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Application of C-reactive Protein/Albumin Ratio (CAR) in Kawasaki Disease

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Abstract

Objective: To investigate the association between the C-reactive protein/albumin ratio (CAR) and coronary artery lesions (CAL), intravenous immunoglobulin (IVIG) resistance in children with Kawasaki disease (KD).

Methods: We retrospectively studied 753 children with KD, categorizing them into the CAL group(n=238) and the No-CAL group(n=515), the IVIG-resistance group(n=61) and the No-IVIG-resistance(n=653) group. The differences in laboratory data, clinical manifestations, the relationship between CAR and CAL as well as IVIG resistance were compared between the two cohort groups.

Results: Compared with No-CAL group, KD with CAL had a higher CAR (2.12 vs 1.69, $p < 0.001$). And CAR was significantly higher in KD children with IVIG resistance (2.42 vs 1.85, $p < 0.001$). Multivariable logistic regression analysis demonstrated that higher CAR was a risk factors of CAL

(OR=1.198, $p<0.001$) and IVIG resistance (OR=1.297, $p<0.001$), respectively. CAL and IVIG resistance interact with each other. ROC curve analysis performed for the prediction of CAL, the best cut-off point for CAR was 1.80(AUC=0.602, sensitivity 64.7%, specificity 54.8%). When predicting IVIG resistance according to the ROC curve analysis, the optimal cutoff point for CAR was 2.20(AUC=0.621, sensitivity 59.0%, specificity 61.1%).

Conclusions: CAR is a valid indicator in KD children. Higher CAR may be helpful in predicting CAL and IVIG resistance in KD.

Keywords: Kawasaki disease, C-reactive protein, albumin ratio, CAR, Coronary artery lesions, IVIG resistance

1. Introduction

Kawasaki disease (KD) is an extensive inflammation of small and medium blood vessels throughout the body. The major serious complication of KD is coronary artery lesions (CAL), which is also the most concerned and focused part to the majority of researchers. As an acute, self-limited febrile illness, KD predominantly affects children <5 years of age^[1]. Timely intravenous administration of high-dose immunoglobulin (IVIG) can reduce the risk of heart disease complications, but CAL still occurs in 5% of KD children, making it a major cause of childhood acquired heart disease^[2]. In addition, about 10-20% of KD patients expressed IVIG resistance, despite the initial IVIG therapy, which increases the risk of cardiac complications^[3]. In recent years, the incidence rate reported in Japan and China has been increasing year by year^[4-7]. How to identify early Cal and IVIG resistance in KD is very important for clinical work.

Inflammation plays an important role in KD. C-reactive protein (CRP) and albumin, commonly used

as inflammatory markers, are known as positive and negative acute reaction products, respectively, and are considered to be associated with coronary artery lesions and adverse cardiovascular events. The newly introduced parameter CRP/ albumin ratio (CAR) is considered to be more accurate than CRP or albumin alone in responding to inflammatory states^[8]. It reflects the balance between CRP and albumin levels and has been used to assess coronary artery lesions and its severity, monitor rheumatoid arthritis disease activity and the prognosis of cancer patients^[9-11]. CRP and/or albumin alone have been investigated in KD, but it is not clear whether CAR is associated with CAL and IVIG resistance. The purpose of this study was to investigate the relationship between CAR and coronary artery lesions as well as IVIG resistance among KD children.

2. Materials and Methods

2.1. Subject

We reviewed the data of children with KD at the Second Affiliated Hospital of Wenzhou Medical University from 1 January 2018 to 31 December 2019. Overall, 818 were collected, 46 excluded due to the following reasons: 3 children received the initial treatment before hospitalization, 19 patients were recurrent cases, 5 children were in convalescence of KD and the data were incomplete in 38 patients. Finally, 772 children were included in the study. We classified all KD children into the non-coronary artery lesions group (No-CAL group, n=515) and the coronary artery lesions group (CAL group, n=238) according to their coronary artery status. Then, according to the resistance of IVIG, they were divided into the IVIG non-resistance group (n=653) and the IVIG resistance group (n=61).

All children were diagnosed with reference to the Scientific Statement for Health Professionals

From the American Heart Association^[1]. Children who met the 5 or 6/6 diagnostic criteria (fever >5 days; extremity changes; rash conjunctivitis; oral changes; cervical lymphadenopathy) were defined as KD, and those with less than 5 diagnostic criteria were defined as atypical KD. All the children received echocardiography before treatment, 2 weeks after onset, and 3-4 weeks after onset.

