Clinical significance and influencing factors of fibrinogen in ANCA-associated vasculitis
A single-center retrospective study from Southwest China

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Abstract

Hypercoagulable is an important pathological state in anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV). Fibrinogen (FIB) is the main protein in coagulation process. In this study, we aimed to investigate the clinical significance and influencing factors of FIB in AAV from Southwest China.

A retrospective study was performed on AAV patients from Peoples Hospital of Deyang City from January 2007 to December 2018. Demographic and clinical characteristics were collected.

A total of 463 AAV patients were included. In Wilcoxon rank sum test, FIB was significantly higher in AAV active group than inactive group ($P$ = .005). FIB was also higher in bacterial infection group than in non-infection group both in active group ($P$ = .008) and inactive group ($P$ = .017). In receiver operating characteristic (ROC) curve analysis, the critical value of FIB for diagnosis of bacterial infection between AAV active and inactive groups was 3.385 g/L ($P$ = .030), with sensitivity of 70.2% and specificity of 52.9%. In the multivariate analysis of variance (MANOVA), estimated glomerular filtration rate (eGFR) was shown to be an independent factor for FIB ($P$ = .001). Least-significant difference showed the concentration of FIB ($P$ < .05) increased with renal impairment, especially in endstage kidney disease (ESKD).

FIB identified a certain reference value in distinguishing AAV activity from bacterial infection. ESKD had a statistical effect on it. Influencing factors of FIB should be evaluated based on the renal function impairment of patients.

Abbreviations: AAV = anti-neutrophil cytoplasmic antibody associated vasculitis, ANCA = anti-neutrophil cytoplasmic antibody, anti-MPO = anti-myeloperoxidase antibodies, anti-PR3 = anti-proteinase 3 antibodies, AP = acute phase protein, AUC = area under curve, BVAS = Birmingham Vasculitis Activity Score, c-ANCA = cytoplasmic-antineutrophil cytoplasmic antibodies, CI = confidence interval, CKD = chronic kidney disease, CLIA = chemiluminescence immunoassay, CREA = creatinine, CRP = C-reactive protein, DVT = deep venous thrombosis, eGFR = estimated glomerular filtration rate, ESKD = endstage kidney disease, FIB = fibrinogen, IIF = immunofluorescent, IL = interleukin, IQR = interquartile range, KDIGO = Kidney Disease Improving Global Outcomes, LSD = least-significant difference, Mac-1 = macrophage-1, MANOVA = multivariate analysis of variance, nCD64 = neutrophil CD64, p-ANCA = perinuclear-antineutrophil cytoplasmic antibodies, PCT = procalcitonin, ROC = receiver operating characteristic, SD = standard deviation, SPSS = Statistical Package for the Social Sciences, Th17 = T helper cell 17, TLR4 = toll-like receptor 4, TNF-α = tumor necrosis factor alpha, VTE = venous thromboembolism, WBC = white blood cell.

Keywords: anti-neutrophil cytoplasmic antibody-associated vasculitis, bacterial infection, diagnostic efficacy, disease activity, fibrinogen, renal impairment
1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disorder and hypercoagulable state is the important pathological state in AAV. Previous studies have pointed out a high prevalence of venous thromboembolism (VTE) in patients with AAV. In addition, the risk of pulmonary embolism in AAV patients is associated with hypercoagulable state.

Fibrinogen (FIB), also known as coagulation factor 1, is the most abundant coagulation factor in plasma and is directly involved in the common clotting pathway. The coagulation cascade is the process of the conversion of soluble fibrinogen to insoluble fibrin that terminates in production of a clot. At the same time, FIB plays an important role in regulating macrophage function, immune inflammatory response and removal of bacterial infection lesions. The adsorption of fibrinogen to biomaterial surfaces is thought to be important for recruitment of macrophages. Fibrinogen is thought to interact with toll-like receptor 4 (TLR4) and integrins expressed on macrophages including CD11b/CD18 (αMβ2, CR3) and CD11c/CD18 (αMβ2, CR4). These effects increase the inflammatory activation of macrophages and further affect downstream signaling. TLR4 activation of macrophages plays a key role in initiating the rapid expression of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and IL-6, as well as promoting the T helper cell 17 (Th17) response, all of which play a key role in autoimmunity.

