Biomedical Research 2017; 28 (1): 41-45 *ISSN 0970-938X*
www.biomedres.info

Laboratory findings in a large population of inflammatory arthritis patients: a retrospective cohort analysis.

Yüksel Maraş[1*], Berat Meryem Alkan[2], Fatma Fidan Yıldız[2], Sevgi Gümüş Atalay[2], Saygın Engin Yamçici[2], Sinem Bozkurt[2], Nebahat Sezer[3]

[1]Department of Rheumatology, Ankara Atatürk Educational and Research Hospital, Ankara, Turkey

[2]Ankara Atatürk Educational and Research Hospital, Physical Medicine and Rehabilitation Clinic, Ankara, Turkey

[3]Yıldırım Beyazıt University, Physical medicine and Rehabilitation Clinic, Ankara, Turkey

Abstract

Objectives: We aimed to determine the prevalence of laboratory findings in a large group of patients with inflammatory arthritis (IA) and the sensitivity and specificity level of anti-cyclic citrullinated peptide (anti-CCP) antibodies and rheumatoid factor (RF) antibodies in the diagnosis of rheumatoid arthritis (RA).

Material and Methods: We recorded the medical findings of 4439 patients with IA, including their demographic and clinical characteristics as well as their laboratory test results. We assessed the inflammatory diseases of patients with positive anti-CCP antibodies tests.

Results: The medical records of 4439 subjects were analysed: the mean age was 49.06 ± 14.06 years, and the sensitivity and specificity of anti-CCP antibodies for the diagnosis of rheumatoid arthritis (RA) were 56% and 97%, respectively. This was compared with the sensitivity and specificity of RF for RA at 75% and 93%. The combination of anti-CCP antibodies and IgM RF resulted in a higher positive predictive value of 92% and a slightly lower negative predictive value of 93% as compared with the use of IgM RF alone. We detected spondyloarthritis in 27 (7.2%), Sjögren's syndrome in 22 (6%), familial Mediterranean fever (FMF) in 13 (3.4%), and gout in 9 (2.4%) patients in the anti-CCP antibodies positive group.

Conclusions: Anti-CCP antibodies have a higher specificity than Ig RF for RA. Although rheumatoid arthritis is seen frequently in patients with anti-CCP antibodies, including other inflammatory diseases in the differential diagnosis is recommended.

Keywords: Anti-cyclic citrullinated peptide (anti-CCP) antibodies, Rheumatoid arthritis (RA).

Accepted on April 5, 2016

Introduction

Inflammatory types of arthritis include a wide range of rheumatic diseases. Rheumatoid arthritis (RA), gout, juvenile RA, lupus arthritis, and spondyloarthropathies are common types of inflammatory arthritis. One of the most common inflammatory diseases is RA, affecting 0.5-1% of the population. It is important to distinguish RA from the other types of inflammatory arthritis because this systemic disease is marked by chronic inflammation of the synovial joints, which leads to the destruction of cartilage and bone and eventually to disability in a great number of patients [1,2].

Complete blood count, C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and erythrocyte sedimentation rate (ESR) are useful laboratory tests for the diagnosis and follow-up in patients with inflammatory arthritis. The RF autoantibody system, directed against the Fc part of immunoglobulin (Ig) G molecules, has had an important role in the diagnosis and prognosis of RA [3]. RF can be identified with a sensitivity of 60-70% and a specificity of 80-90%.

Citrulline is a rare amino acid found in filagrin molecule as an organic part of antigenic epitope.

In recent years, anti-CCP, the most important member of anti-Citrullinated Peptide Antibody (ACPA) family, has a satisfactory specificity and was shown to have significant contribution to the RA diagnosis [4]. In one sense, the importance of anti-CCP is certified, by the inclusion of ACPA serum markers into 2010 RA classification criteria. These antibodies, mostly in immunoglobulin (IgG) class, can easily be identified with ELISA method thanks to the enhancement of synthetic peptides including Cittrulline. However, currently available assays detecting anti-CCP antibodies have a higher specificity of 98% and a sensitivity of 68-80% [5,6].

