Original Paper

Crosstalk of Various Biomarkers That Might Provide Prompt Identification of Acute or Chronic Cardiorenal Syndromes

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Key Words

Cardiorenal syndromes · Cystatin C · Modification of Diet in Renal Disease formula · Xanthine oxidoreductase

Abstract

Introduction: Pathophysiological interaction between the heart and kidneys represents the basis for clinical entities called cardiorenal syndromes. The purpose of the study was to assess the relations between acute and chronic cardiorenal syndromes and biomarkers [advanced oxidation protein products, brain natriuretic peptide, malondialdehyde, xanthine oxidoreductase (XOD), xanthine oxidase, xanthine dehydrogenase, interleukin 8, cystatin C, plasminogen activator inhibitor-1, high-sensitive troponin T, C-reactive protein and glomerular filtration rate, measured by the Modification of Diet in Renal Disease (MDRD) formula], to hypothesize biomarkers that might provide a prompt identification of acute or chronic cardiorenal syndromes, and to distinguish acute versus chronic types of these syndromes. **Methods:** A total of 114 participants were enrolled in this study, i.e. 79 patients divided into subgroups of acute and chronic cardiorenal syndromes and 35 volunteers. **Results:** Nonadjusted odds ratio (OR) showed that there was a significant risk for acute cardiorenal syndrome with increased XOD activity ($p = 0.037$), elevated cystatin C concentration ($p = 0.038$) and MDRD ($p = 0.028$). Multivariable adjusted OR, on the other hand, revealed that only glomerular filtration rate measured by the MDRD formula had a significance for acute cardiorenal syndrome ($p = 0.046$). Nonadjusted OR showed a significant risk for chronic cardiorenal syndrome only in elderly ($p = 0.002$). Multivariable adjusted OR exhibited that age was the only risk factor for chronic cardiorenal syndrome ($p = 0.012$). **Conclusion:** Cystatin C, glomerular filtration rate measured by the MDRD equation and XOD were independent risk factors for acute cardiorenal syn-

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drome, while age remained an independent risk factor for chronic cardiorenal syndrome. When comparing ORs of evaluated parameters, the highest significance for acute cardiorenal syndrome was plasma concentration of cystatin C.

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Introduction

The pathophysiological interaction between the heart and kidneys represents the basis for clinical entities called cardiorenal syndromes (CRSs) [1]. An impairment in the function of one of them results in a dysfunction of or an injury to the other [2]. There is a need for early detection and monitoring of patients with CRSs; therefore, many novel cardiac and renal biomarkers have emerged to supplement traditional markers which have limited specificity and sensitivity. The most investigated biomarkers are: cardiac troponins, natriuretic peptides, and creatinine, as well as cystatin C and parameters of oxidative stress or proinflammatory cytokines.

Cystatin C was proposed as a marker of the glomerular filtration rate (GFR) in order to overcome the limitation of serum creatinine [3], especially for a small reduction in the GFR [4]. It is a member of a family of competitive inhibitors of lysosomal cysteine protease synthesized in all nucleated cells [5].

Xanthine oxidoreductase (XOD) in tissues and circulation exists in two forms, dehydrogenase (XD) and oxidase (XO), whose activity in the circulation is mainly elevated in coronary disease and endothelial dysfunction [6]. Malondialdehyde (MDA) is one of the most well-studied markers of lipid peroxidation, representing an indicator of oxidative stress in a number of cardiovascular disease models.

Advanced oxidation protein products (AOPP) measure highly oxidized proteins, mostly albumin. Recent studies have shown that the key molecule responsible for the AOPP reaction in human plasma is oxidized fibrinogen, resulting in an inhibition of fibrinolysis, thus the development of atherosclerosis, and cardiovascular risk.

Plasminogen activator inhibitor-1 (PAI-1) activation results in the suppression of the normal fibrinolytic system, followed by a prothrombotic state, and induced tissue damage. Increased expression of PAI-1 is connected with thrombosis, fibrosis, and cardiovascular disease [7].

Brain natriuretic peptide (BNP) is synthesized mostly in the conditions characterized by electrolyte and fluid retention, and therefore also by the expansion of effective plasma volume [8]. It is documented that ventricular hypertrophy and fibrosis can also induce the secretion of BNP [9].

