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IMPAIRMENT OF RENAL FUNCTION DETERMINED BY CREATININE AND CYSTATIN C LEVELS IN PATIENTS WITH HYPERTENSION AND FREQUENT EXTRASYSTOLES

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156 patients with essential hypertension stage II were examined, among them 124 had frequent extrasystoles, and 32 did not have heart rhythm disorders. Another 30 practically healthy individuals entered the control group. All participants of the study underwent a complete clinical, laboratory, and instrumental examination, including the level of microalbuminuria, electrolytes, creatinine, and cystatin C with the calculation of the glomerular filtration rate. In patients with hypertension, the level of cystatin C was significantly higher compared to the control group ($p<0.001$). In patients with essential hypertension and extrasystoles, the average level of cystatin C was significantly higher than in patients without extrasystoles ($p<0.05$). The highest level of cystatin C was noted in patients with hypertension and ventricular extrasystoles. It was significantly higher compared to patients with supraventricular extrasystoles ($p<0.05$), patients without arrhythmias ($p<0.001$), and practically healthy subjects ($p<0.001$). In patients with stage II essential hypertension, the extrasystoles of ventricular origin were associated with an increase in the frequency of microalbuminuria, the highest level of cystatin C, the decrease in the glomerular filtration rate (both creatinine and cystatin), and an increase in the number of patients with a glomerular filtration rate of less than 60 ml/min/1.73 m^2. The mean values of the glomerular filtration rate calculated with cystatin C were higher than the corresponding values of the glomerular filtration rate calculated by creatinine.

Key words: essential arterial hypertension, extrasystole, microalbuminuria, blood electrolytes, creatinine, cystatin C, glomerular filtration rate.

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ПОРУШЕННЯ ФУНКЦІЇ НИРОК, ВИЗНАЧЕНІ ЗА РІВНЯМИ КРЕАТИНІНУ ТА ЦИСТАТИНУ С, У ПАЦІЄНТІВ З ГІПЕРТОНІЧНОЮ ХВОРОБОЮ І ЧАСТОЮ ЕКСТРАСИСТОЛІЄЮ

Було обстежено 156 хворих з гіпертонічною хворобою II стадії, серед них 124 мали часту екстрасистолію, а 32 не мали порушень серцевого ритму. Ще 30 практично здорових осіб увійшли до групи контролю. Усім включеним у дослідження було проведено повне клініко-лабораторне та інструментальне обстеження, в тому числі визначення рівня мікроальбумнурії, електролітів, креатиніну та цистатину С з розрахунком швидкості клубокової фільтрації. Виявлено, що у хворих на гіпертонічну хворобу рівень цистатину С був суттєво вищий, в порівнянні з контролем ($p<0,001$), при цьому при наявності екстрасистолії середній вміст цистатину С був достовірно вищий, ніж у пацієнтів без екстрасистол ($p<0,05$). Найвищий рівень цистатину С був зафіксований у хворих з гіпертонічною хворобою і шлуночковою екстрасистолією, що достовірно відрізнялось від відповідного рівня цистатину С у пацієнтів з суправентрикулярною екстрасистолією ($p<0,05$), пацієнтів без аритмій ($p<0,001$) та практично здорових осіб ($p<0,001$). У хворих з гіпертонічною хворобою II стадії шлуночковий варіант екстрасистолії асоціювався зі збільшенням частоти реєстрації мікроальбумінурії, найвищим рівнем цистатину С, зменшенням швидкості клубочкової фільтрації (як за креатиніном, так і за цистатином) та збільшенням кількості пацієнтів, що мають швидкість клубочкової фільтрації менше 60 мл/хв/1,73 $м^2$. Середні значення швидкості клубочкової фільтрації, розрахованої за цистатином С, були вищими відповідних значень швидкості клубочкової фільтрації, розрахованої за креатиніном.

Ключові слова: есенціальна артеріальна гіпертензія, екстрасистолія, мікроальбумінурія, електроліти крові, креатинін, цистатин С, швидкість клубочкової фільтрації.

The study is a fragment of the research project "Metabolic risk factors, cardiovascular remodeling and functional status of the kidneys in patients with cardiovascular disease. Possibilities of pharmacological correction", state registration No. 0119U101849.

