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Glasgow prognostic score and its derived scores predicts contrast-associated acute kidney injury in patients undergoing coronary angiography

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ABSTRACTS

Background: Glasgow prognostic score (GPS) is a reliable scoring system reflecting both nutritional and inflammatory factors. The association of inflammation and nutrition with contrast-associated acute kidney injury (CA-AKI) has been validated. This study set out to determine the impact of GPS and its derived scores on CA-AKI incidence.

Methods: Populations treated with coronary angiography with/without percutaneous coronary intervention were screened retrospectively. According to C-reactive protein and albumin, three kinds of GPSs were involved: GPS, modified GPS (mGPS), and the cutoff-based GPS (cGPS) which was derived by calculating the optimal cutoff values of two parameters. Primary endpoint was CA-AKI. Pearson' r correlation, linear/logistic regression, receiver operating characteristic curve as well as subgroup analyses were conducted.

Results: Totally, 3150 patients were valid for analysis, and the mean age was 67.5 years old, with 66.4 % male. Of these, 610 patients suffered CA-AKI. All three kinds of GPSs were independently associated with the SCr elevation proportion (GPS: $\beta = 4.850$, 95%CI [3.700 to 8.722], $P < 0.001$; mGPS: $\beta = 3.450$, 95%CI [1.896 to 6.888], $P = 0.001$; cGPS: $\beta = 3.992$, 95%CI [2.368 to 6.940], $P < 0.001$). GPS, mGPS and cGPS were proved to be the independent risk factors for CA-AKI risk (all P for trend <0.05). Compared with GPS and mGPS, cGPS was of greater prognostic value for predicting CA-AKI incidence (cGPS: AUC = 0.633; mGPS: AUC = 0.567; GPS: AUC = 0.611). Main findings were also consistent in all subgroup analysis.

Conclusion: Preprocedural GPS and its derived scores (mGPS and cGPS), especially cGPS, were correlated with the incidence of CA-AKI, which might assist in clinical decision making in treating CA-AKI.

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1. Introduction

Coronary artery disease (CAD) is one of the most dangerous cardiac disorders [1]. Interventional technique of coronary arteries has been the commonest means of diagnosis and treatment in CAD population [2]. However, intravascular injection of contrast agent also implies risks for complications [3,4].

Contrast-associated acute kidney injury (CA-AKI) is a common side effect after iodinated contrast agents injection, normally occurring within 3 days following coronary angiography (CAG) and percutaneous coronary intervention (PCI) [5]. CA-AKI is an important cause of poor short- and long-term prognosis, increasing the total costs of therapy [6]. However, to date, there is no consensus on optimal surveillance strategies or prognostic markers for CA-AKI management [7]. The mechanisms of CA-AKI occurrence are complicated and multifactorial [8]. Successive studies report that both inflammation and nutritional condition are closely related to the occurrence and progression of CA-AKI [9]. This calls for the identification of a more comprehensive and accurate surrogate marker that reflect both systemic inflammation and nutritional conditions for predicting CA-AKI.

Glasgow Prognostic Score (GPS), consisting of C-reactive protein (CRP) and serum albumin, is a reliable and composite scoring tool which can effectively reflect systemic inflammation and nutrition [10,11]. Later, modified GPS (mGPS) has been developed [12]. Different from GPS, mGPS stratifies hypoalbuminemia without elevated CRP into risk categories, which places greater emphasis on inflammatory factors [13]. Based on objective biomarkers, GPS/mGPS is simple and convenient to measure, and has been widely used for the prediction of cancer prognosis [12,14]. Recently, the roles of GPS and mGPS for the prediction of prognosis in patients with cardiovascular diseases have also been successively reported [15,16]. However, the application of GPS or mGPS has not been yet determined in evaluating the incidence of CA-AKI.

The purpose of this study was therefore to determine the associations between GPS/mGPS and the incidence of CA-AKI in patients who underwent CAG with/without PCI. Besides, based on optimal cutoff values of CRP and serum albumin, this study creatively constructed the cutoff-based GPS (cGPS) and further compared the predictive values of three GPSs for CA-AKI.

