Original Article

Microbial Profile, Peritoneal Fluid White Blood Cell Count, and Outcome of Peritoneal Dialysis-Related Peritonitis at Indonesian Tertiary Hospital

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Abstract

Introduction: Peritonitis caused by peritoneal dialysis (PD) remains a common complication of continuous ambulatory PD (CAPD). The purpose of this study is to determine the microbial profile in CAPD-related peritonitis, the optimal cutoff of white blood cell (WBC) count, and the percentage of polymorphonuclear (PMN) in CAPD fluid in the prediction of CAPD-related peritonitis, together with the outcome of CAPD-related peritonitis at an Indonesian tertiary hospital. This is a retrospective cohort study of CAPD-related peritonitis patients at Indonesian tertiary hospitals from November 2020 to October 2022. **Methods:** Patients with suspected CAPD-related peritonitis who were tested for CAPD fluid culture and WBC count in CAPD fluid were eligible for this study. Patient's diagnosis and outcome obtained from medical records. Differences in clinical outcomes by category of microorganisms were analyzed with Fisher exact test. The Mann–Whitney test and receiver operating characteristic curve were used to determine optimal WBC and PMN cutoff. **Results:** This study included 58 patients and 102 episodes of CAPD-related peritonitis. CAPD-related peritonitis was caused by 29.4% Gram-negative bacteria, 21.5% Gram-positive bacteria, 7.8% fungi, and 6.9% polymicrobial bacteria. CAPD fluid WBC count >79 cells/μL and PMN percentage >50% had a sensitivity of 76.4% and a specificity of 92.9% in predicting CAPD-related peritonitis. There was a significant difference in outcome between Gram-negative and Gram-positive bacterial peritonitis. **Conclusions:** It is critical to understand the microbial profile in CAPD-related peritonitis. Lower WBC count cutoff points in CAPD fluids may improve sensitivity in predicting CAPD-related peritonitis.

Keywords: Continuous ambulatory peritoneal dialysis, microbiological profile, peritonitis

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is one of the two main modalities of renal replacement therapy and an alternative to hemodialysis. Despite advances in technology and antibiotic therapy, peritoneal dialysis (PD)-related infections, including peritonitis, remain a common and serious complication of PD.[1-4]

Peritonitis is associated with significant morbidity, structural and functional changes in the peritoneal membrane, temporary loss of ultrafiltration, permanent membrane damage, catheter loss, transfer to hemodialysis, and death. Therefore, information regarding microbial causes and predisposing factors of peritonitis is important for the proper management and prevention of PD-related peritonitis.[1-3,5]

This study aims to determine the microbial profile in peritonitis associated with CAPD at Indonesian tertiary hospitals, the optimal cutoff of white blood cell (WBC) count, and the percentage of polymorphonuclear (PMN) in CAPD effluent in the prediction of PD-related peritonitis and the outcome of peritonitis CAPD-related peritonitis.

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Methods

This is a retrospective cohort study of CAPD-related peritonitis patients at an Indonesian tertiary hospital from November 2020 to October 2022. Patients with suspected CAPD-related peritonitis who were tested for CAPD fluid culture and WBC count in CAPD fluid were eligible for this study. Suspected CAPD-related peritonitis is defined as suspicion of possible CAPD-related peritonitis so that the patient is examined for effluent CAPD analysis and culture examination. Patients whose diagnoses and monitoring data were incomplete were excluded from the study.

All patients who met the inclusion criteria were included in the study. Medical records are used to obtain information such as age, gender, duration of use of CAPD, comorbidities, and diagnosis. The laboratory information system was used to obtain data on the culture examination results, WBC count, and PMN percentage in peritoneal fluid. A Sysmex XN-3000 mode body fluid hematology analyzer was used to count WBCs and determine the percentage of PMN in the peritoneal fluid. The diagnosis of CAPD-related peritonitis is determined by the clinician based on International Society for Prenatal Diagnosis (ISPD) criteria where there are at least two out of three findings consist of clinical findings consistent with CAPD-associated peritonitis, dialysis effluent WBC >100/μL with >50% PMN leukocytes, and positive dialysis effluent culture. Diagnosis data are obtained from the medical record. Patients whose data were complete but were not diagnosed with CAPD-related peritonitis were put into the nonperitonitis group. Outcomes in this study include peritonitis resolution, removal of CAPD catheters, and mortality obtained from medical records from the beginning of the patient's peritonitis diagnosis to the outcome.