Interleukin 8 (IL-8) is a proinflammatory chemokine associated with the promotion of neutrophil chemotaxis and degranulation, and is an important mediator of the immune reaction in the innate immune system response. C-reactive protein (CRP) is a part of the acute-phase response to acute and chronic inflammation.

The levels of high-sensitive troponin T (hsTnT) serve as a risk stratification in patients with stable coronary artery disease, heart failure, and noncardiac disease conditions, and are detectable at a very low concentration.

Due to these findings, the purpose of the present study was to assess relations and differences between acute and chronic CRSs and the following biomarkers: AOPP, BNP, MDA, XOD, XO, XD, IL-8, cystatin C, PAI-1, hsTnT, CRP and GFR measured by the Modification of Diet in Renal Disease (MDRD) formula. Another aim of the present study was to hypothesize among them, by multivariate modeling, the biomarkers that might provide a prompt identification of acute or chronic CRSs, as well as to distinguish acute versus chronic types of these syndromes.

Methods

A total of 114 participants (79 patients and 35 healthy volunteers) were enrolled in this study at the Clinic for Nephrology, Dialysis and Transplantation, Clinic for Cardiology, Clinical Centre Nis, and the Medical Faculty, University of Nis, Serbia, between March and November 2013. The main clinical group consisted of 79 patients, 50 (63.3%) men and 29 (36.7%) women, mean age 70.72 ± 9.26 years, divided into 5 different subcategories of CRSs according to ADQI (Acute Dialysis Quality Initiative) consensus [10], each of them with different pathophysiological mechanisms. Within the main clinical group, we formed two subgroups: acute versus chronic CRSs. Subtypes 1 and 3 of the CRSs were considered as acute CRS, and types 2, 4, and 5 were regarded as chronic CRS. Subtype 5 [35 (44.3%) participants] consisted exclusively of patients with type 2 diabetes mellitus.

The subgroup of patients with the acute CRSs consisted of 31 (39.24%) patients, 18 men and 13 women, mean age 69.74 ± 9.46 years, while the subgroup of patients with chronic CRSs consisted of 48 (60.75%) patients, 32 men and 16 women, mean age 71.35 ± 9.18 years. The Ethics Committee of the Medical Faculty, University of Nis approved the study (number 01-6481-9), and fully informed written consent was obtained from each patient prior to the investigation. The control subjects (18 men and 17 women), without renal and cardiovascular disease, were obtained from hospital staff and were age and sex matched with the patients in the clinical group.

A fasting blood sample (5 ml) was obtained from each participant and stored at -80°C until biochemical analysis. Biochemical measurements were obtained using standard clinical laboratory methods, and the analysis was performed on Erba XL600, Germany. hsTnT was measured with apparatus T Cobas 411 Roche®. CRP was measured using immunonephelometric assays (Olympus AU400). PAI-1 (DSE100), IL-8 (D8000C), and cystatin C (DSCTC0) were measured in plasma samples using a commercially available ELISA kit from R&D Systems, Quantikine, Abingdon, UK.

AOPP were determined in plasma mixed with H_2O , acetic acid and potassium iodide. The absorbance was read spectrophotometrically at 340 nm and compared with a solution of chloramine T dissolved in the same buffer. The data were expressed as millimoles per liter of chloramine equivalents and related plasma total protein [11].

The MDA content was assayed in plasma and red blood cells according to the method of Andreeva et al. [12]. XOD and XO were measured in plasma according to the liberation of uric acid by using xanthine as a substrate [13], in the presence of NADH (for XOD) or absence of NADH (for XO) when only molecular oxygen was an electron acceptor [14]. The XD activity was calculated by subtracting the XO activity from XOD. For the estimation of GFR, we used the MDRD formula [15].

Statistical Analyses

The characteristics of the study group were expressed as mean $\pm$ SD (continuous variables) with number and percentages in brackets (categorical variables). We compared clinical and biochemical data of patients in the clinical group with different types of CRSs and the control group using the Student t test for normally distributed data (expressed as mean $\pm$ SD) and the Mann-Whitney U test for data that were not normally distributed. Evaluated parameters between acute and chronic CRSs and the control group were compared with the Kruskal-Wallis test, and post hoc examination was done with the Mann-Whitney U test. Univariate logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for GFR <60 ml/min/1.73 m². Adjusted OR was calculated for statistically significant factors in the univariate model and factor with $p < 0.10$. All analyses were performed with SPSS version 10.0 (SPSS, Chicago, Ill., USA) at the significance level set at $p < 0.05$.

