

BMJ Open Clinical characteristics of infective endocarditis in patients with antineutrophil cytoplasmic antibody or antiphospholipid antibody: a retrospective study in Shanghai

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To cite: Zhou Z, Ye J, Teng J, *et al*. Clinical characteristics of infective endocarditis in patients with antineutrophil cytoplasmic antibody or antiphospholipid antibody: a retrospective study in Shanghai. *BMJ Open* 2020;**10**:e031512. doi:10.1136/bmjopen-2019-031512

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-031512>).

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Received 18 May 2019
Revised 16 December 2019
Accepted 28 January 2020



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ABSTRACT

Objective This study aimed to characterise rheumatic manifestations and autoantibodies in 432 patients diagnosed with infective endocarditis (IE) in Shanghai.

Design, setting and participants A retrospective study was conducted in Ruijin Hospital from 1997 to 2017. The clinical and laboratory characteristics of a total of 432 patients were analysed. In addition, the differences between patients with positive and negative antineutrophil cytoplasmic antibodies (ANCA) and antiphospholipid (aPL) antibodies as well as the survival rates of these patients were compared.

Results A total of 432 patients, including 278 male patients and 154 female patients, were included. The mean age of the patients was 46±16 years. A total of 346 patients (80%) had cardiac surgery, and 55 patients (13%) died in the hospital. Among the IE patients, 104 were tested for either ANCA or aPL and were analysed in different groups. Twenty-one (24%) positive ANCA patients were proteinase 3-ANCA positive. Compared with the ANCA-negative group, patients with positive ANCA had higher IgM (p=0.048), lower haemoglobin (p=0.001) and a higher likelihood of arthritis (p=0.003). Twenty-one (40%) aPL-positive patients had a higher erythrocyte sedimentation rate than was found in the aPL-negative group (p=0.003). In addition, the survival rate of the ANCA-positive IE patients was lower (p=0.032) than that of the ANCA-negative group, while there was no difference between patients with or without aPL antibodies (p=0.728).

Conclusion This study supports the claim that rheumatic manifestations and autoantibodies are frequently present in patients with IE and might lead to early misdiagnosis. Physicians should pay more attention to the measurement of autoantibodies in these patients.

INTRODUCTION

Infective endocarditis (IE) is a microbial infection of the endocardium that usually involves the heart valves. Despite being relatively rare worldwide, IE has been reported in a steady incidence over the past three

Strengths and limitations of this study

- It was a retrospective study in a tertiary clinical centre spanned over 20 years.
- This study filled the gap in the study of the infective endocarditis (IE) population related to antineutrophil cytoplasmic antibodies (ANCA) or antiphospholipid (aPL) antibodies in China.
- The study analysed the clinical characteristics and survival rates of IE patients with and without ANCA or aPL antibodies.
- As it was a retrospective study, not all patients underwent analysis for ANCA and aPL autoantibodies.
- Deaths occurring at home or in other hospitals were not registered.

decades ranging from 2 to 6 per 100 000 individuals in the general population per year and has a considerable associated mortality rate that varies from 10% to 30%.¹ Predisposing factors for IE include conditions such as congenital heart diseases, rheumatic valve disease, artificial valves and other factors such as intravenous drug use (DU), dental procedures and haemodialysis.² The diagnosis of IE is made based on symptoms, blood cultures, echocardiography and pathological biopsy from valve surgery.³ However, superantigens induced by some bacteria, such as *Staphylococcus aureus*, can stimulate an immune response, which could interfere with antibody production.⁴ Rheumatic manifestations, such as myalgia, arthralgia and arthritis are prevalent, occurring in nearly 40% of patients with IE at presentation of weeks to months before the diagnosis of IE.⁵ When classic IE manifestations are less evident, patients can be misdiagnosed as having a rheumatological disease, which might lead to delayed

initiation of antibiotic treatment. Thus, the distinction between IE and rheumatic diseases is not always easy, and to improve the understanding concerning differences between these conditions is of great importance.

