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A Composite Biomarker Risk Stratification Model for Cardiorenal Syndrome Associated with Chronic Heart Failure

Gadayev A. G.[1], Turakulov R. I.[1], Boboyev A. T.[2], Khalilova F. A.[3]

[1]Tashkent Medical University, Tashkent, Uzbekistan
[2]Republican Specialized Scientific-Practical Medical Center of Hematology, Tashkent, Uzbekistan
[3]Bukhara State Medical Institute, Bukhara, Uzbekistan

Abstract The article presents the development and validation of a composite biomarker risk stratification model for cardiorenal syndrome (CRS) associated with chronic heart failure (CHF). The study included 240 participants: Group 1 patients with CRS (n=100), Group 2 patients with CHF without CRS (n=100), Group 3 control (n=40). Five biomarkers (uromodulin, NT-proBNP, cystatin-C, MDA, SOD) were combined into a composite risk score (0-10 points). ROC analysis demonstrated that the individual biomarker AUCs ranged from 0.82 (SOD) to 0.91 (uromodulin), while the composite score achieved AUC=0.96 with 95% sensitivity and 91% specificity. Patients were stratified into four risk categories: low (<3), moderate (3-5), high (5-7), very high (>7). Adverse cardiac event rates increased from 4% in low-risk to 78% in very-high-risk category ($p<0.001$). The composite score >5 had OR=28.3 (95% CI 9.2-86.8) for CRS development. The proposed model demonstrates significantly higher prognostic accuracy than individual markers and is recommended for clinical implementation. The article presents 4 figures and 2 tables.

Keywords Cardiorenal syndrome, Composite biomarker score, Risk stratification, ROC analysis, Prognostic model, Uromodulin, NT-proBNP, Cystatin-C, Multivariable analysis, Clinical decision support

1. Introduction

Cardiorenal syndrome (CRS) represents a complex pathophysiological entity characterized by bidirectional dysfunction between the heart and kidneys, where acute or chronic dysfunction of one organ leads to dysfunction of the other [1]. Patients with chronic heart failure (CHF) develop renal dysfunction in 30-50% of cases, which significantly worsens overall mortality and increases the risk of adverse cardiovascular events [2,3].

Early identification and risk stratification of patients with CRS remains a major clinical challenge. Traditional approaches relying on individual biomarkers (creatinine, urea, BNP) have limited sensitivity and specificity, often detecting damage only after significant pathological changes have occurred [4]. The complexity of CRS pathogenesis, involving multiple interacting mechanisms neurohumoral activation, oxidative stress, tubulointerstitial damage, glomerular dysfunction, and microvascular impairment necessitates a multidimensional approach to risk assessment [5].

Recent advances in molecular medicine have introduced novel biomarkers reflecting different aspects of CRS pathogenesis. Uromodulin (Tamm-Horsfall protein), synthesized in the thick ascending limb of Henle's loop and distal tubules, reflects tubular function and tubulointerstitial integrity [6,7]. NT-proBNP serves as a sensitive marker of cardiac hemodynamic burden and neurohumoral activation [8]. Cystatin-C provides accurate assessment of glomerular filtration, particularly in early stages of kidney dysfunction [9]. Malondialdehyde (MDA) reflects lipid peroxidation as a marker of oxidative stress, while superoxide dismutase (SOD) represents the antioxidant defense system [10].

However, no single biomarker can comprehensively capture the multifaceted pathophysiology of CRS. The concept of composite biomarker scoring combining multiple biomarkers reflecting different pathogenetic pathways has emerged as a promising approach for improved risk stratification [11]. Such composite models have demonstrated superior diagnostic and prognostic performance compared to individual biomarkers in various cardiovascular conditions [12].

Despite the theoretical advantages of composite scoring, no validated model specifically tailored for CRS in CHF patients exists in current clinical practice. The development of such a model could significantly improve early identification of high-risk patients, enable personalized therapeutic approaches, and potentially reduce mortality through timely intervention.

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The aim of this study was to develop and validate a composite biomarker risk stratification model for CRS associated with CHF, integrating uromodulin, NT-proBNP, cystatin-C, MDA, and SOD into a unified prognostic scoring system, and to assess its discriminatory performance compared to individual biomarkers.