Fibrinogen (FIB) is a kind of acute phase protein (AP) and increases during inflammation. Fibrinogen can promote host defense against bacterial pathogens, through multiple mechanisms including: providing barrier function to prevent microbial entry, encapsulation of microbes within host tissues, and modulation of the host immune response to promote microbial clearance. Recent studies have suggested that FIB is related to AAV. Meanwhile, aggressive treatment of AAV incurs infection, which is getting more and more arrestive in clinical application.

The clinical significance and influencing factors of FIB in AAV patients varies significantly among different ethnic groups. The application of FIB in AAV patients from China was not well elucidated. Until recently, only a few studies have explored this issue, mainly focusing on enhanced coagulation in active renal AAV. In this study, we performed a retrospective study, aiming to investigate the clinical significance and influencing factors of FIB in AAV from Southwest China.

2. Materials and methods

2.1. Patients

We performed a retrospective study on the AAV patients from Peoples Hospital of Deyang City from January 2007 to December 2018. AAV was diagnosed by rheumatologist according to the definitions of the Chapel Hill nomenclature. AAV activity in 509 patients was assessed by 2 experienced rheumatologists based on the Birmingham Vasculitis Activity Score (BVAS) and treatment algorithm for AAV. Data on patients without a complete medical history were excluded. “Active group” was defined as follows:

1. the BVAS was greater than 15 in the last 4 weeks,
2. relapse, including major relapse and minor relapse,
3. refractory disease;
4. low-activity disease state.

“Inactive group” was defined as follows:

1. absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy (complete remission),
2. at least 50% reduction of disease activity score and absence of new manifestations (partial remission).

Finally, 463 AAV patients with 258 in activity group and 205 in inactive group were included in Table 1. In the AAV active group, 258 cases including 105 males and 153 females, showed an average age of 57.69 ± 17.35 years and an average BVAS score of 17.6 ± 3.9. In the inactive group, 205 cases including 76 males and 129 females, showed an average age of 57.52 ± 19.51 years and an average BVAS score of 6.5 ± 3.4. There was no statistically significant difference between the 2 groups in gender (P = .329) and age (P = .783), but the difference in average BVAS score was statistically significant (P = .001). This study was approved by the Ethics Committee of Peoples Hospital of Deyang City (Registration number: ChCTR2000032468). Patients were treated according to the Declaration of Helsinki’s ethical principles for medical research involving human subjects. Because of the retrospective nature of the study, patient consent for inclusion was waived.

Table 1

| Characteristics          | Active group | Inactive group | P value |
|-------------------------|--------------|----------------|---------|
| Number of cases         | 258          | 205            |         |
| Female (%) / male (%)   | 59.31 / 40.69| 62.93 / 37.07  | .329    |
| Age, mean ± SD (years)  | 57.69 ± 17.35| 57.52 ± 19.51  | .783    |
| BVAS, mean ± SD         | 12.6 ± 3.9   | 6.5 ± 3.4      | .001    |
| CRP, median (mg/L)      | 18.5 (4.8–62.7)| 10.4 (4.1–36.2)| .018    |
| PCT, median (ng/mL)     | 0.34 (0.16–1.68)| 0.12 (0.05–1.18)| .001    |
| eGFR, median (ml/min/1.73m²) | 63.3 (14.3–107.6) | 105.1 (75.1–129.3) | .001 |
| FIB, median (g/L)       | 4.43 (2.90–6.02)| 3.50 (2.47–5.18)| .019    |
| WBC, median (×10⁹/L)    | 7.39 (2.47–12.69)| 6.21 (3.11–11.47)| .047    |
| Anti-MPO, median (RU/ml)| 5.4 (2.6–6.1) | 1.0 (1.0–1.0) | .001    |
| Anti-PR3, median (RU/ml)| 3.1 (1.5–4.5) | 1.0 (1.0–1.0) | .001    |

Anti-MPO = anti-myeloperoxidase antibodies, Anti-PR3 = anti-proteinase 3 antibodies, BVAS = Birmingham Vasculitis Activity Score, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, FIB = fibrinogen, PCT = procalcitonin, WBC = white blood cell.
2.2. Definition of bacterial infection

Bacterial infection was considered on the basis of clinical manifestation, laboratory data, radiographic imaging, and response to antibiotics. It was confirmed if causative agents were isolated.

