

# Panel of serum biomarkers for non-invasive assessment of glomerular and tubular injury in patients with chronic glomerulonephritis with and without arterial hypertension

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**Aim:** to analyze histological kidney features in patients with chronic glomerulonephritis (CGN) with and without arterial hypertension (AH) and to assess the relationship between serum cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and interleukin-18 (IL-18) levels and histological signs of glomerular and tubulointerstitial kidney injury in patients with preserved renal function.

**Material and methods.** This observational study included 219 patients with biopsy-proven CGN and preserved renal function. Patients were stratified into two groups: CGN with AH (n = 149) and CGN without AH (n = 70). A control group consisted of 60 apparently healthy individuals. Serum levels of cystatin C, NGAL, and IL-18 were measured using enzyme-linked immunosorbent assay. Renal biopsy specimens were evaluated using standard semi-quantitative criteria. Statistical analyses included group comparisons, Spearman's rank correlation and receiver operating characteristic curve analysis.

**Results.** Patients with CGN and AH demonstrated significantly higher serum levels of IL-18, cystatin C, and NGAL compared with patients without AH and controls ( $p < 0.05$ ). Median IL-18 levels were highest in the CGN with AH group, followed by the CGN without AH group and controls. Similar patterns were observed for cystatin C and NGAL. Serum cystatin C levels correlated with histological markers of glomerular injury, whereas NGAL and IL-18 were associated with tubulointerstitial damage. Biomarker elevations were more pronounced in patients with concomitant AH.

**Conclusions.** A serum multimarker approach combining cystatin C, NGAL, and IL-18 effectively reflects compartment-specific glomerular and tubulointerstitial kidney injury in patients with CGN and preserved renal function. Arterial hypertension significantly enhances biomarker expression and structural kidney damage, supporting the clinical value of multimarker strategies for non-invasive assessment of renal injury in CGN.

## Ключові слова:

біопсія нирок, хронічний гломерулонефрит, біомаркери, цистатин С, асоційований з желатиназою нейтрофілів ліпокалін (NGAL), інтерлейкін-18, патологія нирок.

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## Панель сироваткових біомаркерів для неінвазивної оцінки гломерулярного та тубуло-інтерстиціального ушкодження нирок у пацієнтів із хронічним гломерулонефритом з артеріальною гіпертензією та без неї

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**Мета роботи** – проаналізувати гістологічні особливості нирок у пацієнтів із хронічним гломерулонефритом (ХГН) з артеріальною гіпертензією (АГ) та без неї, а також оцінити зв'язок між рівнями сироваткового цистатину С, ліпокаліну, асоційованого з желатиназою нейтрофілів (NGAL), та інтерлейкіну-18 (IL-18) і гістологічними ознаками гломерулярного та тубуло-інтерстиціального ушкодження у пацієнтів зі збереженою функцією нирок.

**Матеріали і методи.** Обстежено 219 пацієнтів із біопсійно підтвердженим ХГН та збереженою функцією нирок. Пацієнтів поділили на дві групи: ХГН з АГ (n = 149) та ХГН без АГ (n = 70). До контрольної групи залучено 60 умовно здорових осіб. Рівні цистатину С, NGAL та IL-18 визначено імуноферментним методом (ELISA). Зразки біопсії нирки оцінено за стандартними напівкількісними критеріями. Статистичний аналіз передбачав порівняння груп, кореляційний аналіз Спірмена та ROC-аналіз.

**Результати.** Пацієнти з ХГН та АГ мали достовірно вищі рівні IL-18, цистатину С та NGAL порівняно з пацієнтами без АГ і групою контролю ( $p < 0,05$ ). Медіана рівня IL-18 найвища в групі ХГН з АГ, нижча у групі ХГН без АГ, найнижча – в контролі. Аналогічні патерни зафіксовано для цистатину С та NGAL. Рівень сироваткового цистатину С корелював із маркерами гломерулярного ушкодження, а NGAL та IL-18 асоціювалися з тубуло-інтерстиціальним ураженням. Підвищення рівнів біомаркерів більш виражене у пацієнтів із супутньою АГ.