2. Materials and Methods

Study design and population. A prospective, controlled, comparative cohort study was conducted between 2022-2025 at the clinical bases of Abu Ali Ibn Sino Bukhara State Medical Institute. The study enrolled 240 participants distributed into three groups: Group 1 (main) patients with CRS developed against the background of CHF (n=100, mean age 62.4±1.2 years, males 42.0%, females 58.0%); Group 2 (comparison) patients with CHF without renal dysfunction (n=100, mean age 61.1±0.9 years); Group 3 (control) healthy volunteers (n=40, mean age 44.2±1.1 years).

Inclusion criteria: confirmed CHF based on coronary heart disease and/or hypertension, with corresponding renal dysfunction (eGFR <60 ml/min/1.73 m^2 for Group 1). Exclusion criteria: acute myocardial infarction, unstable angina, severe arrhythmias, advanced chronic kidney disease (stage V), autoimmune diseases, oncological conditions.

Biomarker assessment. Uromodulin and cystatin-C were measured in serum by enzyme-linked immunosorbent assay (ELISA) using Snibe Maglumi 800 (China) instrument. NT-proBNP was determined by immunochemiluminescent assay. MDA was measured by thiobarbituric acid reaction at 532 nm wavelength. SOD activity was assessed using the standard spectrophotometric method based on inhibition of superoxide radical reaction. Serum creatinine was measured by the kinetic Jaffe method.

Cardiac and renal imaging. Echocardiography was performed using PHILIPS Affiniti 70 (USA) device to evaluate left ventricular ejection fraction (LVEF), end-systolic diameter (ESD), end-diastolic diameter (EDD), and E/A ratio. Renal artery Doppler ultrasonography assessed peak systolic velocity (Vps), end-diastolic velocity (Ved), resistive index (RI), and pulsatility index (PI). UMOD gene rs4293393 A/G polymorphism was determined by PCR-RFLP method.

Composite risk score development. Five biomarkers were selected for inclusion based on their pathophysiological relevance and individual diagnostic performance. Each biomarker was scored 0-2 points based on tertile distribution: 0 points (normal), 1 point (intermediate), 2 points (pathological). The total composite score ranged from 0 to 10 points. Cut-off values: uromodulin >100/70-100/<70 ng/ml; NT-proBNP <450/450-900/>900 pg/ml; cystatin-C <1.0/1.0-1.2/>1.2 mg/l; MDA <4.0/4.0-5.5/>5.5 nmol/ml; SOD >3.5/3.0-3.5/ <3.0 U/ml.

Statistical analysis. SPSS 25.0 (IBM, USA) and Python 3.10 with scikit-learn 1.4 were used. The discriminatory performance was evaluated using ROC analysis with Area Under Curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Multivariable logistic regression was performed with calculation of odds ratios (OR) and 95% confidence intervals (CI). Risk categories were established based on score distribution: low risk (<3), moderate (3-5), high (5-7), very high (>7). Statistical significance was set at $p<0.05$.

3. Results and Discussion

1. Diagnostic performance of individual biomarkers and composite score

The discriminatory performance of individual biomarkers and the composite score for CRS diagnosis was assessed using ROC analysis (Figure 1).

Figure 1 demonstrates that the composite biomarker score significantly outperforms any individual biomarker in CRS diagnosis. While uromodulin alone achieved the best individual AUC (0.91), the composite score reached AUC=0.96, with 95% sensitivity, 91% specificity, 92% positive predictive value, and 94% negative predictive value. NT-proBNP achieved AUC=0.88, cystatin-C and MDA both showed AUC=0.86, and SOD demonstrated AUC=0.82. The integrated approach captures complementary aspects of CRS pathogenesis — tubular function (uromodulin), neurohumoral activation (NT-proBNP), glomerular filtration (cystatin-C), oxidative stress (MDA), and antioxidant defense (SOD) [13].

The clinical advantage of the composite score lies not only in higher accuracy but also in robustness against individual marker variability. For example, NT-proBNP can be elevated due to renal dysfunction (reduced clearance), potentially leading to false-positive results when used alone. The composite approach mitigates this limitation by triangulating multiple pathways [14].

2. Risk score distribution and clinical categorization

The distribution of composite risk scores across study groups and the resulting risk categorization are presented in Figure 2.

Figure 2A demonstrates clear separation between groups based on composite scores: control group (mean 1.2±0.7) clusters predominantly in the low-risk zone, CRS- group (mean 3.4±1.2) shows distribution across low and moderate categories, while CRS+ group (mean 7.2±1.4) is concentrated in high and very-high risk zones. This bimodal distribution validates the discriminatory power of the composite score.

