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Optimal peritoneal fluid white blood cell count for diagnosis of peritonitis in peritoneal dialysis patients

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Background: The diagnosis of peritonitis among peritoneal dialysis (PD) patients is based on clinical presentation, dialysis effluent white blood cell (WBC) count, and dialysis effluent culture. Peritoneal fluid WBC count is very important in the initial diagnosis of peritonitis. The purpose of this work was to determine the optimal number of peritoneal WBCs with different clinical presentations at admission to define PD-related peritonitis.

Methods: Medical records of chronic PD patients who underwent work-up for suspected peritonitis between 2008 and 2019 were reviewed retrospectively. Results of all peritoneal WBC count tests during this period were collected. Clinical manifestations and follow-up analysis of each peritoneal WBC count were performed.

Results: The peritoneal WBC count cutoff of 100/μL recommended by International Society for Peritoneal Dialysis provided specificity of only 35%. Increasing peritoneal WBC count cutoff to 150, 200, and 250/μL provided sensitivity around 98% and gradually increasing specificity. The chi-square automatic interaction detector model of statistical analysis determined that peritoneal WBC count below 230/μL combined with absence of inflammatory markers (fever, increased C-reactive protein) ruled out peritonitis with 99.8% sensitivity. Peritoneal fluid WBC count cutoff of 230/μL provided specificity of 89% and good positive and negative likelihood scores of 8.3 and 0.03, respectively. Peritoneal fluid polymorphonuclear count has lower discriminating ability for peritonitis compared to peritoneal fluid WBC count.

Conclusion: Increasing peritoneal fluid WBC count cutoff to 230/μL in suspected PD-related peritonitis could improve specificity without compromising the sensitivity of the test.

Keywords: Abdominal pain, Peritoneal dialysis, Peritonitis, White blood cells

Introduction

The prevalence of kidney failure requiring replacement therapy is increasing due to an aging population and increase in the incidence of diabetes and hypertension. The estimated number of patients needing renal replacement therapy by 2030 is to be between 4.9 and 9.7 million around the world [1]. Peritoneal dialysis (PD) is a commonly used treatment modality for kidney failure. PD-related peritonitis remains a major cause of technique failure as well as

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The results of the study presented in this paper have never been published previously in abstract format.

mortality in maintenance PD patients [2,3]. According to the International Society for Peritoneal Dialysis (ISPD), peritonitis in PD patients can be diagnosed when at least two of the following are present: 1) clinical features consistent with peritonitis, e.g., abdominal pain and/or cloudy dialysis effluent; 2) dialysis effluent WBC count of >100/μL or >0.1 × 10^9/L (after a dwell time of at least 2 hours), with >50% polymorphonuclear leukocytes (PMNs); and 3) positive dialysis effluent culture [4]. Dialysis effluent WBC count cutoff of 100/μL was determined in 3–4 decades-old studies [5–8]. No study focusing on PD-related peritonitis diagnosis was performed in the last decades. In everyday practice, the clinical picture of peritonitis at presentation can be unclear. The severity and character of the associated abdominal pain are not specific and cannot be differentiated from those of other causes. Differential diagnosis of abdominal pain and other gastrointestinal symptoms includes such common diseases as urinary tract infection, gastroenteritis, and cholecystitis. Pancreatitis can cause cloudy peritoneal fluid with increased neutrophil count. There is also a variety of conditions causing cloudy dialysate without peritonitis [9]. In addition, patients undergoing automated PD (APD), compared with chronic ambulatory PD (CAPD), commonly present with no history of cloudy fluid [8]. Peritoneal fluid WBC count is very important in the diagnosis of peritonitis since peritoneal microbial culture results are not available at patient presentation. From our clinical experience, the great majority of PD-related peritonitis cases presented with much higher peritoneal WBC count than recommended by ISPD [4]. Misdiagnosis of the true source of infection, especially when assessed by less experienced medical staff and emergency department personal can result in false diagnosis of peritonitis and lack of necessary investigation for alternative diagnoses. When mistakenly diagnosed with peritonitis, patients receive improper or unnecessary antibiotics, and further investigation, for example, imaging such as ultrasonography or computed tomography, for an alternative diagnosis is delayed.

The purpose of this work was to determine the optimal number of peritoneal fluid WBCs at different clinical presentations at admission to define PD-related peritonitis.