Statistical analysis

Study results were expressed as frequencies and percentages for categorical variables and a Kolmogorov–Smirnov test was used to check the distribution of data variables. $P \geq 0.05$ indicated that the data were normally distributed. The abnormally distributed data were presented with median, minimum, and maximum values. Differences in clinical outcomes by category of microorganisms were analyzed with Fisher exact test. The Mann–Whitney nonparametric test was used to examine the relationship between WBC count and PMN percentage with peritonitis diagnosis, followed by the creation of a receiver operating characteristic curve (ROC) to determine the ability to discriminate based on area under the curve (AUC) and the optimal predictive cut point based on the Youden Index. $P < 0.05$ was thought to be significant. Data were analyzed using SPSS Statistics version 19 for Windows (IBM, New York, USA).

Results

In this study, 183 episodes from 80 patients with suspected peritonitis were obtained and WBC counts in CAPD fluid and CAPD fluid cultures were tested. A diagnosis of CAPD-associated peritonitis yielded 102 episodes from 58 patients who met the inclusion and exclusion criteria for the analysis. One hundred and thirty-three episodes of patients tested for WBC and peritoneal effluent cultures dan 102 episodes obtained complete WBC count data, peritoneal effluent cultures, diagnosed CAPD-related peritonitis given intraperitoneal antibiotic therapy, and complete follow-up data. Fifty-seven episodes obtained complete WBC count examination data, cultures of peritoneal fluid, not diagnosed CAPD-related peritonitis, and complete follow-up data. Twenty-four episodes were excluded for incomplete data. Fifty-seven episodes were not diagnosed with CAPD-associated peritonitis and were classified in the nonperitonitis group. Of the 58 patients, 68.9% ($n = 40$) had one episode of peritonitis, 8.6% ($n = 5$) had two episodes, and 22.4% ($n = 13$) had three or more episodes. Demographic data are shown in Table 1.

In this study, the most common etiology of CAPD-related peritonitis was Gram-negative bacteria at 29.4%, followed by Gram-positive at 21.5%, fungi at 7.8%, and polymicrobial at 6.9%. The most widely identified Gram-negative bacterial species in this study is *Acinetobacter* sp. (7.8%), followed by *Pseudomonas* sp. (4.9%) and *Enterobacter* sp. (3.9%). For Gram-positive, the most identified is coagulase-negative staphylococci (CoNS) (14.7%). Among fungi, the most found species is *Candida* sp. (6.9%). The percentage of negative cultures in this study was 34.3%. The profile of microorganisms that cause CAPD-related peritonitis in this study is shown in Figure 1.

Based on clinical outcomes, out of 102 episodes, 83 episodes (81.3%) experienced resolution, 4 episodes (3.9%) had catheter removal, and 15 episodes (14.7%) experienced mortality. Patient outcomes by category of microorganisms are shown in Table 2.

Fisher's exact test yielded all-cause mortality in CAPD-associated peritonitis based on the Gram-positive and Gram-negative categories, which was statistically significant at $P = 0.046$. In this study, 50% of CAPD peritonitis mortality were due to sepsis. The comorbidities of patients who died in this study were cardiac disease (50%) consisting of heart failure, coronary artery disease, and arrhythmias.

Table 1: Demographics of continuous ambulatory peritoneal dialysis peritonitis patients

Parameter	Total patients ($n=58$)
Age (years), median (minimum–maximum)	
Child (n=28)	15 (1–18)
Adult (n=30)	45 (20–77)
CAPD usage duration (months)	33 (1–133)
Gender, n (%)	
Male	34 (58.6)
Female	24 (41.3)

CAPD: Continuous ambulatory peritoneal dialysis

In 57 episodes included in the nonperitonitis group, all caused mortality outcomes were obtained in 7 patients (12.2%). The diagnosis in patients with mortality outcomes was gastrointestinal bleeding, iliac artery stenosis, metabolic encephalopathy, multisystem inflammatory syndrome in children, heart failure, and pneumothorax with respiratory distress. Three episodes in the nonperitonitis group with elevated WBC count were diagnosed with exit site infection, pneumothorax with respiratory distress, and bloodstream infection.

As shown in Table 3 and Figures 2 and 3, the group of subjects with CAPD-related peritonitis had statistically different WBC counts and PMN percentages compared to the group with non-CAPD-related peritonitis ($P < 0.05$).