2.3. Clinical data

Demographic and clinical data were collected from the medical records. Bacterial infection was described above. Laboratory data included FIB, C-reactive protein (CRP), procalcitonin (PCT), white blood cell (WBC) count, estimated glomerular filtration rate (eGFR), perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA)/anti-proteinase 3 antibodies (c-ANCA/anti-PR3). FIB was detected by von Clauss method (SYSMEX, Japan). If FIB < 0.8 g/L or FIB > 4.0 g/L, the original plasma should be diluted in-machine and redetermined. CRP and PCT were performed by chemiluminescence immunoassay (CLIA). Creatinine (CREA) was performed by jaffe assay and eGFR was calculated according to calculation formula. WBC count was performed by XN2000 (SYSMEX, Japan). Serum samples were tested for p-ANCA and c-ANCA by immunofluorescent (IIF) assay (Euroimmun, Germany). MPO-ANCA and PR3-ANCA were detected by enzyme linked immunosorbent assay (Euroimmun, Germany).

2.4. Statistical analysis

The statistical analyses were applied by using the Statistical Package for the Social Sciences (SPSS) software (version 22.0). Normally distributed data were presented as mean ± standard deviation (SD), while non-normal variables were expressed as median (interquartile range, IQR). Categorical variables were presented as percentage and frequency. Comparison between groups was evaluated with Chi-Squared test for continuous variables with normal distribution. Comparison between groups was evaluated with Wilcoxon rank sum test for continuous variables with non-normal distribution. For the diagnostic efficacy of bacterial infection between groups, the significant difference was first calculated, then area under curve (AUC) was obtained by receiver operating characteristic (ROC) curve. The Youden index and 95% confidence interval (CI) were calculated. Clinically significant variables in between-group comparison were adjusted by multivariate anova (MANOVA) analyses to identify the factors associated with FIB. Effects of different chronic kidney disease (CKD) stages on FIB were calculated by least-significant difference (LSD). A P value < .05 was considered statistically significant.

3. Results

3.1. The main characteristics of the study population

The demographics and clinical characteristics of all the AAV patients were illustrated in Table 1. In the AAV active group, patients showed higher preoperative levels of CRP (18.5 (4.8–62.7) vs 10.4 (4.1–36.2), P = .018), PCT (0.34 (0.16–1.68) vs 0.12 (0.05–1.18), P = .001), FIB (4.43 (2.90–6.02) vs 3.50 (2.47–5.18), P = .019), WBC (7.39 (5.47–10.43) vs 6.21 (4.43–8.47), P = .047), anti-MPO (5.4 (2.6–6.1) vs 1.0 (1.0–1.0), P = .001) and anti-PR3 (3.1 (1.5–4.5) vs 1.0 (1.0–1.0), P = .001) in comparison with those in the inactive group. However, patients showed a lower preoperative level of eGFR in comparison with that in the inactive group (63.3 (14.3–107.6) vs 105.1 (75.1–129.3), P = .001).

3.2. Comparison between FIB and AAV activity in bacterial infection and non-infection groups

A comparison between bacterial infection and AAV activity was calculated by Chi-Squared test. The infection ratio (44.96%) vs 54.63%, P = .020 was statistical difference with AAV activity (Supplement 1, http://links.lww.com/MD/E921). Clinical examination comparisons between FIB and AAV activity in bacterial infection were illustrated in Table 2.

In bacterial infection group, patients of active group showed higher preoperative levels of PCT (0.34 (0.14–1.68) vs 0.17 (0.09–0.52), P = .002), FIB (4.96 (3.32–6.33) vs 3.41 (2.50–5.27), P = .016), anti-MPO (5.8 (1.1–9.1) vs 1.0 (1.0–1.0), P = .001) and anti-PR3 (6.1 (3.9–11.5) vs 1.0 (1.0–1.0), P = .001) in comparison with those in the inactive group. But patients of active group showed a lower preoperative level of eGFR in comparison with that in the inactive group (55.6 (24.3–98.3) vs 97.5 (76.7–105.7), P = .001).