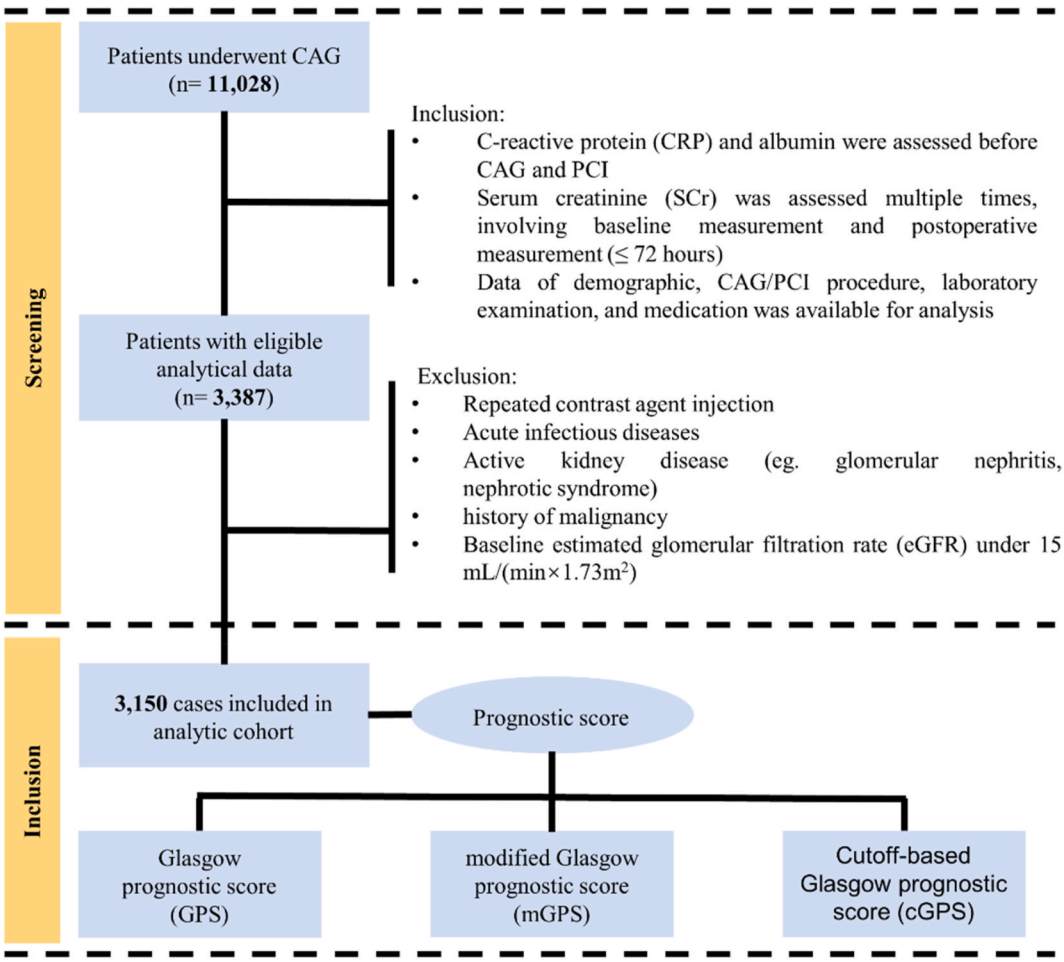


Fig. 1. The study flowchart. CAG indicates coronary angiography; CRP, C-reactive protein; PCI, percutaneous coronary intervention; SCr, serum creatinine; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; cGPS, cutoff-based Glasgow prognostic score.

2. Methods

2.1. Study design

From December 2006 to December 2019, the CAD patients undergoing selective CAG/PCI at Sir Run Run Shaw Hospital and its medical consortium hospitals were retrospectively reviewed (Fig. 1). The inclusion criteria were outlined below: (1) CRP and serum albumin were assessed before CAG and PCI; (2) serum creatinine (SCr) was assessed multiple times, involving baseline measurement and postoperative measurement (≤72 h); (3) data of demographic, PCI procedure, laboratory examination, and medication were available for analysis. The exclusion criteria included: (1) repeated contrast agent injection; (2) acute infectious diseases; (3) active kidney diseases (eg. glomerular nephritis, nephrotic syndrome); (4) history of malignancy; (5) baseline estimated glomerular filtration rate (eGFR) under 15 mL/(min × 1.73m2). As a result, 3150 patients were included.

The present study was done following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the Helsinki declaration. Ethical clearance was provided by the Medical Ethical Review Committee of Sir Run Run Shaw Hospital with Ethical Clearance Certificate No. 20220228-30.

2.2. The definitions of three kinds of GPSs

GPS, mGPS and cGPS are used to evaluate the grade of systemic inflammation and nutritional status, using two objective biomarkers: CRP and serum albumin.

GPS was proposed by Forrest et al. at first, ranging from 0 to 2 points: "CRP levels ≤10 mg/L and albumin ≥35 g/L″ is scored as "0"; "CRP levels >10 mg/L or albumin <35 g/L″ is scored as "1"; "CRP levels >10 mg/L and albumin <35 g/L″ is scored as "2" [10].

The mGPS is developed on the basis of the original GPS, which defines a score of "0" is given if CRP ≤10 mg/L regardless of the levels of albumin [12]. That is, "CRP levels ≤10 mg/L and any albumin level" is scored as "0". Other scoring definitions are the same as GPS.

In this study, according to the optimal cutoff values (CRP: 2.65 mg/L; albumin: 35.93 g/L) determined by receiver operating characteristic (ROC) curves, cGPS is constructed: "CRP levels ≤2.65 mg/L and albumin ≥35.93 g/L″ is scored as "0"; "CRP levels >2.65 mg/L or albumin <35.93 g/L″ is scored as "1"; "CRP levels >2.65 mg/L and albumin <35.93 g/L″ is scored as "2".

2.3. Endpoint

The primary endpoint measure was CA-AKI. Following the consensus guideline (European Society of Urogenital Radiology, ESUR), CA-AKI can be diagnosed when meeting the following conditions: (1) patients receive the injections of contrast agent; (2) patients' SCr concentrations begin to rise after contrast injection; (3) patients have a SCr concentration elevation greater than or equal to 0.5 mg/dL or 25 % from baseline within 72 h [17].

2.4. Data collection

All clinical data were obtained from hospital's clinical information system. The baseline data included demographic features, laboratory data, procedure data and medication data. The baseline variables were selected as the first measurement on admission. SCr was measured on baseline and ≥3 times within 72 h postoperatively, and the highest one was taken. SCr elevation (%) was defined as (baseline SCr - postoperative SCr)/baseline SCr.

In this study, all blood samples were measured by experienced operators in the hospital laboratory department using commercial auto-analysers. SCr and serum CRP levels were detected by enzymatic and immunoturbidimetry method, respectively. Ejection fraction was measured on echocardiography by M-type or Simpson method. Diabetes and hypertension were defined based on the current guidelines [18,19]. All results were reported as International System of Units.

2.5. Statistical analysis

Continuous parameters were represented by mean ± standard deviation (SD) if normally distributed and represented by median (interquartile range) if not normally distributed. Categorical parameters were represented by count (proportion). Independent student's t-test and Mann-Whitney *U* test were employed for examining the continuous variables. The chi-square test and Fisher's exact test were employed for examining the categorical variables.

ROC curves were prepared to ascertain the cutoff values of CRP and serum albumin. In order to reduce skewness as much as possible, in ROC analysis, albumin values were natural log-transformed. Between-group comparison was performed by One way ANOVA with least significant difference (LSD) post-hoc tests. Corresponding results were represented using boxplot graphs. Correlations between GPS-related variables and SCr were assessed using Pearsons correlative analysis and presented as a correlation matrix. Linear regression analysis and logistic regression analysis were conducted to identify the associations of three GPSs with SCr elevation and CA-AKI incidence. In addition, to control for potential confounders, multivariable analysis was conducted and three models were constructed: Model 1: without adjustments; Model 2: adjustments for age, gender, diabetes, systolic blood pressure (SBP), eGFR, ejection fraction (EF), hemoglobin, volume of contrast agent and type of contrast agent; Model 3: additional adjustments for medicine administration (statin, furosemide injection and dopamine). Additionally, tests for linear trend were performed by treating ordered

GPSs as continuous variables. ROC analysis was performed to determine the diagnostic performance of three GPSs as predictors of CA-AKI. Finally, exploratory subgroup analyses were conducted using the pre-specified subgroups of age, eGFR, SBP and the volume of contrast agent.

