Indian J Surg (February 2018) 80(1):61–67
DOI 10.1007/s12262-016-1558-y

ORIGINAL ARTICLE

Efficacy of the Evaluation of Inflammatory Markers for the Reduction of Negative Appendectomy Rates

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Received: 3 May 2016 / Accepted: 7 October 2016 / Published online: 18 October 2016

Abstract Unnecessary appendectomy can cause complications; ways of reducing negative appendectomy rates (NAR) using biochemical and imaging methods are desirable. We retrospectively examined 640 patients who underwent appendectomy for suspected AA. Patients with histologically confirmed appendicitis were designated the positive appendectomy group (n = 565), whereas those with unconfirmed appendicitis were designated the negative appendectomy group (n = 75). The positive appendectomy group was subdivided into the non-perforated (n = 511) and perforated (n = 54) appendectomy groups according to pathology reports. We compared the age, sex, lymphocyte count, neutrophil percentage, pathologic positivity or negativity for appendicitis, C-reactive protein (CRP) level, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) of the patients. When the perforated, non-perforated, and negative appendectomy groups were compared, the highest CRP level, NLR, and PLR were evident in the perforated appendectomy group (p = 0.001), whereas the lowest neutrophil percentage was found in the non-perforated appendectomy group (p = 0.001). Multiple logistic regression analysis identified neutrophil percentage, CRP value, and NLR as independent variables and demonstrated that AA could be diagnosed with 88.9 % accuracy using the cutoff values determined. In patients with suspected AA, particularly in rural areas with limited access to advanced imaging modalities, the evaluation of neutrophil percentage, CRP level, and NLR, in combination with the findings of a physical examination, may aid diagnosis and reduce NAR.

Keywords Acute appendicitis · Negative appendectomy rate · Neutrophil-to-lymphocyte ratio · C-reactive protein · Neutrophil percentage

Introduction

Acute appendicitis (AA) is among the most common diseases requiring emergency surgery [1]. Despite reductions in the mortality rate due to AA, negative appendectomy rates (NAR) remain high [2]. The primary causes of high NAR are as follows: many conditions cause pain in the right lower quadrant, an atypical presentation is evident in approximately 20–33 % of patients [3], and diagnostic parameters such as white blood cell (WBC) count and C-reactive protein (CRP) level are elevated in multiple inflammatory conditions [4]. Unnecessary appendectomy causes complications such as stump leakage at a similar rate to appendectomy performed for inflammation, intestinal obstructions secondary to adhesions, and incisional hernia. Unnecessary appendectomies also incur additional expense [5]. Therefore, numerous studies using various biochemical parameters, advanced imaging methods, and clinical scoring systems have attempted to reduce NAR [5, 6]. However, access to imaging modalities may be limited, particularly in rural areas; thus, easy, inexpensive tests that do not require advanced imaging techniques are in demand [7].

The examination of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which were recently

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introduced as systemic markers of inflammation [7, 8], may constitute an effective, easy, and inexpensive method of reducing NAR. Based on the understanding that systemic inflammation and the immune response play a key role in tumor progression, several studies are currently underway to test the utility of these parameters as prognostic markers for tumor progression [9, 10].

In this study, we evaluated whether biochemical parameters such as NLR, PLR, CRP level, and neutrophil percentage are beneficial for the reduction of NAR. These are easily determined, do not require expertise for their imaging or interpretation, do not increase the complication rates of the disease, and do not confer an additional financial burden on the patient or hospital, particularly in rural areas where access to advanced modalities is limited.

Patients and Methods

This retrospective study included 640 patients who presented to our clinic, were hospitalized with suspected appendicitis, and underwent appendectomy between January 2010 and January 2015. Patient data were obtained from electronic hospital records and patient files. Patients' preoperative diagnoses were established based on their clinical history, the findings of a physical examination, the results of conventional laboratory tests such as a hemogram and the measurement of CRP level, ultrasonography (USG) findings, and the results of advanced imaging modalities such as computed tomography (CT) in patients in whom a diagnosis could not be achieved using a USG. Laboratory outcomes were evaluated from blood samples collected from patients at admission. Patients whose surgically removed appendix tissues were confirmed to exhibit appendicitis were designated the positive appendectomy group (n = 565), and those with tissues confirmed to be normal appendix were designated the negative appendectomy group (n = 75). Patients in the positive appendectomy group were further subdivided into the non-perforated appendectomy group (n = 511) and the perforated appendectomy group (n = 54) according to their intraoperative findings and pathology reports. The age, sex, lymphocyte count, neutrophil percentage, pathologic positivity or negativity for appendicitis, CRP level, NLR, and PLR of the patients were compared.

