Activities of Daily Living Predict Contrast-Associated Acute Kidney Injury among Population Undergoing Coronary Angiography

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Jiang *et al.*: Activities Predict Contrast-Associated Acute Kidney Injury among Coronary Angiography Patients

The Barthel index is a widely used assessment tool for evaluating physical performance in activities of daily living. The present study investigated the relationship between activities of daily living measured by Barthel Index at hospital admission and the occurrence of contrast-associated acute kidney injury among patients undergoing coronary angiography or percutaneous coronary intervention. In this retrospective cross-sectional study, 3148 patients undergoing coronary angiography or percutaneous coronary intervention were enrolled. Activities of daily living were stratified into 5 degrees according to Barthel index scores. Contrast-associated acute kidney injury was defined as an increase of either 25 % or 0.5 mg/dl (44.2 µmol/l) in basal serum creatinine level within 72 h, following the use of contrast agent. Univariable and multivariable linear and logistic regression analysis were used to determine the associations of Barthel index with the proportion of serum creatinine elevation and contrast-associated acute kidney injury, respectively. The exploratory subgroup analysis was further conducted. Totally, 16.7 % of patients suffered from contrast-associated acute kidney injury and the mean age was 67.07±10.71 y old, 65.7 % for males. Multivariable linear regression analysis demonstrated that Barthel index scores were significantly associated with the proportion of serum creatinine elevation (beta=-10.150, 95 % confidence interval=-11.788 to -8.511, p<0.001). Multivariable linear regression analysis demonstrated that Barthel index scores were independent predictors of contrast-associated acute kidney injury incidence (p<0.001). With the increase in Barthel index scores, the incidence of contrast-associated acute kidney injury showed a significant downward tendency. Subgroup analysis showed consistent results. Activities of daily living measured by Barthel index at hospital admission was an independent prediction indicator to assess contrast-associated acute kidney occurrence among patients undergoing coronary angiography or percutaneous coronary intervention.

Key words: Activities of daily living, Barthel index, contrast-associated acute kidney injury, coronary angiography, percutaneous coronary intervention

Contrast-Associated Acute Kidney Injury (CA-AKI), known as Contrast-Induced Acute Kidney Injury (CI-AKI), is one of the major complication after Coronary Angiography (CAG) or Percutaneous Coronary Intervention (PCI) and the incidence is about 2.7 %-20.6 %[1-3]. CA-AKI pathophysiology includes both direct and indirect damages caused by contrast agents, mainly involving tubular injury, vascular dysfunction and inflammation[4]. The occurrence of CA-AKI directly or indirectly causes prolonged hospital stays, more expensive hospitalizations and increased mortality[5,6]. Setting up a facile and economic prediction model to identify patients at high risk is crucial. Currently, several models for predicting CA-AKI occurrence have been developed based on traditional risk factors, mainly involving test results and procedural characteristics[7-9]. However, few studies have been conducted to explore the impact of a patient's physical function on the occurrence of CA-AKI.

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Activities of Daily Living (ADL) are defined as the ability of physical performance required for independent living, such as feeding, dressing, bathing and toileting. The decline of ADL leads to functional dependence, a condition in which a person cannot complete basic activities without assistance, which is thought to be an intuitive external presentation of the adverse effects of various diseases on physical function. Developed in 1965[10], the Barthel Index (BI) is still widely used today as a well-established score to assess the functional capacity for ADL on a clinical basis because of its simplicity, communicability and ease of scoring[11,12]. Although healthcare professionals routinely evaluate patients at hospital admission through BI scores, research has been mainly exclusive to neurological disorders or terminal cancers[13,14] and BI's role in CAG-related complications remains unclear.

The present study aimed to investigate the relationship between ADL measured by BI at hospital admission and CA-AKI occurrence among patients undergoing CAG or PCI.

MATERIALS AND METHODS

Study population:

This study was a retrospective review of all consecutive eligible patients undergoing CAG or PCI from December 2006 to December 2019 at Sir Run Run Shaw Hospital and its medical consortium hospitals. Additional details about the study subjects are listed in fig. 1.