Significance was taken at $P < 0.05$ (two-tailed). Data were analyzed with SPSS version 22.0 (SPSS Inc, Chicago, USA) and R version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Table 1 showed the baseline characteristics. Totally, 3150 patients were valid for analysis, and the mean age was 67.5 years old, with 66.4 % male. Two groups were created according to the primary endpoint: non-CA-AKI group (n = 2540) and CA-AKI group (n = 610). In this study, compared to non-CA-AKI group, CA-AKI patients had higher CRP levels (15.5 ± 28.3 *vs.* 9.5 ± 21.6 mg/L, $P < 0.001$) and lower albumin levels (36.6 ± 5.7 *vs.* 39.1 ± 4.7 g/L, $P < 0.001$). CA-AKI group showed a lower proportion of male participants (60.8 % *vs.* 67.8 %, $P = 0.001$) and higher BMI (24.7 ± 5.1 *vs.* 24.3 ± 5.3 kg/m^2, $P = 0.040$). Patients with CA-AKI exhibited worse cardiac function, lower hemoglobin, lower total cholesterol, while higher proportion of several medications (statin, aspirin, oral furosemide, furosemide injection and dopamine) (all $P < 0.05$). However, there was no difference in the history of diabetes and

Table 1
Baseline characteristics.

Characteristics		CA-AKI		
	Overall (n = 3150)	No (n = 2540)	Yes (n = 610)	*P* value
Demographic features				
Age, years old	67.5 ± 10.5	67.1 ± 10.5	69.4 ± 10.2	<0.001*
Male, n (%)	2093 (66.4)	1722 (67.8)	371 (60.8)	0.001*
Diabetes, n (%)	770 (24.4)	603 (23.7)	167 (27.4)	0.068
Hypertension, n (%)	2004 (63.6)	1611 (63.4)	393 (64.4)	0.678
BMI, kg/m^2	24.3 ± 5.3	24.3 ± 5.3	24.7 ± 5.1	0.040*
Prior PCI, n (%)	213 (25.0)	177 (25.7)	36 (21.8)	0.346
Prior MI, n (%)	67 (8.0)	54 (8.0)	13 (8.0)	1.000
Cardiac function				
Average heart rate, beats/min	73.7 ± 35.7	73.2 ± 38.6	76.1 ± 19.8	<0.001*
Average SBP, mmHg	123.4 ± 14.2	124.0 ± 13.8	121.0 ± 15.5	<0.001*
Average DBP, mmHg	69.5 ± 8.8	70.1 ± 8.8	66.7 ± 8.3	<0.001*
Ejection fraction, %	60.2 ± 12.9	60.8 ± 12.8	57.6 ± 12.9	<0.001*
NT-proBNP, μg/ml	1.7 ± 2.7	1.4 ± 2.4	2.7 ± 3.5	<0.001*
Laboratory data				
Serum creatinine elevation, %	14.4 ± 41.2	2.1 ± 11.6	66.0 ± 70.0	<0.001*
C-reactive protein, mg/L	10.7 ± 23.1	9.5 ± 21.6	15.5 ± 28.3	<0.001*
Serum albumin, g/L	38.6 ± 5.0	39.1 ± 4.7	36.6 ± 5.7	<0.001*
Hemoglobin, g/L	127.5 ± 19.8	129.4 ± 18.7	120.0 ± 21.9	<0.001*
HbA1c, %	6.5 ± 1.4	6.4 ± 1.4	6.8 ± 1.7	0.002*
eGFR, ml/(min × 1.73 m^2)	78.6 ± 23.1	79.2 ± 21.9	76.3 ± 27.3	0.169
Total cholesterol, mmol/L	4.1 ± 1.2	4.1 ± 1.2	3.9 ± 1.2	<0.001*
Total bilirubin, μmol/L	16.0 ± 19.0	15.8 ± 20.1	17.1 ± 13.7	0.129
Low density lipoprotein, mmol/L	2.21 ± 0.92	2.23 ± 0.93	2.15 ± 0.87	0.100
PCI procedure data				
Volume of contrast agent, mg	100.6 ± 69.1	101.1 ± 69.1	98.6 ± 69.2	0.297
FFR/IVUS/OCT examination, n (%)	176 (18.1)	157 (19.7)	19 (10.9)	0.008*
CTO, n (%)	127 (13.1)	105 (13.4)	22 (12.2)	0.752
Multivessel lesions, (%)	55 (6.0)	45 (6.0)	10 (5.9)	1.000
Total length of stents, mm	45.8 ± 25.3	46.2 ± 25.5	43.8 ± 24.6	0.247
Direct PCI, (%)	125 (13.8)	99 (13.4)	26 (15.4)	0.576
Medication, n (%)				
ACEI	549 (17.4)	435 (17.1)	114 (18.7)	0.393
ARB	901 (28.6)	746 (29.4)	155 (25.4)	0.058
CCB	847 (26.9)	689 (27.1)	158 (25.9)	0.574
Beta blocker	1614 (51.2)	1280 (50.4)	334 (54.8)	0.059
Statin	2567 (81.5)	2117 (83.3)	450 (73.8)	<0.001*
Aspirin	2493 (79.1)	2083 (82.0)	410 (67.2)	<0.001*
Oral furosemide	969 (30.8)	670 (26.4)	299 (49.0)	<0.001*
Furosemide injection	479 (15.2)	296 (11.7)	183 (30.0)	<0.001*
Dopamine	815 (25.9)	605 (23.8)	210 (34.4)	<0.001*

BMI indicates body mass index; PCI, percutaneous coronary intervention; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NT-proBNP, N-terminal pro brain natriuretic peptide; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker. *$P < 0.05$.

hypertension, or in ACEI/ARB/CCB/beta blocker use between groups (all $P > 0.05$).

To construct the cGPS, ROC curves were plotted and the cutoff values (albumin: 35.93 g/L; CRP: 2.65 mg/L) were computed (Fig. 2A and B). As shown in Table 2, patients with CA-AKI had higher GPS/mGPS/cGPS scores (all $P < 0.001$). The population distribution histograms in Fig. 2C showed that the higher GPSs scores, the higher incidence of CA-AKI.

3.2. Correlation analysis

Correlation analysis was carried out to determine the correlations between GPS-related variables and SCr (Fig. 3). All GPS, mGPS, cGPS showed close correlations with their two components: positive correlation with CRP levels while negative correlation with albumin levels. GPS had a relatively higher positive correlation with SCr elevation proportion than with mGPS and cGPS (GPS: r = 0.19; mGPS: r = 0.15; cGPS: r = 0.18). Later, comparison among groups were performed and the results showed that SCr elevation proportion was comparable among all three GPSs groups (Fig. 4A–C).

3.3. Linear and logistic regression analysis

Linear regression analysis of three kinds of GPSs on the proportion of SCr elevation was performed. As shown in Table 3, univariate linear regression analysis demonstrated the proportion of SCr elevation was positively related to GPS, mGPS, cGPS (all $P < 0.001$). In Model 3, multivariate analysis indicated that higher GPS/mGPS/cGPS scores were significantly associated with the increased risk of SCr elevation proportion (GPS: $\beta = 4.850$, 95%CI [3.700 to 8.722], $P < 0.001$; mGPS: $\beta = 3.450$, 95%CI [1.896 to 6.888], $P = 0.001$; cGPS: $\beta = 3.992$, 95%CI [2.368 to 6.940], $P < 0.001$).

