Advances in Rheumatology

RESEARCH

Open Access

Measurement of superoxide dismutase: clinical usefulness for patients with anti-neutrophil cytoplasmic antibody-associated vasculitis

Zhihuan Zhang[1], Wenhan Huang[1], Feifeng Ren[1], Lei Luo[1], Jun Zhou[1] and Lin Tang[1*]

Abstract

Objective To investigate the clinical usefulness of serum superoxide dismutase (SOD) measurement in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods In this single-center retrospective study, demographic data, serum SOD levels, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), the Birmingham Vasculitis Activity Score (BVAS), ANCA, organ involvement, and outcomes were analyzed for 152 AAV patients hospitalized in the Second Affiliated Hospital of Chongqing Medical University. Meanwhile, the serum SOD levels of 150 healthy people were collected as the control group.

Results Compared to the healthy control group, serum SOD levels of the AAV group were significantly lower ($P<0.001$). SOD levels of AAV patients were negatively correlated to ESR, CRP, and BVAS (ESR rho = −0.367, $P<0.001$; CRP rho = −0.590, $P<0.001$; BVAS rho = −0.488, $P<0.001$). SOD levels for the MPO-ANCA group were significantly lower than the PR3-ANCA group ($P=0.045$). SOD levels for the pulmonary involvement group and the renal involvement group were significantly lower than those for the non-pulmonary involvement group and the non-renal involvement group ($P=0.006$; $P<0.001$, respectively). SOD levels in the death group were significantly lower than the survival group ($P=0.001$).

Conclusions In AAV patients, low SOD levels might indicate disease associated oxidative stress. SOD levels in AAV patients were decreased with inflammation, suggesting that SOD levels could potentially be a surrogate marker for disease activity. SOD levels in AAV patients were closely related to ANCA serology, pulmonary involvement, and renal involvement, with low SOD levels an important indicator of a poor prognosis for AAV patients.

Keywords ANCA, Vasculitis, Superoxide dismutase, Oxidative stress

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an autoimmune disease with primary pathologic manifestations of inflammation and necrosis of small blood vessel walls [1]. Multiple organ system involvement is common in AAV, especially the lung and kidney, with resultant alveolar hemorrhage, acute renal failure, and a high risk of death [2, 3]. Due to differences in clinical manifestations of AAV, many

*Correspondence:
Lin Tang
300344@hospital.cqmu.edu.cn
[1] Department of Rheumatology and Immunology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

patients have acute onset and rapid progression of the disease, which often brings difficulties to disease assessment [4]. Erythrocyte sedimentation rate (ESR), C reactive protein (CRP) levels, and Birmingham Vasculitis Activity Score (BVAS), as well as other biomarkers are commonly used to evaluate disease activity[5]. However, those biomarkers are less than satisfactory, with ESR and CRP easily impacted by other factors, and the BVAS cumbersome to use [5, 6]. Therefore, it is necessary to find other simple and effective biomarkers for AAV patient evaluation of disease severity and prognosis.

Studies show that autoimmune diseases are closely related to oxidative stress [7–9]. Oxidative stress is an imbalance between cellular reactive oxygen species (ROS), reactive nitrogen species (RNS), and endogenous antioxidants. ROS/RNS can cause protein, DNA, and membrane damage that promote cell stress and/or death by inducing apoptosis and autophagy [9]. Superoxide dismutase (SOD) is a key endogenous antioxidant enzyme, which reduces the harmful effects of superoxide anion by converting harmful superoxide into hydrogen peroxide, protecting cells from internal and external oxidative damage [10]. There are three isoforms of SOD in mammals, including cytosolic SOD1 (Cu, Zn-SOD), mitochondrial SOD2 (Mn-SOD), and extracellular SOD3 (EC-SOD). SOD not only reduces the level of ROS, but also inhibits inflammatory responses by regulating cellular signaling[10]. Numerous studies have proved that SOD plays an important role in rheumatoid arthritis, systemic lupus erythematosus, scleroderma, anti-MDA5-positive dermatomyositis and other autoimmune diseases [10–13]. Recent studies have shown that the pathogenesis of AAV is related to oxidative stress induced by excessive ROS production in vivo [14, 15], but the relationship between SOD and AAV is unclear. The purpose of this study was to explore the clinical value of serum SOD measurement as a guide for AAV patient management.

