Platelet indices and neutrophil to lymphocyte ratio in adults with acute appendicitis

I D Kostakis, N Machairas, C Damaskos, C Doula, P Tsaparas, P Charalampoudis, E Spartalis, G C Sotiropoulos, G Kouraklis

Second Department of Propedeutic Surgery, Laiko General Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece

Corresponding author: *Ioannis D Kostakis (i.d.kostakis@gmail.com)*

Background: A study was performed in adults with acute appendicitis and matched controls to assess the utility of the platelet indices and neutrophil to lymphocyte ratio, as a diagnostic adjunct
Methods: Data were retrospectively collected from a complete blood count test of 155 adult patients (72 men and 83 women) with histologically proven acute appendicitis upon admission, and of 50 healthy adults (20 men and 30 women). The parameters for white blood cells and platelets were compared between the two groups, and for each gender separately.
Results: A higher white blood cell count, neutrophil count, neutrophil percentage, neutrophil to lymphocyte ratio and lower lymphocyte percentage was reported in patients with acute appendicitis than that in the healthy controls, with high areas under the curve (AUC), sensitivities, specificities, positive predictive values (PPVs) and moderate negative predictive values (NPVs). The lymphocyte count was lower in patients than it was in the healthy controls. The platletcrit was lower in the female patients than that in the female controls, whereas a difference was not detected in the male participants. Differences were not detected with regard to platelet count, mean platelet volume and platelet distribution width for both genders.
Conclusion: The neutrophil to lymphocyte ratio increases and lymphocyte percentage decreases in acute appendicitis, and can be used as an additional diagnostic marker. Plateletcrit, and therefore total platelet mass, is reduced in women with acute appendicitis, indicating the involvement of platelets in its pathophysiology. However, it is neither a reliable predictor or excluder of the disease.

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Acute appendicitis is an inflammatory disease, constituting a common cause of acute abdominal pain,[1–4] and with an estimated lifetime risk of 8%.[2] However, diagnosis is often difficult because many other clinical entities also cause right lower quadrant pain, and acute appendicitis can present with atypical symptoms and signs.[2] Blood tests (leukocytosis, neutrophilia and increased C-reactive protein) and imaging studies (abdominal ultrasound and/or computed tomography) are adjuncts used to establish the diagnosis.[1,3,4]

It is known that the neutrophil to lymphocyte ratio is increased in many inflammatory diseases. Thus, it is a marker of inflammatory response.[5–9] It has also been found that platelets are involved in inflammatory processes.[10-16] Their involvement in various inflammatory diseases has been emphasised in several studies.[10,11,17,18] However, the role of the aforementioned parameters in acute appendicitis has only been investigated in a few studies. The aim of the study was to examine the probable changes of the neutrophil to lymphocyte ratio and platelet indices in adults with acute appendicitis.

Method

Patients

One hundred and fifty-five patients (72 men and 83 women, with a mean age of 31 years, a median age of 27 years, and an age range of 15−77 years) with histologically proven acute appendicitis who had undergone appendectomy in our department from August 2008 until November 2013 were included in the study. Data were retrospectively collected on white blood cell count, neutrophil count, neutrophil percentage, lymphocyte count, lymphocyte percentage, neutrophil to lymphocyte ratio, platelet count, mean platelet volume, platelet distribution width and plateletcrit from the complete blood count test performed on patients upon their admission to the emergency department of the hospital. The same data were collected from a complete blood count test of 50 healthy volunteers (20 men and 30 women, with a mean age of 34 years, median age of 34 years, and an age range of 18−58 years), who were used as controls. The study

conformed to the World Medical Association's Declaration of Helsinki.

Complete blood count measurement

Three millilitres of blood were collected in EDTA Vacutainer® tubes with lavender stoppers, and the specimens processed within 20 minutes of the blood having been drawn, using the Sysmex® XT-4000i automated haematology analyser (Sysmex, Kobe, Japan).

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of the data distribution. The t-test and Mann-Whitney U test was used for the two group comparisons when the values were, and were not, normally distributed, respectively. The receiver operating characteristic (ROC) curve was used to assess the optimal cut-off points of the parameters for which significant differences were found. Sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated for these parameters, taking these cut-off points into account. The tests were two-tailed. The results were considered to be statistically significant if $p = \leq 0.050$.

