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV),[11] and (2) were aged between 30 and 74 years.

Potential participants were excluded from the study if they: (1) had CVD, (2) had an inflammatory disease, or (3) had an hs-CRP of ≥10mg/L.

Of 1031 potential participants, the research team excluded 296 because they didn't meet the criteria for age. Of the remaining 735 participants, the team excluded 47 because they had CVD and 47 because their hs-CRP was ≥10 mg/L. Participants with missing data were excluded, including 229 missing hs-CRP, 4 missing blood lipid testing, 20 missing fasting blood glucose, and 1 missing blood pressure.

All participants received information about the study's purposes and protocol and signed an informed consent before any of the study's procedures occurred. The Medical Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University (2016-031) approved the study.

Procedures

Data collection and measurements. The clinical data were extracted from the medical records, and the Medical Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University approved this study. The research team consecutively included the data of participants, obtaining participants' medical histories, demographic information, and clinical laboratory data and collected fasting venous blood after participants fasted overnight and sent the venous blood samples to the hospital's clinical laboratory for immediate testing.

The team also performed blood lipid testing: (1) using an enzymatic method for measurement of total cholesterol (TC) and the glycerol-phosphoric acid oxidase peroxydase method for triglycerides (TG), with both methods using original reagents from Beckman Coulter Experimental Systems (Suzhou) Co., Ltd (Suzhou, Jiangsu Province, China) and (2) using the direct method for high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

In addition, the team performed hs-CRP testing using latex-enhanced immunoturbidimetry (Hunan Yonghe-Sun Biotechnology Co., Ltd, Changsha, Hunan Province, China). The range of measurement was 0-320 mg/L. The coefficient of variation within the analysis was 4.6%, and the coefficient of variation between analyses was 5.2%. The test instrument was an AU5800 automatic biochemical analyzer (Beckman).

Framingham risk calculation. The research team evaluated participants' cardiovascular risk using the Framingham function[12,13] to estimate the general risk of any fatal or nonfatal CVD,[14] and used a model calculation (General CVD Risk Prediction Using Lipids. Excel spreadsheets download for lipids from https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/) for the general cardiovascular risk.

Outcome Measures

Framingham Cardiovascular Risk Score. The measure is one of the most classic tools for risk screening assessment,[12] and researchers have confirmed it use for participants with schizophrenia.[13] According to the risk, the team divided participants into three groups: low <10%, moderate = 10%-20%, and high >20%.

Statistical Analysis

The research team used SPSS 25.0 software (IBM Corp., Armonk, NY, USA) for the analysis. The team expressed: (1) the continuous data as means ± standard deviations (SDs) or medians and interquartile ranges, and (2) the counting data as numbers and percentages (%s). The team divided the data into four groups—Quartile 1 (Q1), Q2, Q3, and Q4—according to the interquartile of hs-CRP.

The research team compared the relationship between the demographics and traditional cardiovascular risk factors and the prevalence of high cardiovascular risk for the groups: (1) using the Kruskal-Wallis test or the Wilcoxon test for the

continuous data, and (2) using Chi-square analysis or the Fisher's exact test for the categorical variables.

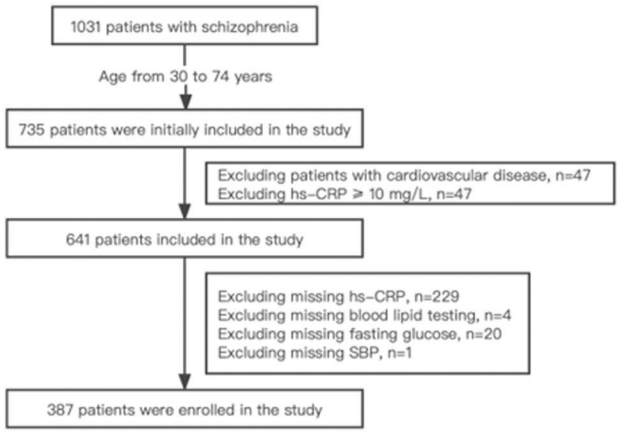
The research team: (1) used the Cochran-Armitage test to analyze the trends in prevalence; (2) determined the cutoff value of hs-CRP for high cardiovascular risk using receiver operating characteristic (ROC) curves; and (3) used univariate and multivariate logistic regression analyses to assess the association between hs-CRP and the high cardiovascular risk. The multivariate logistic regression analysis included duration of illness of ≥20 years, alcohol use, elevated TG, elevated LDL-C, use of antihyperlipidemic drugs, and use of olanzapine or clozapine. *P* values were double-tailed, and $P < .05$ indicated statistically significant differences.