Materials and methods

Participants

This single-center retrospective study took place from January 2016 to October 2022 and included 152 AAV patients hospitalized in the Second Affiliated Hospital of Chongqing Medical University with complete clinical data. All of them were newly diagnosed and fulfilled the 1990 American College of Rheumatology criteria and/or 2012 Chapel Hill Consensus definitions for GPA, MPA and EGPA [1, 16, 17]. AAV patients combined with other connective tissue diseases were excluded. The control group was comprised of healthy individuals in the same hospital and they were free from any common comorbidities or conditions that could interfere at the oxidative state, such as hypertension, diabetes, tabagism and obesity. In accordance with the the Declaration of Helsinki, all patients and control individuals gave their informed consent to participate and agreed to publication of their data. The Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University approved this study.

Data collection

By looking at the medical records, we extracted clinical and laboratory data(demographic data, serum SOD, ESR, CRP, ANCA, and organ involvement) of AAV patients in the hospital, and the information regarding patient's survival or death was recorded. In addition, disease activity was calculated for each patient based on the Birmingham Vasculitis Activity Score (BVAS) [6]. Patient data were collected after first admission but before treatment, reflecting baseline characteristics of the disease.

Materials

Serum SOD levels were assessed by colorimetry using a superoxide dismutase test kit(Reebio, Ningbo, China). ESR was determined by ESR-30 dynamic monitor. CRP was tested with Sysmex XN-3000 and its supporting reagents. ANCA was detected by enzyme linked immunosorbent assays(Westang, Shanghai, China) [18]. All samples in this study were tested according to the above standard procedures.

Statistical analysis

SPSS 25.0 (version 25.0; IBM, Armonk, NY, USA) was used for data processing. Data with normal distribution were expressed as means (standard deviation; SD), with comparisons between groups by Student's t test. Data with a non-normal distribution were expressed as medians (interquartile range; IQR). The Mann–Whitney U test was used for inter-group comparisons. Count data were expressed as percentage or rate, and the Chi-square test was used for comparison between groups. The Spearman test was used for correlation analysis. Risk factors influencing outcomes were analyzed by multivariate logistic regression. A $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

The healthy control group was comprised of 150 individuals, 74 of which were males and 76 females, with an average age of 63.56 years (SD, 13.67). There were 152 AAV patients, 74 of which were males and 78 females, with an average age of 64.07 years (SD, 14.81). The most common AAV organ involvement was pulmonary (76.32%), followed by renal (55.92%). For AAV patients, there were 127 (83.55%) myeloperoxidase

Table 1 Characteristics of 152 AAV patients and the healthy control group of individuals

	AAV (n = 152)	Control (n = 150)	*P*
Female, n(%)	78 (51.32)	76 (50.67)	0.910
Male, n (%)	74 (48.68)	74 (49.33)	
Age, years, mean (S.D.)	64.07 (14.81)	63.56 (13.67)	0.755
Organs involvement, n (%)			
Eye	15 (9.87)	–	–
ENT	50 (32.89)	–	–
Pulmonary	116 (76.32)	–	–
Cardiovascular	10 (6.58)	–	–
Abdominal	11 (7.24)	–	–
Renal	85 (55.92)	–	–
Cutaneous	10 (6.58)	–	–
Musculoskeletal	44 (28.95)	–	–
Nervous	16 (10.53)	–	–
MPO-ANCA, n (%)	127 (83.55)	–	–
PR3-ANCA, n (%)	25 (16.45)	–	–
Died, n (%)	23 (15.13)	–	–

ANCA anti-neutrophil cytoplasmic antibody, *AAV* ANCA-associated vasculitis, *SD* standard deviation, *MPO* myeloperoxidase, *PR3* protease3, *ENT* ear, nose, and throat

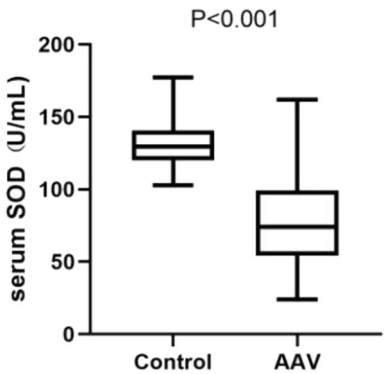

Fig. 1 SOD levels in the healthy control group and in AAV patients. T-test was employed for comparing the mean SOD level between the two groups ($P < 0.001$)

(MPO)-ANCA patients and 25 (16.45%) protease3 (PR3)-ANCA patients. In addition, 23 (15.13%) of the 152 AAV patients died, Table 1.