2.2. Data Collection and Laboratory Tests

We collected the following information: age (month), sex, time and method of IVIG treatment, and IVIG response. Before the IVIG treatment, we collected laboratory data including white blood cell count, hemoglobin level, neutrophil count, platelet levels, lymphocyte count, eosinophil count and levels of ALT, AST, erythrocyte sedimentation rate, fibrinogen, D-dimer, brain natriuretic peptide and c-reactive protein (CRP) and serum albumin. And calculate the CAR value (CRP/albumin). At least 3 times of Echocardiography y should be performed.

2.3. Resistance to IVIG and CAL

Patients develop recrudescence or persistent fever at least 36 hours after the end of first IVIG infusion (body temperature >37.3°C) were defined as IVIG resistance^[1].

Echocardiography was used to assess CAL. CAL are defined according to the Z-Score recommended in the guidelines^[1]. The Z-Score is classified as follows. (1) No involvement: Always, <2; (2) Dilation only: 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥ 1 ; (3) Small aneurysm: ≥ 2.5 to <5; (4) Medium aneurysm: ≥ 5 to <10, and absolute dimension <8 mm; (5) Large or giant aneurysm: ≥ 10 , or absolute dimension ≥ 8 mm. Any one of the three

echocardiographic results suggested that coronary artery lesions, including aneurysmal dilatation, were included in the CAL group.

2.4. Statistical Analysis

SPSS version 22.0 was used for statistical analysis. count data were expressed as the Mean \pm standard deviation or median and interquartile range, and measurement data were expressed as numbers and percentages. Categorical variables were compared using the Chi-square test. The receiver operating characteristic curve was used to examine the predictive value of CAR in patients with CAL and IVIG resistance. The area under the curve was calculated. In the ROC curve, the sensitivity and specificity, for the prediction of CAL and IVIG resistance were calculated by combining the optimal cut-off values for each index using the Youden index. Logistic regression analysis was used to identify predictors of KD patient with CAL and IVIG resistance. The results were considered statistically significant when p values were <0.05 .

3. Result

3.1. Demographic Characteristics and Clinical Data

As shown in table 1, the proportion of male children in CAL group was slightly higher than that in No-CAL group ($P=0.049$), and the age was slightly younger (17.4months vs 24.4months; $P<0.001$). The proportion of main clinical symptoms such as oral changes and lymph in CAL group was lower than that in No-CAL group (85.5% vs 93.8%, $p<0.001$; 28.2% vs 39.9%, $P=0.002$, respectively), and there was no statistical difference in other clinical manifestations. In addition, typical KD was dominant in CAL group, but the proportion was lower than that in No-CAL group (57.1% vs 64.9%; $P=0.042$). The treatment duration of IVIG in both

groups was 6 days, but there was no statistically significant difference. The proportion of IVIG resistance in CAL group was higher than that in No-CAL group (15.7% vs 5.20%; $P < 0.001$).

3.2. CAL group Laboratory Tests

As shown in table 2, the levels of Hb and Hct were slightly lower ($111 \pm 9.97 \text{g/l}$ vs $115 \pm 10.2 \text{g/l}$, $P < 0.001$; $0.335 \pm 0.030\%$ vs $0.347 \pm 0.030\%$, $P < 0.001$, respectively) in CAL group. In the liver function test, compare with No-CAL group, the level of ALT and γ -GT were higher in CAL group ($36.0 \mu\text{L}$ vs $28.0 \mu\text{L}$, $P = 0.017$; $52.0 \mu\text{L}$ vs $26.0 \mu\text{L}$, $P = 0.003$, respectively). Other indexes were no significant difference between the two groups. In the indexes of coagulation function test, the level of PT and D-dimers were significantly higher in CAL group than that in No-CAL group ($14.2 \pm 1.11 \text{s}$ vs $13.8 \pm 1.08 \text{s}$, $P < 0.001$; $1.47 \mu\text{g/ml}$ vs $1.31 \mu\text{g/ml}$, $P = 0.040$, respectively). The levels of NT-pro BNP were significantly higher in CAL group than in No-CAL group (836pg/ml vs 509pg/ml , $P < 0.001$).