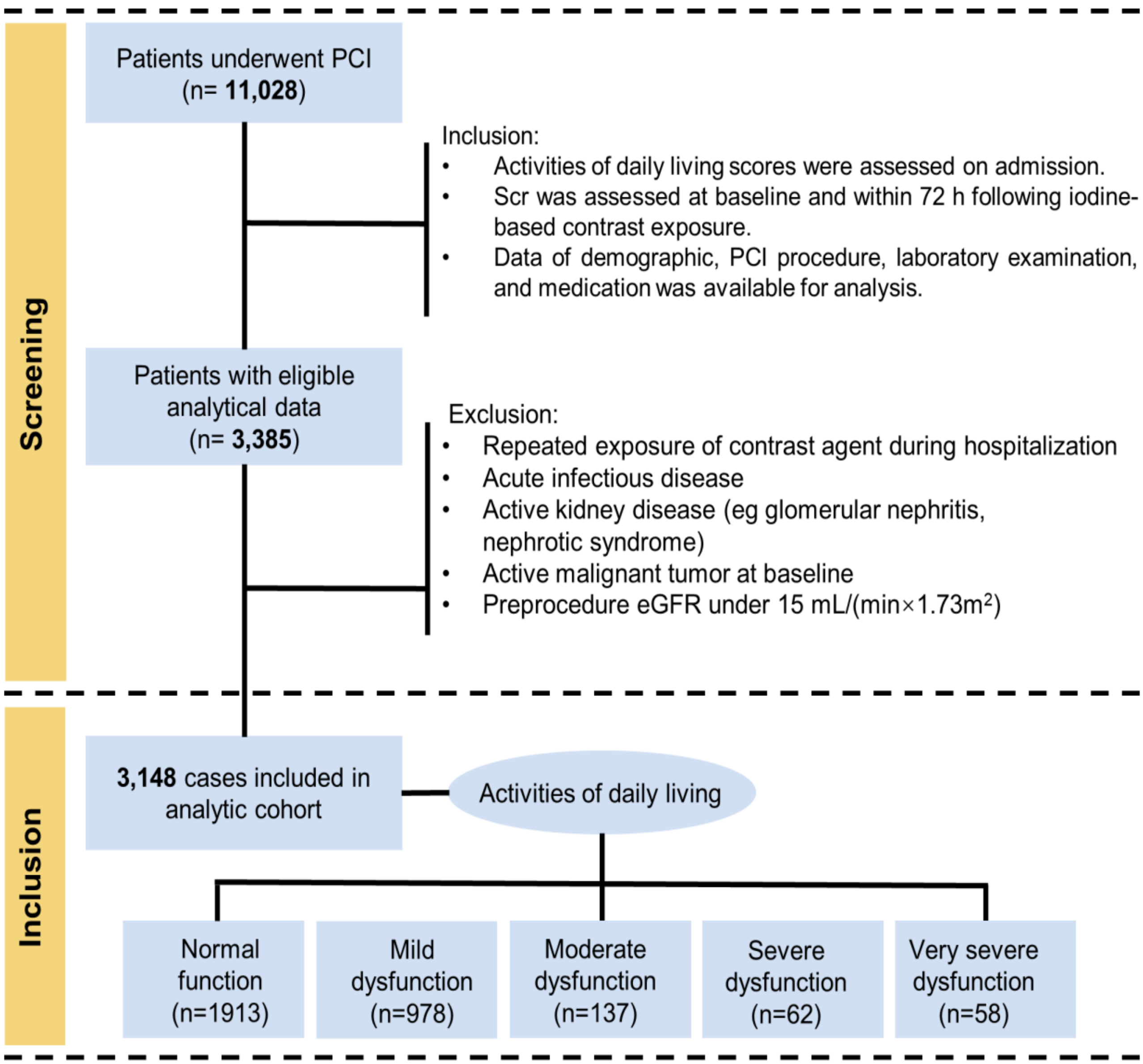

Fig. 1: Flow chart of study design

Selection criteria: The inclusion criteria include patients with ADL scores assessed at hospital admission; patients with documented Serum creatinine (Scr) before the procedure and at 72 h after the procedure; patients with complete data of demographics, angiographic procedure, laboratory examination and medication. Exclusion criteria include patients with repeated contrast exposure within 1 w or less from the procedure; patients with a pre-existing end-stage renal disease requiring hemodialysis, estimated Glomerular Filtration Rate (eGFR)<15 ml/min/1.73 m^2; patients with active kidney disease (e.g., glomerular nephritis, nephrotic syndrome); patients with an acute infectious disease or active malignant tumor. Finally, 3148 patients were enrolled. The study was carried out according to the Declaration of Helsinki and was approved by the Ethics Committee of Sir Run Run Shaw Hospital (No. 20201217-36).