SOD levels among AAV patients and healthy controls

The SOD level for the healthy control group was 131.03 U/ml (SD, 14.23) and that of AAV patients was 78.97 U/ml (SD, 31.36), which was significantly lower than that of the healthy control group ($P < 0.001$, Fig. 1).

The relationship between SOD level and ESR, CRP and BVAS

By analysis of the relationships among SOD levels and disease activity in AAV patients, we found that SOD levels in AAV patients were negatively correlated with ESR, CRP, and BVAS (ESR rho = −0.367, $P < 0.001$, CRP rho = −0.590, $P < 0.001$, and BVAS rho = −0.488, $P < 0.001$, Fig. 2).

Relationship between SOD and ANCA serology

AAV patients (n = 152) were divided into two groups based on ANCA serology (Fig. 3). SOD levels in the MPO-ANCA group (n = 127) were 72.20 U/ml (IQR.5 3.20, 89.90). SOD levels in the PR3-ANCA group (n = 25) were 89.40 U/ml (IQR.66.70, 114.90), the difference was statistically significant ($P = 0.045$).

Relationship between SOD and organ involvement in AAV patients

We assessed SOD levels based on organ involvement. SOD levels in the pulmonary involvement group (n = 116) were 70.35 U/ml (IQR.52.58, 88.95), which was significantly lower than that in the non-pulmonary involvement group (n = 36; 89.65 U/ml (IQR.65.1, 130.75)) ($P = 0.006$). SOD levels in the renal involvement group (n = 85) were 65.10U/ml (IQR.47.95, 84.95), which was significantly lower than the non-renal involvement group (n = 67; 85.50 U/ml (IQR.66.00, 123. 70)) ($P < 0.001$). SOD levels in the ear, nose, and throat(ENT) involvement group (n = 50) were 89.40 U/ml (IQR.70.23, 115.18), which were significantly higher than the non-ENT involvement group (n = 102; 67.30 U/ml (IQR.50.28, 85.85)) ($P < 0.001$). SOD levels did not significantly differ for other involved organs, Fig. 4.

With the high incidence of pulmonary and renal involvement in AAV patients, we further assessed the ENT involvement group for pulmonary and renal involvement. Results showed that the proportion of patients with renal involvement in the ENT involvement group (40.0%) was significantly lower than that in the non-ENT involvement group (63.7%) ($P = 0.006$, Table 2).

Relationship between SOD levels and outcomes for AAV patients

Based on outcomes, 152 AAV patients were divided into a survival group (n = 129) and a death group (n = 23). SOD levels of the death group were significantly lower than those of the survival group ($P = 0.001$) with CRP and BVAS significantly higher than the survival group ($P = 0.048$, $P < 0.001$, Table 3). Based on the data in Table 3, variables with a $P < 0.05$ were included