Many specific antibodies, such as antineutrophil cytoplasmic antibodies (ANCA) and anti-phospholipid (aPL) antibody, might be related to the pathophysiology of IE.^{6 7} Due to positive ANCA tests, IE has been reported to mimic ANCA-associated vasculitis (AAV). Patients with IE may present with multiple pulmonary nodules and glomerulonephritis, which mimics granulomatosis with polyangiitis.⁸ One study further underscored that ANCA might be associated with multiple valve involvement.⁶ In addition, infection-associated elevated aPL levels in patients with IE are related to endothelial cell activation, thrombin generation and impairment of fibrinolysis, which may contribute to the increased risk of major embolic events in these patients.⁷ Therefore, ANCA and aPL are not specific to IE patients.

The objective of this study was to compare the clinical characteristics and survival rates of IE patients with and without ANCA or aPL autoantibodies in a tertiary hospital in Shanghai, China from 1997 to 2017.

METHODS

Patients

This study was a retrospective study. We continuously included 432 patients hospitalised in Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine who were diagnosed with IE from 1997 to 2017 after ruling out 33 patients with primary rheumatic disease or in immunosuppression condition. The clinical and laboratory data of the patients were mainly obtained from the medical records system of Ruijin Hospital.

Only patients with definite IE determined by either the Duke criteria (up to 2000) or the modified Duke criteria (from 2000 onwards) were included.^{3 9} Duration of disease was defined as the period from the time when the patients presented with the first clinical feature to a definite IE diagnosis. In patients with long-term fever, the autoantibodies were tested to rule out rheumatic diseases. Cardiac surgery and death were recorded during the period of hospitalisation. The study followed the ethical standards for human experimentation established in the Declaration of Helsinki.

In this study, patients positive for either myeloperoxidase (MPO)-ANCA or proteinase 3 (PR3)-ANCA were defined as ANCA-positive patients. Patients with any positive test for anticardiolipin antibodies (ACL), lupus anticoagulant (LAC) or anti- β 2 glycoprotein I antibodies (a β 2GPI) were defined as aPL-positive patients. Congestive heart failure was defined according to the New York Heart Association classification system.¹⁰ In-hospital mortality was defined as IE patients who died during hospitalisation. There was a 4-month observation period for patient mortality from the day of diagnosis. The survival rates of subgroups positive or negative for ANCA and aPL were then analysed.

Laboratory features and echocardiography

Levels of anti-PR3, anti-MPO and aPL antibodies in serum were measured by ELISA. The following laboratory data were recorded: white blood cell counts in blood, haemoglobin, platelets, C-reactive protein, erythrocyte sedimentation rate (ESR), lactate dehydrogenase, rheumatoid factor (RF), IgG, IgA, IgM, antinuclear antibody (ANA), ACL, LAC, a β 2GPI antibodies, anti-PR3 antibodies (PR3-ANCA), anti-MPO antibodies (MPO-ANCA), haematuria and proteinuria. All IE patients underwent transthoracic or transoesophageal echocardiography. Furthermore, each patient underwent abdominal ultrasounds.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences for Windows (V.23.0; SPSS, IBM). Statistical analyses were performed by t-test or χ^2 test according to the type of data (continuous or categorical, respectively). Survival curves were obtained using the Kaplan-Meier method. Significance was obtained by a log-rank test. A p value of less than 0.05 was considered statistically significant.

Patient and public involvement

Patients were not informed by the development of the research question and outcome measures. Patients were not involved in the design, the recruitment to and conduct of the study as the study was retrospective. The results were not shared with study participants.

RESULTS

Characteristics of patients

As shown in [table 1](#), a total of 432 patients, including 278 (64%) male patients and 154 (36%) female patients (male:female ratio=1.8:1), were analysed. The mean age \pm SD of patients was 46 \pm 16 years. The median duration of disease was 1.56 (0.75, 3) months. The mitral valve (54%) was the most frequently involved valve followed by the aortic valve (43%). The most common complication of IE patients was congestive heart failure in 141 patients (33%). For embolic events discovered or presented in the hospital, brain (14%) and spleen (6%) infarction were most commonly seen. For predisposing factors, dialysis accounted for 1%, dental procedures accounted for 1%, and intravenous DU accounted for 0.5%. In addition, 58 (13%) patients had rheumatic valvulopathy. During hospitalisation, 346 patients (80%) had cardiac surgery, and 55 patients (13%) died. The pathogens associated with IE patients are listed in online supplementary table 1.