The close cooperation between the cardiovascular system and the kidneys is well known. It is multifaceted and based on a feedback type. In this context, the kidney can act both as a target organ and an active part of systemic metabolic and vascular pathological processes. Malfunction of any link leads to activation of the renin-angiotensin-aldosterone system and sympathetic hyperactivation, development of endothelial dysfunction, and chronic systemic inflammation. Thus, a complex pathogenetic circle is closed, leading to the progression of heart and kidney dysfunction, myocardial and vascular wall remodeling, and increased morbidity and mortality. This pathophysiological condition in modern medicine is called the cardiorenal continuum [3, 6, 8].

In this context, the glomerular filtration rate (GFR) is of great importance, and a decrease in it should be considered an independent risk factor for the development and progression of cardiovascular

disease and an increase in cardiovascular mortality. A series of large population-based studies have shown that even an initial decline in renal function, when serum creatinine levels are within the reference range or slightly elevated, is accompanied by a huge increase in cardiovascular morbidity and mortality [1, 4, 5]. The results of numerous studies have confirmed that impaired kidneys' functional state in patients with hypertension is associated with a worsening of the cardiovascular prognosis [2, 12, 13]. Such data prompted researchers to identify and study in detail earlier markers of renal dysfunction, such as microalbuminuria (MAU) and cystatin C (CysC).

The ESH and ESC in their appendices to the guidelines for the treatment of arterial hypertension (AH) consider MAU as the most convenient, simple, and inexpensive marker of target organ damage and a risk factor for CV morbidity and mortality. MAU is the recommended test for all patients with hypertension. Its presence in patients with hypertension indicates a high risk of CV complications and requires appropriate approaches to hypertension therapy [10].

CysC is being actively studied as an early and most informative marker of renal dysfunction. Many studies have revealed a link between an increase in serum CysC and a decrease in GFR, calculated on its basis, and the incidence of cardiovascular events. It has been proven that this indicator is a more sensitive indicator of GFR decline than creatinine because it is not affected by such factors as age, gender, muscle mass, diet, physical activity, and race. At the same time, it serves as an effective marker for the early detection of renal failure even with a normal creatinine level [2, 3, 7, 9, 14].

The purpose of the study was to evaluate functional renal impairment in patients with hypertension and frequent extrasystoles by creatinine and cystatin C levels.

Materials and methods. The study included 124 patients with essential arterial hypertension (EH) of stage II and frequent symptomatic extrasystoles aged 27 to 75 (mean 58.2±0.9) years, who formed the main clinical population of the study. Among them, 74 patients had supraventricular (SVE) and 50 ventricular (VE) variants of this arrhythmia. In addition, we examined 32 patients with stage II EH without any cardiac arrhythmias (according to the Holter electrocardiogram monitoring (HM ECG)) aged 32 to 72 (mean 55.9±1.7) years, who formed the comparison group contrary to the main clinical population. We also examined 30 patients without cardiovascular and renal pathology, mean age of 53.1±0.3 years, who were included in the control group. In terms of the average age of patients and the percentage of men and women, the main group, the comparison group, and the control group had no significant differences ($p>0.05$), which indicated the age and gender homogeneity of the study participants.

All patients underwent a comprehensive clinical, instrumental, and laboratory examination, which included: 1) general clinical and anthropometric examination, blood pressure measurement; 2) ECG in 12 standard leads; 3) HM ECG; 4) echocardiography in M-, B-, and D-mode; 5) assessment of the functional state of the kidneys (presence and level of MAU, blood electrolytes, cystatin C and creatinine levels with GFR calculation).

The statistical processing of the study results was carried out using the software StatSoft Statistic v. 12.0. The results were presented in the form of median and interquartile range with the indication of the 25th and 75th percentiles and in the form of percentages (%), which reflected the frequency of the parameter in the sample. Comparison of relative values (%) was performed using the χ^2 criterion, and quantitative values of independent samples - using the Kruskal-Wallis criterion.

Results of the study and their discussion. To assess the functional state of the kidneys, in addition to the routine electrolytes levels, creatinine, and calculation of GFR using the CKD- EPI formula, we also revealed the presence and the level of MAU, CysC level, and calculated GFR by cystatin C (adapted CKD-EPI formula, online calculators https://www.mdcalc.com/calc/3939/ckd-epi-equations-glomerular-filtration-rate-gfr (Table 1).

