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Original Article

Correlation between serum urea nitrogen, cystatin C, homocysteine, and chronic heart failure

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Abstract: Objective: To explore the correlation between uric acid (UA), cystatin C (Cys-C), homocysteine (Hcy), and chronic heart failure (CHF). Methods: 45 patients with CHF were selected as the research group; 45 healthy people were selected as the control group. The levels of serum UA, Cys-C and Hcy were detected. Results: The in The research group had much higher levels of serum UA, Cys-C and Hcy than the control group (all P<0.05). The levels of above indexes also increased with an increase in cardiac function classification. Patients with major adverse cardiovascular events (MACE) had much higher levels of serum UA, Cys-C, and Hcy than those without MACE in the research group (all P<0.05). In addition, the levels of these above indexes in the research group were all positively correlated with the left ventricular end diastolic diameter (LVEDD) (all P<0.05), and all negatively correlated with the f left ventricular ejection fraction (LVEF) (P<0.05). What is more, the levels of these above indexes in the research group were all positively correlated with New York Heart Association (NYHA) grade (all P<0.05). The diagnostic sensitivity of serum UA level, Cys-C level, and Hcy level in joint diagnosis of CHF patients was higher than that of any single index diagnosis (P<0.05), and the specificity of combined diagnosis was lower than that of single index diagnosis (P<0.05). Conclusion: The levels of serum UA, Cys-C, and Hcy in CHF patients may be used as reference indexes for clinical screening of early CHF patients and could provide a certain reference for clinical evaluation.

Keywords: Uric acid, cystatin C, homocysteine, chronic heart failure, cardiac function, correlation

Introduction

Chronic heart failure (CHF) is a well-known public health problem [1]. However, associated pathogenesis and progression mechanism of CHF are very complex and diverse. Studies have pointed out that some CHF patients will still be hospitalized repeatedly because of symptom recurrence or ineffective symptom relief even after clinical symptomatic treatment and intervention [2]. Therefore, early and effective screening and symptomatic treatment for CHF patients have positive clinical significance, which can delay the progression of patients' conditions and improve the related clinical symptoms [3]. Purine metabolism produces Uric acid (UA) and UA is related to cardiac function. The significant increase in UA level is also a marker of oxygen metabolism damage at the time of CHF occurrence [4]. Serum cystatin C (Cys-C) exists in all nucleated cells as the inhibitor of cysteine protease. Cys-C protects cells from being hydrolyzed by inappropriate proteases through regulating cell protein hydrolysis [5]. Homocysteine (Hcy) is a common amino acid substance, which directly damages the vascular endothelium [6]. At present, few comprehensive studies on the relevance between serum levels of UA, Cys-C, Hcy, and CHF have been conducted. Therefore, 45 patients with CHF diagnosed and treated in our hospital during August 2019 to August 2020 were selected as main research objects. Then, the expression levels of serum UA, Cys-C, and Hcy were detected and their correlation with CHF was explored as follows.

Materials and methods

General materials

45 patients with CHF diagnosed and treated in Linyi Central Hospital during August 2019 to August 2020 were adopted as the research

group; 45 healthy people who received health screening in Linyi Central Hospital during the same period were selected as the control group.

Inclusion criteria of the research group: (1) In accordance with the clinical diagnosis of chronic heart failure [7]. (2) The clinical data were complete. (3) 30-80 years old. (4) All patients signed informed consent before entering the group.

According to the gender ratio of patients in the study group, 45 healthy people who came to Linyi Central Hospital for health screening during the same period were selected as the control group.

Inclusion criteria of the control group: (1) No abnormality was found in the clinical examination. (2) Left ventricular ejection fraction (LVEF) was larger than 55.0%. (3) The index levels involved in this study are within the normal range. (4) 30-80 years old.

Common exclusion criteria of the two groups: (1) Combined with renal insufficiency. (2) Combined with hepatic insufficiency. (3) Combined with malignant tumor. (4) Combined with hyperthyroidism. (5) Combined with hypothyroidism. (6) Combined with anemia.

25 males and 20 females were included in the control group, with an average age of (54.6± 1.6) years; there were also 25 males and 20 females in the research group, with an average age of (54.9±1.5) years. According to the standard of NYHA for cardiac function grade, of the cases of Grade II, Grade III, and Grade IV were 18, 15, and 12 respectively in the study group. The study had been reviewed and approved by the Ethics Committee of Linyi Central Hospital.