**Висновки.** Мультимаркерний підхід, що поєднує цистатин С, NGAL та IL-18, ефективно характеризує компартмент-специфічне гломерулярне та тубуло-інтерстиціальне ушкодження нирок у пацієнтів із ХГН і збереженою функцією нирок. Артеріальна гіпертензія значно посилює експресію біомаркерів і структурне ураження нирок, що підтверджує клінічну цінність мультимаркерних стратегій для неінвазивного оцінювання ниркового ушкодження при ХГН.

Chronic glomerulonephritis (CGN) remains a major cause of chronic kidney disease (CKD) worldwide and is associated with substantial morbidity, particularly among patients of working age. Importantly, structural kidney damage may already be present at early stages of CGN, even when glomerular filtration rate (GFR) is preserved, contributing to long-term disease progression and adverse outcomes [1,2]. In this context, the identification of non-invasive biomarkers capable of reflecting subclinical glomerular and tubulointerstitial injury is of significant clinical importance.

Renal biopsy is considered the gold standard for assessing histopathological changes in CGN, providing essential information on disease activity, chronicity, prognosis, and therapeutic decision-making [3]. However, the invasive nature of biopsy, limited repeatability, and potential complications restrict its routine use, particularly for longitudinal monitoring. These limitations have stimulated increasing interest in circulating biomarkers that may serve as surrogates for histological kidney injury [4,5,6].

Traditional laboratory parameters, including serum creatinine, estimated GFR, and proteinuria, have well-recognized limitations in detecting early kidney damage. Serum creatinine is influenced by non-renal factors and lacks sensitivity in patients with preserved renal function, while proteinuria demonstrates limited specificity for the underlying structural lesions [5,7,8]. Consequently, contemporary nephrology has increasingly focused on biomarkers that reflect distinct compartments of renal injury.

Cystatin C has emerged as a sensitive marker of glomerular dysfunction and structural damage. Beyond its role as an alternative marker of GFR, elevated serum cystatin C levels have been associated with glomerulosclerosis and increased renal risk, even in patients with preserved renal function [7,8]. These properties make cystatin C a valuable indicator of early glomerular injury in CGN.

In parallel, biomarkers of tubular and tubulointerstitial injury have attracted growing attention, given the pivotal role of tubulointerstitial damage in CKD progression. Neutrophil gelatinase-associated lipocalin (NGAL) is widely recognized as a marker of tubular injury and interstitial fibrosis. Initially investigated in the setting of acute kidney injury, NGAL has subsequently demonstrated diagnostic and prognostic relevance in chronic kidney diseases, including glomerulonephritis [9,10]. Elevated serum NGAL levels have been associated with tubulointerstitial structural alterations and disease severity, independent of conventional renal function measures [6].

Interleukin-18 (IL-18), a pro-inflammatory cytokine involved in innate and adaptive immune responses, has also been implicated in kidney injury. Experimental and clinical data indicate that IL-18 contributes to tubular epithelial cell damage and inflammatory processes within the renal interstitium. Increased circulating levels of IL-18 have been linked to tubular injury and fibrosis, supporting its potential role as a biomarker of tubulointerstitial involvement in CGN [11,12].

While individual biomarkers provide valuable information, accumulating evidence suggests that a multimarker approach may offer superior diagnostic performance compared with single-marker strategies. Given the heterogeneous nature of CGN, no single biomarker can comprehensively reflect the full spectrum of glomerular

and tubulointerstitial injury. The combined assessment of markers reflecting different structural compartments of the kidney may therefore improve non-invasive evaluation and strengthen correlations with histopathological findings [4,6,13].

Arterial hypertension (AH) represents a critical modifier of disease severity in CGN and is closely associated with accelerated structural kidney damage. Patients with CGN and concomitant hypertension frequently exhibit more pronounced glomerular and tubulointerstitial lesions, emphasizing the importance of accounting for blood pressure status when interpreting biomarkers of renal injury [14,15].