Data collection and assessment of clinical parameters:

Different parameters involving patient demographics, clinical features, laboratory results, medications and angiographic characteristics were obtained from the hospital information system.

Healthcare professionals evaluate BI score routinely at the patient's hospital admission. The BI score is recommended as an assessment of ADL, consisting of 10 items about feeding, dressing, bathing, grooming, toileting, bowel control, bladder control, ambulation, chair transferring and stair climbing, with scoring from 0 to 100 (0=completely dependent; 100=completely independent)[10]. ADL were stratified according to BI scores into the following 5 degrees, normal function (BI=100), mild dysfunction (60-99), moderate dysfunction (40-59), severe dysfunction (20-39) and very severe dysfunction (BI<20).

The concentrations of Scr were measured at hospital admission and the postoperative Scr concentrations recorded were the highest for at least three measurements within a 72 h timeframe. CA-AKI was defined as an increase of either 25 % or 0.5 mg/dl (44.2 µmol/l) in basal Scr concentrations within 72 h following the implementation of the contrast agent[15].

Statistical analysis:

Statistical analyses were performed using R version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria) and Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, Illinois (IL), United States). Continuous variables were expressed as mean±Standard Deviation (SD) and compared using Student t-test in case of normal distributed, while expressed as median (Interquartile Range [IQR]) and compared using Mann-Whitney U-test in case of non-normal distributed. Categorical variables were expressed as counts (percentage) and compared using Chi-Square test or Fisher's exact test.

Univariant and multivariate linear regression analyses was done to evaluate the relationship between BI on admission and the proportion of Scr elevation and Locally Estimated Scatterplot Smoothing (LOESS) curve was used to fit the relationship between BI score and the proportion of Scr elevation. Univariant and multivariate logistic regression were used to determine the association of BI on admission with CA-AKI and Restricted Cubic Spline (RCS) curve was performed for visualization analysis. The previously recognized risk factors variables of CA-AKI from previous studies were included as covariates in the multivariate regression analysis[16]. Tests for trend (p for trend) were carried out by the predefining ordered categorical variable (BI: 100, 60-99, 40-59, 20-39, <20) acting as a continuous variable in the logistic regression analysis. Finally, the exploratory subgroup analysis was conducted to assess the relationship between BI and CA-AKI. The p-values<0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Totally, 3148 patients were enrolled in the study and the mean age was 67.07±10.71 y old, 65.7 % for males. The mean BI among the whole population was 87.98±20.99 scores. The incidence of CA-AKI was 16.9 % (533/3148). Table 1 shows the details of the baseline clinical and procedural characteristics.

Compared with non-CA-AKI, CA-AKI patients were significantly older (69.61±10.25 *vs.* 66.55±10.25 y old, p<0.001), had fewer male sex (60.2 % *vs.* 66.8 %, p=0.004) and a higher proportion of diabetes mellitus (28.0 *vs.* 23.4%, p=0.028). CA-AKI patients had higher levels of Body Mass Index (BMI), Hemoglobin A1c (HbA1c), Creatine Kinase-Myocardial Band (CK-MB), cardiac Troponin I (cTnI) and lower levels of eGFR and Ejection Fraction (EF) (all p-values<0.05). Besides, the medication characteristics of CA-AKI patients were reflected in a lower proportion of use of statin (p-value<0.05). Additionally, CA-AKI patients had a significantly lower BI than non-CA-AKI (76.56±28.05 *vs.* 90.31±18.39 scores, p<0.001).

The population was divided into 5 degrees according to BI scores (predefined cut points: 100, 60-99, 40-59, 20-39, <20). Fig. 2 shows the population distribution and the incidence of CA-AKI in 5 groups. With the decrease in BI score, a decline in population counts and elevation of CA-AKI incidence was observed in the present study. The blue histograms described the overall distribution in each BI group. The gold dashed line depicts the trend in incidence of CA-AKI. The relationship between BI and proportion of Scr elevation was shown here. As shown in fig. 3, LOESS smooth curve was conducted to fit the relationship between BI score and the proportion of Scr elevation. With the elevation of the BI score, the proportion of Scr elevation showed an overall downward tendency.