RESULTS

Participants

The study included and analyzed the data of 387 participants (Figure 1). Of the 641 participants originally in the study, the team didn't include 254 patients in the analysis because of missing data in their records: 229 for missing

Figure 1. Flowchart Depicting the Selection of Participants With Schizophrenia



Abbreviations: hs-CRP, high-sensitivity C-reactive protein; SBP, Systolic blood pressure.

Table 1. Characteristics of the Study's Participants (N = 387)

Characteristic	Participants n (%) Mean ± SD Med (Min, Max)	Q1, ≤0.91 n (%) Mean ± SD Med (Min, Max)	Q2, 0.92 - 1.98 n (%) Mean ± SD Med (Min, Max)	Q3, 1.99 - 3.78 n (%) Mean ± SD Med (Min, Max)	Q4, ≥3.79 n (%) Mean ± SD Med (Min, Max)	Z/χ^2 Value	*P* value
Gender						2.335	.506
Men	204 (52.7)	40 (48.8)	51 (50.5)	61 (59.8)	52 (51.0)		
Women	183 (47.3)	42 (51.2)	50 (49.5)	41 (40.2)	50 (49.0)		
Age, y	44.28 ± 10.18	42.75 ± 8.90	42.84 ± 10.16	45.72 ± 10.90	45.86 ± 10.38	7.798	.050
Weight, kg	63.48 ± 12.46	59.14 ± 10.89	61.99 ± 9.57	65.86 ± 14.05	67.00 ± 13.43	21.741	.000[a]
Duration of illness, y	13.14 (6.07, 21.19)	10.41 (5.36, 19.15)	11.14 (6.04, 18.56)	14.24 (4.19, 24.75)	15.28 (6.09, 26.19)	4.045	.257
Days in hospital, d	65 (35, 129)	60 (35, 89)	64 (33, 115)	68 (36, 177)	71 (33, 154)	2.683	.443
TC, mmol/L	5.24 ± 1.24	5.05 ± 0.92	5.13 ± 1.31	5.40 ± 1.24	5.37 ± 1.43	5.093	.165
TG, mmol/L	1.72 ± 1.08	1.35 ± 0.73	1.65 ± 0.88	1.95 ± 1.23	1.94 ± 1.27	23.393	.000[a]
HDL-C, mmol/L	1.24 ± 0.33	1.33 ± 0.35	1.27 ± 0.31	1.18 ± 0.32	1.20 ± 0.31	9.174	.027[a]
LDL-C, mmol/L	3.00 ± 0.93	2.76 ± 0.67	2.95 ± 0.94	3.17 ± 0.92	3.14 ± 1.11	9.695	.021[a]
SBP, mmHg	112.85 ± 12.33	111.89 ± 11.97	110.60 ± 11.15	113.78 ± 12.47	115.18 ± 13.33	7.079	.069
DBP, mmHg	73.21 ± 8.31	72.27 ± 8.04	72.14 ± 7.34	73.11 ± 8.93	75.35 ± 8.58	8.437	.038[a]
Fasting glucose, mmol/L	5.00 ± 1.66	4.65 ± 1.13	4.87 ± 1.22	5.33 ± 2.03	5.16 ± 2.01	8.446	.038[a]
Smoking, yes	40 (10.3)	11 (11.3)	6 (6.1)	10 (10.4)	13 (13.5)	3.048	.384
Alcohol use, yes	12 (3.1)	0 (0)	5 (5.1)	2 (2.1)	5 (5.2)	6.580	.069
Antipsychotic, yes						1.475	.688
≤1	202 (52.2)	48 (49.5)	49 (50.0)	50 (52.1)	55 (57.3)		
≥2	185 (47.8)	49 (50.5)	49 (50.0)	46 (47.9)	41 (42.7)		
Olanzapine/clozapine, yes	223 (57.6)	53 (54.6)	52 (53.1)	63 (65.6)	55 (57.3)	3.710	.294
Antihyperlipidemic drugs, yes	47 (12.1)	4 (4.1)	7 (7.1)	17 (17.7)	19 (12.1)	16.193	.001[a]
Hypoglycemia drugs, yes	45 (11.6)	7 (7.2)	13 (13.3)	16 (16.7)	9 (9.4)	4.939	.176
Antihypertensive drugs, yes	22 (5.7)	4 (4.1)	6 (6.1)	5 (5.2)	7 (7.3)	0.979	.806