Results

A comparison of the patients and the healthy controls

There were no significant differences between patients and healthy controls concerning age ($p = 0.199$) or gender ($p = 0.425$). Higher values pertaining to white blood cell count ($p = \leq 0.000$), neutrophil count (p = ≤ 0.000), neutrophil percentage ($p = \leq 0.000$) and neutrophil to lymphocyte ratio ($p = \leq 0.000$) were reported in patients with acute appendicitis, when compared to the values reported for the healthy controls. Moreover, a lower lymphocyte count ($p = \leq 0.000$), lymphocyte percentage ($p = \leq 0.000$) and plateletcrit ($p = 0.003$) was noted in patients with acute appendicitis, when compared with that in the healthy controls, whereas no significant differences concerning platelet count ($p = 0.056$), mean platelet volume ($p = 0.058$) and platelet distribution width ($p = 0.558$) were found. The mean values, median values, standard deviations (SDs) and ranges for each parameter of each group are shown in Table 1.

The ROC curve analysis provided the following optimal cut-off points with which to distinguish between cases of acute appendicitis and those of healthy controls:

- White blood cell count: ≥ 9 000/µl [AUC: 0.96, 95% confidence interval (CI): 0.94–0.99, SE: 0.01, $p = \leq 0.000$, sensitivity: 91% (141/155), specificity: 92% (46/50), PPV: 97% (141/145), NPV: 77% (46/60), accuracy: 91% (187/205)].
- Neutrophil count: ≥ 5 500/µl [AUC: 0.97, 95% CI: 0.95–0.99, SE: 0.01, $p = \leq 0.000$, sensitivity: 92% (142/155), specificity: 92% (46/50), PPV: 97% (142/146), NPV: 78% (46/59), accuracy: 92% (188/205)].
- Neutrophil percentage: ≥ 70% [AUC: 0.94, 95% CI: 0.91–0.97, SE: 0.02, $p = \leq 0.000$, sensitivity: 87% (135/155), specificity: 88% (44/50), PPV: 96% (135/141), NPV: 69% (44/64), accuracy: 87% (179/205)].
- Lymphocyte count: < 2 000/µl [AUC: 0.71, 95% CI: 0.64–0.77, SE: 0.04, $p = \leq 0.000$, sensitivity: 71% (110/155), specificity: 64% (32/50), PPV: 86% (110/128), NPV: 42% (32/77), accuracy: 69% (142/205)].
- Lymphocyte percentage: ≤ 24% [AUC: 0.94, 95% CI: 0.92–0.97, SE: 0.02, $p = \leq 0.000$, sensitivity: 90% (140/155), specificity: 86% (43/50), PPV: 95% (140/147), NPV: 74% (43/58), accuracy: 89% (183/205)].
- Neutrophil to lymphocyte ratio: ≥ 3 [AUC: 0.94, 95% CI: 0.92–0.97, SE: 0.02, p = ≤ 0.000, sensitivity: 90% (139/155), specificity: 88% (44/50), PPV: 96% (139/145), NPV: 73% (44/60), accuracy: 89% (183/205)].
- Plateletcrit: ≤ 0.25 [AUC: 0.64, 95% CI: 0.55–0.72, SE: 0.04, $p = 0.003$, sensitivity: 62% (96/155), specificity: 56% (28/50), PPV: 81% (96/118), NPV: 32% (28/87), accuracy: 61% (124/205)].

A comparison of the male patients and the healthy male controls

There was an increased white blood cell count ($p = \leq 0.000$), neutrophil count ($p \leq 0.000$), neutrophil percentage ($p = \leq 0.000$) and neutrophil to lymphocyte ratio ($p = \leq 0.000$), in male patients with acute appendicitis, when compared with that in the healthy male controls. Furthermore, there was a decreased lymphocyte count ($p = 0.014$) and lymphocyte percentage ($p = \leq 0.000$) in the male patients with acute appendicitis, when compared with that in the healthy male controls, whereas no significant differences were detected regarding platelet count ($p = 0.576$), mean platelet volume ($p = 0.306$), platelet distribution width ($p = 0.160$) and plateletcrit ($p = 0.290$). The mean values, median values, SDs and ranges for each parameter of each group are shown in Table 1.