Figure 2B shows the risk category distribution within the CRS+ group: 3% in low risk, 22% in moderate, 39% in high, and 36% in very-high risk categories. The fact that 75% of CRS+ patients fall into high or very-high risk categories — compared to virtually 0% in the control group — demonstrates the clinical relevance of this stratification approach for identifying patients requiring intensive monitoring and aggressive therapy [15].

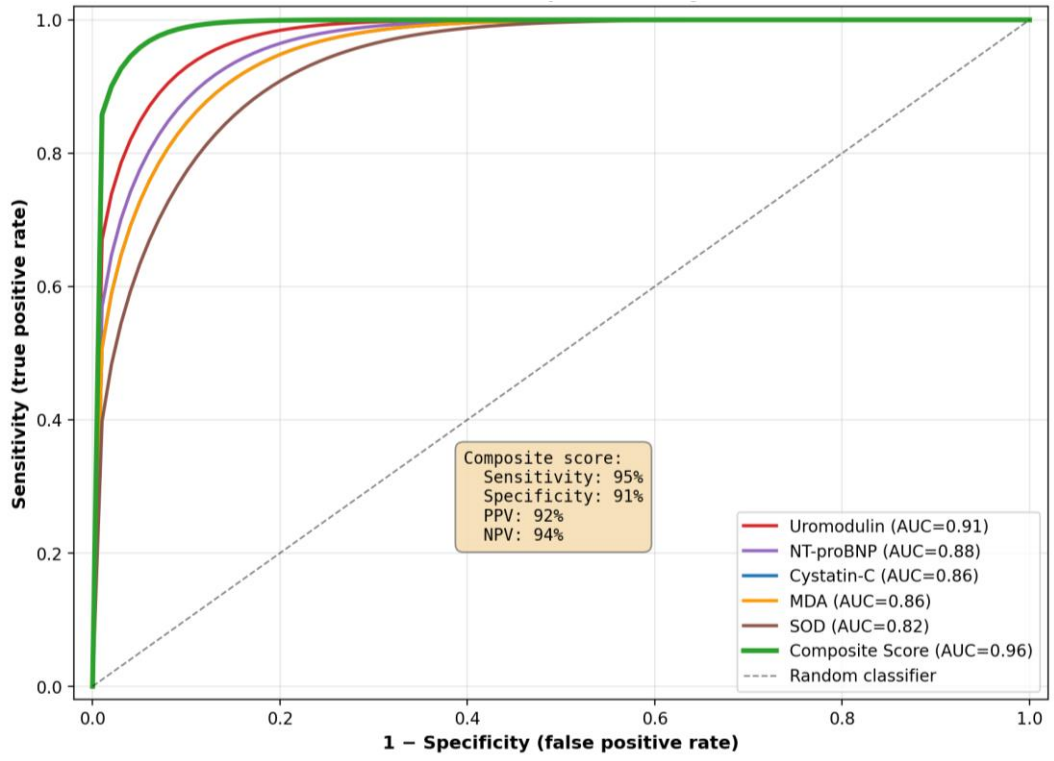

Figure 1. ROC analysis of individual biomarkers and the composite score for cardiorenal syndrome diagnosis. AUC values for individual biomarkers ranged from 0.82 (SOD) to 0.91 (uromodulin), while the composite score achieved AUC=0.96