Methods

3 mL blood samples from elbow of every research object were collected after 12 hours fasting and blood samples centrifugation was conducted at 3000 r/min for 10 min.

Serum uric acid (UA) and homocysteine (Hcy) levels were detected by automatic biochemical analyzer (Shandong Boke Regenerative Medicine Co., Ltd., China), and specialized kits were used (Shanghai Zhenke Biotechnology Co., Ltd., China); the level of serum cystatin C (Cys-C) was detected through immunoturbidimetry (Shanghai Jining Research Co., Ltd., China).

Color Doppler ultrasound (GE, China) was used to detect the cardiac ultrasound index, and the frequency of the probe was set at 3.0 MHZ. All the research objects were examined according to the clinical routine cardiac color Doppler ultrasound examination method.

All data were analyzed retrospectively.

Outcome measures

Main outcome measures: Gender and age; serum levels of UA, Cys-C, and Hcy of two groups; Difference of serum levels in UA, Cys-C, and Hcy of patients with different cardiac function grade in the research group [8]; Difference in levels of UA, Cys-C, and Hcy between patients with different prognosis in the research group. Patients in the research group were divided into groups according to the occurrence of major adverse cardiac events (MACE) or not.

Secondary outcome measures: Difference in related echocardiographic indexes between the two groups, including longitudinal diameter of left atrium (LAD), left ventricular end diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF).

The correlation between UA, Cys-C, and Hcy levels with LVEDD and LVEF levels in the research group was explored.

The correlation between UA, Cys-C and Hcy levels with different cardiac function grade of NYHA in the research group was explored.

Statistical analysis

SPSS 22.0 was used for data analysis. The measurement data were expressed by mean ± standard deviation ($\bar{x} \pm sd$). Two groups were compared by the independent sample t test, and difference in the intragroup was compared by the paired t test; the enumeration data were expressed as rate, and the comparison between groups was conducted by χ^2 test. Spearman rank correlation was used to analyze the correlation. $P<0.05$ indicates asignificant difference.

Table 1. Difference in gender and age between the control group and the research group

Group	Control group (n = 45)	Research group (n = 45)	Statistic	P
Male (cases, %)	25, 55.6%	25, 55.6%	1.254	1.263
Female (cases, %)	20, 44.4%	20, 44.4%		
Mean age (year, $\bar{x}$ ± sd)	54.6±1.6	54.9±1.5	0.485	2.847
Drinking (Cases, %)	5 (11.1)	6 (13.3)	1.139	1.025
Body weight (kg/m^2)	25.23±3.22	26.15±3.39	1.320	0.190
Total cholesterol (mmol/L)	4.53±1.12	4.47±1.09	0.258	0.797
Triglyceride (mmol/L)	1.56±0.64	1.62±0.51	0.492	0.624
Low density lipoprotein cholesterol (mmol/L)	2.57±0.68	2.43±0.71	0.955	0.342
High density lipoprotein cholesterol (mmol/L)	1.24±0.32	1.19±0.41	0.645	0.521

Table 2. Serum levels of UA, Cys-C, and Hcy in the control group and the research group ($\bar{x}$ ± sd)

Group	Cases	UA level (μmol/L)	Cys-C level (mg/L)	Hcy level (μmol/L)
Control group	45	273.12±31.24	0.97±0.23	10.81±2.43
Research group	45	416.21±54.67	1.65±0.46	15.61±5.64
t		15.244	8.870	5.243
P		0.000	0.000	0.000

Note: UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine.

Results

Difference in general data between the control group and the research group

No significant difference existed in gender distribution, average age, drinking, body weight, levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) between two groups (P>0.05). See **Table 1** for details.

Serum levels of UA, Cys-C, and Hcy in the control group and the research group

The serum levels of UA, Cys-C, and Hcy in the research group were (416.21±54.67) μmol/L, (1.65±0.46) mg/L and (15.61±5.64) μmol/L in the research group, which were much higher than those in the control group of (273.12±31.24) μmol/L, Cys-C level (0.97±0.23) mg/L and Hcy level (10.81±2.43) μmol/L, respectively (all P<0.001). See **Table 2** and **Figure 1** for details.