[a]$P < .05$, indicating that weight, TG, HDL-C, LDL-C, DBP, fasting glucose, and use of antihyperlipidemic drugs were significantly different among the quartiles

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 2. Relationship Between High-sensitivity C-reactive Protein and Cardiovascular Risk Factors (N = 387)

Risk factor	Participants n (%)	Q1 (hs-CRP ≤0.91) n (%)	Q2 (hs-CRP 0.92-1.98) n (%)	Q3 (hs-CRP 1.99-3.78) n (%)	Q4 (hs-CRP ≥3.79) n (%)	χ^2 value	*P* value	*Z* Value	*P*-trend value
Male, >55 OR female, >65 years	38 (9.8)	5 (5.2)	9 (9.2)	13 (13.5)	11 (11.5)	4.222	.238	2.958	.085
Smoking, yes	40 (10.3)	11 (11.3)	6 (6.1)	10 (10.4)	13 (13.5)	3.048	.384	0.618	.432
Alcohol use, yes	12 (3.1)	0 (0)	5 (5.1)	2 (2.1)	5 (5.2)	6.580	.069	2.547	.111
Duration of illness, ≥20 years	124 (32.0)	21 (21.6)	23 (23.5)	38 (39.6)	42 (43.8)	16.669	.001[a]	15.070	.000
Antipsychotic, ≥2	185 (47.8)	49 (50.5)	49 (50.0)	46 (47.9)	41 (42.7)	1.475	.688	1.257	.262
Olanzapine/clozapine	223 (57.6)	53 (54.6)	52 (53.1)	63 (65.6)	55 (57.3)	3.710	.294	0.838	.360
Hypertension, yes	37 (9.6)	5 (5.2)	9 (9.2)	7 (7.3)	16 (16.7)	8.372	.039[a]	5.935	.015
Diabetes, yes	59 (15.2)	7 (7.2)	14 (14.3)	21 (21.9)	17 (17.7)	8.625	.035[a]	5.715	.017
TC, ≥5.2mmol/L	183 (47.3)	41 (42.3)	44 (44.9)	49 (51)	49 (51)	2.291	.514	2.044	.153
TG, ≥1.7mmol/L	139 (35.9)	23 (23.7)	29 (29.6)	45 (46.9)	42 (43.8)	15.549	.001[a]	12.588	.000
HDL-C, <1.0mmol/L	88 (22.7)	15 (15.5)	18 (18.4)	29 (30.2)	26 (27.1)	8.068	.045[a]	6.006	.014
LDL-C, ≥3.4mmol/L	110 (28.4)	18 (18.6)	21 (21.4)	39 (40.6)	32 (33.3)	15.161	.002[a]	9.603	.002

[a]$P < .05$, indicating that a duration of illness of ≥20 years, hypertension, diabetes, TC levels ≥5.2 mmol/L, LDL-C levels ≥3.4 mmol/L, and HDL-C levels <1.0 mmol/L were significant cardiovascular risk factors ($P < .05$), and the risk increased with an increase in the hs-CRP level (*P*-trend <.05)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

hs-CRP, 4 for missing blood-lipid testing, 20 for missing fasting glucose, and 1 for missing SBP levels.