Linear regression analysis done to assess the relationship between BI score and the proportion of Scr elevation was shown in Table 2. After adjusting for age, gender, diabetes mellitus, hypertension, EF, eGFR, volumes and type of contrast agent, and medications (statin, Beta-Blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI)/ Angiotensin Receptor Blockers (ARBs) and Calcium Channel Blockers (CCBs), multivariable linear regression analysis demonstrated that BI scores were independent predictors for the proportion of Scr elevation (beta (β)=-10.150, 95 % Confidence Interval [CI]: -11.788 to -8.511, p<0.001). BI scores were negatively correlated with the proportion of Scr elevation.

TABLE 1: BASELINE CHARACTERISTICS OF THE STUDY

Characteristics	CA-AKI			
	Overall (n=3148)	No (n=2615)	Yes (n=533)	p value
Demographic features				
Age, years old	67.07±10.71	66.55±10.73	69.61±10.25	<0.001*
Male, n (%)	2067 (65.7)	1746 (66.8)	321 (60.2)	0.004*
Diabetes, n (%)	760 (24.1)	611 (23.4)	149 (28.0)	0.028*
Hypertension, n (%)	2005 (63.7)	1652 (63.2)	353 (66.2)	0.198
BMI, kg/m^2	24.42±5.31	24.31±5.32	24.97±5.21	0.023*
EF, %	59.36±12.97	60.04±12.76	56.03±13.53	<0.001*
BI, score	87.98±20.99	90.31±18.39	76.56±28.05	<0.001*
Laboratory data				
eGFR, ml/(min×1.73 m^2)	78.78±23.34	79.57±22.15	74.89±28.16	<0.001*
Low-Density Lipoprotein Cholesterol (LDL-C), mmol/l	2.22±0.90	2.23±0.91	2.19±0.87	0.409
cTnI, μg/l	0.78±2.59	0.61±2.24	1.62±3.75	<0.001*
CK-MB, U/l	25.05±38.77	23.54±32.90	32.72±59.81	<0.001*
HbA1c, %	6.42±1.33	6.38±1.28	6.65±1.60	0.001*
PCI procedure data				
Volume of contrast agent, mg	102.07±71.53	101.35±71.70	105.61±70.64	0.21
Chronic Total Occlusion (CTO), n (%)	136 (16.4)	110 (16.1)	26 (17.8)	0.708
Multivessel lesions, n (%)	50 (6.6)	40 (6.4)	10 (7.9)	0.673
Direct PCI, n (%)	105 (14.1)	85 (13.7)	20 (15.7)	0.644
Medication				
Statin, n (%)	2626 (83.4)	2209(84.5)	417 (78.2)	0.001*
BB, n (%)	1588 (50.4)	1298 (49.6)	290 (54.4)	0.05
ACEI/ARB, n (%)	1398 (44.4)	1181 (45.2)	217 (40.7)	0.066
CCB, n (%)	886 (28.1)	740 (28.3)	146 (27.4)	0.711

Note: Categorical data are presented as n (%) and continuous data are expressed as mean±SD, *p<0.05