Serum levels of UA, Cys-C, and Hcy with different NYHA grade in the research group

The levels of UA, Cys-C, and Hcy in patients with NYHA grade IV were obviously higher than those in patients with grade III and grade II (all P<0.05). At the same time, the patients with grade III also had much higher levels of UA, Cys-C, and Hcy than patients with grade II (P<0.05) (all P<0.05). In general, serum levels of UA, Cys-C, and Hcy increased with an increase of cardiac function classification. See **Table 3** and **Figure 2** for details.

Related echocardiographic indexes of the control group and the research group: LAD level, LVEDD level, and LVEF level

Among related echocardiographic indexes, the LAD level and LVEDD level of the research group were (41.31±3.92) mm and (59.81±3.92) mm, which were much higher than those of the control group (32.13±4.12) mm and (46.53±3.71) mm (P<0.001). At the same time, the research group had much lower LVFE level (40.64±5.83)% than the control group (64.71±4.27)% (P<0.001). See **Table 4** for details.

Difference of serum levels of UA, Cys-C and Hcy between patients with different prognosis

All patients in the research group were followed up for 90 days, and 7 cases of MACE occurred. Serum UA, Cys-C, and Hcy levels of patients with MACE in the research group were (398.62±134.33) μmol/L, (1.92±0.74) mg/L and (19.72±3.21) μmol/L, respectively. Serum UA, Cys-C, and Hcy levels of patients without MACE in the research group were (311.61±125.42) μmol/L, (1.42±0.31) mg/L and (14.81±2.62) μmol/L, respectively. The corresponding index of the patients with MACE was much higher than those without MACE in the research group (all P<0.05). See **Table 5** for details.

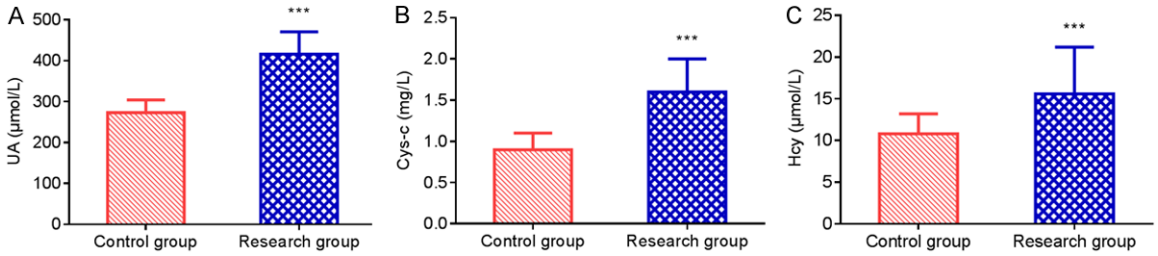

Figure 1. Serum levels of UA, Cys-C, and Hcy in the control group and the research group. A: UA level; B: Cys-C level; C: Hcy level. Compared with control group, ***P<0.001. UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine.

Table 3. Serum levels of UA, Cys-C, and Hcy with different NYHA grade in the research group ($\bar{x}$ ± sd)

Group	Cases	UA level (μmol/L)	Cys-C level (mg/L)	Hcy level (μmol/L)
Grade II	18	325.12±78.43	1.25±0.23	13.16±3.21
Grade III	15	374.15±84.51	1.51±0.33	16.13±4.97
Grade IV	12	446.82±146.22	1.97±0.25	19.81±6.32
F		5.093	25.245	6.984
P		0.024	0.000	0.002

Note: NYHA: New York Heart Association; UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine.

Correlation between serum levels of UA, Cys-C, and Hcy with the level of LVEDD and LVEF in the research group

The levels of serum UA, Cys-C, and Hcy in the research group showed positive correlation with the level of LVEDD (r value = 0.325, 0.318, 0.251, all P<0.05), and showed negative correlation with the level of LVEF (r value = -0.294, -0.289, -0.216, P<0.05). See **Table 6** for details.

Correlation between serum levels of UA, Cys-C, and Hcy with NYHA grade

UA, Cys-C and Hcy levels in the research group were all positively correlated with NYHA grade (all P<0.05). See **Table 7** for details.

Diagnostic efficacy of serum levels of UA, Cys-C, and Hcy in patients with CHF

The ROC curve showed that the diagnostic sensitivity of serum UA level, Cys-C, level and Hcy level in joint diagnosis of CHF patients were higher than that of single index diagnosis (P<0.05), and the specificity of combined diagnosis was lower than that of single index diagnosis (P<0.05). See **Table 8** and **Figure 3** for details.