Clinical manifestations and laboratory features

Fever (84%) and new heart murmur (79%) were present in most patients with IE (online supplementary table 2). The most common rheumatic manifestations were

Table 1 General characteristics of IE patients

Item	N
N	432
Female/male	154 (36)/278 (64)
Age (years, mean±SD)	46±16
Duration (months, median, IQR)	1.56 (0.75,3)
Predisposing factors	
Dialysis	6 (1)
Dental procedure	4 (1)
Intravenous drug use	2 (0.5)
Congenital heart disease	66 (15)
Rheumatic valvulopathy	58 (13)
Complications	
Congestive heart failure	141 (33)
Hypertension	82 (19)
Diabetes	27 (6)
Cancer	11 (3)
Embolic events	
Brain	67 (14)
Spleen	26 (6)
Kidney	8 (2)
Extremity	8 (2)
Coronary	4 (1)
Lung	4 (1)
Infected valve	
Prosthetic valve	42 (10)
Native valve	
Mitral valve	234 (54)
Aortic valve	185 (43)
Tricuspid valve	17 (4)
Pulmonary valve	10 (2)
Outcome	
Cardiac surgery	346 (80)
Relapse	13 (3)
In-hospital mortality	55 (13)

IE, infective endocarditis.

arthritis (15%) and myalgia (6%). In addition, a few patients had non-specific manifestations such as hepatomegaly (4%), splenomegaly (23%) and fatigue (20%). Eighteen patients had Janeway lesions (4%), 11 patients had Osler nodes (3%) and five patients had Roth spot (1%).

Blood cultures were positive in 50% of IE patients. Echocardiographic data showed that 266/432 (62%) patients had IE-specific characteristics such as vegetation, abscess, pseudoaneurysm, intracardiac valvular perforation and abnormal activity around the site of the

Table 2 Antibodies in 38 patients tested for both ANCA and aPL

	N
aPL-positive	15
ACL-positive	1(IgM ACL)
aβ2GPI-positive	1
LAC-positive	10
ACL+LAC	3 (2 IgM ACL +1 IgA ACL)
ANCA-positive	9
Both aPL- and ANCA-positive	3(LAC, LAC +IgMAACL, IgM ACL)

ACL, anticardiolipin; aβ2GPI, anti-β2 glycoprotein I; ANCA, antineutrophil cytoplasmic antibody; aPL, anti-phospholipid; LAC, lupus anticoagulant.

prosthetic valve. Regarding immunologic features, 89 patients were tested for ANCA, 21 (24%) of these were ANCA-positive, and all of these were PR3-ANCA positive. Fifty-three patients were tested for aPL, and 21 were positive (45%). One patient had positive IgG aPL (2%), 4 patients had IgM aPL (8%), 1 patient had IgA aPL (2%), 2 patients had aβ2GPI (4%) and 17 patients had LAC (32%). Eight (13%) patients were positive for ANA, and one was positive for extractable nuclear antigen (ENA) (2%). Proteinuria (109/432, 25%) and haematuria (181/432, 42%) were most commonly observed. Of 38 IE patients tested for both aPL and ANCA, 15 were aPL-positive, 9 were ANCA-positive and 3 were positive for both antibodies (table 2). The clinical features and laboratory features of patients tested for antibodies or not are presented in online supplementary table 3. Arthritis was more common in patients tested for antibodies than in those who were not, indicating the relevance between autoantibodies and rheumatic features.