Methods

Medical records of patients on chronic PD who underwent work-up for suspected peritonitis between 2008 and 2019 were reviewed retrospectively. Results of all peritoneal WBC count tests at presentation during this period of time were collected. Clinical status of each peritoneal fluid sample was analyzed at presentation and further follow-up, including bacteriological culture, antibiotics treatment, and laboratory tests (WBC count and culture of peritoneal fluid). Demographic data, cause of kidney disease, and PD modality were gathered.

Primary renal disease diagnosis was determined and recorded by an unbiased nephrologist. Concise criteria of major etiologies include: diabetic kidney disease diagnosis was based on long standing diabetes mellitus with albuminuria progressing to proteinuria, and progressive decline of kidney function, without significant hematuria or abnormalities on imaging, and after ruling out other etiologies through serologic testing. In cases where kidney biopsy was performed, the diagnosis of diabetic nephropathy was based on the consensus Renal Pathology Society criteria [10]. Patients with symptomatic congestive heart failure and renal failure having urine protein of <0.5 g/24 hours, normal urine microscopy and normal kidneys per sonography were classified as having cardiorenal syndrome. Chronic glomerulonephritis diagnosis was based on course of disease, previous urine sediments, and serology testing, usually accompanied by a diagnostic biopsy. Hypertensive nephrosclerosis was diagnosed in patients with kidney dysfunction, proteinuria, small kidneys on imaging, and after ruling out other etiologies based on urine sediment and serology testing. In cases where kidney biopsy was performed, the diagnosis of hypertensive nephrosclerosis was based on clinicopathologic criteria which include clinical hypertension associated with the histopathologic findings of vascular wall medial thickening, intimal fibrosis, arteriolar hyalinosis, and glomerular ischemic changes of capillary wall wrinkling [11].

The laboratory parameters collected during peritonitis investigation were peritoneal WBC count, peritoneal PMN percentage, blood WBC count, blood PMN percentage, and serum C-reactive protein (CRP) level. Information concerning antibiotics treatment and peritonitis course was also collected.

The final diagnosis of peritonitis was made when peritoneal culture results were available, usually 2 to 3 days after the first presentation, when at least two of the following were present: 1) clinical features consistent with peritonitis, i.e., abdominal pain and/or cloudy dialysis effluent; 2) dialysis effluent WBC of >100/μL after a dwell time of at least 2 hours; and 3) positive dialysis effluent culture [4]. Clinical features leading to the peritoneal fluid WBC examination were 1) abdominal pain; 2) cloudy dialysate; 3) fever or increased serum CRP; 4) exit site infection; 5) difficulties with peritoneal catheter flow; 6) gastrointestinal symptoms other than abdominal pain, such as diarrhea, vomiting, or nausea; 7) other symptoms. "Other symptoms" included complaints of weakness, chest pain, general deterioration, dyspnea, confusion, unexplained weight loss, drowsiness, hypotension, and syncope.

An exit-site infection was defined by the presence of purulent drainage, with or without erythema of the skin around the catheter. Relapsing peritonitis was defined as an episode with the same organism that occurred within 4 weeks of completion of therapy for a prior episode or one sterile episode.

The initial empirical antibiotic treatment included intraperitoneal vancomycin or cefamezin (based on severity of clinical presentation and previous microbiological results if available) with ceftazidime. After the culture results were available, antibiotic treatment was changed accordingly.

Statistical analysis

Categorical variables were described as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and Q-Q plot. These results were reported as mean and standard deviation if they were normally distributed or as median and interquartile range (IQR) if they were skewed. A generalized estimating equation using a binary logistic model was used to study the association between each predictor and peritonitis. Continuous variables that were extremely skewed were natural logarithm transformed before regression. The area under the receiver operating characteristic (ROC) curve was used to evaluate the discrimination ability. A chi-square automatic interaction detector (CHAID) was applied to identify threshold values [12]. CHAID is a classification method for building decision trees using chi-square statistics to identify optimal splits [13]. The method first examines the cross-tabulations between each of the input fields and the outcome and tests for significance using a chi-square independence test. If more than one of these relations is statistically significant, CHAID will select the input field that is the most significant. If an input has more than two categories, these are compared, and categories that show no differences in outcome are combined by successively joining the pair of categories showing the smallest significant difference. This category-merging process stops when all remaining categories differ at the specified testing level. For nominal input fields, any categories can be merged; for an ordinal set, only contiguous categories can be merged [13]. The following variables were included in the CHAID analysis: age at first dialysis; sex; etiology of renal disease; underlying diabetes mellitus; dialysis mode; clinical presentation including abdominal pain, cloudy fluid, inflammatory marker, or fever; exit site infection; catheter occlusion or sterility disruption; other gastrointestinal symptoms; and other symptoms, PD WBC, PD PMN, blood WBC, blood PMN, and CRP.