Patients with incomplete data and those with a history of oncologic or hematologic malignancy or any infectious viral, bacterial, or parasitic disease were excluded from the study because of the potential effect of these conditions on hemogram values. Based on these criteria, three patients with upper respiratory tract infections and one patient who had leukemia in the preoperative period were excluded.

This study was approved by the local Scientific Research Ethics Committee.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows Version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc Version 9 (MedCalc Software bvba, Ostend, Belgium). The Shapiro–Wilk test was used to ascertain the normal distribution of the data, and the Levene test was used to determine the homogeneity of variance. The independent-sample t test was used to compare two independent groups, whereas the Mann–Whitney U test was used with exact results. One-way analysis of variance (robust test: Brown–Forsythe) and the Kruskal–Wallis H test were used to compare multiple groups, whereas the nonparametric post hoc test and the least significant difference test were used for post hoc analyses. Pearson's chi-squared test (exact) and Fisher's exact test (exact) were used to compare categorical data. Correlations between classifications, which were separated by the cutoff values calculated according to the variables in the patient groups, were expressed by an examination of sensitivity and specificity using receiver operating characteristic (ROC) curve analysis. Multivariate logistic regression analysis was used to define the cause–effect relationship between the categorical response variable and the explanatory variables in diotom and multinominal categories. Quantitative data were expressed as the mean ± standard deviation, median ± interquartile range, and median and range (maximum–minimum) in the tables. Categorical data were expressed as n (number) and percentages (%). Data were analyzed with a 95 % confidence interval, and the statistical significance was set at a p value of less than 0.05.

Theory

When the decision to operate is made in patients on whom advanced imaging modalities cannot be used, the evaluation of biologic parameters such as NLR, PLR, CRP level, and neutrophil percentage may be equally effective for preventing unnecessary appendectomy.

Results

In our analysis of 640 patients, we found that the mean age was 39.23 ± 18.02 years in the positive appendectomy group and 35.27 ± 14.8 years in the negative appendectomy group. In the subgroup analysis of the positive appendectomy group, we found that the mean age was 53.31 ± 17.44 years in the perforated appendectomy group and 37.74 ± 17.44 years in the non-perforated appendectomy group. There was a significant difference between the mean ages of the perforated appendectomy group and the other groups (p = 0.036). Of the

patients in the positive appendectomy group, 45.3 % were women; conversely, 54.7 % of the patients in the negative appendectomy group were women.

The mean WBC count was statistically significantly higher in the perforated appendectomy group than in the non-perforated appendectomy and negative appendectomy groups ($p = 0.001$). Of all the groups, the lowest mean lymphocyte percentage was observed in the perforated appendectomy group ($p < 0.001$), whereas the highest mean lymphocyte percentage was evident in the negative appendectomy group. The lowest mean platelet count was observed in the non-perforated appendectomy group, which was significantly different from the perforated appendectomy group ($p = 0.027$) alone. The mean neutrophil percentages were 81.9 ± 11.4, 83.5 ± 9.1, and 70.9 ± 10.5 in the perforated, non-perforated, and negative appendectomy groups, respectively. There was a significant difference between the negative appendectomy group, which exhibited the lowest mean neutrophil percentage, and the other two groups ($p = 0.001$). The mean CRP values were significantly higher in the perforated appendectomy group than in both the other groups ($p = 0.001$). In contrast, the mean CRP value in the non-perforated appendectomy group was significantly higher than in the negative appendectomy group ($p = 0.001$). Similarly, the highest mean NLR value was found in the perforated appendectomy group ($p = 0.001$). Again, there was a statistically significant difference between the non-perforated appendectomy and negative appendectomy groups in terms of NLR ($p = 0.001$). Among all three groups, the highest mean PLR was found in the perforated appendectomy group, whereas the lowest mean PLR was found in the negative appendectomy group. Although PLR in the perforated appendectomy group was significantly different from the other groups ($p = 0.001$), no statistically significant difference was evident between the non-perforated and negative appendectomy groups. The results of the comparisons among the three groups are shown in Table 1.