Comparison of patients with positive and negative ANCA or APL

Of 432 IE patients, the 104 who were tested for either ANCA or aPL were analysed. Finally, 89 patients were classified as 'ANCA-positive IE' or 'ANCA-negative IE', and 53 patients were classified as 'aPL-positive IE' or 'aPL-negative IE' according to their antibodies test (online supplementary figure 1). Thirty-eight patients were tested for both ANCA and aPL antibodies, and their characteristics were analysed. Of 89 patients who were tested for ANCA, 21 (24%) were ANCA-positive, and 68 (76%) were ANCA-negative. Arthritis (p=0.003) was more frequent in ANCA-positive patients than in ANCA-negative patients, while more cardiac surgery was done in ANCA-negative patients (p=0.002) (table 3). Other clinical manifestations such as fever, fatigue, embolic events, myalgia, splenomegaly, heart murmur and weight loss were not significantly different between the two groups (p>0.05). Compared with ANCA-negative patients, in ANCA-positive patients, IgM (p=0.048) was

Table 3 Clinical features of patients with positive or negative ANCA and aPL

Item	ANCA			aPL		
	ANCA (+), N (%)	ANCA (-), N (%)	P value	aPL (+), N (%)	aPL (-), N (%)	P value
Item	21 (24)	68 (76)	/	21 (40)	32 (60)	/
Positive blood culture	13 (62)	37 (58)	0.741	10 (50)	17 (53)	0.826
Fever	19 (90)	57 (84)	0.688	18 (86)	23 (72)	0.400
Arthritis	11 (52)	13(19)	0.003	5 (24)	8 (25)	0.922
Fatigue	3 (14)	16 (24)	0.549	7 (33)	9 (28)	0.686
Pleural effusion	3 (14)	15 (22)	0.642	6 (29)	9 (28)	0.972
Pericardial effusion	4 (19)	12 (18)	0.884	6 (29)	8 (25)	0.773
Thrombosis	3 (14)	17 (25)	0.466	8 (38)	10 (31)	0.607
Myalgia	0	6 (9)	0.362	2 (10)	2 (6)	1.000
Splenomegaly	6 (29)	20 (29)	0.941	5 (24)	6 (19)	0.922
Heart murmur	10 (48)	43 (63)	0.202	18 (86)	28 (88)	1.000
Weight loss	3 (14)	9 (13)	1.000	3 (14)	7 (22)	0.740
Cardiac surgery	5 (24)	42 (62)	0.002	16 (76)	19 (59)	0.206
In-hospital mortality	4 (19)	3 (4)	0.087	2 (10)	4 (13)	1.000

ANCA, antineutrophil cytoplasmic antibody; aPL, anti-phospholipid.

higher, Hb ($p=0.001$) was significantly lower and elevated RF ($p=0.053$) seemed to be more common (table 4). Of 53 patients who were tested for aPL, 21 (40%) were aPL-positive, and the remaining 32 (60%) were aPL-negative. ESR was significantly higher in patients who were positive for aPL than in those who were negative ($p=0.003$) (table 4).

Survival rate

Overall, 9 patients tested for aPL or ANCA antibodies died in the hospital. Among these patients, 4 were ANCA-positive, and 2 patients were aPL-positive. One patient died of renal failure, four of acute heart failure, two of septic shock and two of stroke. The survival rate was significantly lower in ANCA-positive IE patients ($p=0.032$), but there was