Maximum tree depth was organized into three levels, with the minimum number of required cases in parent and child nodes set as 100 and 50, respectively.

All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analysis was performed with IBM SPSS version 24 (IBM Corp).

Table 1. Baseline parameters of peritoneal dialysis patients presenting with suspected peritonitis

Variable	Data
No. of patients	147
Age (yr)	65 (27–92)
Sex, female:male	35/112
Renal disease	
Cardiorenal	41 (27.9)
Diabetic nephropathy	41 (27.9)
Nephrosclerosis	11 (7.5)
Glomerulonephritis	35 (23.8)
Others	19 (12.9)
Prevalent diabetes mellitus	72 (49.0)
Peritoneal dialysis modality (APD)	63 (42.9)

Data are expressed as number only, value (range), or number (%).
APD, automated peritoneal dialysis.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Sheba Medical Center (No. 6479-19-SMC) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, informed consent is not required.

Results

Patient baseline characteristics

A total of 176 chronic PD patients were treated in our unit between 2008 and 2019. Of them, 29 were never investigat-

Table 2. Peritoneal culture results of peritonitis cases in peritoneal dialysis patients (n = 165)

Organism identified	No. of patients (%)
Coagulase-negative *Staphylococcus*	38 (23.0)
Staphylococcus aureus	26 (15.8)
Streptococcus sp.	13 (7.9)
Enterococcus	13 (7.9)
Escherichia coli	12 (7.3)
Pseudomonas sp.	10 (6.1)
Klebsiella sp.	8 (4.8)
Enterobacter	5 (3.0)
Diphtheroids	5 (3.0)
Listeria	3 (1.8)
Fungi	3 (1.8)
Mycobacterium	3 (1.8)
Others	7 (4.2)
Culture negative	18 (10.9)

Table 3. Probability of peritonitis in peritoneal dialysis patients according to clinical and laboratory parameters (n = 753)

Variable	Peritonitis		p-value
	No (n = 588)	Yes (n = 165)	
Age (yr)	65.6 ± 11.3	64.7 ± 12.1	0.63
Sex			0.81
Male	451 (78.4)	124 (21.6)	
Female	137 (77.0)	41 (23.0)	
Etiology of renal disease			0.34
Diabetic nephropathy	190 (78.5)	52 (21.5)	
Chronic glomerulonephritis	130 (77.8)	37 (22.2)	
Cardiorenal syndrome	126 (84.0)	24 (16.0)	
Nephrosclerosis	65 (73.0)	24 (27.0)	
Other	77 (73.3)	28 (26.7)	
Diabetes mellitus	299 (78.9)	80 (21.1)	0.56
Dialysis mode			0.30
CAPD	259 (80.4)	63 (19.6)	
APD	329 (76.3)	102 (23.7)	
Abdominal pain	93 (48.2)	100 (51.8)	<0.001
Cloudy fluid	26 (28.6)	65 (71.4)	<0.001
Fever/inflammation	126 (77.3)	37 (22.7)	0.59
Exit site infection	21 (91.3)	2 (8.7)	0.14
Catheter occlusion	22 (84.6)	4 (15.4)	0.57
Gastrointestinal symptoms	72 (72)	28 (28)	0.13
Other symptoms	341 (93.9)	22 (6.1)	<0.001
Peritoneal WBC (cells/μL)	138.7 ± 79.3	2,651.1 ± 3,285.5	<0.001
Peritoneal PMN (%)	34.8 ± 15.2	64.6 ± 23.3	<0.001
Blood WBC (cells/μL)	10,070.1 ± 5,037.9	11,685.7 ± 6,173.2	0.005
Blood PMN (%)	77.0 ± 9.6	82.0 ± 10.4	<0.001
C-reactive protein (mg/L)	75.0 ± 147.7	141.1 ± 128.9	<0.001

Data are expressed as number (%) or mean ± standard deviation.
APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; PMN, polymorphonuclear leukocytes; WBC, white blood cells.

ed for peritonitis and were excluded from analysis. In the remaining 147 patients, 753 cases of suspected peritonitis were analyzed. The baseline characteristics of the patients are shown in Table 1. The median age of patients was 65 years (range, 27–92 years), and 76.2% were males. Diabetic nephropathy and cardiorenal syndrome were the most frequent causes of renal failure, at 27.9% each. Glomerulonephritis was the cause of renal failure in 23.8% of patients, nephrosclerosis in 7.5%, and other diseases in 12.9% of cases. Underlying diabetes mellitus was found in 49.0% of patients, and 42.9% of patients were on APD. Microbiological culture results of peritoneal culture are presented in Table 2. Peritoneal WBC count was measured in asymptomatic patients: the median peritoneal WBC count was 80 cells/mm^3 (range, 20–160 cells/mm^3), with a PMN cell percentage of 28.6% (range, 6.7%–52.1%).