Despite growing interest in non-invasive biomarkers, data integrating serum cystatin C, NGAL, and IL-18 within a unified, histology-correlated framework in patients with CGN and preserved renal function remain limited. In particular, the combined evaluation of glomerular and tubular injury markers in relation to renal histopathology and arterial hypertension has not been sufficiently explored.

## Aim

To analyze histological kidney features in patients with CGN with and without arterial hypertension and to assess the relationship between serum cystatin C, neutrophil gelatinase-associated lipocalin, and interleukin-18 levels and histological signs of glomerular and tubulointerstitial kidney injury in patients with preserved renal function.

## Material and methods

This observational study included a total of 219 patients with biopsy-proven CGN who were examined at Municipal Nonprofit Enterprise Zaporizhzhia Regional Clinical Hospital of Zaporizhzhia Regional Council. The diagnosis of CGN was established based on clinical presentation, laboratory findings and renal histopathology. All included patients had preserved renal function.

Patients were stratified into two clinical groups according to the presence or absence of AH: Group 1 (CGN with AH) included 149 patients, of whom 101 were men and 48 were women; Group 2 (CGN without AH) included 70 patients, including 52 men and 18 women.

A control group of 60 apparently healthy individuals without a history of kidney disease, AH, diabetes mellitus or cardiovascular disorders was included for comparison of serum biomarker levels. Hemoglobin and total cholesterol levels were within normal reference ranges.

Arterial hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg, or current use of antihypertensive medication.

Inclusion criteria: age  $\geq 18$  years; biopsy-confirmed diagnosis of CGN; preserved renal function, defined as estimated glomerular filtration rate (eGFR)  $\geq 60$  mL/min/1.73 m<sup>2</sup>; availability of renal biopsy material suitable for histopathological evaluation.

Exclusion criteria: acute kidney injury or rapidly progressive glomerulonephritis; diabetes mellitus; systemic inflammatory or autoimmune diseases other than CGN; active infection or malignancy; advanced chronic kidney disease (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>).

**Table 1.** Baseline clinical and laboratory characteristics of the study population

| Parameter, units of measurement            | CGN with AH, n = 149 | CGN without AH, n = 70 | Control, n = 60 |
|--------------------------------------------|----------------------|------------------------|-----------------|
| Age, years                                 | 34.6 ± 3.4           | 39.2 ± 8.1             | 32.8 ± 4.2      |
| Male, n (%)                                | 101 (67.8)           | 52 (74.3)              | 42 (70.0)       |
| Female, n (%)                              | 48 (32.2)            | 18 (25.7)              | 18 (30.0)       |
| Disease duration, months                   | 96.5 ± 7.8           | 49.3 ± 7.2             | –               |
| Nephrotic syndrome, %                      | 10                   | –                      | –               |
| Urinary syndrome, %                        | 88                   | –                      | –               |
| Remission, %                               | –                    | 71                     | –               |
| Proteinuria >1 g/day, %                    | 8                    | –                      | –               |
| Proteinuria, g/day                         | 1.1 ± 0.1            | 0.3 ± 0.02             | –               |
| Hemoglobin, g/L                            | 132.4 ± 1.1          | 135.5 ± 0.5            | –               |
| Serum albumin, g/L                         | 42.2 ± 0.5           | 45.0 ± 0.3             | –               |
| Total cholesterol, mmol/L                  | 5.4 ± 0.3            | 4.8 ± 0.3              | –               |
| Serum creatinine, μmol/L                   | 101.2 ± 3.0          | 95.1 ± 2.0             | –               |
| Serum urea, mmol/L                         | 5.5 ± 0.2            | 5.6 ± 0.1              | –               |
| eGFR (CKD-EPI), mL/min/1.73 m <sup>2</sup> | 90.5 ± 2.0           | 92.0 ± 2.2             | –               |

Data are presented as mean ± SD or n (%).

All participants underwent standardized clinical evaluation, including medical history and blood pressure measurement. Routine laboratory testing included serum creatinine, blood urea nitrogen, serum albumin, lipid profile and daily proteinuria assessment.