Results

Clinical and biochemical data of the clinical and control groups are presented in table 1. Significant differences were found between these groups in the following: creatinine ($p < 0.001$), GFR ($p < 0.001$), uric acid ($p = 0.002$), urea ($p < 0.001$), albumin ($p = 0.002$), urinary albumin creatinine index ($p = 0.030$), glycemia ($p < 0.001$), triglycerides ($p = 0.001$), systolic ($p < 0.001$) and diastolic blood pressure ($p = 0.031$), ejection fraction ($p = 0.001$) and left

Table 1. Clinical and biochemical data of the clinical and control group

Parameter	Clinical group	Control group	t/Z	p
Age, years	70.72±9.26	69.55±32	1.079	0.286
Creatinine, µmol/l	361.00±282.94	77.42±14.92	3.897	<0.001***
GFR by MDRD, ml/min/1.73 m ²	53.15±23.61	92.32±17.92	6.428	<0.001***
Uric acid, µmol/l	435.58±203.09	249.67±44.16	2.881	0.002**
Urea, mmol/l	20.88±14.40	3.37±0.64	4.037	<0.001***
Albumin, g/l	35.09±5.45	42.67±3.38	3.169	0.002**
UACI, mg/mmol	68.89±134.04	0.73±0.43	2.155	0.030*
Hemoglobin, g/l	116.15±24.79	131.50±11.62	1.738	0.082
Na, mmol/l	137.75±4.77	139.67±0.82	1.513	0.130
K, mmol/l	4.89±0.99	4.27±0.45	1.870	0.061
CaxP, mmol/l	3.35±1.50	2.55±0.45	1.500	0.134
Glycemia, mmol/l	7.06±3.12	4.72±0.39	2.992	<0.001***
Triglycerides, mmol/l	1.96±0.89	0.89±0.42	3.056	0.001***
Total cholesterol, mmol/l	4.91±1.42	4.08±0.73	1.487	0.137
LDL cholesterol, mmol/l	2.84±1.23	2.44±0.62	0.754	0.451
HDL cholesterol, mmol/l	1.21±0.53	1.30±0.29	1.269	0.204
Systolic blood pressure, mm Hg	130.67±26.75	101.82±8.15	7.219	<0.001***
Diastolic blood pressure, mm Hg	69.89±15.36	62.27±8.76	2.160	0.031*
Ejection fraction, %	46.84±14.08	72.80±2.95	4.091	0.001***
Left ventricular mass index, g/m ²	302.94±94.94	133.24±24.56	3.596	<0.001***

Data are expressed as means ± SD, compared with the Student t test and the Mann-Whitney U test (coefficient of variation >30%). Figures in bold are significant. * p < 0.05, ** p < 0.01, *** p < 0.001. UACI = Urinary albumine creatinine index; CaxP = calcium phosphorus product; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

ventricular mass index (p < 0.001); all data are presented in table 1. Clinical and biochemical data of patients with acute and chronic CRSs are given in table 2. Significant differences were found between these subgroups in creatinine (p = 0.040) and albumin concentration (p < 0.001).

Evaluated parameters between acute and chronic CRSs and the control group are presented in table 3. There were significant differences between the plasma concentration of BNP (p < 0.001), AOPP (p = 0.003) and MDA (p = 0.002), the plasma activity of XOD (p < 0.001) and XD (p < 0.001), the plasma concentration of hsTnT (p < 0.001) and the GFR measured by the MDRD formula (p < 0.001), EPI creatinine (p = 0.020) and EPI cystatin C (p < 0.001), as well as the plasma concentration of cystatin C (p < 0.001) in acute and chronic CRS compared to the control group. The plasma concentration of CRP differed between all three groups (p < 0.001). There were no significant differences in the plasma concentration of IL-8 and PAI-1 between all three groups (table 3).