Participants' ages ranged from 30 to 73 years, with a mean age of 44.28 ± 10.18 years. Among them, 204 (52.7%) were male and 183 (47.3%) were female (Table 1).

hs-CRP

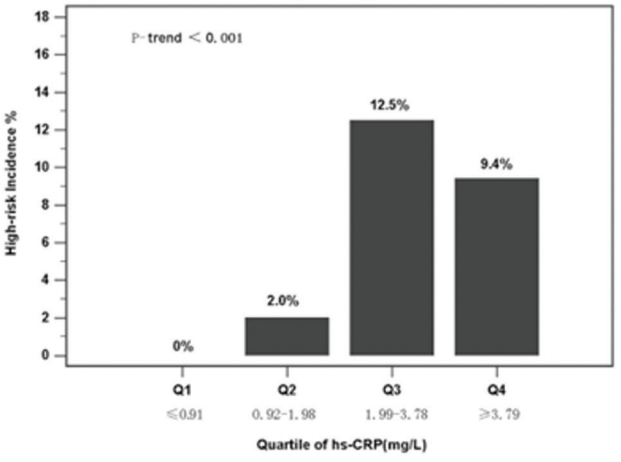
Participants' median hs-CRP was 1.98 (0.91, 3.78) mg/L, of which participants with an hs-CRP of >1.0 mg/L accounted for 73%. The quartiles of hs-CRP were Q1 ≤0.91 mg/L, Q2 = 0.92-1.98 mg/L, Q3 = 1.99-3.78 mg/L, and Q4 ≥3.79 mg/L (Table 2).

Among the four quartiles, duration of illness of ≥20 years, hypertension, diabetes, TC levels ≥5.2 mmol/L, LDL-C levels ≥3.4 mmol/L, and HDL-C levels <1.0 mmol/L were significant cardiovascular risk factors ($P < .05$), and the risk increased with an increase in the hs-CRP level (*P*-trend <.05).

High Cardiovascular Risk

Of the 387 participants, 23 (5.9%) had a high cardiovascular risk, a 10-year general CVD risk of >20%. Figure 2 shows that the incidence of high cardiovascular risk in the Q1, Q2, Q3 and Q4 groups were 0%, 2.0%, 12.5%, and 9.4%, respectively, and the differences among the groups in hs-CRP were statistically significant ($P < .001$).

Figure 2. Relationship Between High-sensitivity C-reactive Protein (hs-CRP) and High Cardiovascular Risk. The association between hs-CRP and the percentage of participants with a high cardiovascular risk was significant, with $P < .001$ overall and as a trend



hs-CRP and High Cardiovascular Risk

The ROC curve analysis showed that an hs-CRP threshold of ≥2.13 mg/L exhibited 91.3% sensitivity and 56% specificity for detecting high cardiovascular risk, with a C statistic of 0.74 (Figure 3). Univariate analysis showed that an hs-CRP of ≥2.13 mg/L was a highly significant predictor of high cardiovascular risk (OR = 13.39; 95% CI: 3.09 - 57.94; *P* = .001).

Multivariate logistic regression analysis found that an hs-CRP of ≥2.13 mg/L was an independent risk factor for high cardiovascular risk (OR=7.81; 95% CI: 1.73 - 35.39; *P* = .008). In addition, a duration of illness of ≥20 years and an LDL-C of ≥3.40 mmol/L were independent risk factors for high cardiovascular risk (Table 3).

DISCUSSION

In the current study, hs-CRP was associated with a variety of cardiovascular risk factors in schizophrenia. With an increase in hs-CRP, the risk increased for a duration of illness of ≥20 years, hypertension, diabetes, elevated TC, elevated LDL-C, and decreased HDL-C, which is similar to Casper et al's previous findings.[5]

The current study used the Framingham Cardiovascular Risk Score,[12,13] as the diagnostic criterion and found that the high-risk group had a higher hs-CRP than the non-high-risk groups (*P* < .001), that the risk increased with the increase in hs-CRP (*P*-trend < .001), and that hs-CRP ≥2.13 mg/L was an independent risk factor for high cardiovascular risk. The study's diagnostic threshold of hs-CRP was lower than the recommended threshold in guidelines of 3 mg/L.