Estimated glomerular filtration rate was calculated using the CKD-EPI equation. Renal function parameters were assessed at the time of blood sampling for biomarker analysis.

Measurement of serum biomarkers. Serum concentrations of cystatin C, NGAL, and IL-18 were measured using commercially available enzyme-linked immunosorbent assay kits (IL-18 – Bender Medsystems (Austria); cystatin C, NGAL – BioVendor (Czech Republic) according to the manufacturers' protocols. All samples were analyzed in duplicate, and mean values were used for statistical analysis.

Renal biopsy was performed using a percutaneous ultrasound-guided technique according to standard clinical practice. Biopsy specimens were fixed in buffered formalin, embedded in paraffin, and processed for light microscopic evaluation.

Histopathological analysis of renal biopsy specimens was performed at the Laboratory of Pathohistological and Immunohistochemical Diagnostics of the Educational and Scientific Medical Center "University Clinic" of Zaporizhzhia State Medical and Pharmaceutical University under the supervision of Professor Valerii O. Tumanskyi, MD, PhD, DSc.

Glomerular and tubulointerstitial injury was evaluated using light, immunofluorescence, and electron microscopy blinded to biomarker data. Serial sections were stained with hematoxylin and eosin, Masson's trichrome, Van Gieson, periodic acid–Schiff (PAS), and periodic acid – methenamine silver (PAMS).

Histological assessment focused on parameters reflecting glomerular and tubulointerstitial injury. Glomerular lesions were evaluated using the following criteria: mesangial cellularity score; expansion of mesangial matrix; presence of glomerulosclerosis; endocapillary hypercellularity; thickening of the glomerular basement membrane; presence of fibrocellular crescents.

Tubulointerstitial lesions were assessed based on dystrophic and necrotic changes in tubular epithelial cells; thickening of the tubular basement membrane; interstitial inflammatory infiltration; interstitial fibrosis.

Histological findings were graded according to standard semi-quantitative criteria.

Statistical analysis was performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normality using the Shapiro–Wilk test. Data with normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median with interquartile range (25<sup>th</sup>;75<sup>th</sup> percentile). Categorical variables were reported as counts and percentages. Comparisons between groups (CGN with AH vs. CGN without AH) were conducted using the Student's t test or Mann–Whitney U test, as appropriate. Comparisons between patient groups and the control group were performed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test with post hoc analysis. Associations between serum biomarker levels (cystatin C, NGAL, and IL-18) and histopathological parameters were evaluated using Spearman's rank correlation coefficient. Diagnostic performance of serum biomarkers for the detection of specific histological lesions was assessed using receiver operating characteristic curve analysis. Sensitivity, specificity, and area under the curve (AUC) were calculated, and optimal cut-off values were identified using the Youden index. A two-sided p value <0.05 was considered statistically significant.

## Results

**Baseline clinical and laboratory characteristics.** The study included 219 patients with biopsy-proven CGN. Among them, 149 patients had AH (101 men and 48 women), while 70 patients had CGN without AH (52 men and 18 women). A control group consisted of 60 apparently healthy individuals (42 men and 18 women).