Nonadjusted ORs for acute CRS are presented in table 4, showing that there was a significant risk for acute CRS with increased XOD activity (OR = 1.015; 95% CI 1.001–1.030, p = 0.037), elevated cystatin C concentration (OR = 1.821; 95% CI 1.034–3.205, p = 0.038) and GFR measured by the MDRD formula (OR = 0.970; 95% CI 0.943–0.997, p = 0.028) (table 4). When comparing predictive values of evaluated parameters, the highest significance for acute CRS was plasma concentration of cystatin C (OR = 1.821). Multivariable adjusted OR showed that only MDRD had a significance for acute CRS (OR = 0.950; 95% CI 0.900–1.003, p = 0.046; table 5).

Nonadjusted ORs for chronic CRS are presented in table 6, showing that there was a significant risk for chronic CRS only in the elderly (OR = 1.058; 95% CI 1.021–1.096, p =

Table 2. Clinical and biochemical data of patients with acute and chronic CRSs

Parameter	Acute CRS	Chronic CRS	t/Z	p
Age, years	69.74±9.46	71.35±9.18	0.748	0.457
Creatinine, µmol/l	437.56±312.38	303.58±247.82	2.056	0.040*
GFR by MDRD, ml/min/1.73 m ²	23.62±17.55	30.89±21.08	1.496	0.135
Uric acid, µmol/l	481.45±288.51	408.06±125.20	0.330	0.741
Urea, mmol/l	24.24±16.31	18.62±12.68	1.298	0.194
Albumin, g/l	31.77±5.06	37.34±4.51	3.944	<0.001**
ACI index, mg/mmol	55.26±126.03	116.60±162.42	1.013	0.220
Hemoglobin, g/l	88.20±71.91	77.84±33.60	0.583	0.893
Na, mmol/l	137.48±4.48	137.92±5.01	0.379	0.449
K, mmol/l	4.92±0.96	4.88±1.03	0.166	0.969
CaxP, mmol/l	3.07±1.05	3.54±1.72	0.890	0.373
Glycemia, mmol/l	6.98±2.11	7.10±3.59	0.899	0.368
Triglycerides, mmol/l	2.02±0.81	1.92±0.96	0.689	0.491
Total cholesterol, mmol/l	4.76±1.68	5.01±1.24	0.728	0.466
LDL cholesterol, mmol/l	2.84±1.48	2.85±1.07	0.029	0.977
HDL cholesterol, mmol/l	1.06±0.35	1.31±0.60	1.944	0.052
Systolic blood pressure, mm Hg	125.15±28.52	127.96±26.07	0.432	0.651
Diastolic blood pressure, mm Hg	68.79±17.68	68.94±12.84	0.697	0.966
Ejection fraction, %	46.27±14.31	47.22±14.10	0.154	0.877
Left ventricular mass index, g/m ²	293.52±94.98	309.44±96.12	0.509	0.611

Data are expressed as means ± SD, compared with the Student t test and Mann-Whitney U test (coefficient of variation >30%). Figures in bold are significant. * p < 0.05, ** p < 0.001. ACI = Albumine creatinine index; CaxP = calcium phosphorus product; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3. Evaluated parameters between patients with acute and chronic CRSs and the control group

Parameter	Acute CRS	Chronic CRS	Control group	χ^2_{kw}	p
BNP, pg/ml	1,478.11±1,815.96	1,439.62±1,513.76	19.43±9.18 ^{a,b}	23.986	<0.001***
AOPP, µm/l	156.58±29.28	162.27±42.59	120.98±42.40 ^{a,b}	11.937	0.003**
MDA, µm/l	7.70±2.96	7.52±2.85	4.14±1.40 ^{a,b}	12.287	0.002**
XOD, IJ/l	132.55±33.37	121.19±44.36	76.62±21.25 ^{a,b}	22.877	<0.001***
XO, IJ/l	63.47±11.31	63.46±17.19	63.95±20.08	0.106	0.948
XD, IJ/l	69.08±33.19	57.73±50.40	12.66±30.85 ^{a,b}	16.609	<0.001***
IL-8, pg/ml	222.60±644.63	123.60±307.64	35.46±26.05	3.963	0.138
PAI-1, ng/ml	8.48±8.55	5.66±6.36	0.50±0.15	5.312	0.070
hsTnT, ng/ml	818.40±2,142.41	311.32±802.16	3.52±0.59 ^{a,b}	24.131	<0.001***
MDRD, ml/min/1.73 m ²	23.62±17.55	30.89±21.08	75.50±6.45 ^{a,b}	16.594	<0.001***
EPI, ml/min/1.73 m ²	29.19±25.85	29.38±24.89	78±7.75 ^{a,b}	7.786	0.020*
Cystatin C, mg/l	1.99±0.76	1.85±0.71	120.98±42.40 ^{a,b}	26.871	<0.001***
EPI cystatin C, ml/min/1.73 m ²	39.43±29.22	41.34±25.55	105.5±14.32 ^{a,b}	23.184	<0.001***
CRP, mg/l	112.42±85.13	18.42±31.88	1.27±0.73 ^{a-c}	24.420	<0.001***