In this study, we aimed to determine the prevalence of laboratory findings in a large group of patients with inflammatory arthritis (IA) and the sensitivity and specificity level of anti-CCP and RF antibodies in the diagnosis of RA. Additionally, we assessed the inflammatory diseases of patients with positive anti-CCP antibodies tests.

Materials and Methods

We conducted this retrospective cohort study with approval from the ethical committee of Yıldırım Beyazıt University. We retrospectively reviewed the records of 4439 patients with a diagnosis of inflammatory arthritis (IA) for anti-CCP antibodies, IgM RF, ESR and C-reactive protein (CRP) levels in serum. RF was determined by nephelometry on an IMMAGE 800 (Beckman-Coulter). A positive result was recorded when the RF concentration was >20 IU/ml. Serum samples for anti-CCP antibodies measurement were studied by the electrochemiluminescence immunoassay (ECLA) method using a commercial anti-CCP antibodies assay.

We recorded the medical findings of the study population, including their demographic and clinical characteristics as well as laboratory test results. Rheumatic diagnoses were established by reviewing laboratory, radiological, clinical notes, and applying the ACR/EULAR 2010 classification criteria by specialists in the Physical Medicine and Rehabilitation and/or Rheumatology clinics [7]. The sensitivity and specificity of anti-CCP antibodies, RF and the combination of anti-CCP antibodies and RF values were calculated.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 17.0 was used to analyse the data. Descriptive statistics were used to describe demographic characteristics. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for anti-CCP antibodies, RF, and the combination of anti-CCP antibodies and RF. Spearman correlation tests were used to determine the relationships between the anti-CCP antibodies and other variables. In all tests, p-values<0.05 were considered significant.

Results

In this study, it was revealed that 4439 patients had arthritis in least one joint for at least two months, with a final diagnosis of RA, n=510; spondyloarthritis, n=627; psoriatic arthritis (PsA), n=127; systemic lupus erythematosus (SLE), n=172; Sjogren's syndrome, n=129; reactive arthritis, n=1250; osteoarthritis (OA), n=1081; other non-inflammatory arthritis, n=544 (Table 1). We assessed the inflammatory diseases in 372 patients with positive anti-CCP antibodies tests in 4439 patients with IA. The mean age of the subjects was 49.06 ± 14.06 years and 78.2% (3473) of the subjects were females. 14.1% (627) of the subjects were positive for RF and 8.4% (372) were positive for anti-CCP antibodies. ESR was high in 1110 (25%) and CRP was high in 1176 (26.5%) of 4439 patients. Table 2 shows baseline characteristics of 4439 patients with inflammatory arthritis.

Table 1. *Diagnoses for patients with recent-onset inflammatory arthritis.*

Patient group patients Age, years n(%), female
n(%) mean ± SD (range)
SpA, 627 (14,1%), 47.81 ± 13.2 (19-80), 479 (76.4%)
RA, 510 (11.5%), 52.39 ± 13.2 (25-73), 381 (74.7%)
PsA, 127 (2.9%), 48.01 ± 15.0 (24-85), 92 (72.8%)
Reactive arthritis, 1250 (28.1%), 48.62 ± 14.7 (18-87), 979 (78.2%)
Osteoarthritis, 1081 (24.3%), 48.70 ± 14.0 (18-87), 838 (77.3%)
Sjogren, 129 (2.9%), 54.52 ± 12.2 (28-75), 118 (91.5%)
SLE, 172 (3.9%), 48.71 ± 14.3 (22-78), 138 (80.2%)
Non-inflammatory condition, 544 (12.2%), 48.11 ± 13.5 (18-90), 449 (82.5%)
SpA-Spondyloarthritis; RA-Rheumatoid arthritis; PsA-Psoriatic arthritis; SLE-Systemic lupus erythematosus.