The analysis of the data showed that the mean creatinine level in patients with extrasystole did not exceed the reference values and significantly differed only from the control group (85 μmol/l in patients with SVE and 89 μmol/l in patients with VE vs. 70 μmol/l, $p<0.04$). Patients with extrasystoles had higher sodium levels than patients without extrasystoles (142 mmol/l in patients with SLE and 141 mmol/l in patients with EH vs. 139 mmol/l, $p<0.04$). The sodium level in patients of the control group was 140 mmol/l, which had no significant difference between the hypertensive patients in total and the comparison group. The index (potassium/sodium)*100 in patients with extrasystole was significantly lower than in patients without arrhythmia (2.92 vs. 3.09, $p<0.04$) and patients without CV and renal pathology (2.92 vs. 3.08, $p=0.04$). The largest number of patients with microalbuminuria was recorded in the group of patients with EH and VE, which had significant statistical differences compared to the patients with EH and SVE (52.0 % vs. 32.4 %, $p=0.03$), patients with EH without arrhythmias (52.0 % vs. 25.0 %, $p=0.02$), and the control group (52.0 % vs. 20 %, $p<0.01$). The mean level of microalbuminuria in patients with EH without

extrasystoles was significantly higher than the level of MAU in patients of the control group (280 mg/ml vs. 120 mg/ml, p<0.05). The GFR (calculated by creatinine) in all 3 groups of patients with EH was significantly lower compared with relatively healthy individuals (64 ml/min/1.73 m^2 in patients without extrasystoles, 53 ml/min/1.73 m^2 in patients with SVE and 50 ml/min/1.73 m^2 in patients with EH vs. 91 ml/min/1.73 m^2, respectively, p<0.001) (Fig. 1).

The lowest eGFR was recorded in patients with VE, which was significantly different from patients without extrasystoles (50 vs. 64 ml/min/1.73 m^2, p=0.04). The distribution of patients by eGFR showed that 98.0 % of patients with VE and 97.3 % of patients with SVE had eGFR less than 90 ml/min/1.73 m^2, which was significantly different from patients without arrhythmias, who were 81.3 % (p<0.008). Another 74.0 % of patients with EH and 63.5 % of patients with SVE had a GFR of less than 60 ml/min/1.73 m^2, which was statistically different from patients without extrasystoles (40.6 %, p<0.03). 28.1 % of patients in the comparison group, 20.3 % of patients with EH and SVE, and 30.0 % of patients with EH and VE had a GFR of less than 45 ml/min/1.73 m^2, without a significant difference between them.

Table 1

Functional state of the kidneys in patients with hypertension and different variants of extrasystole

Parameters of the kidneys' functional state	Patients with EH without extrasystoles	Patients with EH and frequent SVE	Patients with EH and frequent VE	P
	Group 1 (n=32)	Group 2 (n=74)	Group 3 (n=50)	
Creatinine, μmol/l	74 (58; 97)	85 (78; 92)*	89 (82; 94)*	ns
Potassium, mmol/l	4.3 (4.0; 4.5)	4.20 (4.00; 4.33)	4.17 (4.02; 4.30)	ns
Sodium, mmol/l	139 (138; 141)	142 (138; 145)	141 (139; 145)	P1-2=0.03 P1-3=0.04
(Potassium/Sodium)*100	3.09 (2.86; 3.26)	2.92 (2.80; 3.08)*	2.92 (2.83; 3.05)*	P1-2=0.04 P1-3=0.03
Presence of MAU, number (%)	8 (25.0 %)	24 (32.4 %)*	26 (52.0 %)**	P1-3=0.02 P2-3=0.03
MAU in mg/ml	280 (105; 330)*	160 (120; 255)	135 (100; 210)	ns
GFR by creatinine, ml/min/1.73 m^2	64 (42; 87)***	53 (46; 67)***	50 (44; 60)***	P1-3=0.04
GFR < 90 ml/min/1.73 m^2	26 (81.3 %)	72 (97.3 %)	49 (98.0 %)	P1-2=0.004 P1-3=0.008
GFR < 60 ml/min/1.73 m^2	13 (40.6 %)	47 (63.5 %)	37 (74.0 %)	P1-2=0.03 P1-3=0.003
GFR < 45 ml/min/1.73 m^2	9 (28.1 %)	15 (20.3 %)	15 (30.0 %)	ns
Cystatin C, mg/l	1.01 (0.85; 1.23)*	1.14 (1.00; 1.38)**	1.25 (1.10; 1.38)***	P1-2=0.02 P1-3=0.001 P2-3=0.04
GFR by cystatin C, ml/min/1.73m^2	74 (55; 94)***	63 (51; 74)***	54 (48; 65)***	P1-2=0.03 P1-3=0.002 P2-3=0.02
GFR < 90 ml/min/1.73 m^2	23 (71.9 %)	68 (91.9 %)	48 (96.0 %)	P1-2=0.007 P1-3=0.002
GFR < 60 ml/min/1.73 m^2	10 (31.3 %)	31 (41.9 %)	32 (64.0 %)	P1-3=0.004 P2-3=0.02
GFR < 45 ml/min/1.73 m^2	2 (6.3 %)	11 (14.9 %)	8 (16.0 %)	ns