The ROC curve analysis provided the following optimal cut-off points with which to distinguish between cases of acute appendicitis and those of healthy controls:

- White blood cell count: ≥ 9 000/µl [AUC: 0.98, 95% CI: 0.96–1.00, SE: 0.01, $p = \leq 0.000$, sensitivity: 94% (68/72), specificity: 95% (19/20), PPV: 99% (68/69), NPV: 83% (19/23), accuracy: 95% (87/92)].
- Neutrophil count: ≥ 5 600/µl [AUC: 0.98, 95% CI: 0.96–1.00, SE: 0.01, $p = \leq 0.000$, sensitivity: 97% (70/72), specificity: 100% (20/20), PPV: 100% (70/70), NPV: 91% (20/22), accuracy: 98% (90/92)].
- Neutrophil percentage: ≥ 73% [AUC: 0.96, 95% CI: 0.93-1.00, SE: 0.01, $p = \leq 0.000$, sensitivity: 90% (65/72), specificity: 100% (20/20), PPV: 100% (65/65), NPV: 74% (20/27), accuracy: 92% (85/92)].
- Lymphocyte count: ≥ 1 900/µl [AUC: 0.68, 95% CI: 0.56–0.80, SE: 0.06, $p = 0.014$, sensitivity: 69% (50/72), specificity: 60% (12/20), PPV: 86% (50/58), NPV: 35% (12/34), accuracy: 67% (62/92)].
- Lymphocyte percentage: ≤ 21% [AUC: 0.97, 95% CI: 0.94–1.00, SE: 0.02, $p = \leq 0.000$, sensitivity: 92% (66/72), specificity: 90% (18/20), PPV: 97% (66/68),

Table 1: The blood test results of the healthy controls and patients with acute appendicitis

Blood test parameter	Healthy controls			Patients with acute appendicitis		
	All controls	Men	Women	All patients	Men	Women
White blood cell count (cells/µl)						
Mean ± SD	6 855 ± 1 438	6 733 ± 1 089	6 936 ± 1 625	14 186 ± 4 034	14 878 ± 3 750	13 586 ± 4 172
Median (minimum to maximum)	6 955 (3 750–10 070)	6 740 (4 210–9 010)	7 020 (3 750–10 070)	14 230 (5 160–25 800)	14 870 (5 200–24 380)	13 370 (5 160–25 800)
Neutrophil count (cells/µl)						
Mean ± SD	3 920 ± 1 167	3 935 ± 989	3 910 ± 1 272	11 466 ± 3 974	12 045 ± 3 498	10 964 ± 4 282
Median (minimum to maximum)	3 650 (1 800–7 400)	3 600 (2 100–5 600)	3 900 (1 800–7 400)	11 800 (2 700–22 300)	12 300 (2 700–22 300)	10 800 (3 200–22 200)
Neutrophil percentage (%)						
Mean ± SD	56.7 ± 8.8	58.3 ± 9.7	55.6 ± 7.9	79.4 ± 9.9	80.3 ± 8	78.6 ± 11.2
Median (minimum to maximum)	55.3 (38.3–73.7)	59 (38.3–72.7)	54.9 (42.4–73.7)	81.8 (48.1–94.7)	81.6 (48.1–93.7)	81.8 (48.6–94.7)
Lymphocyte count (cells/µl)						
Mean ± SD	224 ± 626	2 148 ± 718	2 304 ± 561	1 753 ± 815	1 700 ± 768	1 799 ± 856
Median (minimum to maximum)	2 135 (1 290–4 180)	1 995 (1 310–4 180)	2 210 (1 290–3 370)	1 640 (320–4 550)	1 655 (320–4 280)	1 600 (530–4 550)
Lymphocyte percentage (%)						
Mean ± SD	33.2 ± 7.5	32.1 ± 8.8	33.9 ± 6.6	13.5 ± 8.3	11.9 ± 6	14.9 ± 9.6
Median (minimum to maximum)	34.2 (18.4–49.4)	31.7 (18.4–49.4)	34.3 (19.4–44.5)	11.5 (1.7–43.3)	10.9 (2.7–37.8)	11.9 (1.7–43.3)
Neutrophil to lymphocyte ratio						
Mean ± SD	1.9 ± 0.8	2.1 ± 0.9	1.8 ± 0.7	8.4 ± 5.6	8.8 ± 5.6	8 ± 5.6
Median (minimum to maximum)	1.6 (0.8–4.0)	1.9 (0.8–4.0)	1.6 (0.9–3.8)	7.2 (1.1–34.7)	7.4 (1.3–34.7)	6.8 (1.1–24.8)
Platelet count (cells/µl)						
Mean ± SD	254 480 ± 58 574	232 200 ± 42 439	269 333 ± 62 976	237 794 ± 63 103	229 430 ± 59 553	245 048 ± 65 165
Median (minimum to maximum)	240 000 (174 000–446 000)	224 000 (174 000–318 000)	246 000 (177 000–446 000)	227 000 (120 000–491 000)	218 500 (120 000–398 000)	230 000 (144 000–491 000)
Mean platelet volume (fl)						
Mean ± SD	10.5 ± 0.9	10.4 ± 1.1	10.5 ± 0.7	10.1 ± 1.2	10.1 ± 1.2	10.2 ± 1.1
Median (minimum to maximum)	10.5 (8.3–12.0)	10.7 (8.3–12.0)	10.4 (9.2-11.9)	10.1 (6.5–14)	10.1 (7.2–14)	10.1 (6.5–13.6)
Platelet distribution width (%)						
Mean ± SD	13.4 ± 1.9	14 ± 1.9	13 ± 1.8	13.4 ± 2.6	13.5 ± 2.8	13.2 ± 2.4
Median (minimum to maximum)	13.2 (10.1–16.8)	14.4 (10.5–16.8)	12.7 (10.1-16.5)	12.8 (9.2–25.1)	12.9 (9.8–25.1)	12.5 (9.2–21.1)
Plateletcrit (%)						
Mean ± SD	0.3 ± 0.1	0.2 ± 0.0	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Median (minimum to maximum)	0.3 (0.2–0.5)	0.2 (0.2-0.3)	0.3 (0.2-0.5)	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.5)