Table 2. *Baseline characteristics of 4439 patients with inflammatory arthritis.*

Age (years) [range]	49.06 ± 14.06 [18-90]
Female n (%)	3473 (78.2%)
IgM-RF positive	627 (14.1%)
Anti-CCP antibody positive	372 (8.4%)
IgM-RF positive and anti-CCP positive	220 (5%)
Sedimentation, mean ± SD (range)	23.36 ± 19.4
CRP, mean ± SD (range)	2.87 ± 8.2
Sedimentation positive n (%)	1110 (25%)
CRP positive n (%)	1176 (26.5%)
RF-Rheumatoid factor; CCP-Cyclic citrullinated peptide; CRP-C-reactive protein.	

Among RA patients, RF was found to be positive in 383 (75.1%) patients, but anti-CCP antibodies was found to be positive only in 288 (56.5%) patients. 220 (5%) anti-CCP antibodies+ patients were also RF+; 68 RA patients with RF– and 163 anti-CCP antibodies– patients with RA showed reactivity to RF. By relying on the results of the abovementioned research, we examined the sensitivity, specificity, and the predictive values for baseline testing. Table 3 shows that the sensitivity of the anti-CCP antibodies test among this group of patients was 56% (95% CI 51-60), with a specificity of 97% (95% CI 96–98), a PPV of 77% (95% CI 72–81), and an NPV of 94% (95% CI 93–95).

Also shown in Table 3, the sensitivity of the RF test was 75% (95% CI 71–79), with a specificity of 93% (95% CI 91–95), a PPV of 61% (95% CI 57–65), and an NPV of 96% (95% CI 95–97). The sensitivity of both RF and anti-CCP antibodies

was 43% (95% CI 38-47). The combination of anti-CCP antibodies and IgM RF resulted in a higher positive predictive value of 92% and a slightly lower negative predictive value of 93% as compared with the use of IgM RF alone.

We detected spondyloarthritis in 27 (7.2%), Sjogren's syndrome in 22 (6%), familial Mediterranean fever (FMF) in 13 (3.4%), and gout in 9 (2.4%) patients in the anti-CCP antibodies positive group (Table 4).

Table 3. *Diagnostic properties of the anti-CCP and RF antibodies tests.*

Per cent (95% confidence interval)
Sensitivity of anti-CCP antibodies 56 (51–60)
Specificity of anti-CCP antibodies 97 (96–98)
Positive predictive value of anti-CCP antibodies 77 (72–81)
Negative predictive value of anti-CCP antibodies 94 (93–95)
Sensitivity of RF 75 (71–79)
Specificity of RF 93 (91–95)
Positive predictive value of RF 61 (57–65)
Negative predictive value of RF 96 (95–97)
Sensitivity both of anti-CCP antibodies and RF 43 (38–47)
Specificity both of anti-CCP antibodies and RF 99 (98–99)
Positive predictive value both of anti-CCP antibodies and RF 92 (87–95)
Negative predictive value both of anti-CCP antibodies and RF 93 (92–94)
RF-Rheumatoid factor; CCP-Cyclic citrullinated peptide.

Table 4. *Diagnoses for patients with positive anti-CCP antibodies group.*

Patient group n (%), patients Age, years n(%), female n=372 mean ± SD (range)
RA, 288 (77.4%), 53.12 ± 12.9, 195 (67.7%)
SpA, 27 (7.2%), 47.03 ± 11.9, 16 (59.3%)
Sjogren, 22 (6%), 51.68 ± 11.2, 17 (77.3%)
FMF, 13 (3.4%), 51.69 ± 18.6, 6 (46.2%)
Gut, 9 (2.4%), 60.55 ± 15.8, 6 (33.3%)
Other, 13 (3.5%), 54.06 ± 16.7, 8 (61.5%)
RA-Rheumatoid arthritis; SpA-Spondyloarthritis; FMF-Familial Mediterranean fever.

It was revealed in this study that anti-CCP antibodies had a positive correlation with RF ($p<0.001$, $r=0.416$), but anti-CCP antibodies were not correlated with ESR ($p<0.001$, $r=0.206$), and CRP ($p<0.001$, $r=0.065$). RF was also not correlated with ESR ($p<0.001$, $r=0.299$) and CRP ($p=0.009$, $r=0.159$) (Table 5).