Discussion

CHF is a very complex clinical syndrome and the occurrence of CHF indicates that the heart disease has developed to a very serious stage. The incidence of CHF is very high in the clinic, and is increasing with aging of the population [9]. Therefore, effective clinical evaluation and diagnosis for CHF patients are of great significance to improve the prognosis of patients.

The results of our study showed that the research group had markedly higher level of UA than the control group; the UA level showed positive correlation with LVEDD level and NYHA grade, and was negatively correlated with LVEF level. UA is produced in the process of purine metabolism in the body. When circulatory failure occurs, UA level in serum will be significantly increased due to reduced excretion and increased production [10]. A previous study indicated that the maximal oxygen uptake of patients with CHF would be significantly reduced, and there existed a correlation between the maximum oxygen uptake and NYHA classification. The decrease in range of oxygen uptake increased with the aggravation of the disease, suggesting that oxygen metabolism was impaired in CHF patients [11]. Patients with CHF usually also have some degree of degrees of hypoxemia. The occurrence of hypoxia will enhance anaerobic metabolism and glycolysis, and reduce the production of adenosine triphosphate (ATP) [12]. The consumption of ATP will promote the degradation of adenine to produce related substances including UA, which is also a main reason for the increased UA level in CHF patients [13].

The results of our study showed that the research group had much higher levels of Cys-C than the control group; Cys-C level was posi-

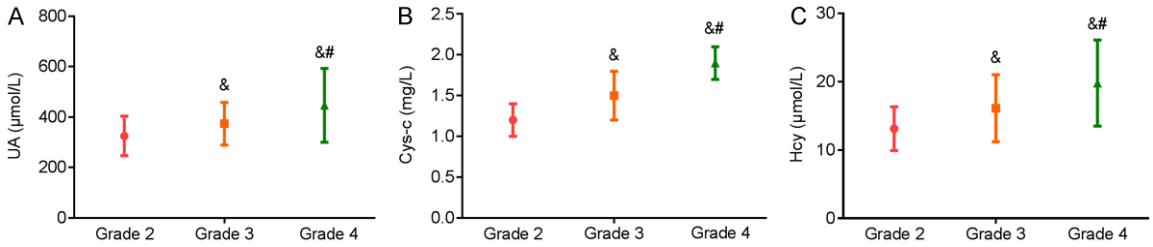

Figure 2. Serum levels of UA, Cys-C, and Hcy with different NYHA grade in the research group. A: UA level; B: Cys-C level; C: Hcy level. Compared to grade II, $^{\&}P<0.05$; compared to grade III, $^{\#}P<0.05$. UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine; NYHA: New York Heart Association.

Table 4. Related echocardiographic indexes of the control group and the research group ($\bar{x}$ ± sd)

Group	Cases	LAD (mm)	LVFE (%)	LVEDD (mm)
Control group	45	32.13±4.12	64.71±4.27	46.53±3.71
Research group	45	41.31±3.92	40.64±5.83	59.81±3.92
T		10.829	22.344	16.506
P		0.000	0.000	0.000

Note: LAD: longitudinal diameter of left atrium; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction.

Table 5. Difference of serum levels of UA, Cys-C, and Hcy between patients with different prognosis ($\bar{x}$ ± sd)

Group	Cases	UA level (μmol/L)	Cys-C level (mg/L)	Hcy level (μmol/L)
Without MACE	38	311.61±125.42	1.42±0.31	14.81±2.62
With MACE	7	398.62±134.33	1.92±0.74	19.72±3.21
T		2.670	3.048	4.405
P		0.011	0.004	0.000

Note: MACE: major cardiovascular adverse events; UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine.

Table 6. Correlation between serum levels of UA, Cys-C, and Hcy with the levels of LVEDD and LVEF in the research group ($\bar{x}$ ± sd)

Index	UA level		Cys-C level		Hcy level	
	r value	*P* value	r value	*P* value	r value	*P* value
LVEDD level	0.325	0.014	0.318	0.005	0.251	0.047
LVEF level	-0.294	0.021	-0.289	0.026	-0.216	0.014

Note: UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction.