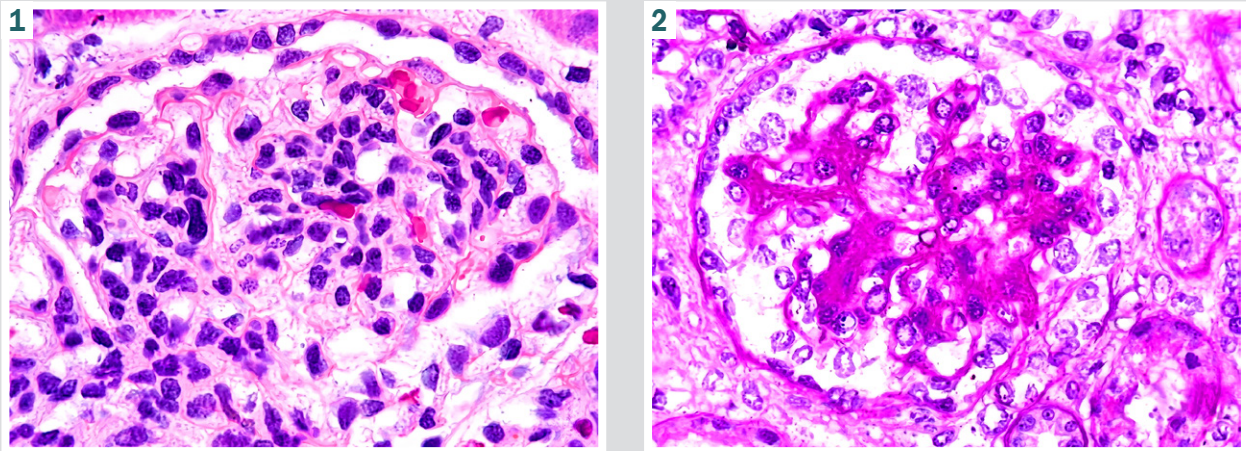
In the CGN with AH group, the mean age was 34.6 ± 3.4 years, and the mean disease duration was 96.5 ± 7.8 months. In patients with CGN without AH, the mean age was 39.2 ± 8.1 years, with a mean disease duration of 49.3 ± 7.2 months. The mean age of the control group was 32.8 ± 4.2 years.

In the CGN with AH group, nephrotic syndrome was observed in 10 % of patients, while urinary syndrome was present in 88 %. Proteinuria exceeding 1 g/day was detected in 8 % of cases, with a mean daily proteinuria of 1.1 ± 0.1 g/day.

In the CGN without AH group, clinical remission was documented in 71 % of patients, and mean daily proteinuria was significantly lower (0.30 ± 0.02 g/day).

Routine laboratory parameters demonstrated preserved renal function in both patient groups. Hemoglobin, serum albumin, cholesterol, creatinine, urea levels, and eGFR (CKD-EPI) were within ranges consistent with preserved kidney function, with no clinically meaningful differences between groups (Table 1).

Histopathological examination revealed that 91 % of patients had mesangial proliferative glomerulonephritis,



**Fig. 1.** Renal biopsy specimen from a patient with chronic glomerulonephritis and arterial hypertension.

**Fig. 2.** Renal biopsy specimen from a patient with chronic glomerulonephritis without arterial hypertension.

5 % membranous nephropathy, and 4 % membranous proliferative glomerulonephritis. Renal biopsy analysis revealed distinct differences in the severity of glomerular and tubulointerstitial lesions between patients with CGN with and without AH.

The glomerulus demonstrates pronounced diffuse mesangial cell proliferation with marked expansion of the mesangial matrix, leading to compression of capillary lumina. Thickening and structural irregularity of the glomerular basement membrane were evident. Features of extracapillary proliferation with crescent formation may be observed, indicating advanced and active glomerular injury. Light microscopy, hematoxylin and eosin / PAS staining,  $\times 400$ .

The microscopic findings in patients with CGN without AH differed from those of the previous group and showed the following features: focal mesangial cell proliferation was identified in 66 % of patients, and a moderate degree of mesangial cell proliferation was observed in 70 % of patients. Focal expansion of the mesangial matrix was noted in 52 % of patients, and the presence of glomerulosclerosis was confirmed in only 10 % of patients. Thickening of peripheral capillary loops and/or their adhesion to Bowman's capsule was detected in 26 % patients, thickening and/or splitting of the glomerular basement membrane in 59 % patients, and an extracapillary component within the lumen of Bowman's capsule was observed in 16 % patients. Fibrous crescents were absent. Fig. 2 demonstrated a milder pattern of glomerular injury in patients with CGN without AH.

The glomerulus showed moderate focal mesangial cell proliferation with limited expansion of the mesangial matrix. The overall glomerular architecture was relatively preserved, with less pronounced basement membrane alterations and absence of extracapillary crescent formation, reflecting a milder pattern of glomerular injury compared to patients with concomitant arterial hypertension. Light microscopy, hematoxylin and eosin / PAS staining,  $\times 400$ .