To verify the independent risk factor of CA-AKI, logistic regression analysis was operated. The results in Table 4 demonstrated that

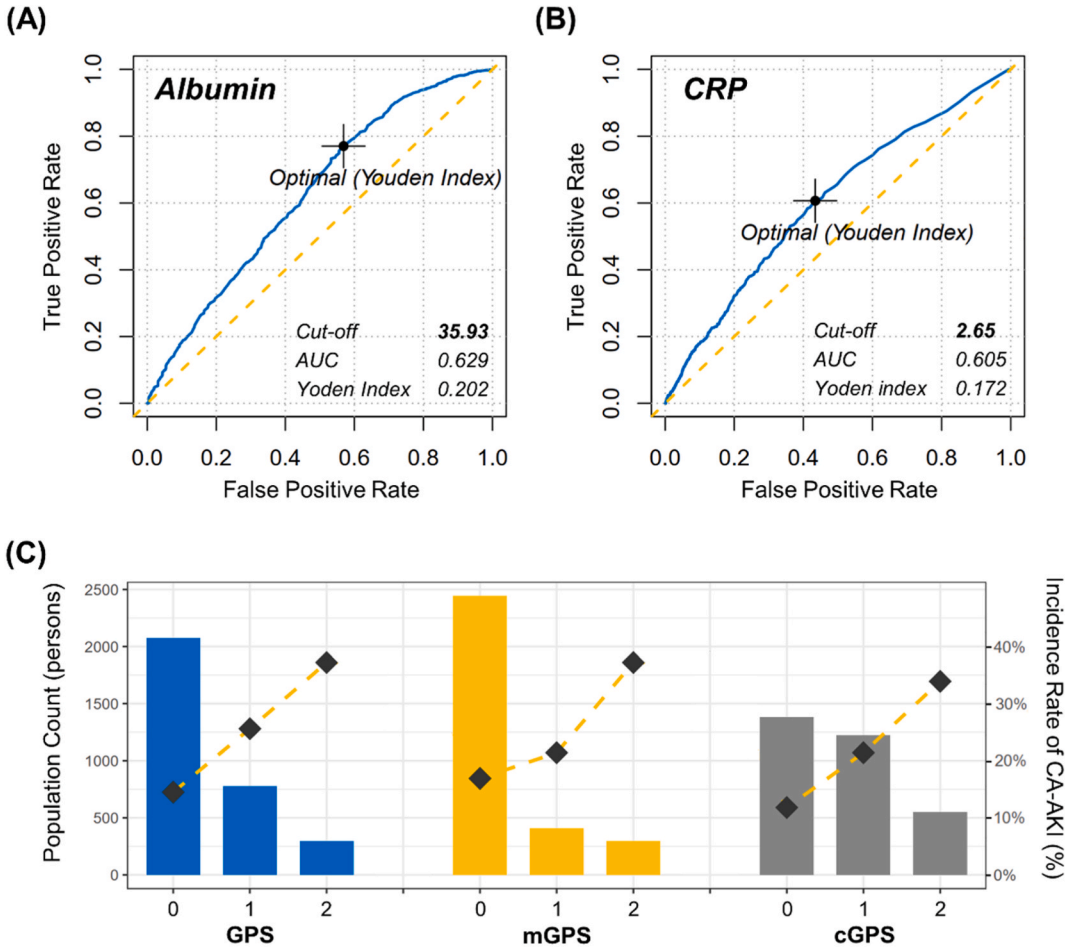


Fig. 2. The cutoff values determined by receiver operating characteristic curve and the population distribution histogram. (A) and (B) Receiver operating characteristic curve of serum albumin and CRP for CI-AKI respectively. (C) The population distribution of CA-AKI incidence according to GPS/mGPS/cGPS. The gold dashed line depicts the changing trend. Left axis, population count (persons); right axis, incidence rate of CA-AKI (%). CA-AKI indicates contrast-associated acute kidney injury; CRP, C-reactive protein; AUC, area under the curve.

Table 2
Baseline characteristics of three GPSs scores.

Characteristics		CA-AKI		
	Overall (n = 3150)	No(n = 2540)	Yes(n = 610)	*P* value
GPS (score, %)				<0.001*
0	2075 (65.9)	1774 (69.8)	301 (49.3)	
1	776 (24.6)	577 (22.7)	199 (32.6)	
2	299 (9.5)	189 (7.4)	110 (18.0)	
mGPS (score, %)				<0.001*
0	2444 (77.6)	2031 (80.0)	413 (67.7)	
1	407 (12.9)	320 (12.6)	87 (14.3)	
2	299 (9.5)	189 (7.4)	110 (18.0)	
cGPS (score, %)				<0.001*
0	1380 (43.8)	1217 (47.9)	163 (26.7)	
1	1221 (38.8)	960 (37.8)	261 (42.8)	
2	549 (17.4)	363 (14.3)	186 (30.5)	

GPS indicates Glasgow prognostic score; mGPS, modified Glasgow prognostic score; cGPS, cutoff-based Glasgow prognostic score. The other abbreviations refer to Table 1. *$P < 0.05$.

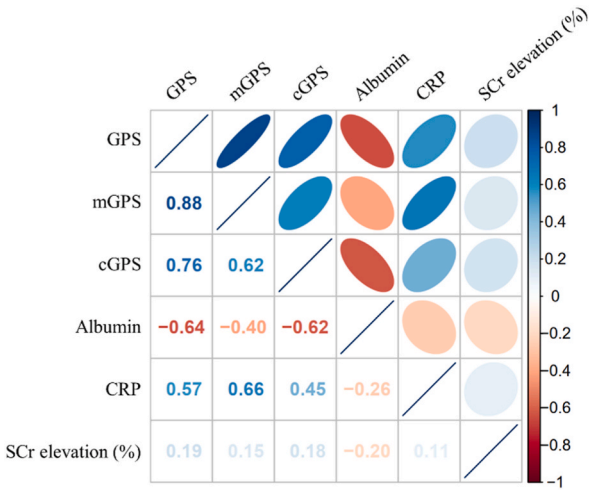


Fig. 3. The correlation matrix. Pearson correlations are displayed on the bottom-left part of the matrix plot. A higher correlation is represented by lower transparency and narrower ellipses. Blue indicates positive correlation and red indicates negative correlation. SCr indicates serum creatinine; other abbreviations are consistent with the above.