In non-infection group, patients of active group showed higher preoperative levels of FIB (4.32 (2.73–6.05) vs 3.14 (2.20–4.25), P = .017), anti-MPO (4.1 (1.0–7.4) vs 1.0 (1.0–1.0), P = .001) and anti-PR3 (3.9 (1.1–8.9) vs 1.0 (1.0–1.0), P = .001) in comparison with those in the inactive group.

3.3. Efficacy value of FIB in diagnosis of bacterial infection between AAV active and inactive groups

We constructed ROC curve to access the efficacy value of FIB and other diagnostic indicators such as CRP, PCT and WBC for bacterial infection between AAV active and inactive groups. As presented in Fig. 1 and Table 3, FIB (P = .030) was statistically significant in identifying bacterial infection in AAV active and inactive groups.

Table 2: Clinical examination comparisons between FIB and activity in bacterial infection.

| Characteristics     | Infection group median (IQR) | P value | Non-infection group median (IQR) | P value |
|---------------------|-------------------------------|---------|----------------------------------|---------|
|                     | Active                        | Inactive|                                  |         |
|                     | FIB (g/L)                     | 4.96 (3.32–6.33) | 3.41 (2.50–5.27) | .016     | 4.32 (2.73–6.05) | 3.14 (2.20–4.25) | .017     |
|                     | CRP (mg/L)                    | 44.0 (11.7–72.9) | 28.1 (6.8–41.8) | .124     | 7.2 (4.1–18.7)  | 6.5 (3.9–11.4)  | .204     |
|                     | PCT (ng/ml)                   | 0.34 (0.14–1.68) | 0.17 (0.09–0.52) | .002     | 0.16 (0.03–0.19) | 0.09 (0.05–0.11) | .075     |
|                     | eGFR (mL/min/1.73m²)          | 55.6 (24.3–98.3) | 97.5 (76.7–105.7) | .001     | 89.9 (58.7–107.6) | 116.1 (84.7–129.3) | .156     |
|                     | WBC (×10^9/L)                 | 9.75 (5.01–12.69) | 7.07 (3.35–10.33) | .331     | 8.34 (7.63–10.48) | 5.97 (3.11–10.85) | .326     |
|                     | Anti-MPO (RU/ml)              | 5.8 (1.1–9.1)  | 1.0 (1.0–1.0)   | .001     | 4.1 (1.0–7.4)   | 1.0 (1.0–1.0)   | .001     |
|                     | Anti-PR3 (RU/ml)              | 6.1 (3.9–11.5) | 1.0 (1.0–1.0) | .001     | 3.9 (1.1–8.9)   | 1.0 (1.0–1.0)   | .001     |

Anti-MPO = anti-myeloperoxidase antibodies, Anti-PR3 = anti-proteinase 3 antibodies, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, FIB = fibrinogen, PCT = procalcitonin, WBC = white blood cell.
inactive groups with an AUC of 0.623, a cut-off value of 3.385, a sensitivity of 70.2% and a specificity of 52.9%, respectively. CRP ($P = 0.028$) was statistically significant with AUC of 0.624, a cut-off value of 80.0, a sensitivity of 34.2% and a specificity of 91.2%. WBC ($P = 0.003$) was statistically significant with AUC of 0.671, a cut-off value of 8.25, a sensitivity of 51.8% and a specificity of 79.4%, respectively. PCT ($P = 0.087$) was not statistically significant in identifying bacterial infection between AAV active and inactive groups.

3.4. Multivariate analysis of variance on the effects of AAV activity, eGFR and bacterial infection on FIB

We constructed the MANOVA analyses to identify the effects of AAV activity, eGFR and bacterial infection on FIB. As presented in Table 4, eGFR ($P = 0.001$) had a significant effect on the dependent variable FIB, while AAV activity ($P = 0.947$) and bacterial infection ($P = 0.564$) had no statistical difference on FIB. In this analysis, there was no statistically significant interaction between AAV activity, eGFR and infection ($P > 0.05$).