All indicators of glomerular apparatus injury and their statistical analysis were presented in Table 2.

Tubulointerstitial structural damage in CGN. The morphological findings in the group of patients with CGN and AH were characterized by the presence of tubular dystrophic changes of varying severity in 94 % of patients. In contrast, in the group of patients with CGN without AH, dystrophy of the tubular epithelium was detected in only 13 % of patients.

Renal biopsy specimens from patients with CGN and AH were characterized by necrotic changes of the tubular epithelium in 35 % of patients, thickening and/or splitting of the tubular basement membrane in 54 % of patients, cellular infiltrates in 17 % of patients, and interstitial fibrosis in 97 % of cases.

Patients with CGN without AH demonstrated different features: necrosis of the tubular epithelium was observed in 13 % of patients, thickening and/or splitting of the tubular basement membrane in 29 % of patients, interstitial fibrosis in 14 % of patients, and cellular infiltrates in 13 % of patients. Interstitial fibrosis was present in almost all patients with CGN and AH, being focal in 45 % and diffuse in 55 % of cases. In the group of patients with CGN without AH, the presence of focal interstitial fibrosis was confirmed in only 13 % of patients. All indicators of tubulointerstitial tissue injury and their statistical analysis were presented in Table 3.

These findings indicate that AH was associated with more severe and diffuse glomerular and tubulointerstitial structural damage in CGN, even in the presence of preserved renal function. In patients with CGN and AH, the severity of glomerular injury was accompanied by pronounced tubulointerstitial damage, indicating a close structural interrelationship between these compartments. In contrast, in patients without AH, glomerular and tubulointerstitial lesions were less severe and showed a more focal and dissociated pattern.

Serum levels of cystatin C, NGAL, and IL-18 differed significantly between patient groups and controls (Table 4).

Median serum IL-18 concentrations were highest in patients with CGN and AH (804.2 [748.6; 991.0] pg/mL), followed by patients with CGN without AH (120.6 [66.5;

**Table 2.** Glomerular changes of the kidneys according to the results of morphological examination in patients with CGN

| Parameter                                                                          | Results of statistical analysis | Interpretation of results                           |
|------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------|
| Mesangial cell proliferation                                                       | $\chi^2 = 14.9$ ; $p < 0.05$    | More pronounced in patients with CGN and AH         |
| Expansion of the mesangial matrix                                                  | $\chi^2 = 18.5$ ; $p < 0.05$    | More pronounced in patients with CGN and AH         |
| Glomerulosclerosis                                                                 | $\chi^2 = 18.3$ ; $p < 0.05$    | More pronounced in patients with CGN and AH         |
| Presence of fibrous crescents                                                      | $\chi^2 = 7.3$ ; $p < 0.05$     | More pronounced in patients with CGN and AH         |
| Thickening of peripheral capillary loops and/or their adhesion to Bowman's capsule | $\chi^2 = 5.5$ ; $p > 0.05$     | No statistically significant differences were found |
| Thickening and/or splitting of the glomerular basement membrane                    | $\chi^2 = 14.9$ ; $p < 0.05$    | More pronounced in patients with CGN and AH         |

**Table 3.** Tubulointerstitial changes of the kidneys according to the results of morphological examination in patients with CGN

| Parameter                                                    | Results of statistical analysis | Interpretation of results                           |
|--------------------------------------------------------------|---------------------------------|-----------------------------------------------------|
| Dystrophic changes of the tubular epithelium                 | $\chi^2 = 40.9$ ; $p < 0.05$    | More pronounced in patients with CGN and AH         |
| Necrotic changes of the tubular epithelium                   | $\chi^2 = 4.1$ ; $p < 0.05$     | More pronounced in patients with CGN and AH         |
| Thickening and/or splitting of the tubular basement membrane | $\chi^2 = 9.5$ ; $p < 0.05$     | More pronounced in patients with CGN and AH         |
| Presence of cellular infiltrates                             | $\chi^2 = 0.73$ ; $p > 0.05$    | No statistically significant differences were found |
| Interstitial fibrosis                                        | $\chi^2 = 63.8$ ; $p < 0.05$    | More pronounced in patients with CGN and AH         |