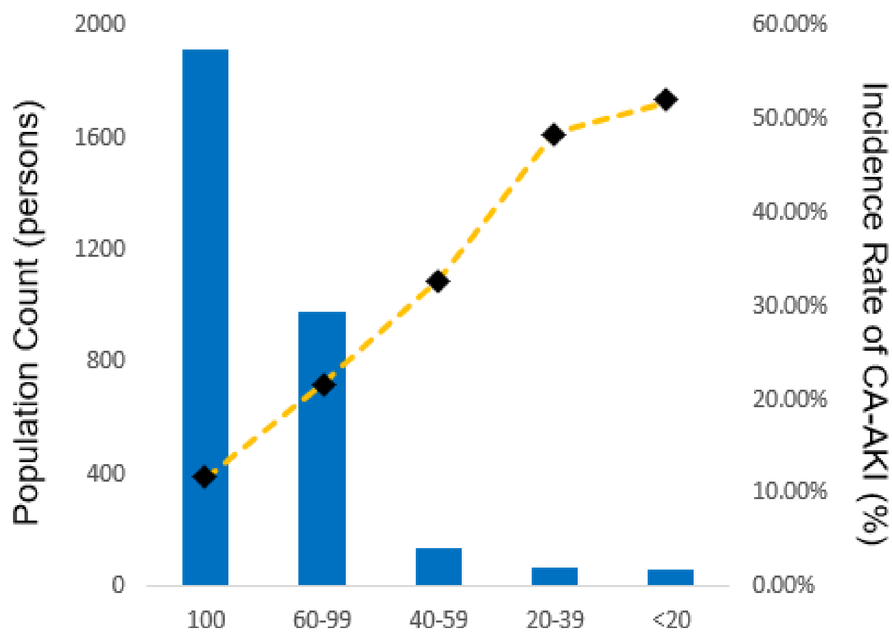

Fig. 2: The population distribution histogram
Note: The population distribution of the incidence of CA-AKI according to BI, (▬) overall distribution in each BI group; (- - -) CA-AKI incidence; Horizontal axis, BI (scores); left axis, population count (persons) and right axis, incidence of CA-AKI (%)

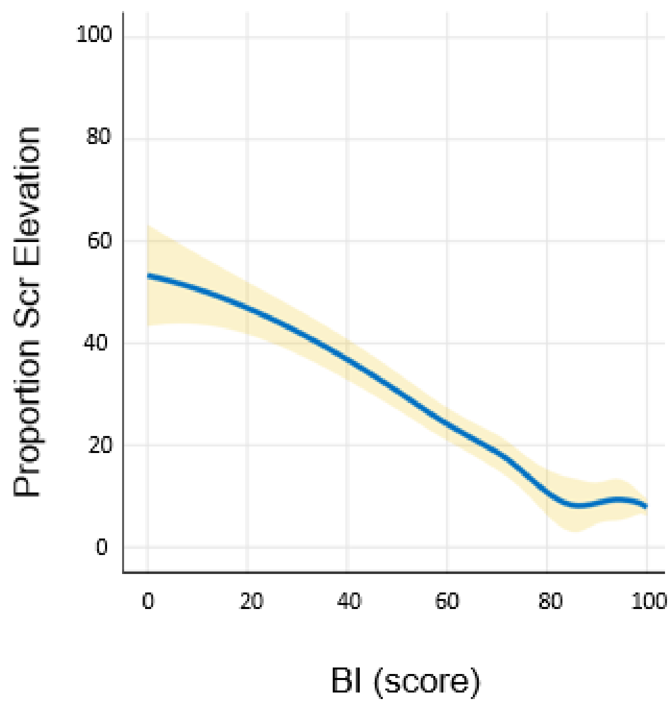

Fig. 3: LOESS smooth curve of BI with the proportion of Scr elevation
Note: The yellow shadow area around the solid line indicated 95 % CI

TABLE 2: LINEAR REGRESSION ANALYSES OF BI ON THE PROPORTION OF SCR ELEVATION

Models	β-coefficient [95 % CI]	p value
Model 1	-10.921 [-12.48 to -9.363]	<0.001*
Model 2	-10.119 [-11.738 to -8.499]	<0.001*
Model 3	-10.150 [-11.788 to -8.511]	<0.001*

Note: *p<0.05

As shown in Table 2, model 1 is adjusted for none; model 2 is adjusted for age (years old), gender (male or female), diabetes (yes or no), hypertension (yes or no), EF (%), eGFR (ml/min/1.73 m^2), contrast volume (mg) and contrast type (isotonic or hypotonic); model 3 is based on model 2, additionally adjusted for medications (administration of statin, BB, ACEI/ARB and CCB) (yes or no).

The relationship between BI and the incidence of CA-AKI was explained here. As shown in fig. 4, restricted cubic spline analysis was conducted to explore the relationship of BI score with CA-AKI. BI scores, the incidence of CA-AKI showed a downward tendency.

The univariable and multivariable logistic regression analysis were used to determine the relationship between BI and the incidence of CA-AKI (Table 3). Model 1 showed BI scores which were negatively correlated with the incidence of CA-AKI (p for trend<0.001; each grade compared with the reference: 60-99 *vs.* 100: 21.4 % *vs.* 11.4 %, Odds Ratio (OR)=2.102, 95 % CI [1.708 to 2.588], p<0.001; 40-59 *vs.* 100: 32.8% *vs.* 11.4%, OR=3.784, 95 % CI [2.579 to 5.551], p<0.001; 20-39 *vs.* 100: 48.4 % *vs.* 11.4 %, OR=7.252, 95 % CI [4.322 to 12.168], p<0.001; <20 *vs.* 100: 51.7 % *vs.* 11.4 %, OR=8.288, 95 % CI [4.859 to 14.135], p<0.001).