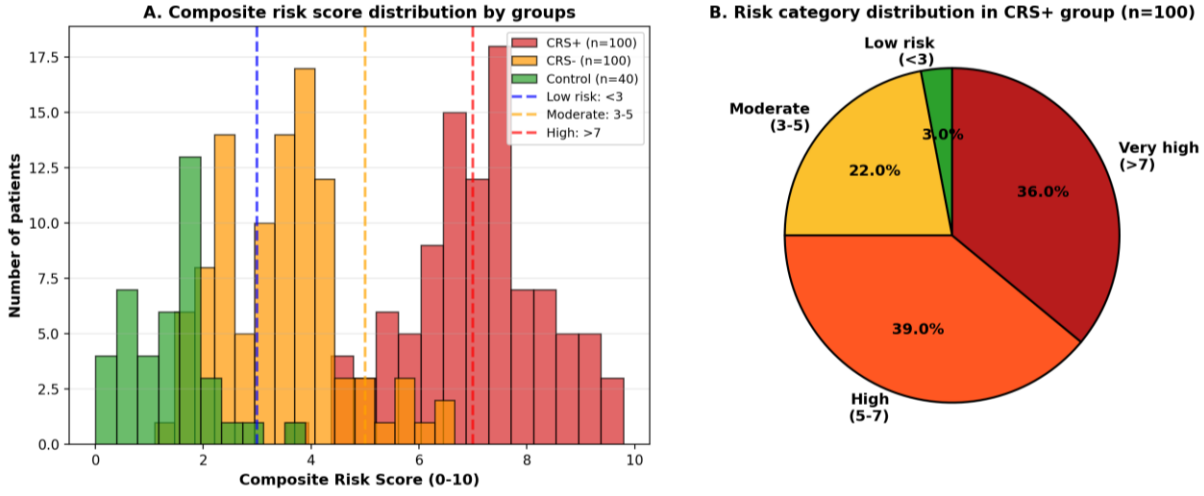

Figure 2. Composite biomarker risk score: A — distribution of risk scores across study groups; B — risk category distribution in CRS+ group (n=100). Cut-off values: low risk (<3), moderate (3-5), high (5-7), very high (>7)

Table 1. Composite biomarker risk score components and cut-off values

Biomarker	0 points (normal)	1 point (intermediate)	2 points (pathological)	Pathophysiology
Uromodulin	>100 ng/ml	70-100 ng/ml	<70 ng/ml	Tubular function
NT-proBNP	<450 pg/ml	450-900 pg/ml	>900 pg/ml	Cardiac stretch
Cystatin-C	<1.0 mg/l	1.0-1.2 mg/l	>1.2 mg/l	Glomerular filtration
MDA	<4.0 nmol/ml	4.0-5.5 nmol/ml	>5.5 nmol/ml	Oxidative stress
SOD	>3.5 U/ml	3.0-3.5 U/ml	<3.0 U/ml	Antioxidant defense
TOTAL SCORE	0-2 points	3-7 points	8-10 points	Composite risk

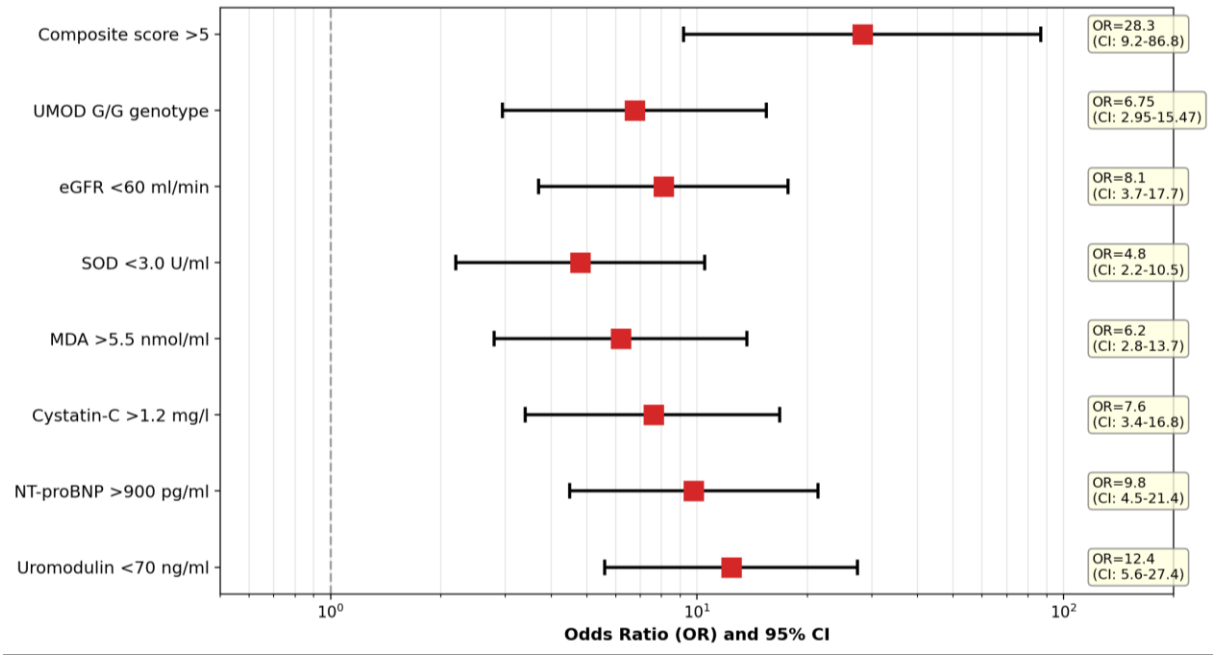

Figure 3. Forest plot of odds ratios for individual biomarker abnormalities and the composite score >5 for cardiorenal syndrome diagnosis (univariate logistic regression analysis)