Possible explanations include: (1) the population was the Chinese patients with schizophrenia; (2) through the correction of participants' poor diet structure and their receipt of systematic medical treatment during hospitalization, their dyslipidemia improved to a certain extent and their blood pressure tended to become normal, while the research team calculated the cardiovascular risk scores based on such factors as TC, HDL-C, and blood pressure, which also decreased. This is consistent with the low 10-year general cardiovascular risk score of 3.6% (1.90, 7.70) in the study's population.

To sum up, the research team believes that hs-CRP levels are strongly associated with cardiovascular risks, and its measurement can have the effect of identifying people with potentially high cardiovascular risk. The team suggests that a hs-CRP cut-off value of 2.13 mg/L is appropriate for identifying patients who have schizophrenia at high cardiovascular risk.

The limitations of this study include the fact that it was a cross-sectional study in which the cardiovascular risk score predicted event probability, which limited further research on the relationship between hs-CRP and cardiovascular risk in patients with schizophrenia. Also, it was a single center study, and the results aren't necessarily extendable to other centers.

Figure 3. Analysis of Receiver Operator Characteristic (ROC) Curve. The analysis showed that high-sensitivity C-reactive protein (hs-CRP), at a cutoff of 2.13, exhibited 91.3% sensitivity and 56% specificity for detecting high cardiovascular risk, with a C statistic of 0.74

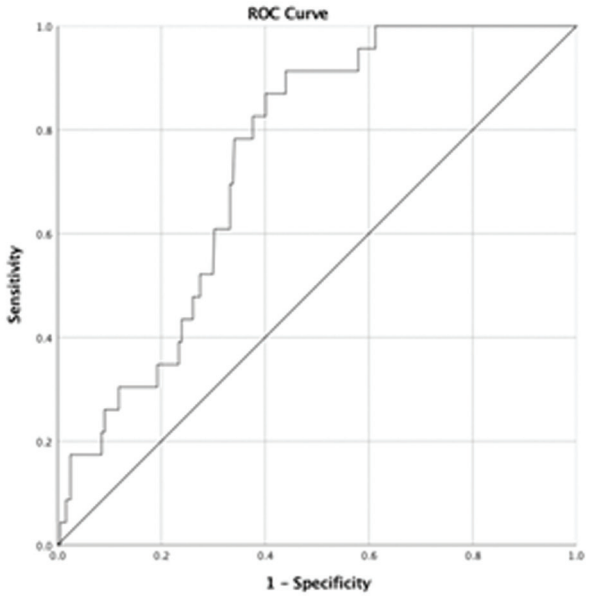


Table 3. Multivariable Association Between High Cardiovascular Risk and High-sensitivity C-reactive Protein (CRP). The factors involved in the cardiovascular risk score weren't adjusted for confounders. The dependent variable was high cardiovascular risk: 0 for the non-high-risk group, ≤20%, and one for the high-risk group, >20%.

Variable	Odds Ratio	95% CI	*P* value
hs-CRP, ≥2.13mg/L	7.81	1.73 - 35.39	.008[a]
Duration of illness, ≥20 years	8.34	2.61 - 26.70	.000[a]
Alcohol use, yes	4.50	0.41 - 48.89	.217
TG, ≥1.70mmol/L	1.44	0.52 - 3.99	.487
LDL-C, ≥3.40mmol/L	2.84	1.03 - 7.83	.043[a]
Antihyperlipidemic drugs, yes	1.41	0.49 - 4.07	.531
Olanzapine/clozapine, yes	0.60	0.22 - 1.67	.331

[a]*P* < .05, indicating that an hs-CRP of ≥2.13mg/L, a duration of illness of ≥20 years, and an LDL-C of ≥3.40mmol/L were significant predictors of high cardiovascular risk

Abbreviations: LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein

CONCLUSIONS

An hs-CRP of ≥ 2.13 mg/L can be an independent predictor of high cardiovascular risk in patients with schizophrenia. Detection of hs-CRP may be beneficial in identifying patients at high risk of cardiovascular events in this population. Further prospective studies are needed to determine the hs-CRP threshold for evaluating cardiovascular risk in schizophrenia.

AUTHORS' DISCLOSURE STATEMENT

The Medical and Health Science and Technology Project of Guangzhou (20171A010280) supported this study. The research team declares that they have no conflicts of interest related to the study.

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