After adjusting for age, gender, diabetes mellitus, hypertension, EF, eGFR, volumes and type of contrast agent, (shown in model 2), and further adjusting for medications (statin, BB, ACEI/ARB and CCB) (shown in model 3), multivariable linear regression analysis demonstrated that BI scores were independent predictive indicators for the incidence of CA-AKI (all p for trend<0.001).

Fig. 5 showed the exploratory analysis performed in subgroups, based on age (<70 or ≥70 y.), eGFR (<60 or ≥60 ml/min/1.73 m^2), contrast volumes (<100 or ≥100 mg) and EF (<40, 40≤EF<50, ≤50%). Compared with the reference (BI=100), the incidence of CA-AKI increased with the decreasing BI, which remained consistent in all subgroups (all p for trend<0.001).

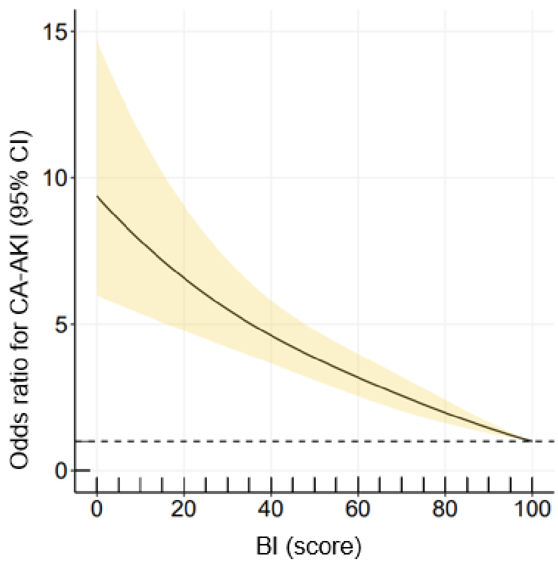

Fig. 4: Restricted cubic spline analyses of the association between BI and CA-AKI
Note: The solid line showed the adjusted OR of BI for CA-AKI and the yellow shadow area around the solid line indicated 95 % CI

TABLE 3: LOGISTIC REGRESSION ANALYSES OF BI ON THE CA-AKI

BI score	ADL grade	Patients/ Overall (%)	Model 1		Model 2		Model 3	
			OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
100	Normal function	219/1913 (11.4 %)	(Reference)		(Reference)		(Reference)	
60-99	Mild dysfunction	209/978 (21.4 %)	2.102 [1.708 to 2.588]	<0.001*	1.828 [1.469 to 2.273]	<0.001*	1.869 [1.499 to 2.330]	<0.001*
40-59	Moderate dysfunction	45/137 (32.8 %)	3.784 [2.579 to 5.551]	<0.001*	3.041 [2.048 to 4.516]	<0.001*	3.131 [2.095 to 4.680]	<0.001*
20-39	Severe dysfunction	30/62 (48.4 %)	7.252 [4.322 to 12.168]	<0.001*	6.176 [3.624 to 10.523]	<0.001*	6.591 [3.838 to 11.318]	<0.001*

<20	Very severe dysfunction	30/58 (51.7 %)	8.288 [4.859 to 14.135]	<0.001*	6.553 [3.769 to 11.394]	<0.001*	6.622 [3.771 to 11.628]	<0.001*
p value				<0.001*		<0.001*		<0.001*