**Table 4.** Serum biomarker levels in patients with chronic glomerulonephritis and controls

| Parameter, units of measurement | CGN with AH, n = 149    | CGN without AH, n = 70 | Control, n = 60       |
|---------------------------------|-------------------------|------------------------|-----------------------|
| Interleukin-18, pg/mL           | 804.2 [748.6; 991.0]    | 120.6 [66.5; 603.6]    | 78.1 [60.1; 92.8]     |
| Cystatin C, ng/mL               | 1804.2 [1223.6; 2014.9] | 1063.6 [933.1; 1303.6] | 992.1 [560.1; 1092.8] |
| NGAL, ng/mL                     | 7.8 [4.9; 8.1]          | 4.2 [3.8; 7.0]         | 2.2 [0.9; 2.8]        |

Data were presented as median [interquartile range].

603.6] pg/mL), and were lowest in the control group (78.1 [60.1; 92.8] pg/mL). Serum IL-18 levels were significantly higher in the CGN with AH group compared with both the CGN without AH group and controls ( $p < 0.05$ ).

Median serum cystatin C levels were significantly elevated in patients with CGN and AH (1804.2 [1223.6; 2014.9] ng/mL) compared with patients without AH (1063.6 [933.1; 1303.6] ng/mL) and controls (992.1 [560.1; 1092.8] ng/mL),  $p < 0.05$ .

Similarly, serum NGAL concentrations were highest in the CGN with AH group (7.8 [4.9; 8.1] ng/mL), intermediate in patients with CGN without AH (4.2 [3.8; 7.0] ng/mL) and lowest in the control group (2.2 [0.9; 2.8] ng/mL). Differences between groups were statistically significant ( $p < 0.05$ ).

Overall, patients with CGN and concomitant AH exhibited the highest levels of all investigated serum biomarkers, indicating more pronounced glomerular and tubulointerstitial injury.

Correlation between serum biomarkers and histological findings. Spearman's rank correlation analysis demonstrated significant associations between serum biomarker levels and histopathological indicators of kidney injury.

Serum cystatin C levels correlated with markers of glomerular damage, including glomerulosclerosis and mesangial matrix expansion. Serum NGAL and IL-18 levels showed significant correlations with indices of tubulointerstitial injury, particularly dystrophic tubular changes and interstitial fibrosis. These associations were stronger in patients with CGN and AH, supporting the role of arterial hypertension as a modifier of structural kidney damage.

Diagnostic performance of serum biomarkers. Receiver operating characteristic curve analysis demonstrated good diagnostic performance of serum cystatin C, NGAL and IL-18 for the identification of specific histological

lesions. Each biomarker showed high sensitivity and specificity for its corresponding compartment of renal injury, with the highest diagnostic accuracy observed in patients with CGN and AH.

## Discussion

The present study demonstrated that CGN accompanied by AH was associated with significantly more pronounced structural kidney damage compared with normotensive CGN, even in the presence of preserved renal function. Morphological analysis revealed diffuse mesangial proliferation, expansion of the mesangial matrix, glomerulosclerosis, and pronounced tubulointerstitial injury in patients with concomitant hypertension. These findings support the concept that AH acts as an important modifier of structural kidney damage in chronic glomerular diseases.

Our results were consistent with previous studies demonstrating the key role of hypertension in accelerating renal structural remodeling. Bazzi et al. reported that AH in patients with CGN was associated with increased severity of glomerulosclerosis and tubulointerstitial fibrosis, contributing to faster disease progression [15]. Similar observations have been described in studies of CKD, where elevated intraglomerular pressure and microvascular injury promote progressive structural damage of both glomerular and tubular compartments [5,16].