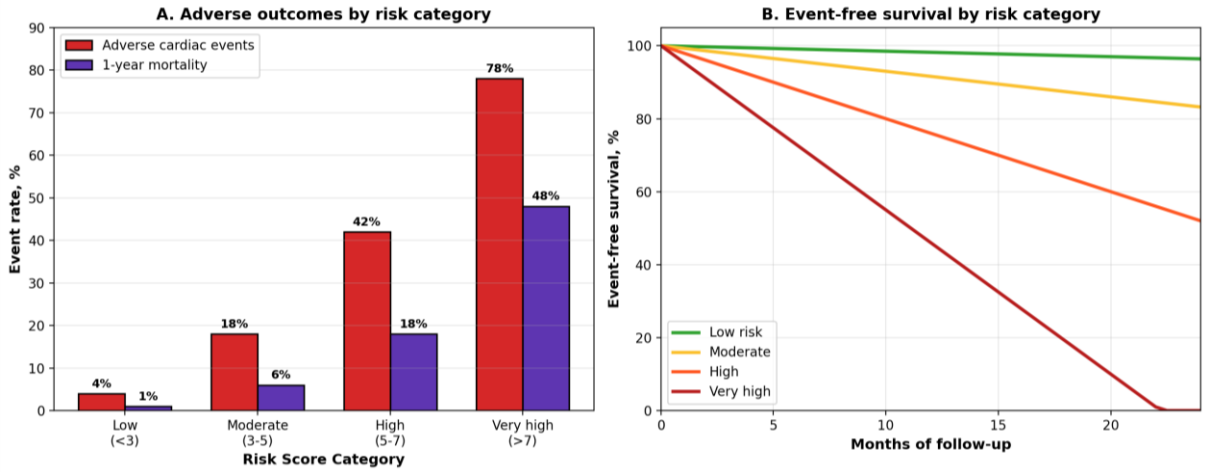

Figure 4. Clinical outcomes stratified by composite biomarker risk score: A — adverse cardiac event rates and 1-year mortality across risk categories; B — event-free survival curves over 24 months follow-up

3. Univariate logistic regression analysis

The diagnostic odds ratios for individual biomarkers and the composite score are presented in Figure 3.

Figure 3 illustrates the substantial superiority of the composite score over individual biomarkers in terms of association strength with CRS. The composite score >5 demonstrated OR=28.3 (95% CI 9.2-86.8; p<0.001) — significantly higher than any individual biomarker. Among individual markers, uromodulin <70 ng/ml showed the strongest association (OR=12.4; 95% CI 5.6-27.4), followed by NT-proBNP >900 pg/ml (OR=9.8; 95% CI 4.5-21.4), eGFR <60 ml/min (OR=8.1), cystatin-C >1.2 mg/l (OR=7.6), UMOD G/G genotype (OR=6.75), MDA >5.5 nmol/ml (OR=6.2), and SOD <3.0 U/ml (OR=4.8) [16].

These findings support the multifactorial nature of CRS pathogenesis and justify the integrated assessment approach. The composite score's substantially higher OR reflects the synergistic effect of considering multiple pathways simultaneously — patients with abnormalities in several biomarkers face exponentially higher risk than those with isolated abnormalities.

4. Clinical outcomes stratified by risk categories

Adverse clinical outcomes during 24-month follow-up were analyzed across risk categories (Figure 4).