Table 7. Correlation between serum levels of UA, Cys-C, and Hcy with NYHA grade in the research group ($\bar{x}$ ± sd)

Index	UA level		Cys-C level		Hcy level	
	r value	*P* value	r value	*P* value	r value	*P* value
NYHA grade	0.294	0.046	0.274	0.024	0.285	0.016

Note: UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine; NYHA: New York Heart Association.

tively correlated with LVEDD level and NYHA grade, and was negatively correlated with LVEF level. At present, serum Cys-C level has been used as a new reference index for the detection of renal function [14]. Compared with traditional renal function indexes, such as serum creatinine and urea nitrogen, Cys-C can reflect glomerular filtration rate more accurately [15]. Studies have shown that serum Cys-C may be associated with cardiovascular disease [16]. Cys-C may damage the cardiovascular system by affecting lipid peroxidation, coagulation function, smooth muscle cell function, and endothelial cell function [17, 18]. Studies have pointed out that one of the main risk grading markers of cardiac disease endpoint events is serum Cys-C. In addition, there exists a close relationship between Cys-C and cardiac dysfunction [19, 20].

The results of our study showed that the research group had a substantially higher level of Hcy than the control group; the Hcy level was positively correlated with LVEDD level and NYHA grade, and was negatively correlated with LVEF. Related studies have pointed out that Hcy can damage the normal function of endothelial cells, stimulate the production of platelet-derived growth factor, and promote the formation atherosclerosis; at the same time, Hcy is closely related with coronary heart disease [21]. Hcy can promote the occurrence of cardiovascular diseases through various mechanisms, such as affecting lipid metabolism, inducing the

Table 8. Diagnostic effect of serum UA, Cys-C, and Hcy levels in patients with CHF

Diagnostic indicator	Area	SE	sig	95% CI	Sensitivity	Specificity
Serum UA	0.832	0.067	0.000	0.735-0.912	0.814	0.681
Cys-C	0.871	0.068	0.000	0.671-0.914	0.723	0.642
Hcy	0.863	0.071	0.000	0.754-0.893	0.802	0.632
Joint diagnosis	0.912	0.050	0.000	0.732-0.895	0.901	0.523

Note: UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine; SE: sensitivity; sig: significance; CI: confidence interval.