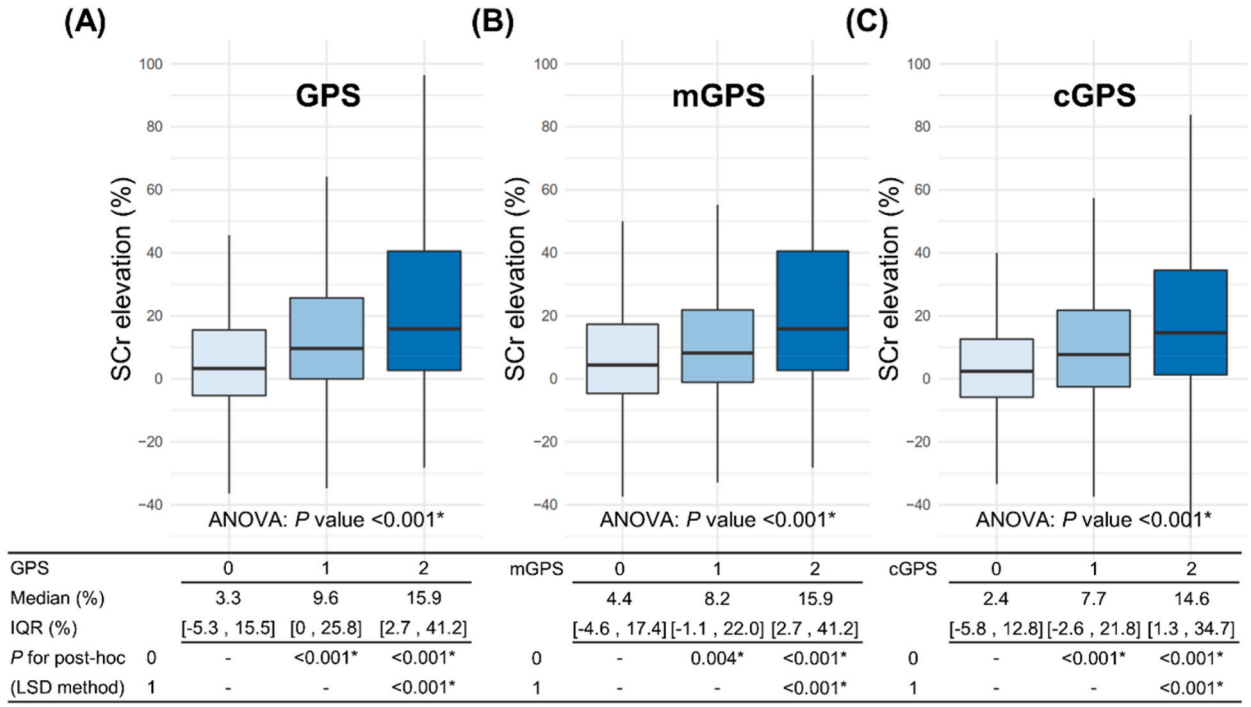
after fully adjusted, higher GPSs scores were independently associated with higher CI-AKI risk when compared to the reference, (GPS: [2 *vs.* 0]: OR = 2.091, 95 % CI [1.538 to 2.843], $P < 0.001$; mGPS: [2 *vs.* 0]: OR = 1.765, 95 % CI [1.314 to 2.370], $P < 0.001$; cGPS: [2 *vs.* 0]: OR = 2.318, 95 % CI [1.742 to 3.085], $P < 0.001$). Besides, tests for linear trend were also performed by treating ordered GPSs score as continuous variables in corresponding logistic regression models. The results further illustrated that GPS, mGPS, and cGPS were independent risk factors for CA-AKI incidence (all *P* for trend <0.05).

3.4. ROC analysis

For determining the predictive power of three kinds of GPSs for CA-AKI incidence, ROC curve analysis was conducted (Fig. 5). The results revealed that all three GPSs had a predictive capability for the incidence of CA-AKI. Among these, cGPS had the strongest predicting power (cGPS: AUC = 0.633; mGPS: AUC = 0.567; GPS: AUC = 0.611).

3.5. Subgroup analysis

To identify potential sources of heterogeneity, subgroup analysis was carried out according to age (<70 or ≥70 yrs), eGFR (<60 or ≥60 ml/(min x1.73m2)), SBP (<120 or ≥120 mmHg) and volume of contrast agent (<100 or ≥100 mg). Figs. 6 and 7 showed that the results from all four subgroup analyses were consistent with the results from the main analyses (all *P* for trend <0.05).



GPS		0	1	2	mGPS	0	1	2	cGPS	0	1	2
Median (%)		3.3	9.6	15.9		4.4	8.2	15.9		2.4	7.7	14.6
IQR (%)		[-5.3 , 15.5]	[0 , 25.8]	[2.7 , 41.2]		[-4.6 , 17.4]	[-1.1 , 22.0]	[2.7 , 41.2]		[-5.8 , 12.8]	[-2.6 , 21.8]	[1.3 , 34.7]
P for post-hoc	0	-	<0.001*	<0.001*	0	-	0.004*	<0.001*	0	-	<0.001*	<0.001*
(LSD method)	1	-	-	<0.001*	1	-	-	<0.001*	1	-	-	<0.001*

Fig. 4. Comparison among three GPSs groups. Comparison among groups of GPS (A), mGPS (B), and cGPS (C) were performed by One way ANOVA and followed with least significant difference (LSD) post-hoc tests. Abbreviations are consistent with the above.

Table 3
Linear regression analysis of three GPSs on the proportion of serum creatinine elevation.

	Model 1 (Crude)		Model 2 (Adjusted)		Model 3 (Adjusted)	
	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
GPS	11.027 [9.893 to 14.172]	<0.001*	6.443 [5.768 to 10.814]	<0.001*	4.850 [3.700 to 8.722]	<0.001*
mGPS	8.439 [7.371 to 11.832]	<0.001*	4.642 [3.447 to 8.488]	<0.001*	3.450 [1.896 to 6.888]	0.001*
cGPS	10.148 [8.028 to 11.873]	<0.001*	5.890 [4.578 to 9.147]	<0.001*	3.992 [2.368 to 6.940]	<0.001*

Model 1 adjusted for none.
Model 2 adjusted for age, gender, diabetes, average SBP, eGFR, ejection fraction, hemoglobin, volume of contrast agent, type of contrast agent.
Model 3 additionally adjusted for administration of statin, furosemide injection, and dopamine.
The abbreviations refer to Table 1. *$P < 0.05$.