An important finding of the present study is the close relationship between serum biomarker levels and histological indicators of kidney injury. Serum cystatin C levels showed significant associations with markers of glomerular damage, including glomerulosclerosis and mesangial matrix expansion. Previous studies have demonstrated that cystatin C is a sensitive marker of early renal dysfunction and structural kidney injury, often

detecting pathological changes earlier than conventional markers such as serum creatinine or estimated GFR [7,8].

In contrast, NGAL and IL-18 were primarily associated with tubulointerstitial injury. NGAL was widely recognized as a marker of tubular epithelial damage and has been shown to correlate with the severity of tubulointerstitial fibrosis and inflammation in both acute and CKD [2,10]. Recent investigations have confirmed that elevated NGAL levels may reflect ongoing tubular stress and structural remodeling even in patients with relatively preserved renal function [9].

Interleukin-18 represented another important biomarker reflecting inflammatory mechanisms of kidney injury. Experimental and clinical studies indicated that IL-18 contributes to inflammatory activation of tubular epithelial cells and the development of interstitial fibrosis [12]. Increased circulating IL-18 concentrations have been observed in various forms of kidney disease and were associated with progression of renal structural damage.

The combined evaluation of cystatin C, NGAL, and IL-18 provided a more comprehensive assessment of renal injury compared with single-marker strategies. Recent studies emphasize that multimarker approaches may improve the non-invasive assessment of kidney pathology by simultaneously reflecting different structural compartments of the kidney [4,17]. In patients with CGN, such strategies may be particularly valuable for identifying early structural damage when conventional markers remain within normal ranges.

Another important observation of the present study was that hypertension amplifies both morphological lesions and biomarker expression. Patients with CGN and AH demonstrated higher levels of all investigated biomarkers together with more pronounced histological abnormalities. This finding supports the concept that hypertension not only reflects disease severity but may also actively contribute to structural kidney injury through hemodynamic stress, endothelial dysfunction, and inflammatory activation [1,14].

Several limitations of the study should be acknowledged. First, the cross-sectional design did not allow assessment of longitudinal changes in biomarker levels and structural kidney damage. Second, renal biopsy, although considered the reference standard for histopathological evaluation, is subject to sampling variability. Nevertheless, the relatively large cohort of biopsy-confirmed CGN patients and the use of standardized histopathological evaluation strengthen the validity of the observed associations.

Overall, the results of the present study supported the clinical value of a multimarker approach for the non-invasive assessment of renal injury in patients with CGN. Integration of serum cystatin C, NGAL, and IL-18 into diagnostic strategies may improve early detection of structural kidney damage and help identify patients at increased risk of disease progression [5,18].

## Conclusions

1. This study demonstrated that a serum multimarker approach combining cystatin C, NGAL, and IL-18 provides an effective non-invasive assessment of glomerular and tubulointerstitial kidney injury in patients with CGN and preserved renal function. Elevated levels of these bio-

markers were associated with histological evidence of structural kidney damage, despite relatively preserved conventional renal function parameters.

2. Patients with AH exhibited significantly higher biomarker concentrations and more pronounced histopathological alterations, highlighting the role of hypertension as a key modifier of renal injury in CGN. The differential associations of cystatin C with glomerular damage and NGAL and IL-18 with tubular and tubulointerstitial injury supported the concept of compartment-specific biomarker profiling.

3. Overall, the integration of serum cystatin C, NGAL, and IL-18 into a multimarker panel may enhance early detection and characterization of renal injury in CGN and represent a promising tool for non-invasive evaluation, particularly in patients with preserved renal function and limited indications for repeated renal biopsy.

## AI statement

The authors did not use artificial intelligence tools in the preparation of the manuscript.

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## Ethical approval

The Bioethics Commission of Zaporizhzhia State Medical and Pharmaceutical University reviewed the materials presented in the article and confirmed that the study complies with applicable ethical standards, including the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, and other relevant legal regulations. Written informed consent was obtained from all participants prior to their inclusion in the study. Ethical approval is documented by an extract from the minutes of the Bioethics Commission meeting (Protocol No. 3, dated February 13, 2026).

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