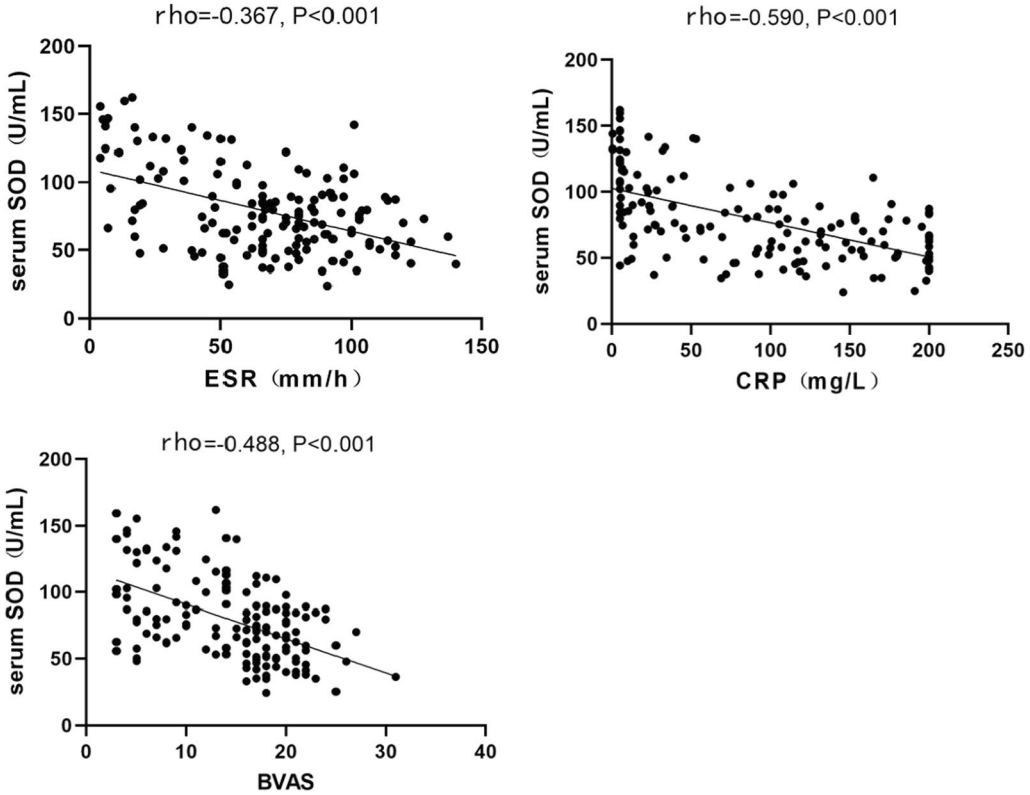

Fig. 2 Correlation analysis of SOD with ESR, CRP, and BVAS in AAV patients. The Spearman test was used for correlation analysis. Abbreviations: ESR: erythrocyte sedimentation rate; CRP: C reactive protein; BVAS: Birmingham Vasculitis Activity Score

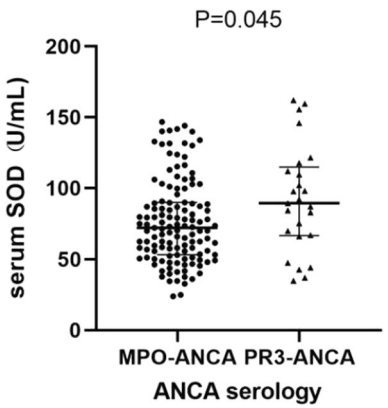

Fig. 3 SOD levels based on ANCA serology. The Mann–Whitney U test was used to compare median SOD level between PR3 and MPO groups ($P=0.045$). Lines and bars indicate the medians (IQR)

in multivariate logistic regression analysis. Results showed that low SOD levels were an independent risk factor for a poor outcome for AAV patients ($P=0.03$, Table 4).

Discussion

Although the survival rate for AAV patients has improved, the mortality rate is still 2.7 times that of the general population [19]. Recent studies have shown that oxidative stress plays an important role in the development of AAV [14, 15]. SOD, as an important antioxidant, regulates oxidative stress by scavenging excessive oxygen free radicals [10]. Numerous studies have demonstrated SOD play an important role in the occurrence and development of autoimmune disease. However, it is unclear whether SOD also plays a role in AAV. Therefore, this study explored the relationship between serum SOD and AAV.

Studies have shown that during the onset of AAV, neutrophils are activated by pathogenic ANCAs and that a large number of oxygen free radicals are produced and released, promoting endothelial injury and vasculitis [20]. SOD, as one of the important enzymatic antioxidant substances in the body, can clean up oxygen free radicals contained in the body. Its activity level reflects the body's ability to scavenge free radicals. Furthermore, the level of SOD is a sensitive index of antioxidant activity in the body [21]. Our research shows that the lower level of SOD among AAV patients, reflect