3.5. Least-significant difference on the effects of different CKD stages on FIB

CKD was staged according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, using estimated glomerular filtration rate (eGFR).[^13] We constructed the LSD to identify whether different CKD stages would affect the concentration of FIB. As presented in Table 5, the concentration of FIB ($P < 0.05$) increased with the increase of renal function damage, especially in endstage kidney disease (ESKD).

4. Discussion

FIB is an important coagulation factor in the process of hemostasis. When inflammation occurs, vascular endothelial cell contraction causes FIB to exudate and stimulates various chemokines to act on T cells, neutrophils, and macrophages, which are closely related to the inflammatory damage.[^13] A recent study had emphasized the importance of inflammatory response mediated by monocyte and neutrophil activation in deep venous thrombosis (DVT).[^14] Studies of hypercoagulability in AAV patients showed that AAV patients were more likely to develop venous thromboembolism due to long-standing vascular endothelial activation or dysfunction.[^4, ^35] Compared with the previous reports, this study focused on the significance of FIB in AAV clinical diagnosis and treatment. Some characteristics of FIB in the Southwest Chinese AAV patients were notable.

Previous studies showed that clotting process related markers have a certain diagnostic value in AAV disease activity. A study from Northern China showed that FIB was higher in AAV patients in active stage than those in remission.[^36] A Japanese

![Figure 1. ROC curves of CRP, PCT, WBC and FIB for bacterial infection. Different ROC curves were represented by curves of different colors. Blue indicated CRP, red indicated PCT, green indicated WBC, orange indicated FIB, yellow indicated reference line. CRP = C-reactive protein, FIB = fibrinogen, PCT = procalcitonin, WBC = white blood cell.](image)
study suggested high concentration of FIB could be accompanied by diffused intravascular coagulation.[37] Our results showed that FIB had a diagnostic value with AAV disease activity. In the current study, FIB was statistical difference with or without bacterial infection, indicating that FIB in AAV patients was also affected by AAV activity itself. Thus, physicians should be aware of the significance of FIB in AAV patients. Proper evaluation of FIB could be important for clinical treatment selection.

We are also interested in the ability of FIB to identify AAV disease activity and bacterial infection in autoimmune diseases. Previous reports showed FIB could induce free radical production by neutrophils without modifying the activation status of macrophage-1 (Mac-1). Another study found that soluble fibrinogen stimulated macrophages to produce high levels of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α). Fibrin (ogen) may be a key switch in regulating macrophage phenotype behavior.[39] Our results showed that FIB had a similar efficiency to clinically common diagnostic markers of bacterial infection, such as CRP, PCT and WBC.

However, the AUC of above experimental indicators in this study were low. In recent years, researches on new markers such as neutrophil CD64 (nCD64) have also attracted the attention of clinicians. A prospective study of infected patients in U.S. emergency rooms showed that nCD64 provided improved diagnostic detection of infection/sepsis compared with CRP, absolute neutrophil count, myeloid left shift and sedimentation rate.[40] A study from Colombia showed that high nCD64 expression was useful to differentiate infections from activity in SLE patients.[32] At present, there are no studies on nCD64 in patients with bacterial infection and AAV disease activity. Further studies are needed to determine whether nCD64 can distinguish AAV disease activity from bacterial infection.

Long-term non-standard treatment of AAV could lead to chronic renal impairment. Previous reports suggested that increased FIB was associated with mortality among subjects with mild to moderate kidney impairment.[41–43] Regarding the influence of AAV disease activity, eGFR and bacterial infection on FIB of AAV patients, our results showed that eGFR had

### Table 4

Test of between subjects effects of activity, estimated glomerular filtration rate and bacterial infection on FIB. Dependent variable: FIB.