Correlations with peritonitis diagnosis

The association of several clinical and laboratory param-

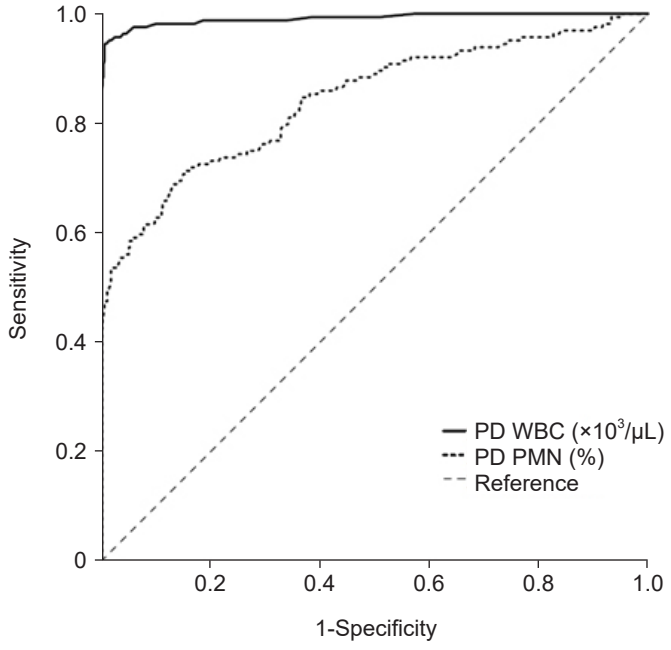

Figure 1. Receiver operating characteristics curve of peritoneal fluid WBCs and peritoneal fluid PMN for diagnosis of peritonitis. The area under the curve for peritoneal fluid WBCs for predicting peritonitis was 0.989 (range, 0.979–0.998), and that for peritoneal fluid PMN was 0.842 (range, 0.803–0.881).
PD, peritoneal dialysis; PMN, polymorphonuclear leukocytes; WBC, white blood cells.

Table 4. Peritoneal WBC counts for peritonitis diagnosis; diagnostic test results (n = 753)

Variable	Peritoneal WBC (cells/μL)							
	≥100	≥150	≥200	≥230	≥250	≥300	≥350	≥440
Sensitivity	1.000 (0.978–1.000)	0.988 (0.957–0.999)	0.982 (0.948–0.996)	0.976 (0.939–0.993)	0.976 (0.939–0.993)	0.958 (0.915–0.983)	0.946 (0.899–0.974)	0.897 (0.840–0.939)
1-Specificity	0.308 (0.271–0.347)	0.612 (0.572–0.652)	0.811 (0.777–0.842)	0.890 (0.861–0.914)	0.898 (0.871–0.921)	0.952 (0.932–0.968)	0.980 (0.965–0.989)	0.995 (0.985–0.999)
PPV	0.289 (0.252–0.328)	0.417 (0.368–0.468)	0.593 (0.533–0.652)	0.712 (0.649–0.771)	0.729 (0.665–0.786)	0.850 (0.790–0.898)	0.929 (0.879–0.963)	0.980 (0.943–0.996)
NPV	1.000 (0.980–1.000)	0.995 (0.980–0.999)	0.994 (0.982–0.999)	0.992 (0.981–0.998)	0.993 (0.981–0.998)	0.988 (0.975–0.995)	0.985 (0.971–0.993)	0.972 (0.955–0.984)
Positive LR	1.445 (1.369–1.525)	2.548 (2.298–2.824)	5.201 (4.393–6.158)	8.827 (7.010–11.115)	9.562 (7.515–12.168)	20.109 (13.989–28.907)	46.327 (26.431–81.200)	175.806 (56.798–544.170)
Negative LR	0.010 (0.000–0.157)	0.020 (0.005–0.079)	0.022 (0.007–0.069)	0.027 (0.010–0.072)	0.027 (0.010–0.071)	0.045 (0.022–0.092)	0.056 (0.030–0.105)	0.104 (0.066–0.163)
AUC	0.654 (0.613–0.695)	0.800 (0.769–0.831)	0.897 (0.873–0.920)	0.933 (0.912–0.953)	0.937 (0.917–0.957)	0.955 (0.935–0.975)	0.963 (0.941–0.984)	0.949 (0.922–0.976)

Data are expressed as number (95% confidence interval).
AUC, area under the curve; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; WBC, white blood cells.

eters with confirmed diagnosis of peritonitis was evaluated. In univariate analysis, abdominal pain and cloudy dialysate were positively correlated with peritonitis, while "other symptoms" correlated negatively (Table 3). Laboratory parameters of peritoneal fluid WBC count, peritoneal fluid PMN cell count, blood WBC count, blood PMN cell count, and CRP were positively correlated with peritonitis (Table 3).