Table 2: Microorganism profile with patient outcome

Etiology-based on culture results	Outcome		
	Resolution, *n* (%)	Catheter loss, *n* (%)	Mortality, *n* (%)
Gram-negative	23 (22.5)	0	7 (6.8)
Gram-positive	21 (20.5)	0	1 (0.9)
Fungi	4 (3.9)	2 (1.9)	2 (1.9)
Polymicrobial	5 (4.9)	0	2 (1.9)
Culture negative	30 (29.4)	2 (1.9)	3 (2.9)
Total	83	4	15

Table 3: White blood cell count and polymorphonuclear percentage in effluent fluid in continuous ambulatory peritoneal dialysis-related peritonitis group compared to nonperitonitis

Parameter	Diagnosis		*P*[a]
	Peritonitis	Nonperitonitis	
WBC count (cell/μL)	836 (18–34,334)	6 (1–369)	0.00
Percentage PMN	81 (14–98)	30 (0–100)	0.00

[a]Analyzed using the Mann–Whitney test (normal nondistributed data), $P<0.05$, statistically significant. PMN: Polymorphonuclear, WBC: White blood cell

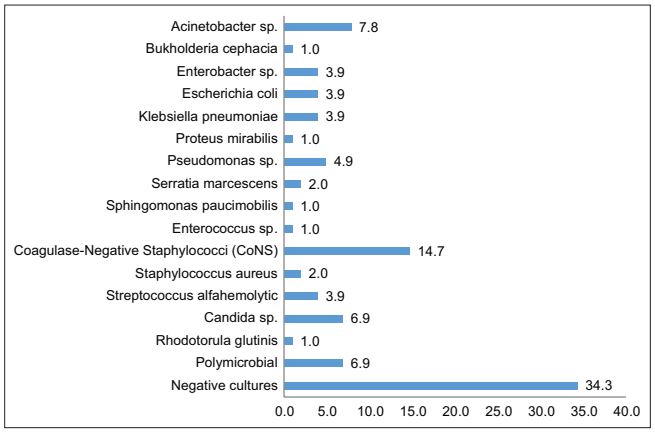

Figure 1: Microbiology profile of CAPD-related peritonitis. CAPD: Continuous ambulatory peritoneal dialysis

ROC curve analysis is performed to determine the intercept, sensitivity, and specificity of WBC and PMN percentage of CAPD fluid in predicting CAPD-associated peritonitis. Based on the highest Youden index, the cutoff point for the CAPD liquid WBC count parameters was >79 cells/μL with 94.1% sensitivity and 93% specificity. The AUC area obtained with the PMN percentage parameter is 0.871. Based on the highest Youden index, the PMN percentage cut point is 52% with a sensitivity of 79.4% and a specificity of 89.5%. AUC area was obtained with a parameter of 0.884. The ROC curve is shown in Figure 4.

As shown in Table 4, a sensitivity of 76.4% and a specificity of 92.9% were achieved using a WBC cutoff >79 cells/μL and a PMN percentage >50%. The positive predictive value (PPV) is 95.1%, and the negative predictive value (NPV) is 68.33%. A sensitivity of 74.5% and a specificity of 92.9% were achieved when comparing the ISPD criteria with leukocyte count cutoff >100 cells/μL and PMN percentage >50%. PPV is 95%, and NPV is 68.83%.

Discussion

In this study, the most common causes were Gram-negative bacteria (29.4%), followed by Gram-positive (21.5%), fungi (7.8%), and polymicrobial (6.9%). This finding contrasts with Seng *et al*,[6] Wang *et al*.,[7] Mujais.,[8] Ghali *et al*.,[9] Özdemir *et al*,[1] and Aldriwesh *et al*.[10] which found the most common causes were Gram-positive.

The findings of this study were similar to those of Abraham *et al*.[11] in India who discovered the most common etiology of Gram-negative bacteria (47.8%), followed by Gram-positive (36.7%), fungi (13.3%), and *Mycobacterium tuberculosis* (2.2%). According to the study, the possibility of Gram-negative predominance was considered due to the high number of negative cultures that also occurred in this study. In this study, the most frequent Gram-negative findings were *Acinetobacter* sp. The study conducted by Özdemir and S.[1] also found the most frequent Gram-negative bacteria were *Acinetobacter* sp. and *Pseudomonas* sp.