SD: standard deviation

NPV: 75% (18/24), accuracy: 91% (84/92).

- Neutrophil to lymphocyte ratio: ≥ 3.5 [AUC: 0.97, 95% CI: 0.94−1.00, SE: 0.02, p = ≤ 0.000, sensitivity: 90% (65/72), specificity: 90% (18/20), PPV: 97% (65/67), NPV: 72% (18/25), accuracy: 90% (83/92).
- Plateletcrit: ≤ 0.23 [AUC: 0.58, 95% CI: 0.44−0.71, SE: 0.07, p = 0.291, sensitivity: 53% (38/72), specificity: 60% (12/20), PPV: 83% (38/46), NPV: 26% (12/46), accuracy: 54% (50/92)].

A comparison of the female patients and the healthy female controls

There was an increased white blood cell count (p = ≤ 0.000), neutrophil count (p = ≤ 0.000), neutrophil percentage (p = ≤ 0.000) and neutrophil to lymphocyte ratio (p = ≤ 0.000) in the female patients with acute appendicitis, when compared with that in the healthy female controls. Moreover, there was a decreased lymphocyte count (p = 0.000), lymphocyte percentage (p = < 0.000) and plateletcrit (p = 0.004) in the female patients with acute appendicitis, when compared with that in the healthy female controls, whereas no significant differences concerning platelet count (p = 0.058), mean platelet volume (p = 0.054) and platelet distribution width (p = 0.938) were detected. The mean values, median values, SDs and ranges for each parameter of each group are shown in Table 1.