Peritonitis diagnosis based on peritoneal white blood cell count

The ROC curves of peritoneal fluid WBCs and peritoneal fluid PMN percentage were used for diagnosis of peritonitis (Fig. 1). The area under the curve (AUC) for peritoneal fluid WBCs for predicting peritonitis was 0.989 (range, 0.979–0.998), indicating good discrimination ability of the biomarker. The AUC for peritoneal fluid PMN for predicting peritonitis was 0.842 (range, 0.803–0.881), a lower discrimination ability for peritonitis compared to peritoneal fluid WBCs. The AUC for peritoneal fluid WBC combined with peritoneal fluid PMN was 0.992, indicating that peritoneal fluid PMN did not improve significantly the discrimination ability of peritoneal fluid WBC count alone.

In order to identify accurate threshold levels of peritoneal fluid WBC count for diagnosis of peritonitis, sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of different peritoneal fluid WBC count values were analyzed (Table 4). While the sensitivity of peritoneal fluid WBC count of 100 cells/μL was 100%, specificity was only 35%. Increasing peritoneal fluid WBC count cutoff to 150, 200, and 250/μL produces a sensitivity around 98% and gradually increased specificity (Table 4).

The CHAID model was used for identification of peritonitis based on peritoneal fluid WBC count and clinical findings. According to the CHAID model, peritoneal fluid WBC count above 440 cells/μL was the best discriminator for peritonitis diagnosis (Fig. 2). Among those with peritoneal fluid WBC count above 440/μL, the next discriminator was abdominal pain at presentation. Patients on PD presenting with abdominal pain and peritoneal fluid WBC