In the ROC analyses, cutoff values were calculated for WBC count (11,300 K/μL, $p < 0.001$), neutrophil percentage (74.9 %, $p < 0.001$), lymphocyte count (1760 K/μL, $p < 0.001$), lymphocyte percentage (16.2 %, $p < 0.001$), CRP level (51 mg/L, $p < 0.001$), NLR (4.64, $p < 0.001$), and PLR (126.44, $p < 0.001$). A WBC count above the cutoff value exhibited 65 % sensitivity and 60 % specificity for diagnosing AA [area under the ROC curve (AUC) = 0.663 ± 0.034]. A neutrophil percentage above the cutoff value demonstrated 74.7 % sensitivity and 80 % specificity for diagnosing AA (AUC = 0.755 ± 0.03). A lymphocyte count under the cutoff value showed 65.1 % sensitivity and 61.3 % specificity for diagnosing AA (AUC = 0.752 ± 0.03). A lymphocyte percentage under the cutoff value demonstrated 72.6 % sensitivity and 82.7 % specificity for diagnosing AA (AUC = 0.752 ± 0.03). CRP values above the cutoff value exhibited 37.5 % sensitivity and 86.7 % specificity for diagnosing AA (AUC = 0.621 ± 0.033). An NLR in excess of the cutoff value demonstrated 72.7 % sensitivity and 82.7 % specificity for diagnosing AA (AUC = 0.752 ± 0.03). A PLR greater than the optimal cutoff value showed 70.7 % sensitivity and 48 % specificity for diagnosing AA (AUC = 0.588 ± 0.037; Table 2).

The statistically significant results of the model created by multiple logistic regression analysis using neutrophil percentage, CRP level, and NLR as independent variables for the diagnosis of AA are given in Table 3. In this model ($p < 0{,}001$), the specified cutoff values of these three parameters were able to establish a diagnosis of AA with 88.9 % accuracy.

Discussion

A diagnosis of AA, one of the most common diseases necessitating emergency surgery, is generally established with the clinic-based, physical examination of patients. However, the efficacy of the clinic-based diagnostic method depends on the experience of the clinician, and NAR range from 15 to 30 % [11]. Like all surgical operations, negative appendectomy can also cause morbidity and mortality in addition to socioeconomic outcomes such as increased hospital costs, labor loss, and reduced efficiency [12].

The addition of advanced imaging methods such as CT and magnetic resonance imaging to clinical evaluations and laboratory tests increases the possibility of an accurate diagnosis of AA, thereby reducing NAR [13]. CT is often used in patients with suspected AA and is thought to decrease NAR by over 10 % [14]. However, additional diagnostic methods are necessary because access to advanced imaging modalities is not always possible, particularly in rural areas; moreover, the use of these modalities increases costs and is infeasible in patients in whom radiation exposure must be limited, such as pregnant women [7, 14]. Based on these assumptions, the objective of this study was to evaluate whether the use of biochemical parameters such as NLR, PLR, CRP level, and neutrophil percentage is beneficial in reducing NAR without introducing further complications.

In this retrospective study, which was conducted in a tertiary referral hospital, patients with a clinical history and results of a physical examination compatible with AA underwent an operation based on USG and CT findings. According to pathology reports, NAR was 11.7 %.

In our study, we observed a significant difference between the negative and positive appendectomy groups in terms of CRP values. Similar to previous studies, CRP values increased with the level of inflammation and were higher in the perforated appendectomy group than in the non-perforated appendectomy group. Furthermore, the sensitivity and specificity of CRP level in this study were similar to those identified in previous studies.