The ROC curve analysis provided the following optimal cut-off points with which to distinguish between cases of acute appendicitis and those of healthy controls:

- White blood cell count: ≥ 9 100/µl [AUC: 0.94, 95% CI: 0.90−0.98, SE: 0.02, p = ≤ 0.000, sensitivity: 87% (72/83), specificity: 93% (28/30), PPV: 97% (72/74), NPV: 72% (28/39), accuracy: 89% (100/113)].
- Neutrophil count: ≥ 5 200/µl [AUC: 0.95, 95% CI: 0.92−0.99, SE: 0.02, p = ≤ 0.000, sensitivity: 88% (73/83), specificity: 90% (27/30), PPV: 96% (73/76), NPV: 73% (27/37), accuracy: 89% (100/113)].
- Neutrophil percentage: ≥ 67% [AUC: 0.93, 95% CI: 0.88−0.98, SE: 0.02, p = < 0.000, sensitivity: 86% (71/83), specificity: 93% (28/30), PPV: 97% (71/73), NPV: 70% (28/40), accuracy: 88% (99/113)].
- Lymphocyte count: ≤ 2 000/µl [AUC: 0.72, 95% CI: 0.63−0.82, SE: 0.05, p = 0.000, sensitivity: 66% (55/83), specificity: 73% (22/30), PPV: 87% (55/63), NPV: 44% (22/50), accuracy: 68% (77/113)].
- Lymphocyte percentage: ≤ 26% [AUC: 0.92, 95% CI: 0.88−0.98, SE: 0.02, p = < 0.000, sensitivity: 88% (73/83), specificity: 87% (26/30), PPV: 95% (73/77), NPV: 72% (26/36), accuracy: 88% (99/113)].
- Neutrophil to lymphocyte ratio: ≥ 2.5 [AUC: 0.93, 95% CI: 0.88−0.98, SE: 0.02, p = < 0.000, sensitivity: 88% (73/83), specificity: 87% (26/30), PPV: 95% (73/77), NPV: 72% (26/36), accuracy: 88% (99/113)].
- Plateletcrit: ≤ 0.27 [AUC: 0.68, 95% CI: 0.57−0.78, SE: 0.06, p = 0.004, sensitivity: 69% (57/83), specificity: 53% (16/30), PPV: 80% (57/71), NPV: 38% (16/42), accuracy: 65% (73/113)].

Discussion

There is increasing evidence in the literature that platelets are involved in inflammatory and immunological processes.[10−16] In particular, platelets interact with endothelial cells, and all categories of leukocytes, through numerous mechanisms, such as adhesive interactions via *P*-selectin, which result in leukocyte activation and recruitment, the production of inflammatory cytokines, such as interleukin-1β and chemokines, and the expression of various immunological modulators, such as toll-like receptors and the CD40 ligand.[10−16] Platelets also interact with the complement system[12] and microorganisms.[10,13] Furthermore, platelets have been implicated in the pathophysiological processes of various disorders in which inflammation plays a major role, such as atherosclerosis, sepsis, infectious disease, autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis), neurological disorders (multiple sclerosis) and transfusion-related acute lung injury.[10,11,17,18]

Changes in platelet indices have been detected in various disorders in which inflammatory processes are implicated. First of all, reactive thrombocytosis is found in chronic inflammatory and infectious diseases, such as connective tissue disorders, inflammatory bowel disease, temporal arteritis, chronic pneumonitis and tuberculosis.[19] Mean platelet volume is a marker of platelet activation, because larger platelets have more and larger pseudopodia, making them more reactive than smaller ones, resulting in an enhanced production rate.[20−23] It increases in metabolic syndrome, myocardial infarction, peripheral artery disease, ischaemic stroke, obstructive sleep apnoea, rheumatoid arthritis, ankylosing spondylitis, psoriasis, infective endocarditis, celiac disease and pre-eclampsia. On the other hand, it decreases in inflammatory bowel disease, familial Mediterranean fever and chronic obstructive pulmonary disease.[23−26] Platelet distribution width is the width of the size distribution curve of the platelets in flat the 20% level when assuming that the peak distribution curve is 80−100%.[23,24] It is higher during platelet activation and represents the variability of platelet size, probably owing to the higher production of larger platelets.[20,22,23] It is increased in many diseases, such as myocardial infarction,[22] obstructive sleep apnoea,[25] pulmonary tuberculosis[27] and pre-eclampsia,[23] whereas it is reduced in various disorders, such as inflammatory bowel disease.[26] Finally, plateletcrit reflects the total platelet mass because it indicates the volume percentage of platelets in the whole blood [pateletcrit (%) = (mean platelet volume (fl) x platelet count (cells/µl)/107].[22,26] It is higher in various diseases, such as pulmonary tuberculosis,[27] autoimmune gastritis[21] and pre-eclampsia,[23] whereas it is lower in some disorders, such as inflammatory bowel disease.[26]