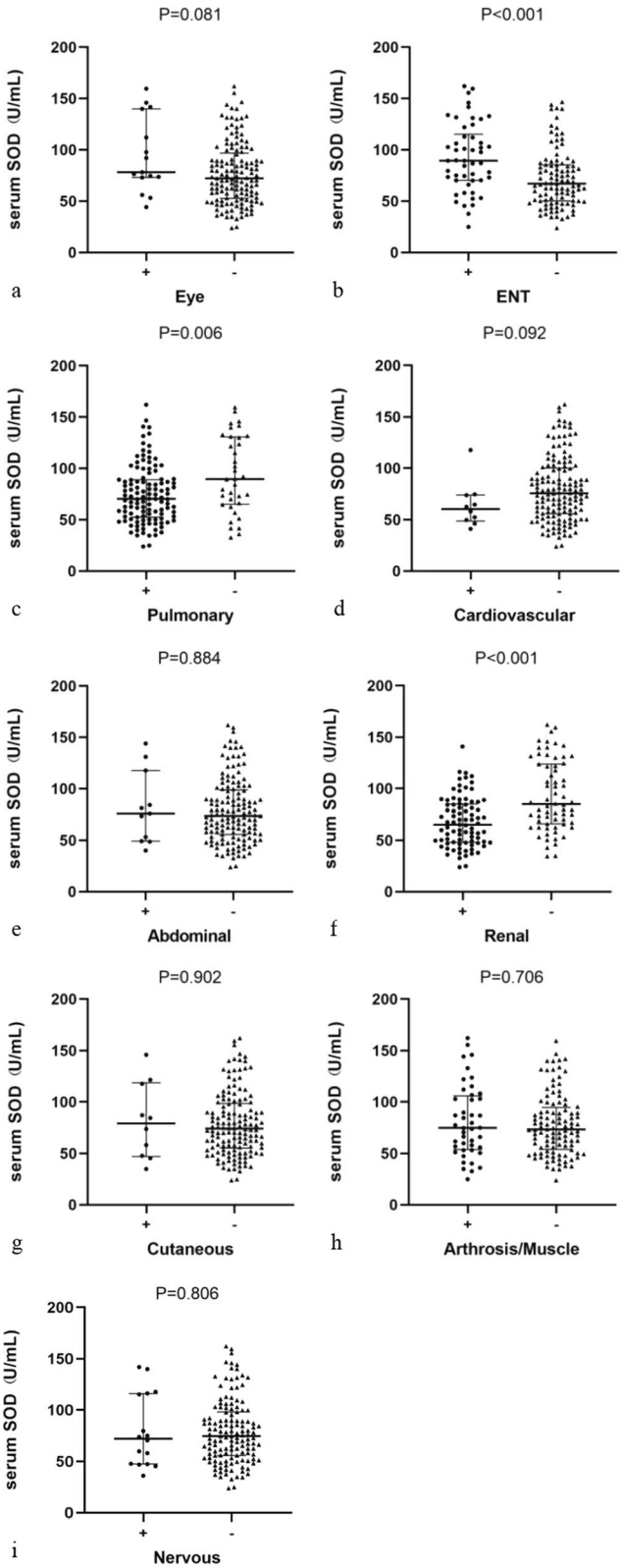

Fig. 4 Comparison of serum SOD level based on the pattern of organ involvement. The Mann–Whitney U test was used to compare median SOD level between the two groups. Lines and bars indicate the medians (IQR). Abbreviations: ENT: ear, nose, and throat

Table 2 Comparison of pulmonary and renal involvement based on ENT involvement

	ENT involvement group (n = 50)	Non-ENT involvement group (n = 102)	*P*
Pulmonary involvement, n (%)	34 (68.0)	82 (80.4)	0.091
Renal involvement, n (%)	20 (40.0)	65 (63.7)	0.006

ENT ear, nose, and throat

Table 3 Comparison of SOD level, inflammatory markers based on outcomes

	Survival group (n = 129)	Death group (n = 23)	*P*
SOD (U/mL), mean (S.D.)	82.59 (31.45)	58.71 (22.18)	0.001
ESR (mm/h), mean (S.D.)	65.69 (33.05)	72.65 (28.47)	0.344
CRP (mg/L), mean (S.D.)	86.60 (71.93)	114.81 (58.79)	0.048
BVAS, mean (S.D.)	13.85 (6.38)	18.48 (3.68)	0.000

SOD superoxide dismutase, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein, *BVAS* Birmingham Vasculitis Activity Score

a higher oxidative stress state compared to healthy controls. Therefore, SOD levels in AAV patients may be a valuable index for rheumatologists.