Note: BI score=100 was set as reference category, where *p<0.05

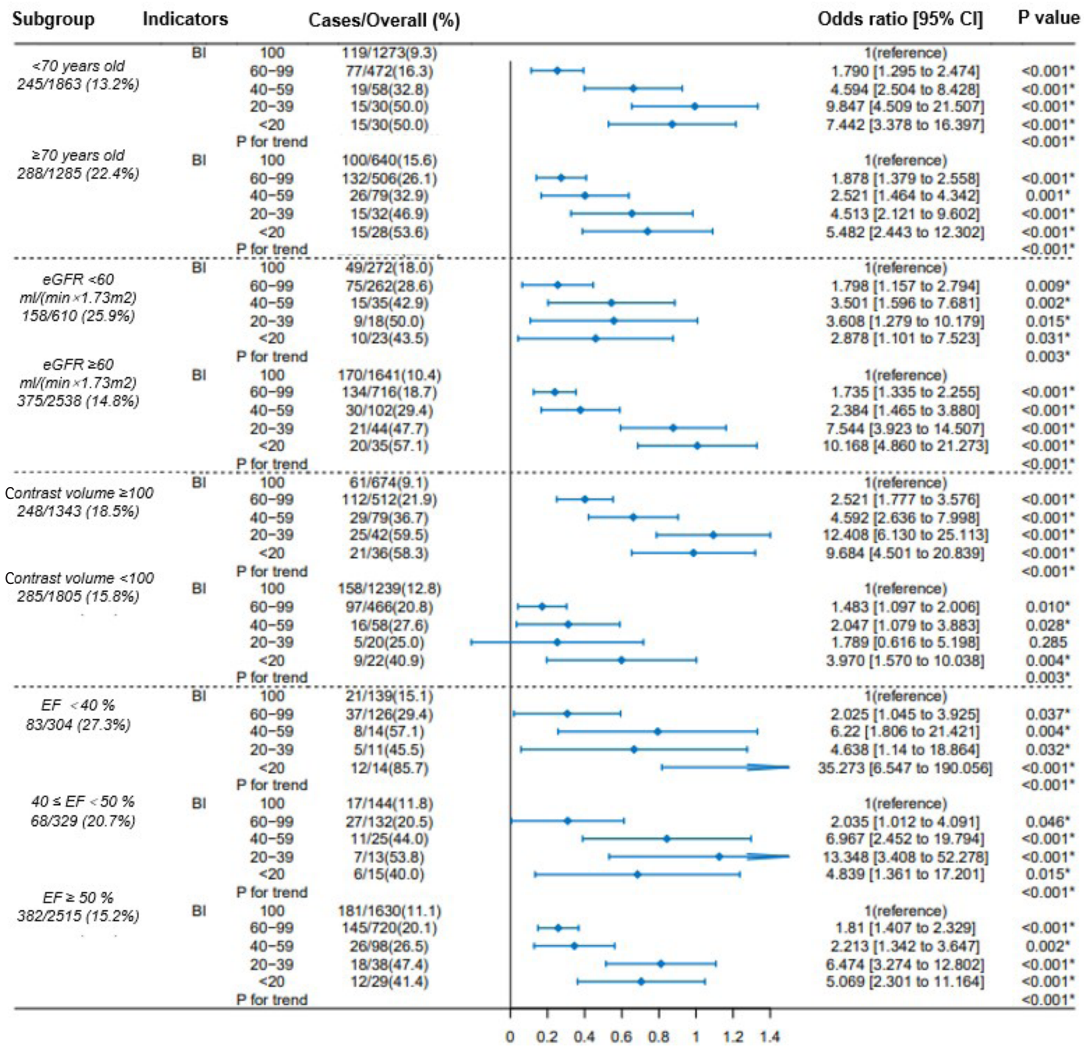

Fig. 5: Forest plots of BI for CA-AKI in prespecified subgroups
Note: In the subgroup analyses, multivariable logistic regression adjusted the same variables of Model 3, *p<0.05

The morbidity of CA-AKI was about 16.9 % in this multicenter retrospective study. The results demonstrated that BI scores were negatively correlated with the proportion of Scr elevation. ADL measured by BI at hospital admission was an independent prediction indicator to assess the incidence of CA-AKI among patients undergoing CAG or PCI, that was, the incidence of CA-AKI increased with decreasing BI scores. Similar results were observed in subgroups by exploratory analysis.