There are only a few studies on platelet indices in acute appendicitis. Albayrak et al. found that mean platelet volume decreased in adult patients with acute appendicitis, in comparison with that in healthy controls,[28] whereas Yang et al. detected this reduction only in adult male patients with acute appendicitis.[29] By contrast, Narci et al. reported that

mean platelet volume increased in adult patients with acute appendicitis, when compared with that in healthy controls.[30] Furthermore, Bilici et al. found that children with acute appendicitis had a lower platelet count and mean platelet volume than healthy children,[31] whereas no significant difference regarding mean platelet volume was detected by Uyanik et al. between children with acute appendicitis and healthy children.[32]

Systemic inflammatory response also causes neutrophilia and lymphocytopenia, thus resulting in an increase in the neutrophil to lymphocyte ratio, a marker of inflammation in many diseases.[5–9,33] Critically ill patients with severe sepsis have a higher neutrophil to lymphocyte ratio, which relates to a worse prognosis.[9] An increased neutrophil to lymphocyte ratio has also been reported in children with cystic fibrosis and with poor clinical status.[7] Moreover, high values of this ratio have been found in many malignant diseases, such as breast, lung, gastric, colorectal and pancreatic cancer, and have been associated with a poor prognosis and more aggressive and/or more advanced disease.[6,8] Higher values of this ratio relate to increased morbidity and mortality, and worse outcomes in patients with acute and chronic coronary artery syndromes.[5,33]

Only a few studies have been conducted on the neutrophil to lymphocyte ratio in patients with acute appendicitis. It has been reported in some studies that there is an increased neutrophil to lymphocyte ratio in cases with histologically confirmed acute appendicitis, when compared with that in cases without it,[34–37] and that this ratio is even higher in complicated acute appendicitis, than in uncomplicated appendicitis.[37-39] Guraya et al. also found that one in two patients with acute appendicitis had lymphopenia.[40] Fergusson et al. and Nordback and Harju reported that the lymphocyte count and percentage were lower in cases with histologically confirmed acute appendicitis, than that in cases with a normal appendix and clinical image mimicking acute appendicitis[41,42] Furthermore, Goulart et al. and Jahangiri and Wyllie reported a decreased lymphocyte count in patients with complicated acute appendicitis, compared to that in patients with uncomplicated appendicitis.[43,44]

Interesting findings were reported in our study. Plateletcrit was the only platelet index found to be altered in acute appendicitis. Significant differences were not detected between the patients and healthy controls concerning the platelet count, mean platelet volume and platelet distribution width. In particular, a lower plateletcrit was reported in adult patients with acute appendicitis, when compared with that in healthy adults. However, this difference only applied to female patients and not to male ones, when gender was taken into account. This finding leads to the conclusion that plateletcrit, and therefore total platelet mass, is reduced only in female adult patients with acute appendicitis, and not in male ones. However, plateletcrit was associated with a moderate AUC and intermediate to insufficient sensitivity, specificity and NPV. Only PPV was satisfactory, with values just above 80%. On the other hand, the neutrophil to lymphocyte ratio (reported to be higher in cases of acute appendicitis), lymphocyte percentage (reported to be lower in acute appendicitis), and white blood cell count, neutrophil count and neutrophil percentage (widely used markers of inflammation and used in the diagnosis of acute appendicitis),[1,3,4] were associated with a very good AUC, and high sensitivities, specificities and PPV. Only the NPV was moderate. However, the lymphocyte count, lower in patients with acute appendicitis, was associated with a moderate AUC and intermediate to insufficient sensitivity, specificity and NPV. Only the PPV was satisfactory, with values above 80%.

Conclusion

The neutrophil to lymphocyte ratio increases, and the lymphocyte percentage decreases, in acute appendicitis, and can be used as additional diagnostic markers which provide results equivalent to those of the usual inflammatory markers used. By contrast, plateletcrit, and therefore total platelet mass, is reduced in female adult patients with acute appendicitis, which while indicating the involvement of platelets in its pathophysiology, is not a sufficient diagnostic index of this disease.

Conflict of interest

The authors declare that there was no conflict of interest when writing this article.

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