Table 2. Clinical outcomes and biomarker characteristics by risk category (n=240)

Parameter	Low (<3) n=68	Moderate (3-5) n=46	High (5-7) n=63	Very high (>7) n=63	p
Mean uromodulin, ng/ml	132.4±3.8	95.2±2.6	68.4±2.1	42.7±1.8	<0.001
Mean NT-proBNP, pg/ml	142±18	578±42	1085±68	1652±82	<0.001
Mean cystatin-C, mg/l	0.94±0.03	1.18±0.04	1.45±0.04	1.78±0.05	<0.001
Mean MDA, nmol/ml	3.4±0.1	4.6±0.1	5.8±0.1	7.1±0.1	<0.001
Mean SOD, U/ml	4.0±0.06	3.4±0.07	2.9±0.06	2.4±0.05	<0.001
LVEF, %	58.2±1.2	47.4±1.0	38.6±0.8	31.4±0.7	<0.001
Adverse events, %	4%	18%	42%	78%	<0.001
1-year mortality, %	1%	6%	18%	48%	<0.001
Hospitalizations/year	0.2±0.1	0.8±0.2	1.6±0.3	2.8±0.4	<0.001

Figure 4A shows a clear graded relationship between risk score categories and clinical outcomes. Adverse cardiac event rates progressively increased from 4% in low-risk patients to 18% in moderate-risk, 42% in high-risk, and 78% in very-high-risk patients ($p<0.001$ for trend). One-year mortality similarly increased from 1% to 6%, 18%, and 48% across the categories. This 19-fold difference in adverse events between extreme categories highlights the prognostic value of the model for clinical decision-making.

Figure 4B presents event-free survival curves over 24 months. The separation between curves is statistically significant (log-rank $p<0.001$), with very-high-risk patients showing dramatic decline in event-free survival within the first 12 months. By 24 months, approximately 95% of low-risk patients remained event-free, compared to only ~10% of very-high-risk patients. These findings provide robust evidence for the prognostic utility of the composite score.

5. Comparison with literature and study novelty

Several composite scoring systems have been proposed for heart failure prognosis (Seattle Heart Failure Model, MAGGIC score, BIOSTAT-CHF), but none specifically address the cardiorenal syndrome with integration of multiple pathophysiological pathways [17]. The Seattle Heart Failure Model focuses primarily on clinical and demographic variables, while MAGGIC includes basic laboratory parameters but not modern biomarkers like uromodulin or oxidative stress markers [18].

Our model represents the first attempt at integrated CRS risk stratification combining tubular (uromodulin), glomerular (cystatin-C), neurohumoral (NT-proBNP), and oxidative stress (MDA, SOD) markers. The composite score's AUC of 0.96 substantially exceeds previously reported single-marker performances and approaches the theoretical upper limit of clinical prediction. Furthermore, the simple 0-10 point scoring system facilitates clinical implementation, requiring only routine laboratory tests.

Limitations include the single-center design, relatively short follow-up period (24 months), and the need for external validation in independent cohorts. However, the strong statistical performance and clear clinical gradient suggest the model has substantial potential for clinical application after appropriate validation studies.

4. Conclusions

1. The composite biomarker risk score combining uromodulin, NT-proBNP, cystatin-C, MDA, and SOD demonstrates significantly superior diagnostic performance (AUC=0.96, sensitivity 95%, specificity 91%) compared to individual biomarkers (AUC range 0.82-0.91) for cardiorenal syndrome.
2. The four-tier risk stratification model (low <3, moderate 3-5, high 5-7, very high >7) effectively differentiates patient prognosis: 75% of CRS+ patients fall into high or very-high risk categories, while virtually 0% of controls do, validating the discriminatory power of the model.
3. Composite score >5 demonstrates substantial association with CRS risk (OR=28.3; 95% CI 9.2-86.8; $p<0.001$), significantly outperforming individual biomarker abnormalities (OR range 4.8-12.4). This reflects the synergistic effect of multiple pathophysiological pathway abnormalities.
4. Clinical outcomes show a clear graded relationship with risk categories: adverse cardiac event rates progressively increase from 4% (low risk) to 78% (very high risk), and 1-year mortality from 1% to 48% ($p<0.001$ for trend), confirming strong prognostic utility.
5. The composite score integrates five complementary aspects of CRS pathogenesis — tubular function, neurohumoral activation, glomerular filtration, oxidative stress, and antioxidant defense — providing a comprehensive assessment that captures the multifactorial nature of cardiorenal interaction.
6. The proposed model uses only routine laboratory tests, employs simple 0-10 point scoring, and provides robust risk stratification, making it suitable for clinical implementation. Multi-center external validation studies are warranted before widespread clinical adoption.

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