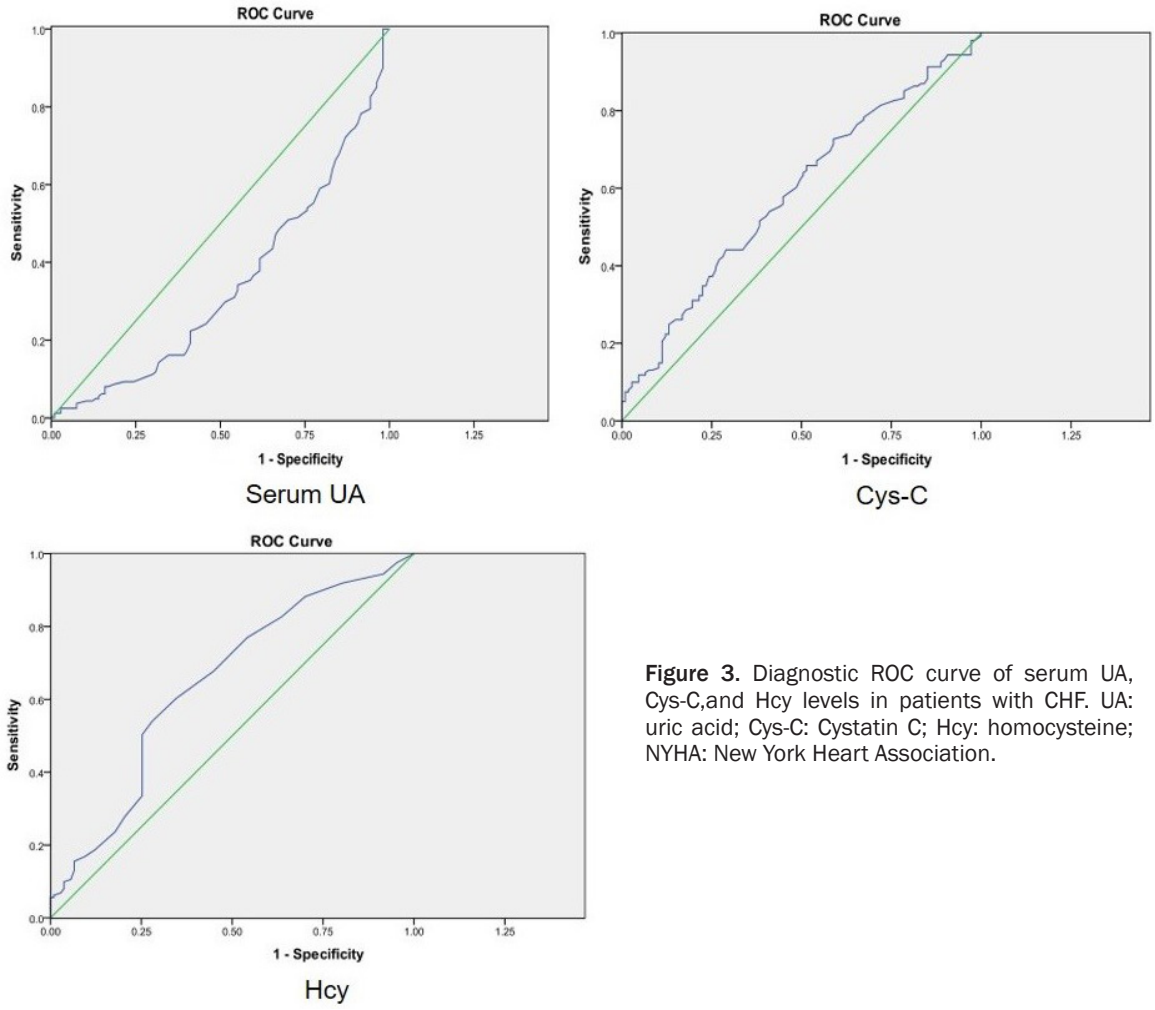

Figure 3. Diagnostic ROC curve of serum UA, Cys-C,and Hcy levels in patients with CHF. UA: uric acid; Cys-C: Cystatin C; Hcy: homocysteine; NYHA: New York Heart Association.

proliferation of smooth muscle cells, promoting the formation of thrombosis, destroying the balance between fibrinolysis and coagulation, and participating in an inflammatory reaction [22]. In our study, we found that the diagnostic sensitivity of serum UA, Cys-C, and Hcy levels in joint diagnosis of CHF patients were higher than that of single index diagnosis, and the specificity of combined diagnosis was lower than that of single index diagnosis. The results suggested that the joint diagnosis of serum UA level, Cys-C level and Hcy level had higher diagnostic sensitivity in patients with CHF.

There are also some deficiencies in this study. For example, the sample size in the study is relatively small, which may lead to some deviation and limitations in the results of the study. In the future clinical research, we will conduct multi-center in depth exploration and research with larger sample size, so as to verify and judge the reliability and accuracy of the present research results. It is hoped that our present study could provide certain reference and scientific basis for the diagnosis and treatment of CHF patients, and provide certain reference for future research.

Taken together, CHF patients had much higher levels of UA, Cys-C, and Hcy than patients in the control group, indicating that these above serum levels could be used as reference indexes for clinical screening of early CHF patients; UA, Cys-C and Hcy levels in CHF patients were all positively correlated with NYHA grade and the level of LVEDD, and were negatively correlated with the level of LVEF. Thus, these three serum indexes could provide a certain reference for clinical evaluation of CHF patients.

Disclosure of conflict of interest

None.

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References

[1] Song GJ, Ruan ZB, Zhu Li, Wang RZ, Li JM and Lin J. Correlation between cardiac function parameters of color doppler ultrasound and serum homocysteine level in patients with chronic heart failure. Prog Mod Biomed 2018; 18: 3653-3656.

[2] Jensen AC, Polcwiartek C, Søgaard P, Mortensen RN, Davidsen L, Aldahl M, Eriksen MA, Kragholm K, Torp-Pedersen C and Hansen SM. The association between serum calcium levels and short-term mortality in patients with chronic heart failure. Am J Med 2019; 132: 200-208.

[3] Ma YX and Zhang J. The relevant study between the serum homocysteine, high-density lipoprotein, high-sensitivity cardiac troponin t and cardiac function in patients with chronic heart failure. J Ningxia Med Univ 2018; 40: 424-428.

[4] Xiang ZT, Cao YL, Wang Y, Zhao GW, Xiao HL, Zhang SQ, Huang SQ and Yu Qin. Correlation analysis of serum homocysteine, methionine and cysteine with chronic heart failure. Chin J Postgrad Med 2020; 43: 585-589.