Data are given as means ± SD. Figures in bold are significant. * p < 0.05, ** p < 0.01, *** p < 0.001. Difference between: ^a acute CRS vs. control, ^b chronic CRS vs. control, ^c acute vs. chronic CRS. Summary p was determined with the Kruskal-Wallis test, and post hoc examination with the Mann-Whitney U test.

Table 4. Nonadjusted OR and 95% CIs for acute CRS

Parameter	OR	95% CI	p
Male	0.982	0.407–2.370	0.968
Age (years)	1.027	0.994–1.061	0.110
Diabetes mellitus	1.828	0.753–4.443	0.183
BNP (pg/ml)	1.000	1.000–1.001	0.442
AOPP (μm/l)	1.001	0.990–1.012	0.861
MDA (μm/l)	1.100	0.945–1.281	0.218
XOD (IJ/l)	1.015	1.001–1.030	0.037*
XO (IJ/l)	1.000	0.972–1.028	0.982
XD (IJ/l)	1.013	1.000–1.026	0.053
IL-8 (pg/ml)	1.001	0.999–1.002	0.290
Cystatin C (mg/l)	1.821	1.034–3.205	0.038*
PAI-1 (ng/ml)	1.049	0.984–1.119	0.142
MDRD (ml/min/1.73 m ²)	0.970	0.943–0.997	0.028*

Figures in bold are significant. * p < 0.05.

Table 5. Multivariable adjusted OR and 95% CI for acute CRS

Parameter	OR	95% CI	p
XOD (IJ/l)	1.002	0.992–1.013	0.647
XD (IJ/l)	1.009	0.989–1.029	0.386
MDRD (ml/min/1.73 m ²)	0.950	0.900–1.003	0.046*
Cystatin C (mg/l)	1.395	0.090–1.735	0.219

Adjusted OR was calculated for statistically significant factors in the univariate model and factors with * p < 0.10. Figures in bold are significant.

Table 6. Nonadjusted OR and 95% CI for CRS

Parameter	OR	95% CI	p
Male	0.455	0.194–1.066	0.070
Age (years)	1.058	1.021–1.096	0.002*
Diabetes mellitus	1.286	0.548–3.017	0.564
BNP (pg/ml)	1.000	1.000–1.001	0.183
AOPP (μm/l)	1.010	0.998–1.021	0.097
MDA (μm/l)	1.094	0.947–1.263	0.223
XOD (IJ/l)	1.002	0.992–1.012	0.710
XO (IJ/l)	0.999	0.973–1.026	0.966
XD (IJ/l)	1.002	0.993–1.011	0.724
IL-8 (pg/ml)	1.000	0.999–1.001	0.609
Cystatin C (mg/l)	1.484	0.882–2.496	0.137
PAI-1 (ng/ml)	0.941	0.877–1.011	0.097
MDRD (ml/min/1.73 m ²)	0.990	0.970–1.011	0.361

Figures in bold are significant. * p < 0.01.

Table 7. Multivariable adjusted OR and 95% CI for chronic CRS

Parameter	OR	95% CI	p
Male	0.411	0.253–1.820	0.441
Age (years)	1.048	1.010–1.088	0.012*
AOPP (μm/l)	1.007	0.994–1.020	0.305
PAI-1 (ng/ml)	0.952	0.885–1.024	0.186

Adjusted OR was calculated for statistically significant factors in the univariate model and factors with *p < 0.10. Figures in bold are significant.