In the inflammatory state, neutrophils are activated and produce large amounts of ROS. SOD not only reduces the level of ROS, but also inhibit the inflammatory response by regulating cellular signaling [10]. Furthermore, Ueda et al. [22] found that SOD mRNA and protein levels decreased during inflammatory conditions, which demonstrated the influence of inflammation on SOD was related to transcription and proteolytic regulation. Herein, we found AAV patient SOD levels to be negatively correlated to ESR, CRP, and BVAS, indicating that SOD levels are decreased with inflammation. These results suggest that SOD levels are closely related to disease activity in AAV patients. Therefore, SOD levels could potentially be a biomarker to access disease activity among AAV patients and this should be explored in prospective studies.

PR3 and MPO are important target antigens of ANCA [18]. Studies have shown that PR3 and MPO are involved in the activation of neutrophils, leading to the release of inflammatory mediators. Subsequently, both PR3 and MPO are released into the circulation where they interact with endothelial cells. PR3 induces apoptosis of the endothelial cell whereas MPO induces the production of intracellular oxidants [23]. We analyzed SOD levels in AAV patients based on ANCA serology, and found SOD levels of the MPO-ANCA group to be significantly lower than those of the PR3-ANCA group. These results indicate that ANCA serology is associated with SOD levels in patients, which may be related to different inflammatory pathways induced by PR3 and MPO. However, further studies are needed. Therefore, this study demonstrated for the first time, that serum SOD levels are associated with ANCA serology.

As for the relationship between SOD and AAV organ involvement, we show lower SOD levels in AAV patients with pulmonary and renal involvement. In the pulmonary system, excessive ROS can induce oxidation of membrane phospholipids and peroxidation of polyunsaturated fatty acids. This process results in dysfunction of membrane receptors and enzymes, increasing tissue permeability, and aggravating damage to the pulmonary extracellular matrix [24]. Moreover, oxidative stress induced by ROS promotes the synthesis and secretion of various cytokines and growth factors, especially transforming growth factor (TGF-β), which promotes the development of pulmonary fibrosis [25]. As an important antioxidant, SOD is highly expressed in the pulmonary system. Reduced levels of SOD result in pulmonary injury, which is characterized by thickening of the alveolar septum, increased inflammatory cell infiltration, pulmonary fibrosis, and alveolar hemorrhage [26, 27]. With regard to the renal system, recent studies have shown that excessive ROS and the accumulation of dityrosine-containing protein products, produced during oxidative stress (advanced oxidation protein products)

Table 4 Multivariate logistic regression analysis

Variable	B	Sb	Wald χ^2	*P*	OR	95% CI	
						Low	High
SOD (U/mL)	− 0.027	0.012	4.714	0.030	0.974	0.950	0.997
CRP (mg/L)	− 0.001	0.004	0.033	0.856	0.999	0.992	1.007
BVAS	0.095	0.052	3.370	0.066	1.099	0.994	1.216
Constant	− 1.355	1.512	0.802	0.370	0.258		

SOD superoxide dismutase, *CRP* C reactive protein, *BVAS* Birmingham Vasculitis Activity Score

are directly related to podocyte injury, proteinuria, the development of focal segmental glomerulosclerosis, and tubulointerstitial fibrosis [28]. Further, vasculitis with renal involvement is common in MPO-AAV patients. Hilhorst et al. [29] found that activated MPO triggered an oxidative burst through HOCl production, which may result in early stage glomerulonephritis. SOD regulates oxidative stress, with a decline in SOD affecting the balance between oxidation and anti-oxidation. Hence, there is a connection between SOD and pulmonary and renal involvement in AAV patients. Interestingly, we found that SOD levels in AAV patients with ENT involvement are significantly higher than in AAV patients without ENT involvement. Further analysis showed that the proportion of AAV patients with renal involvement in the ENT involvement group was significantly lower than that in the non-ENT involvement group. We believe that the relationship between renal involvement and SOD level may result in lower SOD levels in patients without ENT involvement, suggesting a relationship between renal involvement and SOD. However, identification of the involved mechanism(s) requires further study. In conclusion, this study is novel in that it demonstrates that SOD might be used as a simple and effective biomarker to assess organ involvement in AAV patients.