4. Discussion

This retrospective cross-sectional study investigated the impact of a simple risk score based on inflammatory and nutritional status (GPS) and its derived risk scores (mGPS and cGPS) on the incidence of CA-AKI in CAD patients who underwent CAG with/without PCI. Higher GPS, mGPS and cGPS were independent risk factors of CA-AKI. More importantly, compared with GPS and cGPS, cGPS had a higher predictive value for CA-AKI. Overall, the results of present study might be quite clinically valuable for early identification and management of CA-AKI.

CA-AKI is classically determined according to the elevation of SCr levels [17]. However, there may exist uncertainties regarding the degree and reversibility of kidney injury that occurs after contrast agent injection [7]. Delayed treatment of CA-AKI and underlying non-reversible renal injury further aggravates the anticipated poor prognosis [19]. Thus, precise assessment and early prediction are crucial for the incidence of CA-AKI and individualized prognosis. Using combined objective indicators may attribute to more accurate risk assessment for CA-AKI [20]. Several comprehensive scores such as Syntax Score (SS), Syntax Score II (SSII), and PRECISE-DAPT risk score which usually used to identify the CAD risk have been found to be associated with CI-AKI incidence [21–23].Anyway, there remain urgent needs for simpler and more effective methods to identify CI-AKI risk.

In clinical, both CRP and albumin are routine biomarkers and are readily available in standard blood samples [24]. The close correlation between inflammation and CA-AKI has been well-established [25,26]. Multiple inflammation indicators are used to assess CA-AKI risk in clinical, of which the most commonly used is CRP [27]. Laboratory evidence has shown that CRP can impair tubular epithelial cell regeneration and promote acute kidney injury through a variety of signaling pathways [28]. Gao et al. reported that

Table 4
Logistic regression analysis of three GPSs on CI-AKI incidence.

	Score	Cases/Overall (%)	Model 1 (Crude)		Model 2 (Adjusted)		Model 3 (Adjusted)	
			Odds ratio	*P* value	Odds ratio	*P* value	Odds ratio	*P* value
GPS	0	301/2075 (14.5 %)	1 (reference)		1 (reference)		1 (reference)	
	1	199/776 (25.6 %)	2.033 [1.661 to 2.488]	<0.001*	1.742 [1.393 to 2.179]	<0.001*	1.546 [1.229 to 1.945]	<0.001*
	2	110/299 (36.8 %)	3.430 [2.632 to 4.471]	<0.001*	2.497 [1.852 to 3.369]	<0.001*	2.091 [1.538 to 2.843]	<0.001*
	P for trend			<0.001*		<0.001*		<0.001*
mGPS	0	413/2444 (16.9 %)	1 (reference)		1 (reference)		1 (reference)	
	1	87/407 (21.4 %)	1.337 [1.031 to 1.733]	0.028*	1.236 [0.934 to 1.636]	0.138	1.125 [0.845 to 1.498]	0.421
	2	110/299 (36.8 %)	2.862 [2.212 to 3.704]	<0.001*	2.047 [1.536 to 2.728]	<0.001*	1.765 [1.314 to 2.370]	<0.001*
	P for trend			<0.001*		<0.001*		0.001*
cGPS	0	163/1380 (11.8 %)	1 (reference)		1 (reference)		1 (reference)	
	1	261/1221 (21.4 %)	2.030 [1.640 to 2.512]	<0.001*	1.809 [1.432 to 2.285]	<0.001*	1.656 [1.306 to 2.100]	<0.001*
	2	186/549 (33.9 %)	3.826 [3.007 to 4.867]	<0.001*	2.877 [2.181 to 3.795]	<0.001*	2.318 [1.742 to 3.085]	<0.001*
	P for trend			<0.001*		<0.001*		<0.001*

Model 1 adjusted for none.
Model 2 adjusted for age (per 10 years), gender (male or female), diabetes (yes or no), average SBP (<90, 90–114, 115–139, ≥140 mmHg), eGFR (<30, 30–59, 60–89, ≥90 ml/min × 1.73 m2), ejection fraction (<50, 50–64, ≥65 %), contrast volume (<60, 60–119, ≥120 mg), and type of contrast agent (isotonic or hypotonic).
Model 3 additionally adjusted for administration of statin (yes or no), furosemide injection (yes or no), and dopamine (yes or no).
The abbreviations refer to Table 1. *$P < 0.05$.

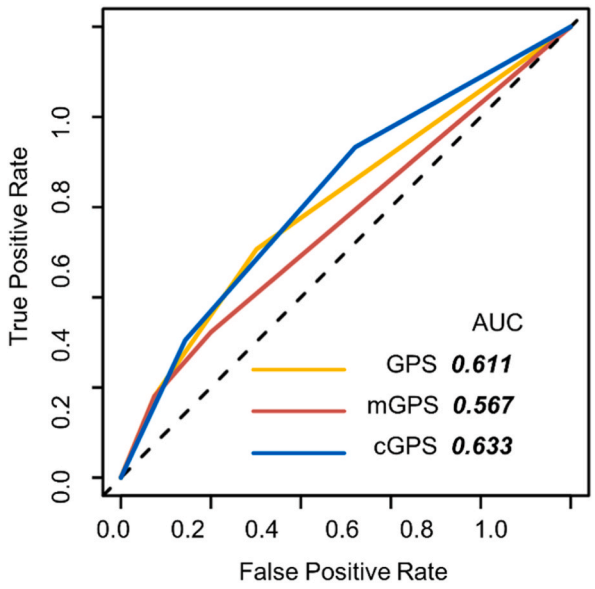


Fig. 5. The receiver operating characteristic (ROC) analysis. The ROC curve of the GPS (solid line, yellow) compares mGPS (solid line, red) and cGPS (solid line, blue). ROC indicates receiver operating characteristic; other abbreviations are consistent with the above.

increased preprocedural CRP was related to higher incidence of CA-AKI [29]. In addition, serum albumin is another biomarker in routine bioanalytical methods. It is well known that serum albumin is an important proxy for nutritional status [30]. Studies have shown that patients with malnutrition and hypoalbuminemia have a higher risk of CA-AKI [31]. Hence, theoretically, preprocedural risk stratification with CRP and albumin can serve as a potential adjunct to predict and manage CA-AKI.