0.002). Multivariable adjusted OR revealed that age was the only risk factor for chronic CRS (OR = 0.048; 95% CI 1.010–1.088, p = 0.012; table 7).

The other evaluated parameters, i.e. AOPP, BNP, MDA, XO, XD, IL-8, PAI-1, hsTnT and CRP, did not have any significance for the occurrence of acute or chronic CRSs.

Discussion

In this study, we have shown that the plasma activity of XOD, the plasma concentration of cystatin C and GFR measured by the MDRD formula were possible parameters for the rapid identification of acute, but not chronic, CRS. Renal function in clinical practice is commonly expressed by serum creatinine levels. There are some serious limitations of this kind of measurement, because serum creatinine concentration depends on the muscle mass, tubular secretion, sex, age, and physical activity. There are two equations that are widely used for the estimation of GFR, i.e. the MDRD and the Cockcroft Gault formula, which can overcome the limitations of creatinine [3]. Cystatin C has a promising potential as a new biomarker of GFR. It is completely filtered in the glomeruli and catabolized in proximal tubules; therefore, plasma cystatin C concentration very likely depends on a GFR. Very recently, cystatin C has been proposed as a marker for cardiovascular diseases [3]. In conclusion, cystatin C plasma concentrations were associated with the progression of heart failure [16]. It was demonstrated that cystatin C was a strong predictor of the composite of mortality or hospitalization and mortality alone [17], and has also remained a strong predictor with multivariable analysis. This was not documented in our study, since after multivariable modeling the only biomarker for acute CRSs was GFR measured by the MDRD formula. The prognostic role of cystatin C was also assessed in the elderly population [18]. This study documented that all-cause mortality and death from cardiovascular events increased with the higher concentration of cystatin C. Other investigators [19] documented that after the comparison of renal function in three different manners (cystatin C, MDRD and creatinine concentration), they found that patients with the highest plasma concentration of cystatin C had the worst cardiovascular risk profile. In our study, cystatin C had the highest OR, compared to XOD and MDRD, indicating that it may have a benefit over potential biomarkers for acute CRS. Cystatin C was also documented as a useful tool in detecting early deterioration of renal function after hospitalization for acute CRS [20], and it has been suggested that it is highly sensitive to 'preclinical' kidney failure. Some studies suggest that cystatin C-GFR was better than creatinine-based estimates of GFR at GFR levels >60 ml/min/1.73 m² (CKD stages 1 and 2) [21].

All of these findings suggest cystatin C as a promising marker in cardiorenal pathology, but the reason why it is so still remains unclear. Moreover, its main advantage seems to be its greater sensitivity for the early detection of kidney dysfunction [22]. We should stress that

the plasma concentration of cystatin C still depends on some factors such as age, smoking, body mass index, sex and inflammatory biomarkers [23, 24]. Finally, in our results, cystatin C did not have any significance in the identification of chronic CRSs.

Still, we have to point out that it was highly expected for the plasma activity of XOD to have a significance for acute over chronic CRS. Higher XOD activity very likely represents acute vascular damage and XOD release from the endothelial cells, rather than de novo XOD formation in the endothelium. Age remained a risk factor for the occurrence of chronic CRS, mostly due to the physiological involution of the organs and numbered comorbidities in the elderly.

Conclusion

We have demonstrated that the plasma concentration of cystatin C, renal function measured by the MDRD equation and XOD plasma activity were potential parameters for the prompt identification of acute, but not for chronic, CRSs. Therefore, these parameters might present a good tool to distinguish acute versus chronic CRSs, independently from the primary organ damage. From our results, we may give some priority to the plasma concentration of cystatin C over MDRD measurement or XOD activity. The other evaluated parameters did not have any significance in distinguishing acute versus chronic CRSs.

Our results indicate that cystatin C is a potential biomarker for the rapid identification of acute compared to chronic CRSs in the group of patients with combined organ damage. These findings may provide to the clinicians a faster and easier differentiation of the patients with an unclear clinical presentation of CRSs, and possible prevention of irreversible changes of the affected organs.

Disclosure Statement

All authors declare no conflicts of interest.

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