Table 4 Laboratory features of patients positive or negative for ANCA and aPL

Item	ANCA			aPL		
	ANCA (+)	ANCA (-)	P value	aPL (+)	aPL (-)	P value
Item	21 (24)	68 (76)	/	21 (40)	32 (60)	/
WBC ($\times 10^9/L$)	8.39 \pm 2.53	8.56 \pm 4.19	0.896	7.66 \pm 2.54	8.58 \pm 4.52	0.403
Hb (g/L)	87.57 \pm 26.83	105.51 \pm 18.76	0.001	99.57 \pm 15.28	102.34 \pm 26.22	0.664
PLT ($\times 10^9/L$)	194.70 \pm 110.91	201.25 \pm 127.06	0.879	184.95 \pm 83.86	193.47 \pm 151.31	0.819
LDH (IU/L)	206.125 \pm 53.45	252.00 \pm 96.73	0.200	278.87 \pm 296.11	247.72 \pm 103.72	0.632
ESR (mm/h)	64.76 \pm 36.87	51.85 \pm 33.47	0.135	69.14 \pm 34.82	39.09 \pm 33.48	0.003
IgG (mg/dl)	2254.29 \pm 1001.40	1660.05 \pm 528.67	0.172	1959.69 \pm 747.29	1751.67 \pm 707.30	0.379
IgA (mg/dl)	232.29 \pm 89.77	301.50 \pm 131.20	0.188	276.63 \pm 94.03	283.38 \pm 130.21	0.859
IgM (mg/dl)	312.71 \pm 183.51	140.70 \pm 64.03	0.048	193.07 \pm 119.30	153.79 \pm 119.39	0.324
IgE (mg/dl)	37.00 \pm 22.39	354.85 \pm 569.90	0.286	357.31 \pm 437.81	351.73 \pm 635.24	0.983
ACL-positive	2 (25)	2 (5)	0.436	5 (24)	0	0.004
a β 2GPI-positive	0	1 (5)	1.000	2 (13)	0	0.057
LAC-positive	2 (29)	11(38)	0.981	17(81)	0	0.000
ANA-positive	2 (15)	6 (12)	1.000	3 (16)	3 (11)	0.618
Elevated CRP	18(90)	51(86)	0.851	14(74)	21(75)	0.921
Elevated RF	10(59)	14(32)	0.053	6 (31)	6 (25)	0.336

ACL, anticardiolipin; a β 2GPI, anti- β 2 glycoprotein I; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; aPL, anti-phospholipid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; LAC, lupus anticoagulant; LDH, serum lactate dehydrogenase; PLT, platelets; RF, rheumatoid factor; WBC, white blood cell.

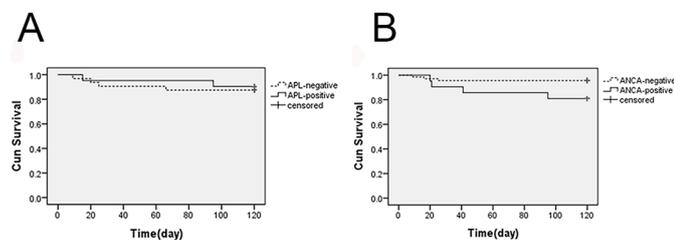


Figure 1 Kaplan-Meier survival curves. (a) Kaplan-Meier survival curves of patients who were tested for anti-phospholipid (aPL). (B) Kaplan-Meier survival curves of patients who were tested for antineutrophil cytoplasmic antibody (ANCA).

no significant difference between the aPL groups ($p=0.728$) (figure 1).

DISCUSSION

Although it has been reported about different aspects of IE,^{11–13} the analysis of the clinical and immunologic features of Chinese IE patients is still limited. The clinical presentations and laboratory findings of IE are similar to those of many rheumatic diseases, making it difficult to diagnose. Thus, it is pivotal to analyse the rheumatic manifestations of IE to help physicians differentiate it when encountering these clinical scenarios. In this study, we analysed the clinical and laboratory features of 432 IE patients in Ruijin Hospital and compared the characteristics of 104 patients tested for ANCA or aPL during the past two decades. The mean age of the IE patients was 46 years. In many studies of IE patients, the mean age was higher than that in our study, while other IE patients were similar to ours.^{2 14 15} In addition, elderly people were more likely to have valve replacement surgery because of degenerative valve disease. With regard to blood culture, it has been reported that blood culture-negative IE (BCNIE) may occur in up to 31% of all cases of IE and often poses considerable diagnostic and therapeutic dilemmas.³ BCNIE most commonly arises as a consequence of previous antibiotic administration. As a tertiary hospital, before hospitalisation in Ruijin Hospital, our patients had been treated with antibiotics empirically in other hospitals with uncertain diagnoses. As a result, only approximately 50% of the patients had a positive blood culture. Patients who were culture-negative were diagnosed based on other criteria such as echocardiography findings and a postoperative histological examination of vegetation. In addition, our study showed that ANCA-positive IE patients had higher IgM and lower Hb levels and were more likely to present with arthritis than was found in ANCA-negative IE patients. Moreover, aPL-positive IE patients had significantly higher ESR than was found in aPL-negative patients.