In addition, the levels of CRP in CAL group was higher than that in No-CAL group (84.0mg/L vs 66.8mg/L , $P < 0.001$), but the level of albumin was lower (39.0g/L vs 40.8g/L , $P < 0.001$). And the level of CAR was significantly higher in CAL group than in No-CAL group (2.12 vs 1.69 , $P < 0.001$).

3.3. IVIG Resistance group Laboratory Tests.

As shown in table 2, there was no statistical difference in blood routine indexes. In the liver function test, the level of ALT and γ -GT were significantly higher in IVIG resistance group than in the No-IVIG resistance group ($56.0 \mu\text{L}$ vs $31.0 \mu\text{L}$, $P = 0.017$; $67.5 \mu\text{L}$ vs $32.0 \mu\text{L}$, $P < 0.001$). Among the coagulation function indexes, only the level of D-dimers was significantly higher in IVIG resistance group than that in No-IVIG resistance group ($2.10 \mu\text{g/ml}$ vs $1.33 \mu\text{g/ml}$, $P = 0.04$), while there was no difference in other indexes. And the level of NT-pro BNP was significantly higher in IVIG resistance group than in No-IVIG resistance group (1320pg/ml vs 609pg/ml , $P < 0.001$).

In addition, compared with No-IVIG resistance group, the levels of CRP was significantly higher (92.6mg/L vs 74.0mg/L, $P < 0.001$) and the level of albumin was lower(38.0g/Lvs40.5g/L, $P<0.001$) in IVIG resistance group. And the level of CAR was significantly higher in IVIG resistance group(2.42 vs 1.86, $P<0.001$).

3.4. CAR, Coronary Artery Outcomes and IVIG Resistance

3.4.1. CAR and Coronary Artery Lesions

Logistic regression analysis was performed for the correlation between CAR and CAL (Table 3). Elevated CAR and IVIG resistance (+) were independent risk factors for CAL. When we adjusted for possible confounding factors that might be associated with CAL, such as age, sex and IVIG treat time, high level of CAR (OR=1.198, 95%CI=1.086-1.322, $P<0.001$) and IVIG resistance (+) (OR=3.439, 95%CI=1.741-5.238, $P<0.001$) remained a significant risk factor for CAL. ROC curves were constructed to determine the discriminatory ability of CAR to predict the occurrence of CAL (Fig 1, Table4), CAR(AUC=0.602), with a sensitivity of 64.7% and a specificity of 54.8%, showed a better performance than CRP (AUC=0.590). The cut-off value of CAR for CAL in KD children was 1.80.

3.4.2. CAR and IVIG Resistance

Logistic regression analysis was performed for the correlation between CAR and VIG Resistance (Table 5). The results showed that CAL (+) before IVIG and high level of CAR were independent risk factors for IVIG resistance. And after we adjusted for possible confounding factors, such as age, sex and IVIG treat time, increased CAR (OR=1.266, 95% CI=1.094-1.464, $P=0.002$) and CAL

(+) before IVIG (OR=3.096, 95% CI=1.784-5.373, P<0.001) remained a significant risk factor for IVIG resistance.

ROC curves were constructed to determine the discriminatory ability of CAR to predict the occurrence of IVIG resistance (Fig 2, Table 6), CAR(AUC=0.621), with a sensitivity of 59.0% and a specificity of 61.1%, showed a better performance than CRP (AUC=0.603). The cut-off value of CAR for CAL in KD children was 2.20.

4. Discussion

KD has been around for decades. Unfortunately, the pathogenesis of KD is still unclear. However, KD is now known to be characterized by systemic inflammation in all the medium-sized arteries and in multiple organs and tissues during the acute febrile phase^[12]. In recent years, the incidence of KD in Japan, South Korea and other regions has shown an increasing trend, and China is no exception^[4, 5]. Even with IVIG treatment following strict guidelines, approximately 4.9% of patients with KD develop coronary artery abnormalities^[13]. According to reports from Beijing, about 12.8% of KD patients have IVIG resistance^[14]. And IVIG resisters are prone to develop CAL^[15]. Thus, early identification of IVIG resistance and risk factors for coronary artery lesions is crucial for pediatricians to actively treat KD and improve prognosis.