Notes: 1. ns – not significant, p>0.05; 2. MAU – microalbuminuria; GFR – glomerular filtration rate; 3. Intergroup difference significance of absolute values was calculated by the Kruskal-Wallis ANOVA test & Median test, and percentages – by the χ^2-test; 4. The sign "*" indicates the significance of the difference between the comparison and the control group (n=30), p<0.05; "**" – p<0.01 and "***" – p<0.001.

The mean level of CysC in patients with frequent extrasystoles was significantly higher compared with patients without arrhythmias (p<0.02) and relatively healthy individuals (p<0.01). At the same time, the highest level of CysC was recorded in patients with a ventricular variant of extrasystole, which was significantly different from patients with a supraventricular variant (1.25 vs. 1.14 mg/l, p=0.04) and patients without extrasystoles (1.25 vs. 1.01 mg/l, p=0.001). It should be noted that the mean values of GFR calculated by CysC were higher than the corresponding values of GFR calculated by creatinine, but without significant differences between them (Fig. 2).

The GFR by CysC in all patients with EH was significantly lower than in the control group (relatively healthy individuals) (74 ml/min/1.73 m^2 in patients without extrasystole, 63 ml/min/1.73 m^2 in patients with SVE and 54 ml/min/1.73 m^2 in patients with EH vs. 94 ml/min/1.73 m^2, respectively, p<0.001). The mean GFR by CysC in patients with extrasystole was significantly lower than in patients

without extrasystole (54 ml/min/1.73 m^2 in patients with VE and 63 ml/min/1.73 m^2 in patients with SVE vs. 74 ml/min/1.73 m^2, p<0.03). Analysis of the level of GFR depending on the topical variant of extrasystole revealed that the lowest level of GFR was recorded in patients with VE, which was significantly different from patients with SVE (54 vs. 63 ml/min/1.73 m^2, p=0.02). The distribution of patients depending on the level of GFR showed that 96.0% of patients with VE and 91.9 % of patients with SVE had a GFR of less than 90 ml/min/1.73 m^2, while the number of patients in the comparison group in this category was significantly lower (71.9 %, p<0.007). The highest percentage of patients with a GFR less than 60 ml/min/1.73 m^2 was recorded in the group of patients with frequent VE, which was significantly different from patients with SVE and patients without arrhythmias (64.0 % vs. 41.9 % and 31.3 %, p<0.02). Another 6.3 % of patients in the comparison group, 14.9 % of patients with SVE, and 16.0 % of patients with VE had a GFR of less than 45 ml/min/1.73 m^2, without significant differences between them.