Table 5. *Correlation with RF, Anti-CCP antibodies and acute phase reactants.*

Variables	RF	ESR	CRP
Anti-CCP antibodies r value	0.416	0.206	0.065
p value	p<0.001	p<0.001	p<0.001

RF-Rheumatoid factor; CCP-Cyclic citrullinated peptide; ESR-Erythrocyte sedimentation rate; CRP-C-reactive protein.

Discussion

In this study, we aimed to find out the prevalence of laboratory findings in a large group of patients with IA, and the sensitivity and specificity level of anti-CCP antibodies and RF antibodies in the diagnosis of RA. It was also aimed to determine the diseases other than RA which could be observed in patients with IA showing anti-CCP antibodies positivity. The present study, among RA patients, the sensitivity of the RF test was 75% (95% CI 71–79) with a specificity of 93% (95% CI 91–95). The presence of RF was the first identified biological marker of RA and is a criterion of the American College of Rheumatology for a diagnosis of RA. Several studies showed that the RF antibody was found in approximately 75% of the patients with RA, but its specificity was limited because patients with other autoimmune diseases and considerably the healthy population and healthy elderly individuals also had RF. [6,8,9]. Even though rheumatoid factor is one of the criteria for an RA diagnosis, RF has a sensitivity of 31% to 80% and a specificity of 91% to 93% [6,8-12]. Van Boekel et al. [13] stated that the presence of RF was widely used as a diagnostic marker for RA regardless of its relatively low specificity.

Anti-CCP antibodies were found to be highly specific in the diagnosis of RA (95%) and only slightly less sensitive than IgM RF (60% to 70%) [14,15]. The present study, which compared RA patients to non-RA patients, the sensitivity of the anti-CCP antibodies test among RA patients was 56% (95% CI 51-60), with a specificity of 97% (95% CI 96–98). Other studies with RA patients have shown that the sensitivity and specificity of anti-CCP antibodies test range from 39% to 50% and from 93% to 98%, respectively, when compared to non-RA patients [6,10,11,15].

Our experience with the anti-CCP assay in patients with RA indicates a sensitivity and specificity for RA of 56% and 97%, respectively (not in comparison with normal subjects but in comparison with patients with other inflammatory types of arthritis). Niewold et al. [16] maintain that the high specificity of a negative anti-CCP antibodies test denote that the patient is most likely to have RA when the result is positive, and the low sensitivity of the test (40–50% in most published cohorts) shows that disease can be observed despite a negative anti-CCP antibodies tests. Niewold et al. stated that anti-CCP antibodies can also be used in order to detect patients who tend

to have evident on-going disease activity, and may be a justification for early aggressive treatment [16].

In this study, 288 (77.4%) of a total of 372 anti-CCP antibodies positive patients were diagnosed with RA at the initial evaluation. Van Gaalen et al. noted that 93% of patients who tested positive for anti-CCP antibodies were categorized as having RA within the next three years, so the presence of anti-CCP autoantibodies can be considered a prominent predictor of RA [15]. Anti-CCP autoantibodies are extremely valuable biomarkers for the diagnosis and prognosis of RA patients. The high probability of diagnosing RA in the earlier stages is also of high importance [17].

We detected a high sedimentation rate in 1110 (25%) patients and CRP was high in 1176 (26.5%) of 4439 patients. CRP and ESR are tests commonly used as markers of inflammation in arthritis [18]. Although ESR has become less widely used because of its slow response following an inflammatory stimulus, this is not important in chronic inflammation where both CRP and ESR are maintained at a steady state [19]. Measurements of ESR and CRP can be useful in assessing inflammatory disease progression or the effectiveness of treatments. In our study, anti-CCP antibodies and RF were not correlated with CRP and ESR while anti-CCP antibodies were positively correlated with RF. It was revealed in a number of other studies that there is a strong correlation between anti-CCP antibodies positivity and significant disease activity [20-22]. Niewold et al. proposed that patients with significantly greater disease activity can be identified more reliably by anti-CCP antibodies than by RF [16].