Table 1 Comparison of patients in terms of age, sex, C-reactive protein level, white blood cell count, lymphocyte count, neutrophil percentage, lymphocyte percentage, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio

	Positive appendectomy groups				All appendectomy groups		
	Non-perforated appendectomy group $n = 511$	Perforated appendectomy group $n = 54$	Negative appendectomy group $n = 75$	p Value	Negative appendectomy group $n = 75$	Positive appendectomy group $n = 565$	p Value
Age (years)[e]	37.74 ± 17.44	53.31 ± 17.44[a]	35.27 ± 14.8	0.036	35.27 ± 14.8	39.23 ± 18.02	0.037
Sex[d]							
Female	230 (45.2)	25 (46.3)	41 (54.7)	0.307	41 (54.7)	255 (45.3)	0.140
Male	279 (54.8)	29 (53.7)	34 (45.3)		34 (45.3)	308 (54.7)	
WBC (K/μL)[f]	12.6 ± 6.11	14.38 ± 4.81	10.89 ± 5.25[a,b]	<0.001	10.89 ± 5.25	12.76 ± 6.03	<0.001
Neutrophil percentage[f]	81.9 ± 11.4	83.5 ± 9.1	70.9 ± 10.5[a,b]	<0.001	70.9 ± 10.5	82 ± 11.4	<0.001
Lymphocyte count (K/μL)[f]	1.59 ± 1.08	1.03 ± 0.88[a]	1.88 ± 0.97[a,b]	<0.001	1.88 ± 0.97	1.47 ± 1.06	<0.001
Lymphocyte percentage[f]	11.1 ± 9.2	7.6 ± 9	20.3 ± 7.7[a,b]	<0.001	20.3 ± 7.7	11.1 ± 9.6	<0.001
Platelet (K/μL)[f]	250 ± 96[b]	268.5 ± 106	263 ± 96	0.027	263 ± 96	250 ± 94	0.339
CRP (mg/L)[f]	25.2 ± 51.6	68.5 ± 49[a]	17.6 ± 33.02[a,b]	<0.001	17.6 ± 33.02	27.9 ± 56.3	0.001
NLR[f]	7.32 ± 6.44	12.43 ± 11.93[a]	3.39 ± 1.73[a,b]	<0.001	3.39 ± 1.73	7.32 ± 7.05	<0.001
PLR[f]	163.09 ± 155.73	298.13 ± 202.19[a]	136.07 ± 144.36	<0.001	136.07 ± 144.36	172.86 ± 161.97	0.013

Independent sample t test; Mann–Whitney U test (exact); one-way analysis of variance (Brown–Forsythe). Post hoc tests: least significant difference test; Kruskal–Wallis H test (exact); nonparametric post hoc test; Fisher's exact test (exact); Pearson's chi-squared test (exact)

[a] Significant compared with the non-perforated appendectomy group

[b] Significant compared with the perforated appendectomy group

Significant compared with the negative appendectomy group

[d] n (%)

[e] Mean ± standard deviation

[f] Median ± interquartile range

Table 2 Sensitivity and specificity of white blood cell count, C-reactive protein level, lymphocyte count, neutrophil percentage, lymphocyte percentage, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio cutoff values to diagnose acute appendicitis

Cutoff	+ Appendectomy	− Appendectomy	AUC ± SE	*p* Value
WBC (K/μL)				
WBC >11.3	367 (92.4) (65)[a]	30 (7.6)[c] (40)	0.663 ± 0.034	<0.001
WBC ≤11.3	198 (81.5)[d] (35)	45 (18.5) (60)[b]		
Neutrophil percentage				
Neutrophil percentage >74.9	422 (96.6) (74.7)[a]	15 (3.4) (20)[c]	0.755 ± 0.03	<0.001
Neutrophil percentage ≤74.9	143 (70.4)[d] (25.3)	60 (29.6) (80)[b]		
Lymphocyte count (K/μL)				
Lymphocyte count ≤1.76	368 (92.7) (65.1)[a]	29 (7.3) (38.7)[c]	0.628 ± 0.033	<0.001
Lymphocyte count >1.76	197 (81.1)[d] (34.9)	46 (18.9) (61.3)[b]		
Lymphocyte percentage				
Lymphocyte percentage ≤16.2	410 (96.9) (72.6)[a]	13 (3.1) (17.3)[c]	0.752 ± 0.03	<0.001
Lymphocyte percentage >16.2	155 (71.4)[d] (27.4)	62 (28.6) (82.7)[b]		
CRP (mg/L)				
CRP >51	212 (95.5) (37.5)[a]	10 (4.5) (13.3)[c]	0.621 ± 0.033	<0.001
CRP ≤51	353 (84.4)[d] (62.5)	65 (15.6) (86.7)[b]		
NLR				
NLR >4.64	411 (96.9) (72.7)[a]	13 (3.1) (17.3)[c]	0.752 ± 0.03	<0.001
NLR ≤4.64	154 (71.3)[d] (27.3)	62 (28.7) (82.7)[b]		
PLR				
PLR >126.44	400 (91.1) (70.8)[a]	39 (8.9) (52)[c]	0.588 ± 0.037	0.018
PLR ≤126.44	165 (82.1)[d] (29.2)	36 (17.9) (48)[b]		