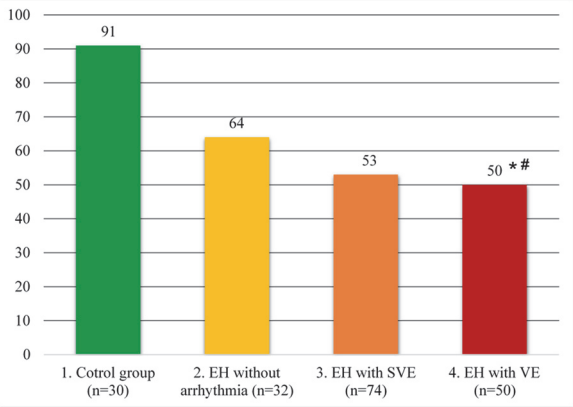

Fig. 1. GFR by creatinine (in ml/min/1.73 m2) in different clinical groups of patients. Notes (hereinafter): * – the significance of the difference compared to EH without arrhythmias p<0.04; # – the significance of the difference compared to the control group p<0.001.

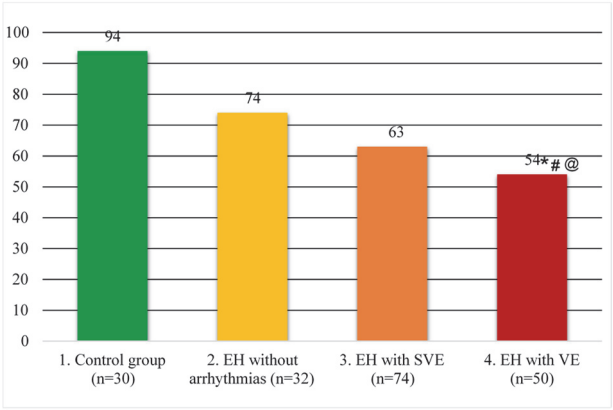

Fig. 2. GFR by Cystatin C (in ml/min/1.73 m2) in different clinical groups of patients. Note: @ – p=0.02 compared to patients with EH and SVE.

Hypertension and extrasystole (especially of ventricular origin) are known to lead to cardiac remodeling and dysfunction. It is known that cardiac remodeling is accompanied by certain inflammatory changes (apoptosis, atrial fibrosis, impaired calcium transport, and regulation of connexin, etc.). CysC is often referred to as an inflammatory marker because it is produced during inflammation by cells containing a nucleus [9, 11], which can explain the increase in the level of this peptide in patients with hypertension and extrasystole.

Our findings are consistent with the statement that CysC is currently the “gold standard” and prognostic marker for renal function [3, 6]. They allow us to consider an increased CysC level as an additional marker of increased cardiovascular risk. In patients with EH and extrasystole, the mean creatinine level (the study included patients whose creatinine level did not exceed the reference values 62–115 µmol/l in men and 53–97 µmol/l in women) was significantly higher only compared to healthy individuals. In patients with stage II EH, the presence of frequent extrasystoles was associated with increased levels of cystatin C, sodium, decreased potassium-to-sodium ratio, and decreased renal filtration function, as determined by the GFR (eGFR). In addition, we divided all patients according to the value of GFR, because several meta-analyses have identified a critical level of GFR at which the risk of cardiovascular and overall mortality begins to increase, which is approximately 75 ml/min/1.73 m^2 [1, 5, 7]. In patients with stage II EH and frequent extrasystoles, there was an increase in the number of patients with a GFR of less than 90 (by creatinine and CysC) and less than 60 ml/min/1.73 m^2 (by creatinine). In patients with stage II EH, the presence of ventricular extrasystoles is associated with the highest level of cystatin C, a decrease in GFR (both by creatinine and cystatin), and an increase in the number of patients with microalbuminuria and GFR less than 60 ml/min/1.73 m^2 (by CysC). The mean values of GFR calculated by CysC were higher than the corresponding values of GFR calculated by creatinine. It is known that CysC is currently used as a more accurate and more sensitive marker of renal dysfunction than creatinine [1, 6, 14].

According to our study, patients with stage II EH showed a decrease in GFR compared with healthy subjects, and the lowest GFR (both creatinine and cystatin C) was recorded in patients with stage II EH and frequent VE, which can be explained, by the literature data, through the more severe

hemodynamic and metabolic disorders in ventricular extrasystolic arrhythmia but this issue requires further study [4, 5, 11].

Conclusions

1. It was determined that in patients with stage II EH, the serum level of CysC was significantly higher (by 23.3 %) than in controls (1.16 (1.00; 1.37) vs. 0.89 (0.63; 1.04) mg/L, $p<0.0001$). The highest level of CysC was recorded in patients with VE, which was 45.3 % ($p<0.0001$) higher than the corresponding level in the control group, 23.8 % ($p<0.001$) higher in patients with stage II EH without arrhythmias, and 9.6 % ($p<0.05$) higher in patients with SVE.