In addition, we detected anti-CCP antibodies in other rheumatic diseases, including Sjogren's syndrome in 22 (6%), spondyloarthritis 27 (7.2%), FMF in 13 (3.4%) and gout in 9 (2.4%) patients. Considerable research concerning other inflammatory diseases has been carried out to determine whether anti-CCP antibodies are observed in these inflammatory diseases or not. Van der Cruyssen et al. found that, of their 192 patients with psoriatic arthritis, 15 (7.8%) tested positive for anti-CCP antibodies [23]. Anti-CCP antibodies were found in 66 patients with SLE, 2 of 10 with erosive arthritis, and 1 of 56 patients with non-erosive disease in another study conducted by Mediwake et al. [24]. Similarly, Atzenil et al. found that 14 (9.9%) of their patients with progressive systemic sclerosis (PSS) had moderate to high levels of anti-CCP antibodies [25]. Gottenberg et al. studied a cohort of 134 patients with PSS and found that 7.5% were positive for anti-CCP antibodies [26]. These results indicate that including other inflammatory diseases in the differential diagnosis is recommended in patients positive for anti-CCP antibodies.

There are several limitations of our study. A major limitation is the retrospective manner of our study. Furthermore, since we used the 2010 ACR/EULAR classification criteria, which include the presence of RF or anti-CCP antibodies, this may lead to falsely high sensitivity and specificity. Therefore, further prospective studies, which use both the present classification and older classification criteria, will be useful to make more accurate interpretation.

Conclusions

Anti-CCP antibodies were found to be more sensitive than RF in RA patients. Our study also suggests that the combination of testing for both RF and anti-CCP antibodies may be more effective in detecting RA. Although rheumatoid arthritis is seen frequently in patients with anti-CCP antibodies, other inflammatory diseases are recommended in the differential diagnosis.

References

1. Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. Cell; 1996; 85: 307-310.
2. Bukhari M, Harrison B, Lunt M, Scott DGI, Symmons DPM, Silman AJ. Time to first occurrence of erosions in inflammatory polyarthritis: results from a prospective community-based study. Arthritis Rheum, 2001; 44: 1248-1253.
3. Kashyap B, Tiwari U, Garg A, Kaur IR. Diagnostic utility of anti-CCP antibodies and rheumatoid factor as inflammatory biomarkers in comparison with C-reactive protein and TNF-α in rheumatoid arthritis. Trop jrnal Medi Res. 2015; 18: 5-9.
4. Agilli M, Ekinci S, Aydin FN, Sener I, Parlak A, Yaman H. Anti-cyclic Citrullinated Peptide Antibody (Anti-CCP) and Diagnostic Value for Rheumatoid Arthritis. TAF Prev Med Bull. 2014; 13: 83-88.
5. Zendman AJW, Venrooij WJ, Pruijn GJM. Use and significance of anti-CCP autoantibodies in rheumatoid arthritis, Rheumatology. 2006; 45: 20-25.
6. Schellekens GA, Visser H, De Jong BAW, Hoogen FHJ, Hazes JMW, Breedveld FC, Venrooij WJ. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000; 43: 155-163.
7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Ann Rheum Dis, 2010; 69: 1580-1588.
8. Smolen JS. Autoantibodies in rheumatoid arthritis. In: van Venrooij WJ, Maini RN, editors. Manual of biological markers of disease. Dordrecht (The Netherlands): Kluwer Academic Publishers, 1996; 1: 1-18.
9. Visser H, Gelinck LBS, Kampfraath AH, Breedveld C, Hazes JMW. Diagnostic and prognostic characteristics of the enzyme linked immunosorbent rheumatoid factor assay in rheumatoid arthritis. Ann Rheum Dis. 1996; 55: 157-161.
10. Jansen AL, Bruinsma I, Schaardenburg D, Stadt RJ, Koning MH, Dijkmans BA. Rheumatoid factor and antibodies to cyclic citrullinated peptide differentiate

rheumatoid arthritis from undifferentiated polyarthritis in patients with early arthritis. J Rheumatol. 2002; 29: 2074-2076.