Studies have shown that SOD can not only remove free radicals but also regulate immune cell function, inhibit inflammatory mediators, and regulate cell signaling [10, 30]. A significant decrease in SOD level indicates a serious oxidative stress imbalance within the body. Overproduction of ROS and decreased antioxidant defense promote inflammation and tissue fibrosis, which aggravate disease progression [9]. In this study, SOD levels in the death group were significantly lower than those in the survival group. Further, multivariate regression analysis showed that low SOD levels were an independent risk factor for a poor outcome for AAV patients. Therefore, low SOD levels are an important biologic indicator of a poor prognosis for AAV patients.

It is worth noting that this is a retrospective study and inherent limitations should not be ignored, including selection bias and recall bias. Also, this single-center retrospective study shows that SOD levels were negatively correlated with ESR, CRP, BVAS in AAV patients, but the usefulness for disease activity should be explored in a prospective study.

Conclusion

In summary, this study explored the relationships among serum SOD levels and disease activity, ANCA serology, organ involvement, and outcomes in patients with AAV, providing relevant information for clinical practice and reliable basis for follow-up studies.

Acknowledgements
This work was supported by grant no. 81771738 from the National Natural Science Foundation of China, the Talents Program of Chongqing, the CQMU Program for Youth Innovation in Future Medicine and the Kuanren Talents Program of the Second Affiliated Hospital of Chongqing Medical University.

Author contributions
ZZ: medical student responsible for the study, participated in all planning, execution and preparation of the manuscript. WH: advisor and supervisor, participated in the analysis, data interpretation and critical review of the content. FR, LL, JZ: participated in the process of execution and content review. LT: responsible for outlining the study, participated in the content execution and review process.

Funding
This work was supported by grant no. 81771738 from the National Natural Science Foundation of China, the Talents Program of Chongqing, the CQMU Program for Youth Innovation in Future Medicine and the Kuanren Talents Program of the Second Affiliated Hospital of Chongqing Medical University.

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

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. All patients and control individuals gave their informed consent to participate and agreed to publication of their data.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 6 February 2023 Accepted: 15 June 2023
Published online: 28 June 2023

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1–11.
2. Quartuccio L, Bond M, Isola M, Monti S, Felicetti M, Furini F, et al. Alveolar haemorrhage in ANCA-associated vasculitis: long-term outcome and mortality predictors. J Autoimmun. 2020;108:102397.
3. Chen Y, Lu Y, Zhou Y, Yu C. Clinical features and prognosis in ANCA associated vasculitis patients with acute kidney Injury. Arch Iran Med. 2022;25(4):235–40.
4. Santacruz-Sandoval E, Lopez-Bonilla J, Guevara-Calderon LA, Nieto-Aristizabal I, Ruiz-Ordonez I, Canas CA, et al. Clinical characteristics and outcomes of patients with ANCA-associated vasculitides in a Colombian hospital. J Clin Rheumatol. 2022;28(2):e491–e7.
5. Csernok E, Bossuyt X. Investigations in systemic vasculitis. The role of the laboratory. Best Pract Res Clin Rheumatol. 2018;32(1):52–62.
6. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity score (version 3). Ann Rheum Dis. 2009;68(12):1827–32.
7. Ramani S, Pathak A, Dalal V, Paul A, Biswas S. Oxidative stress in autoimmune diseases: an under dealt malice. Curr Protein Pept Sci. 2020;21(6):611–21.
8. Smallwood MJ, Nissim A, Knight AR, Whiteman M, Haigh R, Winyard PG. Oxidative stress in autoimmune rheumatic diseases. Free Radic Biol Med. 2018;125:3–14.