CRP, an acute-phase reactant protein, is a sensitive indicator of inflammation, and its change is often associated with the degree of inflammation^[16]. It can be frequently used for the diagnosis, treatment follow-up and prognosis of inflammatory diseases^[17]. In the acute phase of inflammatory diseases, the phenomenon of hypoalbuminemia may be caused by the following reasons: the decreased ability of the liver to produce albumin^[18, 19]. Alternatively, inflammatory cells release

cytokines that increase microvascular permeability and serum albumin extravasation from the blood vessels^[20]. Therefore, albumin is also considered to be closely related to inflammation severity and disease prognosis^[21]. Furthermore, related findings^[22] found that the hypoalbuminemia reflects outcome which CRP and other inflammatory markers can not. Although CRP and albumin are good indicators of inflammation, while previous studies have shown that the CAR is more predictive than CRP or albumin alone^[23-25]. The CAR is a novel inflammation-based prognostic score, which is correlated to the inflammation severity and mortality^[24, 26], and is often used to predict the prognosis of disease such as cancer, sepsis, acute pancreatitis^[24, 27, 28] etc. Higher CAR levels are associated with higher inflammatory status and poorer prognosis^[24, 29].

In our study, we found that compared with the No-CAL group, KD children in the CAL group had higher CAR, and CAR may help to predict the occurrence of CAL. Through regression analysis, we found that high CAR, high CRP and low albumin were risk factors for CAL in children with KD, even after controlling for age, sex and IVIG treat time. High CRP levels and low albuminemia are reported to be risk factors for CAL development^[30]. Our results are consistent with that. CRP stimulates leucocyte-endothelial interaction by regulating endothelium-derived molecules and chemokines, and impairs the number and function of endothelial progenitor cells by promoting apoptosis and attenuating their migration and adherence capacities^[31]. The level of CRP is not only a manifestation of vascular inflammation, but also a good predictor of future cardiovascular events^[32, 33]. Albumin has the ability of antioxidation and free radical-scavenging, capacity to prevent apoptosis, and affinity for binding with lipids, drugs, toxic substances and other ligands^[22]. So, the albumin may have potential clinical biological protective effects^[22]. CAR combines information provided by CRP and albumin to predict coronary artery disease. We found through

ROC curve analysis that CRP had a sensitivity of 63.0% and specificity of 54.2% for predicting CAL at cutoff value of 71.0mg/L but CAR had a sensitivity of 64.7% and specificity of 54.8% for predicting CAL>1.80 cutoff value which shows better accuracy of CAR in predicting CAL than CRP. Therefore, the higher the CAR, the higher ranking risk of CAL.

Our study also found that CAR was associated with IVIG resistance and was a predictor of IVIG resistance in KD children. IVIG is the most effective first-line treatment during the acute phase of KD. The therapeutic efficacy of IVIG might be achieved through reduction of systemic immune response and levels of related cytokines^[34]. However, approximately 10% to 20% of patients with KD have persistent or recurrent fever after primary therapy with IVIG plus aspirin^[1]. So far, there is no consensus regarding the risk factors of IVIG resistance. Based on the reported literature^[15, 35], laboratory levels such as increased CRP and decreased albumin, reduced Hb level, elevated WBC count, increased level of LDH, ESR and PLT could serve as independent risk factors for predicting IVIG resistance. Compared to IVIG-responder, IVIG resistance showed a more intense inflammatory response. Increased microvascular permeability is an important event during the initial process of KD vasculitis^[36]. Hypoalbuminemia caused by vascular leakage is a key feature of pathophysiology of KD. AS Terai et al^[37] revealed that hypoproteinemia was much serious in the IVIG-resistance group than in the IVIG-responsive group. Plasma albumin is a constitutive protein. And the albumin levels are valuable indicators of recovery or deterioration of health^[38]. IVIG resistant children expressed more severe vascular leakage and liver damage. Hypoalbuminemia, is the result and manifestation of inflammation, which indicate the degree of vasculitis, and is associated with IVIG resistance. CAR combines the acute course of inflammation with the chronic outcome nutritional status to reflect the degree of inflammation and the prognosis of the disease.

Thus, CAR is considered to be a good indicator of the state of inflammation. We further examined the association between CRP, CAR, albumin and IVIG resistance. Our data demonstrated that the optimal cut-off point of the CAR for IVIG resistance was 2.20, with a sensitivity of 59.0% and a specificity of 61.1%, and the AUC of the CAR was 0.621, which was higher than that of CRP (AUC 0.603). Therefore, we believed that CAR was associated with IVIG resistance and may be used as a potential predictor of IVIG resistance.