11. Saraux A, Berthelot JM, Devauchelle V, Bendaoud B, Chales G, Henaff CL, Thorel JB, Hoang S, Jousse S, Baron D. Value of antibodies to citrulline-containing peptides for diagnosing early rheumatoid arthritis. J Rheumatol. 2003; 30: 2535-2539.
12. Soderlin MK, Kastbom A, Kautiainen H, Leirisalo-Repo M, Strandberg G, Skogh T. Antibodies against cyclic citrullinated peptide (CCP) and levels of cartilage oligomeric matrix protein (COMP) in very early arthritis: relation to diagnosis and disease activity. Scand J Rheumatol. 2004; 33: 185-188.
13. Van Boekel MAM, Vossenaar ER, Hoogen FHJ, Venrooij WJ. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res. 2002; 4: 87-93.
14. Schellekens GA, Jong BA, Hoogen FH, Putte LB, Venrooij W. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis specific autoantibodies. J Clin Invest. 1998; 101: 273-281.
15. Van Gaalen FA, Linn-Rasker SP, Venrooij WJ, Jong BA, Breedveld FJ, Verweij CL, Toes REM, Huizinga TWJ. Autoantibodies to Cyclic Citrullina Peptides Predict Progression to Rheumatoid Arthritis in Patients With Undifferentiated Arthritis A Prospective Cohort Study. Arthritis Rheum. 2004; 50: 709-715.
16. Niewold TB, Harrison MJ, Paget SA. Anti-CCP antibody testing as a diagnostic and prognostic tool in rheumatoid arthritis. Q J Med. 2007; 100: 193-201.
17. Taylor P, Gartemann J, Hsieh J, Creeden J. A systematic review of serum biomarkers anti-cyclic citrullinated peptide and rheumatoid factors tests for rheumatoid arthritis. Autoimmun Dis. 2011.
18. Van Leeuwen MA, Rijswijk MH. Acute phase proteins in the monitoring of inflammatory disorders. Baillieres Clin Rheumatol. 1994; 8: 531-552.
19. Rhodes B, Merriman ME, Harrison A, Nissen MJ, Smith M, Stamp L, Steer S, Merriman TR, Vyse TJ. A genetic association study of serum acute-phase C-reactive protein levels in rheumatoid arthritis: implications for clinical interpretation. PLoS Med, 2010; 7: e1000341.
20. Pinheiro GC, Scheinberg MA, Aparecida DS, Maciel S. Anti-cyclic citrullinated peptide antibodies in advanced rheumatoid arthritis. Ann Intern Med. 2003; 139: 234-235.
21. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis. 2004; 63: 1085-1089.
22. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis, 2004; 63: 1090-1095.
23. Cruyssen B, Hoffman IE, Zmierczak H, Berghe M, Kruithof E, De Rycke L. Anti-citrullinated peptide antibodies may occur in patients with psoriatic arthritis. Ann Rheum Dis, 2005; 64: 1145-1149.
24. Mediwake R, Isenberg DA, Schellekens GA, Venrooij WJ. Use of anti-citrullinated peptide and anti-RA33 antibodies in distinguishing erosive arthritis in patients with systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis. 2001; 60: 67-68.
25. Atzenil F, Sarzi-Puttini P, Lama N, Bonacci E, Bobbio-Pallavicini F, Montecucco C, Caporali R. Anti-cyclic citrullinated peptide antibodies in primary Sjogren syndrome may be associated with non-erosive synovitis. Arthritis Research & Therapy. 2008; 10: 51.
26. Gottenberg JE, Mignot S, Nicaise-Rolland P, Cohen-Solal J, Aucouturier F, Goetz J, Labarre J, Meyer O, Sibillia J, Mariette X. Prevalence of anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with primary Sjogren's syndrome. Ann Rheum Dis. 2005, 64: 114-117.

*Correspondence to:

Yüksel Maraş

Department of Rheumatology

Ankara Ataturk Educational and Research Hospital

Universities Quarter

Turkey