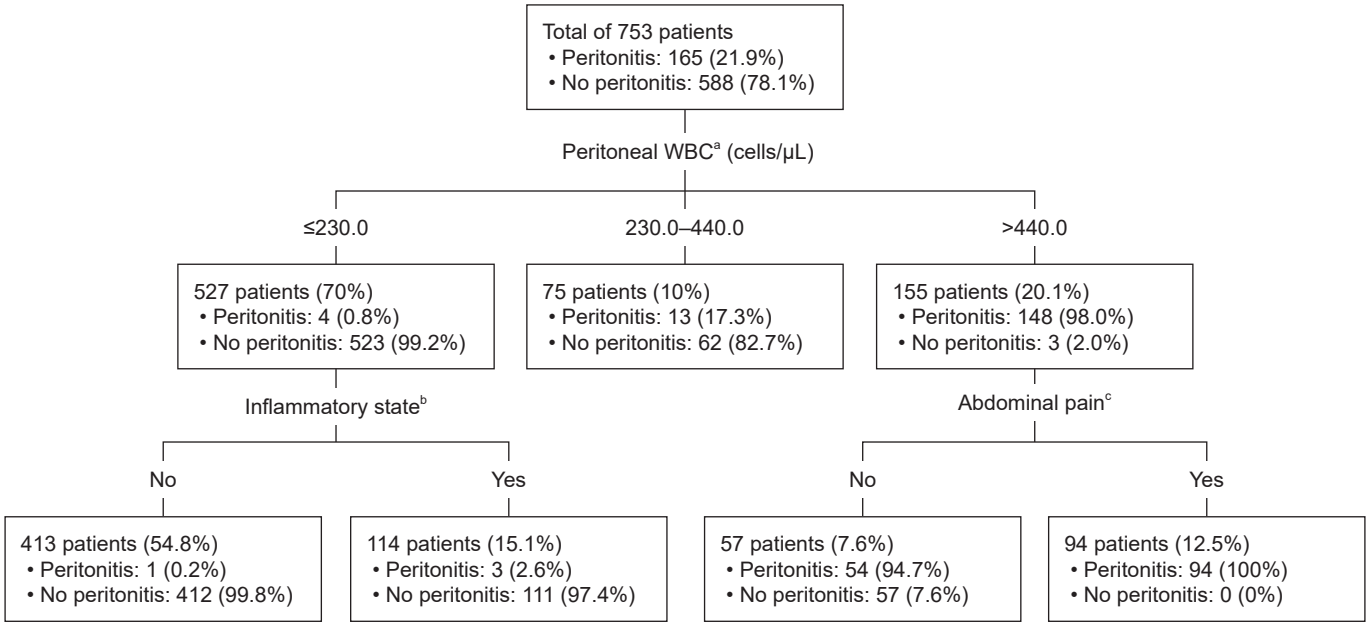

Figure 2. The chi-square automatic interaction detector model of decision tree to identify peritoneal dialysis-related peritonitis.
WBC, white blood cells.
[a]Peritoneal WBC adjusted p-value <0.001, chi-square = 649.810, degree of freedom (df) = 2. [b]Clinical presentation of inflammatory markers or fever, adjusted p-value = 0.009, chi-square = 6.772, df = 1. [c]Clinical presentation of abdominal pain, adjusted p-value = 0.03, chi-square = 5.048, df = 1.

count above 440/μL had 100% probability of having peritonitis. The CHAID model identified peritoneal WBC count less than 230 cells/μL as the best discriminator to rule out peritonitis. After this peritoneal fluid WBC count, the next discriminator was absence of inflammatory markers (fever or increased serum CRP level). Patients on PD without fever or elevated serum CRP level and with peritoneal fluid WBC count less than 230 cells/μL had 99.8% probability of not having peritonitis. Based on the above two analyses, a threshold of peritoneal WBC count of 230 cells/μL will provide a better specificity for diagnosis of peritonitis compared to a cutoff of 100 cells/μL without compromising the sensitivity of the test. We also assessed the peritonitis rate in cases with low WBC count (WBC < 230 cells/μL) and high PMN count (PMN ≥ 50%). Of the 78 such patients identified, none had peritonitis.

Peritoneal white blood cell count and severity of peritonitis

The annual peritonitis rate in our unit was 0.29 cases per year. In 44 episodes of peritonitis (26.7%), patients were hospitalized. Peritoneal WBC count at presentation was significantly higher in episodes of peritonitis when patients were hospitalized compared to episodes treated ambulatorily. Median peritoneal WBC count was 2,325 cells/μL (range, 290–17,860 cells/μL) in episodes requiring hospitalization versus 1,270 cells/μL (range, 120–17,110 cells/μL) in episodes treated ambulatorily (p = 0.02). In 13 peritonitis episodes (7.9%), the Tenckhoff catheter was removed due to partial response to treatment or to subsequent development of fungal infection. There was no difference in peritoneal WBC count at presentation between peritonitis cases that responded to treatment and those who eventually needed Tenckfoff catheter removal—1,450 cells/μL (range, 120–17,860 cells/μL) and 1,610 cells/μL (range, 400–10,470 cells/μL), respectively (p = 0.40). In 17 episodes of peritonitis (10.3%), patients experienced relapse after initial improvement. There was no difference in peritoneal WBC count at presentation between peritonitis cases with and without relapse—1,950 cells/μL (range, 450–17,110 cells/μL) and 1,360 cells/μL (range, 120–17,860 cells/μL) cells, respectively (p = 0.29).

Peritoneal white blood cell count below 230 cells/μL

In only four episodes of established peritonitis in our study, patients presented with peritoneal WBC count above the cutoff suggested by the ISPD of 100 cells/μL but below our proposed cutoff level of 230 cells/μL. One of these four patients presented with the classical clinical symptom of peritonitis; abdominal pain. The three others presented with fever only or with fever and additional abdominal symptoms. In two of the patients, peritoneal WBC count increased later during follow-up. Peritoneal fluid culture returned positive several days after the initial presentation in all four patients. Because of their nonspecific presentation, patients did not receive intraperitoneal antibiotics immediately, but all eventually were treated with oral or intravenous antibiotics. Outcome was not compromised in any of these patients. One of these four patients (25.0%) with peritoneal WBC count below 230 cells/μL had classical presentation of abdominal pain, 126 patients (78.3%) with peritoneal WBC count above 230 cells/μL from the whole studied group had abdominal pain and/or cloudy peritoneal fluid (p = 0.04), typical presentation of peritonitis.