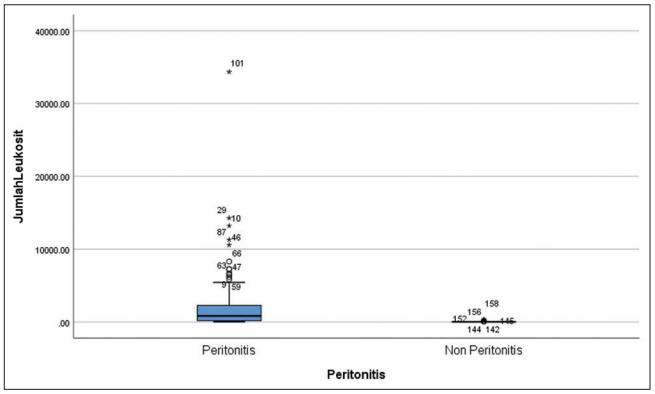

Figure 2: Boxplot of WBC count in the peritonitis group compared to the nonperitonitis group. WBC: White blood cell

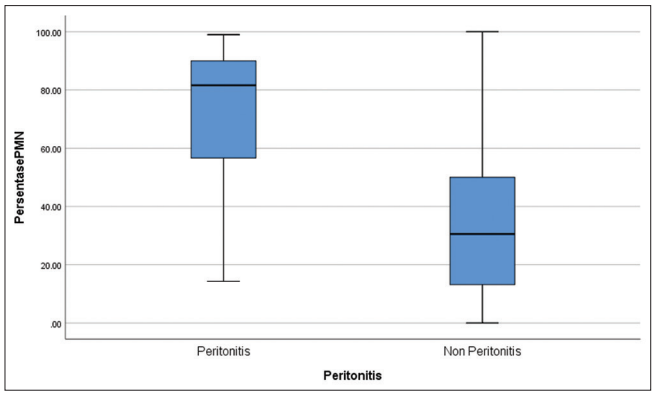

Figure 3: Boxplot PMN% in the peritonitis group compared to the nonperitonitis group. PMN: Polymorphonuclear

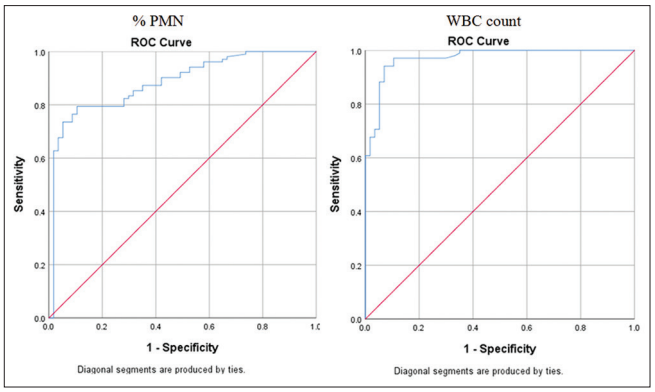

Figure 4: ROC curve WBC count and PMN percentage in predicting peritonitis. ROC: Receiver operating characteristic, WBC: White blood cell, PMN: Polymorphonuclear

Table 4: Diagnostic test with cutoff points white blood cell count >79 cell/μL and percentage polymorphonuclear >50%

	Peritonitis	Nonperitonitis
WBCs count >79 and PMN >50%	78	4
Does not meet the criteria	24	53
Total	102	57

PMN: Polymorphonuclear, WBC: White blood cell

In this study, the most identified Gram-positive species was CoNS (22.3%). The same finding is also found in the studies of Hu *et al*.,[12] Chow *et al*. and Li *et al*.,[13] and Özdemir and S.[1] where Gram-positive, especially CoNS, is the most common cause of PD-related peritonitis. CoNS is generally derived from the normal flora of the skin this is in line with the most frequent source of infection in CAPD-related peritonitis derived from touch contamination.[2,3,14] For fungi, the most found species is *Candida* sp. which is as much as 10.4%. This finding is by a study by Hu *et al*.[12] that found peritonitis due to *Candida* sp. about 7.7%.