| Source of variation                        | Type III sum of squares | Degree of freedom | Mean square | F   | P value |
|------------------------------------------|-------------------------|------------------|-------------|-----|---------|
| Model                                    | 14831.111               | 584              | 25.396      | 37.678 | .000    |
| eGFR                                     | 2602.949                | 447              | 5.823       | 8.639 | .001    |
| AAV activity                             | 0.003                   | 1                | 0.003       | 0.005 | .947    |
| Bacterial infection                      | 0.244                   | 1                | 0.244       | 0.362 | .564    |
| eGFR × AAV activity                      | 0.324                   | 112              | 0.003       | 0.004 | 1.000  |
| eGFR × bacterial infection               | 4.101                   | 2                | 2.050       | 3.042 | .104    |
| AAV activity × bacterial infection        | 0.000                   | 0                | > 0.05      | > 0.05 | > .05  |
| eGFR × AAV activity × bacterial infection| 0.000                   | 0                | > 0.05      | > 0.05 | > .05  |
| Error                                    | 5.392                   | 8                | 0.674       | –     | –       |
| Total                                    | 14836.503               | 592              | –           | –     | –       |

*R Squared = 1.000 (Adjusted R Squared = 0.973), AAV = ANCA-associated vasculitis, eGFR = estimated glomerular filtration rate, FIB = fibrinogen.

### Table 5

Least-significant difference of effects of chronic kidney disease stage on FIB. Dependent variable: FIB.

| (I) Group | (J) Group | Average deviation (I-J) | Standard error | P value | Lower limit | Upper limit |
|----------|-----------|-------------------------|----------------|---------|-------------|-------------|
| CKD 1    | CKD 2     | –0.036                  | 0.262          | .890    | –0.552      | 0.479       |
| CKD 1    | CKD 3     | –0.069                  | 0.290          | .812    | –0.640      | 0.502       |
| CKD 1    | CKD 4     | –0.045                  | 0.207          | .107    | –0.479      | 0.552       |
| CKD 2    | CKD 1     | 0.036                   | 0.262          | .890    | –0.997      | –0.091      |
| CKD 2    | CKD 3     | –0.032                  | 0.237          | .923    | –0.696      | 0.631       |
| CKD 2    | CKD 4     | –0.057                  | 0.207          | .107    | –1.073      | 0.057       |
| CKD 3    | CKD 1     | 0.069                   | 0.291          | .812    | –0.502      | 0.640       |
| CKD 3    | CKD 2     | 0.032                   | 0.237          | .923    | –0.631      | 0.696       |
| CKD 3    | CKD 4     | –0.035                  | 0.405          | .381    | –1.091      | 0.141       |
| CKD 4    | CKD 1     | 0.037                   | 0.217          | .108    | –1.206      | 0.461       |
| CKD 4    | CKD 2     | 0.045                   | 0.367          | .230    | –0.280      | 1.163       |
| CKD 4    | CKD 3     | 0.045                   | 0.424          | .319    | –0.392      | 1.202       |
| CKD 4    | CKD 5     | –0.092                  | 0.386          | .012    | –0.861      | 0.655       |
| CKD 5    | CKD 1     | 0.044                   | 0.230          | .109    | 0.091       | 0.997       |
| CKD 5    | CKD 2     | 0.057                   | 0.287          | .078    | –0.057      | 1.073       |
| CKD 5    | CKD 3     | 0.037                   | 0.313          | .131    | –0.141      | 1.091       |
| CKD 5    | CKD 4     | 0.092                   | 0.386          | .012    | –0.655      | 0.861       |

CKD = chronic kidney disease, CKD 1: eGFR ≥ 90 ml/minutes/1.73 m², CKD 2: eGFR 60–89 ml/minutes/1.73 m², CKD 3: eGFR 30–59 ml/minute/1.73 m², CKD 4: eGFR 15–29 ml/minute/1.73 m², CKD 5: eGFR < 15 ml/minute/1.73 m².
significant influence on FIB. Further multiple comparative studies on different CKD stages showed that ESKD had a statistical effect on FIB. It was consistent with previous studies. Therefore, renal impairment was always a matter of concern when the risk of AAV disease activity was evaluated.

Our study had certain limitations. The prevalence of infection may be underestimated due to the selection bias since outpatients with infection were automatically excluded. Additionally, data were generated from 1 hospital from Southwest China. The interpretation of the results to the general AAV population is cautious.

In summary, FIB has a certain relevance value in distinguishing AAV activity from bacterial infection. However, ESKD has a statistical effect on it. Influencing factors of FIB should be evaluated based on the renal function impairment of patients.

Author contributions

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