Receiver operating characteristic curve analysis (Hanley and McNeil method, Youden index *J*)

[a] Sensitivity

[b] Specificity

[c] False-positive ratio

[d] False-negative ratio

CRP is an acute-phase reactant that may reach measurable levels 6–12 h after the onset of inflammation. Although it is not a specific marker for AA, CRP level is a valuable parameter because it is generally elevated in the early period of inflammatory events related to pathologic conditions [12]. In addition, as reported by John et al. [12], if AA is considered based on the history and physical examination of a patient, the examination of CRP level can be used to achieve a diagnosis with high sensitivity and specificity (98 and 87 %, respectively). However, the sensitivity and specificity of CRP level have not been found to be so high in many studies. For example, in a meta-analysis on the utility of the examination of CRP level in the diagnosis of AA [15], its sensitivity (47–74 %) and specificity (55–89 %) were shown to differ widely. In another meta-analysis [16], the sensitivity of CRP level was reported to be 40–99 %, and its specificity was reported to be 27–90 %. Similar to the results of these meta-analyses, in our study, we determined the sensitivity of the CRP value to be 37.5 % and the specificity to be 86.7 % for the diagnosis of AA. However, CRP level has been demonstrated to increase with an increasing severity of inflammation and with complications such as perforation, gangrene, or plastron [17]. Consistent with the literature, in our study, the highest CRP levels were evident in the group with perforation.

Neutrophils are WBCs generally related to bacterial infection. Neutrophil count was demonstrated to be more valuable than WBC count both in the diagnosis of AA and in the evaluation of the degree of simple and complicated appendicitis

Table 3 Results of multiple logistic regression analysis of C-reactive protein level, neutrophil percentage, and neutrophil-to-lymphocyte ratio to determine independent predictors of acute appendicitis

Independent variables	*B* ± SE	*p* Value	Odds ratio (95 % CI)
Neutrophil percentage	1.035 ± 0.518	0.046	2.815 [1.02–7.77]
CRP (mg/L)	1.124 ± 0.375	0.003	3.076 [1.476–6.411]
NLR	1.852 ± 0.566	0.001	6.371 [2.101–19.32]
Constant	0.242 ± 0.374	0.518	1.274
		Predicted 88.9	*p* model <0.001

Multiple logistic regression analysis [backward stepwise method (Wald)]

[18]. In studies on the value of determining neutrophil count in the diagnosis of AA, the sensitivity of neutrophil count was reported to be 68.6–98.9 %, and its specificity was reported to be 33.1–91 % [19]. Similarly, in a retrospective study [20], increased neutrophil count was identified as a good parameter for the diagnosis of AA, with 70.96 % sensitivity and 65.52 % specificity. In this study, the sensitivity and specificity of neutrophil percentage in the diagnosis of AA were found to be similar to those reported in the literature. However, studies that investigated the correlation between the neutrophil percentage and the severity and complications of AA reported varying results. For example, Şahbaz et al. [20] stated that they did not observe a correlation between complicated appendicitis and neutrophil percentage, whereas other studies reported that values above 85 % correlated with complicated AA [21, 22]. In our study, neutrophil percentage increased as the disease became complicated, and the highest mean neutrophil percentage (83.5 %) was observed in the group with perforation.