The percentage of nongrowing cultures or negative cultures in this study was 34.3%. This is much higher than the ISPD recommendation of <15%.[14] Patients with negative culture results remain included as peritonitis when they meet the criteria for ISPD. Peritonitis with negative culture results can be due to previous exposure to antibiotics, suboptimal sampling, or culture methods that are not optimal for atypical organisms such as mycobacteria and fungi. Research conducted by Seng *et al*.[6] obtained a negative culture rate of around 22.6%, while in a study conducted in India, a higher percentage of negative culture was obtained.[11,15]

ISPD recommends sending specimens within 6 h of collection, inoculating 5–10 mL effluent into two blood culture tubes (aerobic and anaerobic), and obtaining a negative culture percentage of 10%–20% at centers that do so. The culture was conducted in this study in a nonuniform manner, using both conventional methods and direct inoculation into the blood culture bottle. This is thought to lead to a higher percentage of negative cultures than in other studies and ISPD standards.[14,16]

Based on clinical outcomes, it was observed that 83 episodes (81.3%) experienced resolution, 4 episodes (3.9%) experienced catheter loss, and 15 episodes (14.7%) experienced mortality. Hu *et al*.[12] obtained similar data, the percentage of the resolution was 82.4% but the mortality rate was lower (2.9%) in the study. In this study, the etiologies found in mortality outcomes were *Klebsiella pneumoniae, Escherichia coli, Candida* sp., and polymicrobial with a negative culture obtained in one patient. Outcome mortality for Gram-negative etiologies in this study was higher than for other etiologies. Fisher's exact test yields a difference in CAPD-associated peritonitis outcome based on the category of Gram-positive and Gram-negative causative organisms, which is statistically significant with $P < 0.05$. This is similar to other studies that have found mortality more commonly seen in Gram-negative etiologies.[1]

In peritonitis subjects who died from sepsis, the microorganisms that cause it are Gram-negative bacteria, namely *K. pneumoniae* with a proportion of 30% (mono- and polymicrobial). A study conducted by Lin *et al*. in[17] Taiwan found *K. pneumoniae* is the second most common monomicrobial pathogen and the most frequent pathogen also found in polymicrobial. Compared to cases caused by *E. coli*, peritonitis caused by *K. pneumoniae* obtained a higher incidence of sepsis or bacteremia (38%) ($P = 0.11$) and a higher mortality rate (23%) ($P = 0.36$). The most comorbidities in patients who died in this study were heart disease consisting of heart failure, coronary heart disease, and arrhythmias. This is in line with the meta-analysis that found cardiovascular disease increased mortality risk in PD patients.[17,18]

This study shows that using a lower leukocyte cutoff improves sensitivity without compromising specificity. These results are different from the results of the retrospective study by Kunin *et al*.,[19] which get WBC count with a cutoff of 230 cells/μL to have better specificity. In the study of Kunin *et al*.,[19] peritonitis patients with <230 cells, in the follow-up, an increase in the number of cells and positive cultures were obtained. The study conducted by Rubin *et al*. obtained the number of WBC in CAPD patients who

were not infected <50 cells/μL, and in infected patients obtained the dominance of PMN. Williams *et al*. also found in CAPD patients without infection a leukocyte count of 0–50 cells/mm^3 with an average of 11.6/mm^3.[20] The cutoff in the diagnostic criteria used by ISPD come from research conducted in the previous decades where WBC of more than 100 cells/μL accompanied by PMN of more than 50% have better sensitivity and specificity.[19,21]

This was the first study in an Indonesian tertiary hospital to obtain a microbial profile of the cause as well as a cutoff for the number of WBC and PMN in CAPD-related peritonitis patients' dialysis fluid. The study's limitations were that it was conducted retrospectively on a single center, a tertiary hospital in Indonesia. Because the cut point was determined using retrospective data in this study, the results may still be influenced by preanalytical factors such as timing, method of collection, and processing of dialysis fluid specimens.

Conclusions

It is critical to understand the microbial profile in CAPD-related peritonitis. There is a difference in mortality outcome between Gram-positive and Gram-negative bacteria in CAPD-related peritonitis. Lower WBC count cutoff points in CAPD fluids may improve sensitivity in predicting CAPD-related peritonitis.

Research quality and ethics statement

This study was approved by the Institutional Review Board/Ethics Committee of the Faculty of Medicine, University of Indonesia-Cipto Mangunkusumo Hospital (IRB KET-1246/UN2. F1/ETIK/PPM.00.02/2022. The authors followed applicable EQUATOR Network (https://www.equator-network.org/) guidelines during the conduct of this research project.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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