[5] Lin CY, Lee HL, Hwang YT and Su TC. The association between total serum isomers of per- and polyfluoroalkyl substances, lipid profiles, and the DNA oxidative/nitrative stress biomarkers in middle-aged Taiwanese adults. Environ Res 2020; 182: 109064.

[6] Song C and Zheng G. Correlation among homocysteine, brain natriuretic peptide (BNP) and risk stratification of chronic heart. Chin J Cardiovasc Res 2018; 16: 337-339.

[7] Shi SM, Liu Y and Sun Y. Study on the correlation between homocysteine and cardiac function in patients with chronic heart failure. Prev Treat Cardio-Cereb-Vasc Dis 2019; 19: 275-276.

[8] Zhang QS, Ma CL, Zhu H and Yin ZT. N-terminal pro-B-type natriuretic peptide and heart function of the New York Society of Cardiology Comparative analysis of the correlation of classification in the diagnosis of heart failure. The Med J Ind Enterp 2012; 25: 42-43.

[9] Yu JS and Huang ZY. Correlation between plasma homocysteine level and chronic heart failure in patients with dilated cardiomyopathy. Chin J Hypertens 2019; 27: 278-282.

[10] Gao SY, Ji RJ, Yan YL, Yu K, Wang YJ, Li F and Zhu DL. Correlation of serum homocysteine, fibrinogen, cystatin-c levels with NIHSS score in patients with acute cerebral infarction. Chin J Stroke 2020; 15: 389-393.

[11] Fan L, Zhang W, Wang X, Dong W, Tong Y, Dong C and Shuang S. A two-photon ratiometric fluorescent probe for highly selective sensing of mitochondrial cysteine in live cells. Analyst 2019; 144: 439-447.

[12] Wu J, Liu XM, Deng M and Zhu HQ. The application value of serum homocysteine and cystatin C in thediagnosis of acute cerebral infarction. Chin J Lab Diagn 2020; 24: 405-408.

[13] Wang AL and Wang XH. The value of urine retinol binding protein, serum cystatin-C and homocysteine in the early diagnosis of diabetic nephropathy and its correlation with the degree of oxidative stress. Shanxi Med J 2018; 47: 2092-2094.

[14] Zhao G, Zhang YY and Xie Y. Study on the correlation between serum glycosylated albumin, homocysteine and diabetes complicated with cardiovascular disease. Int J Endocrinol Metab 2018; 38: 145-148.

[15] Iyare RN, Volskiy V and Vandenbosch GAE. Study of the correlation between outdoor and indoor electromagnetic exposure near cellular base stations in Leuven, Belgium. Environ Res 2019; 168: 428-438.

[16] Wei Y, He YL, Cai YR, Wang XL and Chang YF. Correlation analysis of serum homocysteine with coronary heart disease patients and multiple biochemical indicators. Mod J Integr Tradit Chin West Med 2018; 27: 3228-3230.

[17] Chen B, Ma ZH, Zhang YJ, Tao JP, Hu Yu, Zeng JM and Chen Z. Correlation analysis between serum cystatin C and Hcy levels and severity of coronary artery disease in patients with acute coronary syndrome. Chin J Integr Med on Cardio-Cerebrovasc Dis 2018; 16: 2054-2056.

[18] Ballew SH and Matsushita K. Cardiovascular risk prediction in CKD. Semin Nephrol 2018; 38: 208-216.

[19] Li S, Guo Y, Zhao XY, Zou YH and Ruan YJ. Correlation study of serum SF, hs-CRP, Hcy, and Cys C levels and blood lipid indexes with carotid intima media thickness in elderly patients with essential hypertension. Prog Mod Biomed 2018; 18: 3892-3990.

[20] Wang H. New insights on cystatin c and cardiovascular risk. Adv Cardiovasc Dis 2018; 039: 1006-1008.

[21] Qin SG, Hu HG, Shao CJ, Liu LH, Bu WJ and Xiao C. The correlation of folic acid, vitamin B6, homocysteine and cystatin C with the degree of lesion of patients with diabetic nephropathy. Lab Med Clin 2018; 15: 2371-2373.

[22] Zhou L, Li JJ, Wang KC and Liao XC. The predictive value of cystatin-C and homocysteine for coronary heart disease and stenosis degree. Pract J Clin Med 2019; 16: 128-130.