GPS and mGPS are reliable and simple prognostic scores combining these two biomarkers [10,12]. Over the years, GPS and mGPS have been widely used to assess cancer progression and prognosis [32]. With the inflammation hypothesis of heart diseases has gained increased support, researchers also link the GPS and mGPS with the clinical outcomes of heart diseases [15,33]. Shigeto et al. found that GPS was a useful prognostic score for hospitalized patients with acute heart failure [34]. Anna et al. reported that mGPS could predict the survival in patients with heart failure with reduced ejection fraction (HFrEF) [35]. Besides, Xu et al. also demonstrated that the additional predictive value of GPS for MACEs during hospitalization in acute myocardial infarction patients [16]. In light of

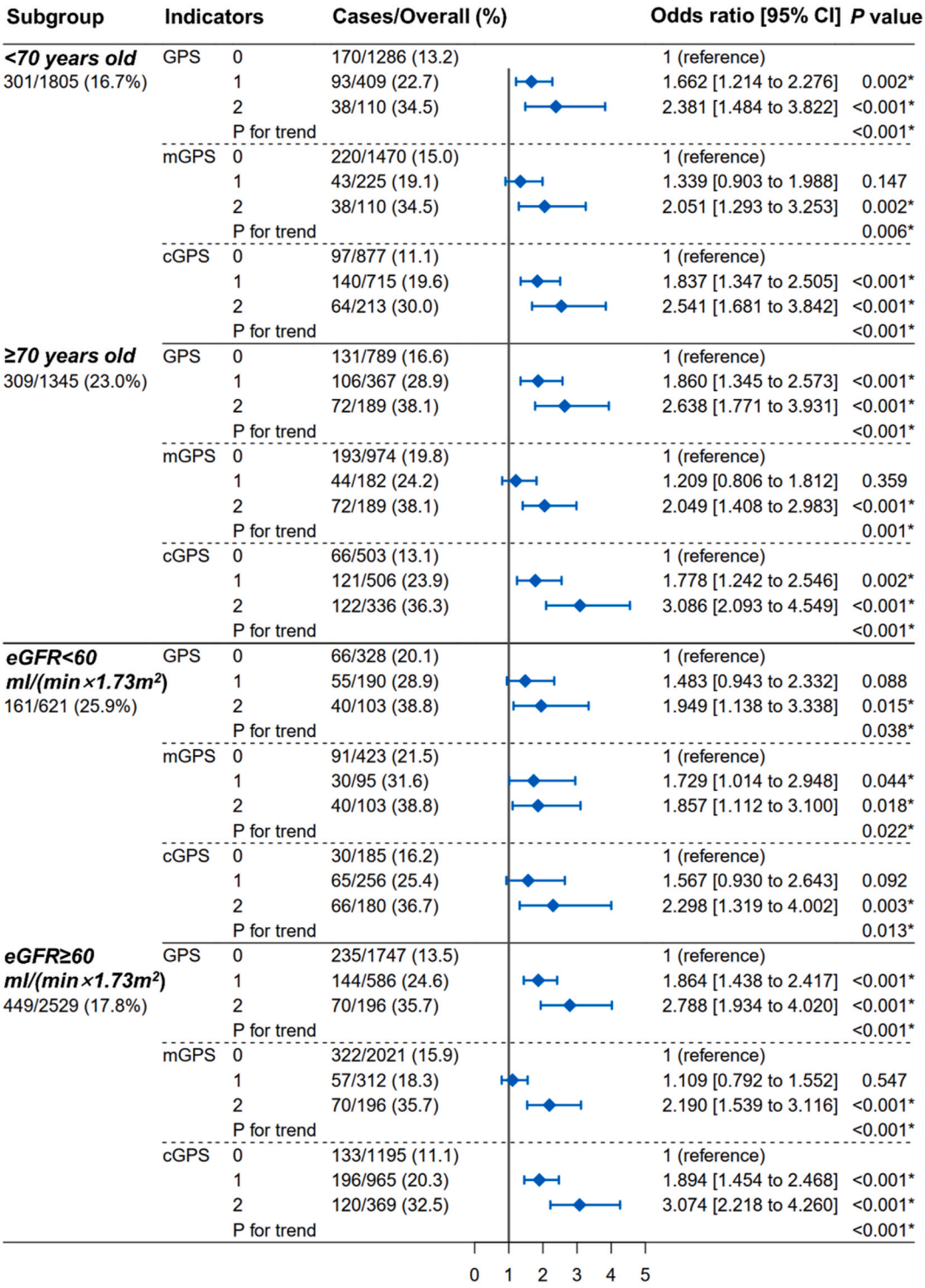


Fig. 6. Subgroup analysis according to the age and estimated glomerular filtration rate (eGFR). Patients were dichotomized according to the age (<70 or ≥70 yrs) and eGFR (<60 or ≥60 ml/(min x1.73m2)). Multivariate logistic regression adjusted the same covariates of Model 3 in Table 3 with the first category of GPSs being the reference. eGFR indicates estimated glomerular filtration rate; other abbreviations are consistent with the above.