9. Scherlinger M, Tsokos GC. Reactive oxygen species: the Yin and Yang in (auto-)immunity. Autoimmun Rev. 2021;20(8):102869.
10. Nguyen NH, Tran GB, Nguyen CT. Anti-oxidative effects of superoxide dismutase 3 on inflammatory diseases. J Mol Med (Berl). 2020;98(1):59–69.
11. Huang W, Chen D, Wang Z, Ren F, Luo L, Zhou J, et al. Evaluating the value of superoxide dismutase in anti-MDA5-positive dermatomyositis associated with interstitial lung disease. Rheumatology (Oxford). 2023;62(3):1197–203.
12. Al-Shobaili HARZ. Immunological studies of oxidized superoxide dismutase in patients with systemic lupus erythematosus. Correlation with disease induction and progression. Saudi Med J. 2012;33(11):1177–84.
13. Jinnin MIH, Yazawa N, Asano Y, Yamane K, Tamaki K. Serum levels of manganese superoxide dismutase in patients with localized scleroderma. Exp Dermatol. 2004;13(6):357–60.
14. Sredoja Tisma V, Bulimbasic S, Galesic Ljubanovic D, Galesic K, Morovic-Vergles J, Mitrovic J et al. The onset of systemic oxidative stress Associated with the Accumulation of lipid peroxidation product acrolein in the skin of patients with small-vessel vasculitis. Molecules. 2021;26(8):2344.
15. Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol. 2018;15(2):91–101.
16. Leavitt RYFA, Bloch DA, Michel BA, Hunder GG, Arend WP, Calabrese LH, Fries JF, Lie JT, Lightfoot RW Jr, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum Arthritis Rheum. 1990;33(8):1101–7.
17. Masi ATHG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33(8):1094–100.
18. Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suarez LF, Guillevin L, et al. Position paper: revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13(11):683–92.
19. Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA. Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies. Ann Rheum Dis. 2017;76(9):1566–74.
20. Falk RJTR, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci USA. 1990;87(11):4115–9.
21. Yan L, Wang B, Chen S, Zhou H, Li P, Zhou L, et al. The ratio of superoxide dismutase to standard deviation of erythrocyte distribution width as a predictor of systemic lupus erythematosus. J Clin Lab Anal. 2020;34(6):e23230.
22. Ueda J, Starr ME, Takahashi H, Du J, Chang LY, Crapo JD, et al. Decreased pulmonary extracellular superoxide dismutase during systemic inflammation. Free Radic Biol Med. 2008;45(6):897–904.
23. Hilhorst M, van Paassen P, Tervaert JW, Limburg Renal R. Proteinase 3-ANCA Vasculitis versus myeloperoxidase-ANCA vasculitis. J Am Soc Nephrol. 2015;26(10):2314–27.
24. Rahman I, Adcock IM. Oxidative stress and redox regulation of lung inflammation in COPD. Eur Respir J. 2006;28(1):219–42.
25. Richter K, Kietzmann T. Reactive oxygen species and fibrosis: further evidence of a significant liaison. Cell Tissue Res. 2016;365(3):591–605.
26. Gongora MC, Lob HE, Landmesser U, Guzik TJ, Martin WD, Ozumi K, et al. Loss of extracellular superoxide dismutase leads to acute lung damage in the presence of ambient air: a potential mechanism underlying adult respiratory distress syndrome. Am J Pathol. 2008;173(4):915–26.
27. Cui Y, Robertson J, Maharaj S, Waldhauser L, Niu J, Wang J, et al. Oxidative stress contributes to the induction and persistence of TGF-β1 induced pulmonary fibrosis. Int J Biochem Cell Biol. 2011;43(8):1122–33.
28. Duni A, Liakopoulos V, Roumeliotis S, Peschos D, Dounousi E. Oxidative stress in the pathogenesis and evolution of chronic kidney disease: untangling Ariadne's thread. Int J Mol Sci. 2019;20(15):3711.
29. Hilhorst MMA, Kavian N, Batteux F, Borderie D, Le Quellec A, van Paassen P, Guilpain P. Impact of MPO-ANCA-mediated oxidative imbalance on renal vasculitis. Am J Physiol Renal Physiol. 2018;315(6):F1769–F76.
30. Shimojima Y, Kishida D, Ichikawa T, Takamatsu R, Nomura S, Sekijima Y. Oxidative stress promotes instability of regulatory T cells in Antineutrophil cytoplasmic antibody-associated vasculitis. Front Immunol. 2021;12:789740.

Publisher's Note