High peritoneal white blood cell count without peritonitis

In 57 cases, peritoneal WBC count was above 230 cells/μL (our suggested cutoff), but peritonitis was not diagnosed according to criteria and further follow-up. The median peritoneal WBC count in those cases was 290 cell/μL (range, 240– 510 cells/μL). These cases were divided into groups based on final diagnosis: 40.4% had sepsis from origin other than peritonitis; 24.6% underwent WBC count for a peritonitis episode during follow-up, usually 2 weeks after antibiotic course completion; 12.3% presented with gastrointestinal symptoms such as diarrhea or vomiting and were suspected to have gastroenteritis; 10.5% were new PD patients not undergoing regular exchange; 8.8% were patients with history of ascites or peritoneal catheter occlusion; and 3.4% presented with unexplained transient episode of cloudy peritoneal fluid.

Validation study

Validation of our results was performed on a more recent

cohort of PD patients treated in our unit between 2020 and 2021. There were 116 cases of suspected peritonitis in 45 patients during this period. The median age of patients was 72 years (range, 29–92 years), and 64.4% were males. Diabetic nephropathy was the most frequent cause of renal failure, found in 44.4% of patients. Glomerulonephritis was a cause of renal failure in 24.4%, nephrosclerosis in 13.4%, cardiorenal syndrome in 4.4%, and other diseases in 13.4% of cases. Diabetes mellitus was found in 60.0% of patients, and 42.2% of patients were on APD. Using the peritoneal WBC cutoff of 230 cells/μL, peritonitis was excluded with 100% sensitivity and 97.9% specificity. The positive predictive value of this cutoff was 91.3%, negative predictive value was 100%, positive likelihood ratio was 47.5, and negative likelihood ratio was 0.024.

Discussion

Bacterial peritonitis is the most common complication of PD and is associated with significant morbidity, catheter loss, transfer to hemodialysis, transient loss of ultrafiltration, possible permanent membrane damage, and occasional death [14–16]. Treatment delay causes patient discomfort, peritoneal membrane damage, and catheter failure and contributes to mortality. However, unnecessary treatment should be avoided as it is costly and can lead to antimicrobial resistance, evolutionary selection of pathogenic organisms such as *Clostridioides* (formerly *Clostridium*) *difficile*, and drug toxicity [17]. Diagnosis of peritonitis is based on clinical presentation, dialysis effluent WBC count, and dialysis effluent culture [4]. However, at presentation, patient treatment can be started based only on clinical features and peritoneal fluid WBC count.

Cellular content of ascitic fluid has been used as an indicator of peritonitis since 1940 [18] when it was shown that nontuberculous peritonitis was associated with an ascites WBC count of ≥1,000/μL and a preponderance of PMN leukocytes. Tenckhoff [19] and Hurley et al. [20] used dialysate cell count and turbidity to diagnose PD-associated peritonitis, demonstrating that dialysate cell count above 500 WBC/μL is frequent in bacterial peritonitis. Hurley et al. [20] showed that peritoneal PMN leukocytosis accompanied peritonitis, while uninfected patients continued to have a predominance of macrophages in their peritoneal fluid. Rubin et al. [21] found that uninfected CAPD patients had dialysate WBC count less than 50/μL, while infected patients had PMN pleocytosis. Williams et al. [5] found that peritoneal WBC count ranged from 0 to 50 cells/mm^3 in 38 control patients on CAPD without peritonitis, and the majority of the cells were mononuclear with a mean cell count of 11.6/mm^3. At peritonitis presentation in 24 patients, the mean cell count was 2,585/mm^3, with a range of 600 to 9,600/mm^3. Their work [5] and the work of Rubin et al. [21] concluded that dialysate cell counts in asymptomatic patients are in the range of 501 cells/mm^3. In a study by Tranaeus et al. [6], the median value for all episodes was 1,032 cells/μL, with a median of 537 cells/μL in asymptomatic cases; 1,580 cells/μL in mild clinical cases; 1,470 cells/μL in moderately severe cases; and 1,110 cells/μL in severe clinical peritonitis. Flanigan et al. [8] measured peritoneal effluent cell count in 28 uninfected CAPD patients on 137 separate occasions. The cell count was 13 ± 2 cells/μL, with a range from 0 to 191 WBC/μL. The percentage of PMN cells was 11.97 ± 2.23. Uninfected patients based on APD systems had a WBC count of 72 ± 16/μL (range, 0–700/μL). In CAPD patients with peritonitis, peritoneal cell count was 2,311 ± 645 cells/μL, with 85.5% PMN; in APD patients with peritonitis, the count was 2,112 ± 761 cells/μL, with 84.8% PMN. In CAPD patients with peritonitis, WBC count generally exceeded 100/mm^3 during infection, and PMN cells accounted for ~50% of the leukocytes [8].