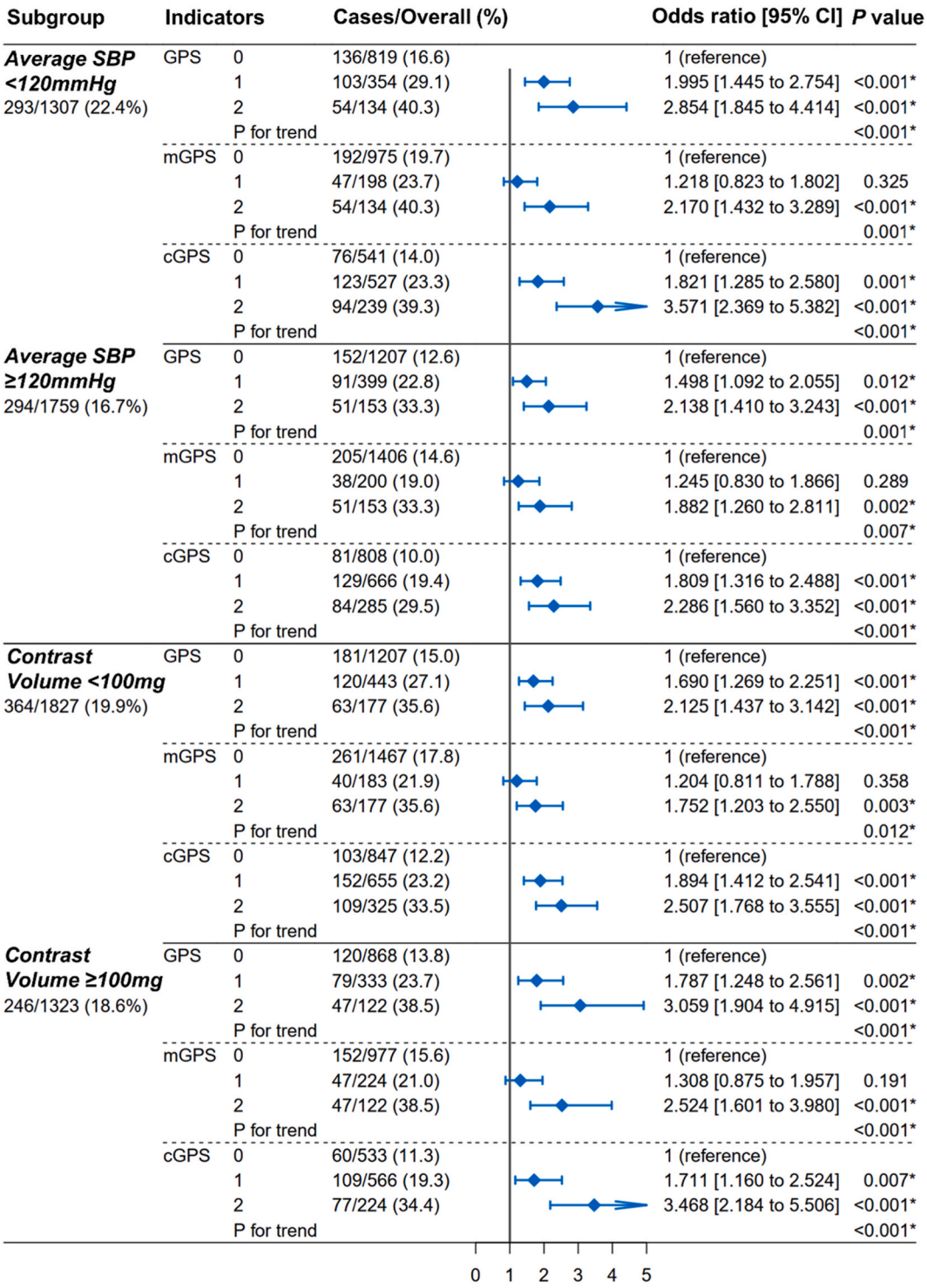


Fig. 7. Subgroup analysis according to the systolic blood pressure (SBP) and the volume of contrast agent. Patients were dichotomized according to the SBP (<120 or ≥120 mmHg) and the volume of contrast agent (<100 or ≥100 mg). Multivariate logistic regression adjusted the same covariates of Model 3 in Table 3 with the first category of GPSs being the reference. Abbreviations are consistent with the above.

available studies, it is plausible to assume that the GPS and mGPS, combining both CRP and albumin, should provide great clinical relevance to CA-AKI. As expected, this study demonstrated that the increased GPS and mGPS were significantly associated with higher risk of CA-AKI during hospitalization after CAG or PCI. These findings might encourage clinicians to pay more attention on baseline

GPS and mGPS for providing predictive values of CA-AKI.

GPS/mGPS and its classification cutoff score are based on the data from cancer patients [10,12]. To a great extent, the optimum cutoff values vary from different populations. It is necessary to reconsider whether such grading criteria is exactly generalizable to CAD populations in real-life settings. Based on the data from CAD patients, the present study calculated the optimal cutoff value of two biomarkers (CRP: 2.65 mg/L; albumin: 35.93 g/L), and further creatively constructed the cGPS. The findings revealed that cGPS could be considered as an independent predictor for CA-AKI, which was in good agreement with that of GPS/mGPS. More importantly, the AUC of ROC analysis revealed that cGPS displayed a stronger ability to predict the incidence of CA-AKI than GPS and mGPS. Further investigations are required to identify the optimal cGPS score which has better discrimination and ability to predict CA-AKI. Although additional optimizations of cGPS are required, the findings of this study suggested that it was important for cardiovascular physicians to use cGPS as a clinical tool to predict CA-AKI risk. In clinical, physicians should pay more attention to cGPS to identify high-risk CA-AKI patients and optimize preoperative rational individual management without delay. For patients with higher cGPS scores, they will be considered to be injected less amount of contrast during CAG and PCI procedure or treated with more aggressive hydration to prevent the incidence of CA-AKI.

The pathogenesis of CA-AKI is complex and the potential mechanisms between GPSs based on inflammatory and nutritional factors and CA-AKI may be explained as follows. On the one hand, inflammation plays a direct role in damaging renal endothelial function, enhancing oxidative stress, activating various inflammatory mediators and so on [25]. On the other hand, malnutrition or hypoalbuminemia means an imbalance in anabolic-catabolic processes which can lead to individual metabolic disorders and increase the renal burden [36]. Importantly, there exists a close relationship between inflammation and serum albumin levels [37]. In inflammatory condition, capillary permeability increases and albumin decreases correspondingly [38]. Lower albumin can also predispose for the increased susceptibility to inflammatory response [39]. In this way a vicious circle is created and therefore lead to the incidence of CA-AKI.

There were several potential limitations to this study. Firstly, because of the retrospective nature, the level of evidence of our findings was restricted and potential selection bias could not be excluded. Secondly, in this study, cGPS was calculated based on a limited sample size, whether such findings apply to all CA-AKI populations requires further study. Thirdly, although we controlled important potential confounding factors, there were residual confounders influencing the results.

5. Conclusion

For CAD patients who underwent CAG with/without PCI, preoperative GPS, mGPS and cGPS were independent predictors of CA-AKI incidence. Among them, cGPS which was constructed by the optimal cutoff value of CRP and albumin demonstrated the higher potential predictive power.

Ethics statement

This study was reviewed and approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University, with the approval number: 20,220,228-30. Informed consent was not required for this study because the retrospective nature of this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Hangpan Jiang: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Siwei Yang:** Formal analysis, Writing – original draft. **Zhezhe Chen:** Formal analysis, Writing – original draft. **Duanbin Li:** Formal analysis, Methodology, Writing – original draft. **Yu Shan:** Methodology. **Yecheng Tao:** Formal analysis. **Menghan Gao:** Formal analysis. **Xiaohua Shen:** Methodology. **Wenbin Zhang:** Funding acquisition, Writing – review & editing. **Shudong Xia:** Writing – review & editing. **Xulin Hong:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

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Abbreviations

CAD	coronary artery disease
CA-AKI	contrast-associated acute kidney injury
CAG	coronary angiography
PCI	percutaneous coronary intervention
GPS	glasgow prognostic score
CRP	C-reactive protein
mGPS	modified GPS
cGPS	cutoff-based GPS
SCr	serum creatinine
eGFR	estimated glomerular filtration rate
ROC	receiver operating characteristic
SD	standard deviation
LSD	least significant difference
EF	ejection fraction
SBP	systolic blood pressure
HFrEF	heart failure with reduced ejection fraction

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