In the study cohort, the CAL group was significantly younger than the No-CAL group, and mainly male, which means CAL mainly affected younger and male patients. In our study, we found that nearly 8.28% of the patients showed immunoglobulin resistance, slightly lower than the previously reported drug resistance rate (10%-20%)^[14, 30]. This may be related to the time of our first dose of IVIG treatment. There were 74.4% of the children with KD were treated with IVIG on the 5th-7th day of the disease. Moreover, we found that the IVIG resistance rate (11.0% VS 7.30%) was significantly higher in CAL group than in the No-CAL group, and the incidence of coronary artery lesions in the IVIG resistance was 47.3%, similar to the previously reported studies (47.5%)^[3]. After all, patients with IVIG resistance are at high risk of developing coronary artery lesions^[39].

Our study also found that, in addition to CAR can being a predictor for KD's occurrence of CAL and IVIG resistance, CAL and IVIG resistance also interact with each other. (1) The occurrence of CAL before treatment may contribute to IVIG resistance. At present, the pathogenesis of Kawasaki disease complicated with CAL is not fully understood. Some scholars believed that oxidative stress, immune activation, and the coronary arteries infiltration of immune system cells associated with secretion of proinflammatory cytokines, elastases, and matrix metalloproteinases in contribute to the occurrence of CAL^[40-43]. The occurrence of CAL before IVIG treatment is a signal of strong

vascular inflammation, which means that vascular leakage is serious, resulting in increased albumin leakage, and thereby increasing the risk of IVIG resistance^[37]. A study from Children's Hospital Colorado^[44] suggested that Children with KD who had CAL at the time of diagnosis were more likely to have IVIG resistance, which is consistent with our findings. (2) IVIG resistance is associated with an increased risk for CAL in children with KD. Systemic inflammatory response is severe in KD children with IVIG resistance, the increase of cytokines damages vascular endothelium, increases vascular endothelial permeability, causes perivascular edema, and then aggravates vascular wall injury^[45]. Albumin not only indicates nutritional status but also a useful factor for predicting patient prognosis^[21]. Thus, IVIG-resistant patients are at higher risk of developing CAL than IVIG-responsive patients^[34, 46]. In summary, attention should be paid to the KD children with CAL before treatment or IVIG resistance after the first dose of treatment. Further research is needed to determine whether pediatricians may consider combining IVIG and aspirin with second-line treatments such as hormones and immunosuppressants to reduce the incidence of IVIG resistance and CAL.

Our study has several limitations. Firstly, our study is a single-center study with a time span of only 2 years. A larger study is needed to confirm our findings. Secondly, whether the predictive role of CAR in KD coronary damage and IVIG resistance is applicable in other populations needs to be verified by larger studies. Finally, due to the different time of visit and treatment for KD children, blood sample collection and determination time were different before treatment, we could not evaluate the changes in CRP, albumin, and CAR over time. This may be the reason why CAR specificity and sensitivity are not high enough. Further studies that investigate the changes in CAR are needed in the future.

5. Conclusion

Our study found that CAR can predict the occurrence of CAL and IVIG resistance in KD to some extent. Therefore, for hospitalized children diagnosed with KD, clinicians should pay attention to CAR value, especially for children with acute stage and high CAR value, and adopt more active treatment measures and cardiac ultrasound follow-up observation.

Table 1: Demographic Characteristics and Clinical Data

Table 2: Laboratory Tests

Table 3: Multiple regression analysis of Coronary Artery Lesions

Table 4: ROC curves of CAR and Coronary Artery Lesions

Figure 1: ROC curves of CAR and Coronary Artery Lesions

Table 5: Multiple regression analysis of IVIG Resistance

Table 6: ROC curve distribution of CAR and IVIG Resistance

Figure 2: ROC curves of CAR and IVIG Resistance

Declarations:**Ethics approval and consent to participate**

This study was approved by the ethical Board of Wenzhou Medical University, Zhejiang, China. Informed consent was signed by the parents of all patients. And all the experiment protocol for involving humans data was in accordance with the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Data Availability

The datasets generated and analysed during the current study are not publicly available due legal reasons. To deposit data in an open depository or send data to a journal where other people (you do not know whom) may access data MAY result in harm. Hence, researchers are not allowed to deposit the data elsewhere. But the data can be made available from the corresponding author on reasonable request.