Positive ANCA and aPL were previously reported to be non-specific in patients with infection.^{6–8} The phenomenon of IE patients positive for ANCA has long been reported. A study from France reported that 8% of IE patients had PR3-ANCA or MPO-ANCA, associated with

young age ($p=0.022$), echocardiographic vegetation ($p=0.043$) and elevated IgG levels ($p=0.017$).¹⁶ It has also been reported that most Gram-positive endocarditis can cause an anti-PR3 specificity. During delayed polymorphonuclear leucocyte apoptosis, PR3 contact with the immune system could possibly cause an increase in the production of anti-PR3 ANCA.¹⁷ It was interesting to find that among our IE patients tested for ANCA, all of them were PR3-ANCA-positive. One important presentation of AAV is glomerulonephritis. However, IE-associated glomerular nephritis often presents with acute kidney injury.¹⁸ The most common biopsy finding was necrotising and crescentic glomerular nephritis (53%), followed by endocapillary proliferative glomerular nephritis (37%).¹⁸ In our study, among IE patients, those with proteinuria and haematuria accounted for 25% and 42%, respectively. However, the kidney biopsy was not routinely performed in these patients.

Apart from ANCA, aPL was also analysed in our study. In terms of the relationship between aPL and IE, it has been indicated that IgG aPL might be associated with Q fever endocarditis and aPL antibodies have previously been shown to be associated with thrombosis during acute Q fever.^{19 20} In our study, aPL-positive patients did not have positive serology of *Coxiella*. Furthermore, the presence of IgM aPL and a β_2 GPI was associated with embolic events, especially cerebral events, which could contribute to assessing the embolic risk of IE.²¹ In our study, there was no difference in thrombosis between aPL-positive patients and aPL-negative patients. APL-positive IE patients had higher ESR, and LAC was the most commonly positive type of aPL in IE patients. This might indicate that aPL was related to an inflammatory status.

In terms of the survival rate found in our study, it was significantly lower in the ANCA-positive IE group than in the ANCA-negative group. ANCA-positive patients were more likely to be mistaken for AAV, leading to a delay in diagnosis. Thus, these antibodies may be associated with a poor prognosis, which might be the reason for a higher mortality. Previously, we reported that the survival rate was significantly lower in ANCA-positive IE patients than in ANCA-negative group.¹³ However, there was no difference in the survival rate between the aPL groups in our study.

There were several limitations of this study. First, it was retrospective. The measurement of autoantibodies was not conducted in all IE patients when they were diagnosed, with only 89 undergoing ANCA and 53 aPL testing, and only 38 patients were tested for both ANCA and aPL antibodies. Second, the duration of the study spanned over 20 years, and some patients were lost to follow-up. Third, although there was a 4-month observation period for patients' mortality from the day of diagnosis during hospitalisation, we did not register deaths occurring in other hospitals or patients who died at home.



CONCLUSIONS

This study supports the hypothesis that rheumatic complications are frequent in patients with IE. For rheumatologists, it is indispensable to routinely exclude IE in patients with rheumatic features such as arthritis, splenomegaly, myalgia, proteinuria and haematuria. For cardiologists, more attention should be paid to the measurement of autoantibodies in IE patients as this might contribute to the evaluation of prognosis.

Acknowledgements We would like to thank the patients and patient advisors for their participation in this study. We also thank Dr Shuzhen Xiao for her critical reading of this manuscript.

Contributors JT, HL, XC, HC and FW collected the clinical data. YSu and YSun analysed the data. ZZ and JY wrote the manuscript. WJ and CY designed the study and critically read the manuscript.

Funding This work is supported by the National Natural Science Foundation of China (81801592, 81370397, 81670266), Science and Technology Commission of Shanghai Municipality (17140902500), Shanghai Sailing Program (18YF1414100), Shanghai Jiao Tong University Interdisciplinary Research Project (YG2016QN60), Excellent Youth B Project (GCQN-2017-B05) and Innovative research team of high-level local universities in Shanghai.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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