While the average value of peritoneal WBC count for peritonitis diagnosis was high, mostly above 1,000 cells/μL [5–8], the minimum cutoff of 100 cells/μL was determined since peritoneal WBC count during peritonitis usually exceeded this value [8]. During the last two decades, the incidence of peritonitis declined substantially, particularly episodes caused by gram-positive organisms [22,23], due to the introduction of Y-set and double-bag disconnect systems. The introduction of "biocompatible" solutions with normal pH could improve peritoneal leukocyte function and further reduce peritonitis rate [24]. Moreover, patients tend to be more aware of the importance of early arrival with suspected peritonitis than in the past, and peritonitis diagnostic techniques have improved. Therefore, new updated studies regarding peritonitis diagnostics in PD patients are needed.

We demonstrated that peritoneal WBC count cutoff level higher than that recommended by the ISPD could improve the specificity of the test without compromising its sensi-

tivity. Peritoneal fluid WBC count below 230/μL effectively ruled out peritonitis given that inflammatory markers were not elevated. This peritoneal fluid WBC cutoff below 230/μL effectively ruled out peritonitis in a more recent PD patient validation group.

We found that severe peritonitis as defined by patient hospitalization was associated with significantly higher peritoneal WBC count. A count of 290 WBC/μL was the lowest limit demonstrated in peritonitis cases that required hospitalization. Two other potential features of severe peritonitis, need for catheter removal and peritonitis relapse, were not associated with higher peritoneal WBC count. These outcomes are probably more significantly related to the type of microbial pathogens, such as *Candida albicans* or *Pseudomonas aeruginosa*, rather than to the severity of inflammation, as represented by initial WBC count [25]. For example, it was demonstrated that *Corynebacterium* peritonitis often resulted in relapse or repeat episodes, catheter removal, permanent hemodialysis transfer, and death [26]. In addition, *Pseudomonas* peritonitis is associated with high rates of hospitalization, catheter removal, and permanent hemodialysis transfer [27,28].

Our patients with less than 230 cells/μL in peritoneal fluid who later were diagnosed as having peritonitis based on ISPD criteria and culture results did not have a classical presentation of PD-related peritonitis and were initially treated according to clinical judgment. In those cases, outcome was not compromised even though intraperitoneal antibiotics administration was delayed. It seems that there is a correlation between severity of peritonitis and peritoneal fluid WBC count. Patients with low peritoneal fluid WBC count at presentation have less severe peritonitis.

Peritoneal PMN cell count was not more sensitive than peritoneal WBC in peritonitis diagnosis in our work. Peritoneal cell differential could be influenced by many factors. Resident peritoneal macrophages can multiply when dwell times are prolonged, while rapid exchanges and protracted handling result in decreased dialysate cell counts through dilution and clotting [5]. The number of leucocytes in the dialysate is influenced by the duration of dwell time [8], differences in dwell time from preceding measurements, and differences in the intensity of the inflammatory response between episodes. It is possible that a repeat peritoneal fluid cell count and differential after several hours from initial presentation could show higher peritoneal PMN percentage.

Our study demonstrates that it might be safe to increase the currently recommended peritoneal fluid WBC count cutoff of 100/μL for peritonitis diagnosis in PD-treated patients. This could decrease the possibility of unnecessary antibiotic treatment and allow a timely search for an alternative diagnosis, such as other intraabdominal pathologies. In this setting, clinical judgment is essential. In unclear cases, where peritoneal fluid WBC count is only slightly elevated, a repeat peritoneal fluid cell count and differential after several hours of observation can be beneficial. In many cases of peritonitis, the dialysate becomes cloudy on subsequent exchanges. In such cases, the patient should be closely monitored and antibiotics should be started if signs, symptoms, and repeat cell count are consistent with peritonitis.

Limitations of the study include a single-center performance and retrospective design. In addition, increasing peritoneal fluid WBC count above the currently recommended value as a diagnostic criterion for peritonitis could put the patient at risk of late diagnosis and delayed treatment. In this regard, in unclear cases, a repeat peritoneal fluid cell count and differential after several hours of observation can be beneficial. If this is not possible, antibiotic treatment should be administered immediately. Prospective studies should be performed to confirm our findings.

To conclude, it seems that the currently recommended cutoff peritoneal fluid WBC count for peritonitis diagnosis in PD patients can be safely increased provided close follow-up and clinical judgment.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization, Formal analysis: MK
Investigation: MK, NAA
Supervision: PB

Validation: SM, NAA
Writing–original draft: MK
Writing–review & editing: SM, PB
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