The determination of NLR is a simple test that does not confer additional expense on the patient, does not require expertise to interpret, and can be easily ascertained using blood parameters involved in the complete blood count [23]. Goodman et al. [23] first proposed that the use of NLR is more informative than total leukocyte count in the diagnosis of AA. In subsequent years, studies have been conducted on the correlation between the NLR and the severity of AA, treatment planning, and complications. In a retrospective study by Shimizu et al. [24] involving 422 patients during a 13-year period, patients were examined in two groups based on whether they had gangrenous or catarrhal appendicitis, and it was determined that it is appropriate to treat patients with an NLR of <5 with medical therapy and those with an NLR of >5 with surgical treatment.

In a retrospective study by Kahramanca et al. [7] that evaluated 1067 patients, patients were divided into the appendicitis and negative appendicitis groups according to pathology results. The authors reported that an NLR cutoff value of 4.68 (sensitivity 65.3 %; specificity 54.7 %) was critical to establish a diagnosis of appendicitis. In the same study, in the subgroup analysis of the appendicitis group, a cutoff value of 5.74 (sensitivity 70.8 %; specificity 48.5 %) was found to be critical for complicated disease. Furthermore, Ishizuka et al. [25] demonstrated that an NLR above 8 was significant for gangrenous appendicitis. Similarly, in our study, the mean NLR increased as AA became complicated. The highest mean NLR was observed in the perforated appendectomy group.

Platelets are known to be associated with various cell types such as endothelial cells, dendritic cells, T lymphocytes, and neutrophils. Recent studies demonstrated a correlation between platelets and mild, moderate, and severe inflammation. In addition, PLR values are known to increase in various inflammatory conditions. Therefore, PLR also represents a marker of inflammation, a fact recently emphasized [26, 27]. In a study comparing 99 patients with the inflammatory disorder Bell's palsy [28] with a control group, the mean PLR among patients with the condition was found to be 137.5 ± 81.04, a statistically significant increase compared with the control group. In another recent study [29], NLR, PLR, mean platelet volume, and red cell distribution width values were evaluated in 153 patients treated for familial Mediterranean fever; PLR was found to be increased in patients with the condition compared with the control group. In a study by İlhan et al. [30] involving pregnant women with pancreatitis, PLR was not significantly different compared with the control group, although it tended to be low. However, because cases of pancreatitis during pregnancy are rare, the small number of patients examined makes interpretation of the low PLR value difficult. In our study, the sensitivity of PLR under the 126.44 K/μL cutoff value was high for the diagnosis of AA, but the specificity was low. In the subgroup analysis, PLR was increased with inflammation and was higher in the perforated appendectomy group (298.13 ± 202.19 K/μL). Multiple logistic regression analysis determined that the examination of PLR is not a significant screening test for the diagnosis of AA.

One limitation of this study was its retrospective design. However, the parameters used are accessible anywhere, suitable for use in multiple settings, and applicable to patients on whom some advanced imaging techniques cannot be used, such as pregnant women.

Although WBC and PLR were statistically significant alone for the diagnosis of AA, they were not significant in a multiple logistic regression analysis. In contrast, CRP level, neutrophil percentage, and NLR were significant alone for the diagnosis of AA, and their combined use predicted AA with an accuracy of 88.9 %. In this study, we were unable to reduce NAR using CRP level, neutrophil percentage, or NLR alone, but by using these three parameters in combination, we obtained diagnostic outcomes much closer to the NAR obtained using USG and CT.

In conclusion, we believe that the examination of CRP level, neutrophil percentage, and NLR in combination with the findings of a physical examination in patients with suspected AA may help to establish a diagnosis of AA, particularly in rural areas with limited access to advanced imaging modalities.

Author's Contribution Each author's contribution to the manuscript: conception and design: Fatih Mehmet Yazar and Murat Bakacak; data collection: Fatih Mehmet Yazar, Murat Bakacak, and Ömer Faruk Boran; writing the article: Fatih Mehmet Yazar and Aykut Urfalioğlu; and critical revision of the article: Ertan Bülbüloğlu.

Compliance with Ethical Standards This manuscript has not been published elsewhere and is not under consideration by another journal.

In this article, there was no conflict with ethical standards as no data of human beings were created and approval for this study was obtained from the institutional Medical Ethics Committee.

Conflict of Interest The authors declare that they have no conflicts of interest.

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