The association of better exercise capacity with fewer complications and better prognosis is well established[17]. A nationwide cohort study from the Danish national geriatric database demonstrated that ADL provided independent evaluation information on the expected survival time of elderly hospitalized patients[18]. The research of ADL have been mostly restricted to neurological disorders or terminal cancers[19,20]. With great reliability, validity and repeatability, the BI score is a standard routine assessment procedure for inpatients[11]. The BI scores can be assessed orally by inquiring the patient or a family member. With rapid and simple properties, BI score is applicable to evaluate patients early at hospital admission. Higuchi *et al.* adapted this valuable indicator in cerebrovascular diseases field to assess the long-term prognosis of patients with Acute Coronary Syndrome (ACS)[21]. This small-scale retrospective study showed that ADL at discharge was a valuable predictive indicator for the long-term prognosis and 1 y mortality among elderly

ACS patients after PCI[21]. Another multi-center retrospective cohort study further supported that BI score at hospital admission was associated with mortality during follow-up in ACS patients[22]. It has not been investigated in depth for the association between ADL and the short-term complications of cardiovascular disease.

As predicted, the incidence of CA-AKI is increasing with the decline in BI scores. The decline in ADL is often accompanied by old age, organ dysfunction and increased comorbidities, such as diabetes and hypertension[23-25]. Advanced age is well recognized as a negative prognostic marker for CA-AKI[26,27]. Patients with preoperative cardiac or renal dysfunction are also more likely to occur CA-AKI[28,29]. With the decline in ADL, patients with impaired swallowing and digestion function can adversely occur nutritional risks to affect their prognosis[30]. Our research center has set up a retrospective cross-sectional study to demonstrate that high nutritional risks will increase CA-AKI morbidity among patients after CAG[31]. Moreover, favorable ADL may be beneficial for cardiovascular health through inducing anti-inflammatory response[32], while low ADL levels may facilitate chronic inflammatory response[33]. Wesolowska *et al.* reported that there was an inverse relationship between ADL and inflammatory markers, particularly in elderly adults[34]. Lian *et al.* also supported that the decline in ADL resulted in the upregulation of inflammatory markers[35]. Inflammatory markers upregulation, involving C-Reactive Protein (CRP), etc., is closely related to the occurrence of CA-AKI[36,37]. In the current research, the predictive value of BI score on the occurrence of CA-AKI was still observed after adjustment for these well-established risk factors.

Furthermore, as shown in model 3 in Table 3, after adjusting covariates, the incidence of CA-AKI significantly increased when BI score<40 (that was, when the degree of ADL reached severe dysfunction or above), while there is no significant difference for morbidity risk between the group of BI 20-39 and the group of BI<20 ([severe dysfunction *vs.* reference] *vs.* [Very Severe dysfunction *vs.* reference], OR=6.622 *vs.* 6.591). The patients of group of BI<40 may represent few physical activities or be bedridden for a long time and easily develop infections and other comorbidities, further increasing the incidence of CA-AKI.

These results stress out the importance of evaluating BI scores at hospital admission of patients who intend to undergo CAG or PCI. The significance of this study lies on the one hand, the study confirms that the BI score is a simple, economical and easy to operate model to predict the occurrence of CA-AKI. The morbidity of CA-AKI increases with the decline in BI scores. The low BI scores warn physicians to be alert to the occurrence of CA-AKI. On the other hand, we speculate that the appropriate increase of rehabilitation exercises and the improvement of ADL, for patients with decreased ADL, especially those with severe dysfunction, may reduce the incidence of CA-AKI.

This study also had some limitations that require to be discussed. First, the inherent bias cannot completely avoid as a retrospective observational study, although statistical correction was performed for confounders to the greatest extent. Therefore, the validity of the results needs to be further verified by carrying out large-scale prospective studies. Second, one of the inclusion criteria is patients with documented Scr before and 72 h after CAG or PCI. Patients in stable conditions were discharged the next day and this group of patients was excluded. This might lead to selection bias. Third, operators might be partially subjective, which could result in error or bias. ADL measured by BI at hospital admission was a useful, easily accessible and independent prediction indicator to assess the incidence of CA-AKI among patients undergoing CAG or PCI.

Ethical approval:

The study was approved by the Ethics Committee of Sir Run Run Hospital, College of Medicine, Zhejiang University (202012217-36).

Author’s contributions:

Yunxiang Wang conceived and designed the study. Qirong Jiang organized these data and drafted the manuscript with the help of Siwei Yang, Qirong Jiang, Changchun Lai and Zakareya Moayed Ali Alsalman analyzed the data. Zakareya Moayed Ali Alsalman, Peng Wang and Xiaolong Hu drew the pictures. Yunxiang Wang detected any errors in the whole process. All authors have read and approved the manuscript for submission.

Conflict of interests:

The authors declare that they have no competing interests.

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