2. Patients with stage II EH showed a significant decrease in GFR compared with controls ($p<0.001$), and in patients with stage II EH and VE, the GFR (both by creatinine and by CysC) was not only the lowest but also less than 60 ml/min/1.73 m^2 (50 (44; 60) and 54 (48; 65) ml/min/1.73 m^2).

References

1. Jin S, Xu J, Shen G, Gu P. Predictive value of circulating cystatin C level in patients with acute coronary syndrome: a meta-analysis. Scand J Clin Lab Invest. 2021; 81 (1): 1–7. https://doi.org/10.1080/00365513.2020.1846212

2. Kuzminova NV, Ivankova AV, Lozinsky SE, Knyazkova II, Ivanova EI, Kulchytska OM, et al. Accordance of clinical and instrumental profile to cystatin c level in patients with stage II hypertension and frequent extrasystole. World of Medicine and Biology. 2022; 2 (80): 89–93.

3. Kuzminova NV, Ivankova AV, Lozinsky SE, Knyazkova II, Kulchytska OM, et al. State of kidney function and features of metabolic status changes in patients with hypertensive disease with different forms of extrasystols. World of Medicine and Biology. 2019; 3 (69): 83–89.

4. Pottel H, Delanaye P, Schaeffner E. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. 2017; Nephrol. Dial. Transplant. 32 (3): 497–507. https://doi.org/10.1093/ndt/gfw425

5. Rothenbacher D, Rehm M, Iacoviello L, Costanzo S, Tunstall-Pedoe H, Belch JJF et al. Contribution of cystatin C- and creatinine-based definitions of chronic kidney disease to cardiovascular risk assessment in 20 population-based and 3 disease cohorts: the BiomarCaRE project. BMC Medicine. 2020; 18 (1): 13. https://doi.org/10.1186/s12916-020-01776-7

6. Stevens PE, Levin A. Kidney Disease: Improving global Outcomes (KDIGO) CKD Work group. KDIGO 2012 Clinical Practice guideline for the for the Evaluation and Management of Chronic Kidney Disease. Ann. Intern. Med. 2013; 158 (11): 825–30. https://doi.org/10.7326/0003-4819-158-11-201306040-00007

7. Sun Y, Lu Q, Cheng B, Tao X. Prognostic value of cystatin C in patients with acute coronary syndrome: A systematic review and meta-analysis. Eur. J. Clin. Invest. 2021; 51 (3): e13440. https://doi.org/10.1111/eci.13440

8. Teslenko YV, Myakonkova LO, Teslenko Early cardiac rehabilitation in acute myocardial infarction patients and its features. World of Medicine and Biology. 2021; 4 (78): 166–171.

9. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D. et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75: 1334–57. https://doi.org/10.1161/HYPERTENSIONAHA.120.15026

10. Wang S, Lin X, Zhou J, Li M, Song D. Association between serum cystatin C level and cognition in older adults: a cross-sectional analysis. Front Neurosci. 2023; 17: 1200763. https://doi.org/10.3389/fnins.2023.1200763

11.Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39 (33): 3021–3104. https://doi.org/10.1093/eurheartj/ehy339

12. Xu TY, Yang Y, Li JJ, Li Y, Wang JG. Left ventricular deformation in relation to the geometric pattern in hypertensive patients. Medicine (Baltimore). 2019; 98 (4): e14257. https://doi.org/10.1097/MD.0000000000014257

13. Yang S, Song L, Zhao L, Dong P, Lai L, Wang H. Predictive value of cystatin C in people with suspected or established coronary artery disease: A meta-analysis. Atherosclerosis. 2017; 263: 60–7. https://doi.org/10.1016/j.atherosclerosis.2017.05.025

14. Zhu Z, Zhong C, Xu T, Wang A, Peng Y, Xu T et al. Prognostic significance of serum cystatin C in acute ischemic stroke patients according to lipid component levels. Atherosclerosis. 2018; 274: 146–51. https://doi.org/10.1016/j.atherosclerosis.2018.05.015

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