Conflicts of Interests

The authors declare that they have no conflicts of interest.

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Authors' Contributions

ZQW and YPS conceptualized and designed the study, collected the data, drafted the initial manuscript. JXW and XTZ carried out the statistics. BYH, ZPX made substantial contributions to the design of the paper, and its interpretation. XR and HXQ reviewed and revised the manuscript for important intellectual content. RZW and MPC reviewed and revised the manuscript. All authors read and contributed to the present manuscript. All authors read and approved the final manuscript.

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Figures

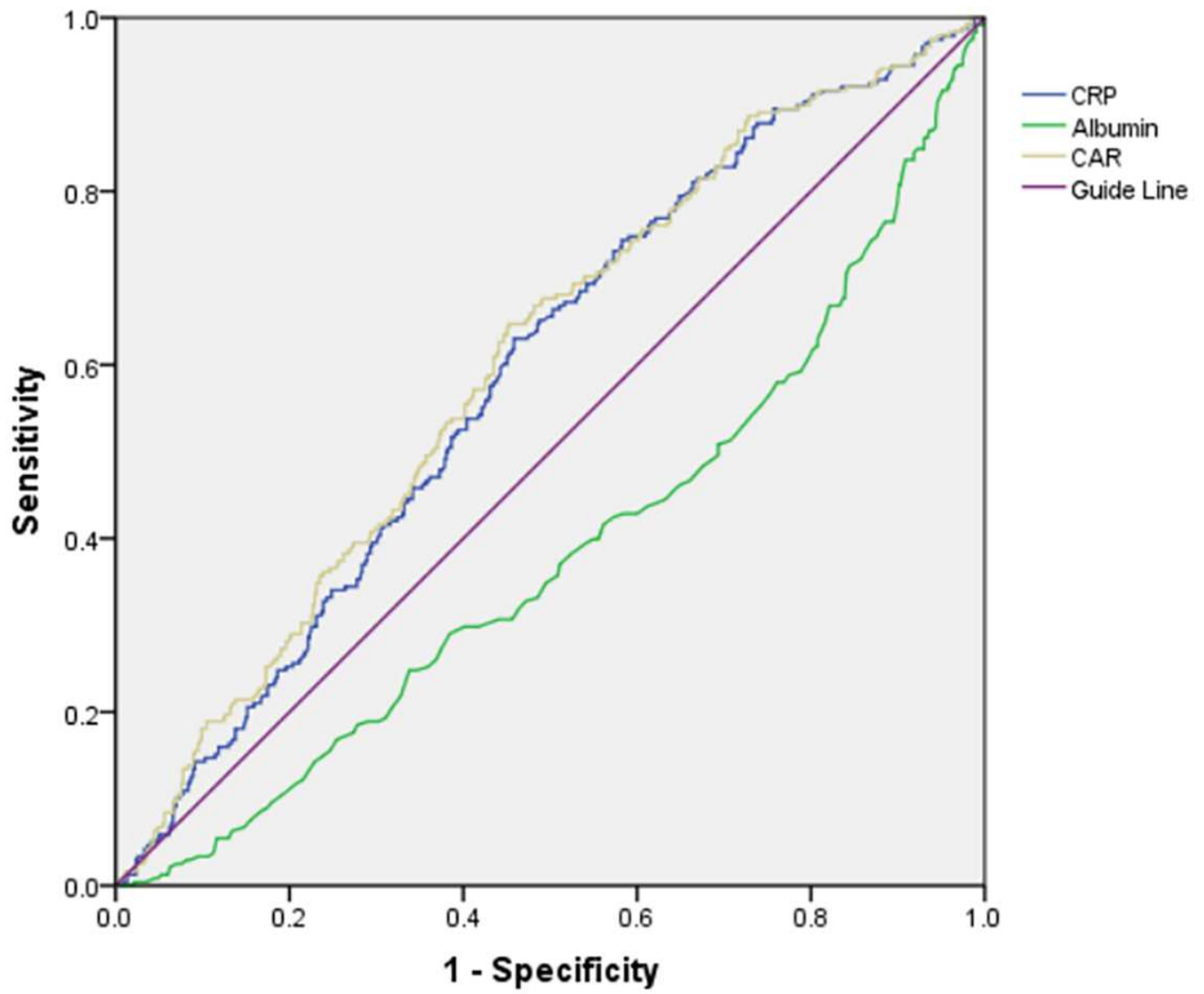


Figure 1

ROC curves of CAR and Coronary Artery Lesions

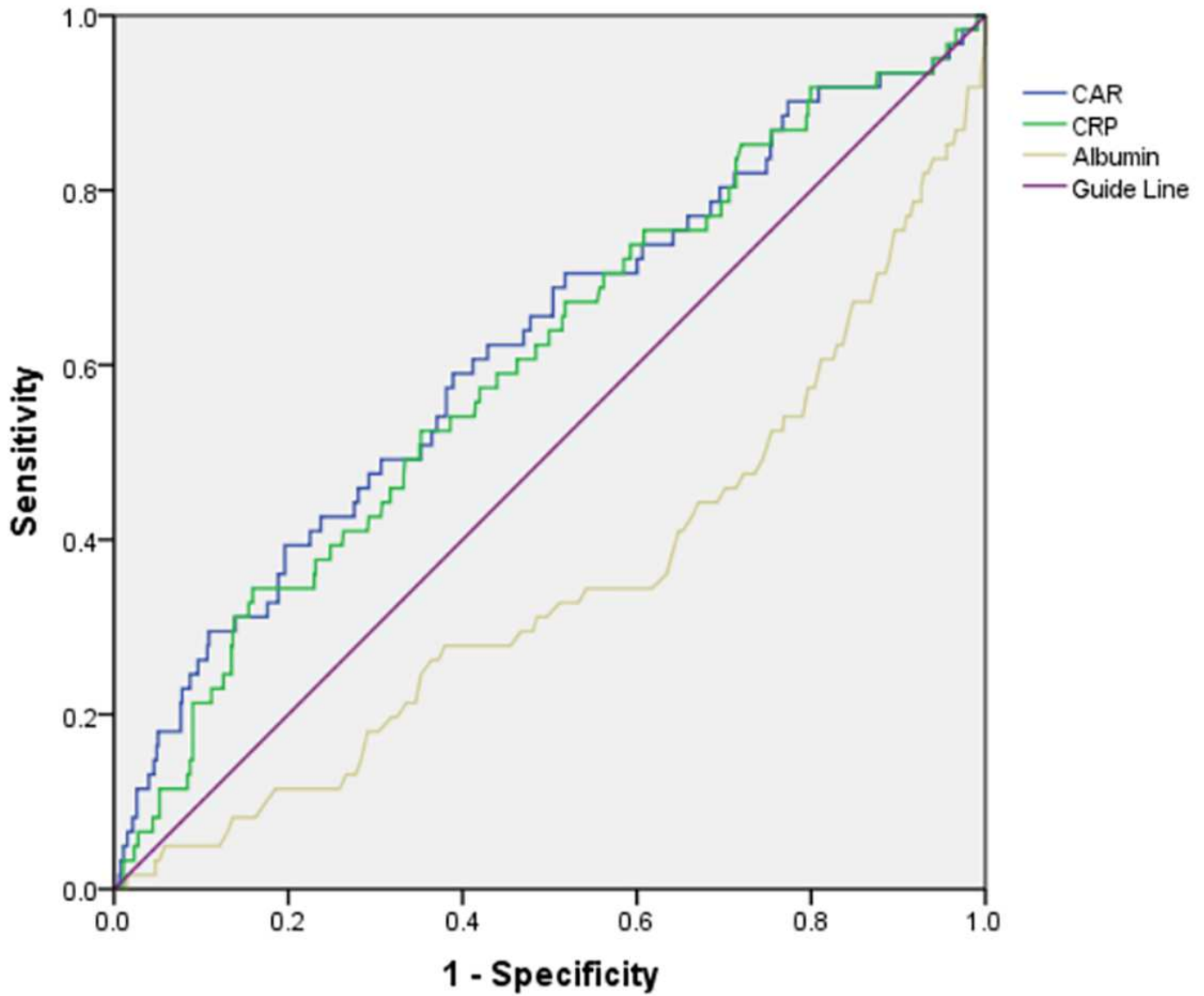


Figure 2

ROC curves of CAR and IVIG Resistance

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