

Original article

# The association between albumin levels, platelet-toalbumin ratio, and the likelihood of peritonitis occurrence in individuals undergoing peritoneal dialysis

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## **ABSTRACT**

BACKGROUND: Since albumin and platelet had been reported to govern the risk of infection, their impact in the case of peritoneal dialysis (PD) – related peritonitis should be investigated.

OBJECTIVES: To assess the association between albumin levels and platelet – to – albumin ratio and the risk of PD-related peritonitis.

METHODS: We conducted a retrospective study in Saiful Anwar General Hospital, Malang, Indonesia during July 2019 and July 2021. Data related to albumin levels and platelet – to – albumin ratio as well as the incidence of PD-related peritonitis were collected from medical record using a standardized pilot form. The association between the albumin levels and platelet – to – albumin ratio and the risk of PD-related peritonitis was analyzed using multiple logistic regression.

RESULTS: We included 123 PD patients during study period. Of them, 20 patients were PD-related peritonitis. Our study found that lower albumin levels were associated with increased risk of PD-related peritonitis with the mean difference was -0.30 (MD: -0.30; 95%CI: [-0.55], [-0.05]). We also found that platelet – to – albumin ratio was observed higher in PD-related to peritonitis compared to control (MD: 14420.10; 95%CI: 832.08, 28008.12). However, the role of albumin levels and platelet – to – albumin ratio had weak association to the risk of PD-related peritonitis with the area under curve were 61% and 59%, respectively.

CONCLUSION: Our study provides the preliminary data regarding the potential role of albumin and platelet – to – albumin ratio for predicting the risk of PD-related peritonitis. However, further large – scale study should be performed to reclarify our findings.

KEYWORDS: Albumin; platelet-to-albumin ratio; peritoneal dialysis; peritonitis.

# INTRODUCTION

The origin of peritoneal dialysis (PD) can be dated back to the pivotal year of 1959.¹ Since its inception, PD has emerged as a valuable therapeutic approach, providing potential benefits for individuals afflicted with end-stage renal disease (ESRD), particularly in mitigating complications and enhancing overall quality of life.² However, the integration of PD into clinical practice is not devoid of challenges, and among these hurdles, PD-related peritonitis stands out prominently.³ Across global landscapes, the incidence of PD-related peritonitis has been approximated to fall within a range of 1.1 to 1.3 episodes per patient per year of treatment. Moreover, the mortality rates linked with this complication exhibit a noteworthy variability spanning from 4% to 16%.⁴ Effectively managing PD-related peritonitis represents a significant clinical endeavor owing to its multifaceted etiology, intricately interwoven with diverse factors including malnutrition, immunosuppression, socioeconomic factors, psychosocial determinants, hypoalbuminemia, and elevated platelet levels. Thus, addressing these multifactorial contributors is paramount for optimizing

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the management and outcomes of PD-related peritonitis.<sup>5</sup> However, among these factors, albumin and platelets hold intriguing potential to be investigated and substantiate their roles in cases of PD-related peritonitis.

Albumin, a protein primarily located in blood plasma, particularly in the serum, represents the major protein circulating in plasma, accounting for approximately half of its total protein composition. It plays multifaceted roles within the immune system, influencing leukocytes, interacting with sphingosine 1-phosphate and heparin-binding protein, and engaging with bioactive lipid mediators. Reduced levels of albumin serve as a surrogate marker for the presence and severity of infections.<sup>6</sup> On the other hand, platelets function as acute-phase reactants, with their levels increasing in response to various stimuli, including systemic infections and inflammatory states. Increased concentrations of proinflammatory cytokines such as interleukin-1, interleukin-6, and interleukin-11 stimulate megakaryocyte growth, leading to enhanced platelet production.<sup>7</sup> Despite this understanding, study that examined the combined roles of albumin and platelets in precipitating PD peritonitis remained limited. Therefore, this study aimed to investigate the contributions of albumin and the platelet to albumin ratio to the risk of PD-related peritonitis occurrence.

### **METHODS**

## Study design

A retrospective study was conducted at Saiful Anwar General Hospital in Malang, Indonesia, employing a comprehensive sampling approach. The participants were stratified into two categories: patients undergoing PD with and without peritonitis. To achieve the study objectives, pertinent data were extracted from medical records utilizing a standardized pilot form and evaluated regarding the influence of albumin and the platelet-to-albumin ratio on PD peritonitis incidence. Approval was obtained from the local Ethical Committee, and due to the retrospective nature of the data analysis, the necessity for written informed consent was waived. The study protocols were aligned with the principles outlined in the Helsinki Declaration<sup>8</sup> and adhered to the checklist outlined in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), ensuring adherence to standardized guidelines.<sup>9</sup>

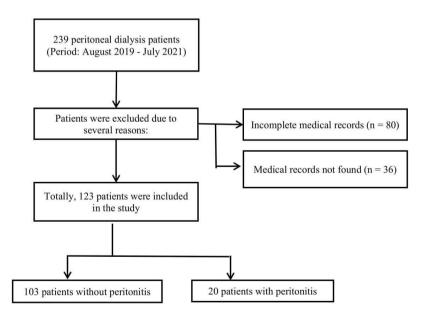


Figure 1. A flowchart of patient selection in our present study.

## Participants & eligibility criteria

The sample selection method employed in this study utilized a total sampling approach. However, it was imperative for the sample size in this study to meet the requisite minimum sample size as determined by the formula for sample calculation in retrospective studies.<sup>10</sup> Given an estimated prevalence rate of peritonitis patients at 9% among all chronic kidney disease patients receiving PD therapy,<sup>11</sup> a case-to-control ratio of 0.2,<sup>12</sup> a 5% margin of error, a 95% confidence interval (CI), and a power exceeding 90%, the requisite sample size was computed to be 98 PD patients (actual power 94%), distributed into 16 patients for the case group

and 82 patients for the control group. The software utilized for sample calculation in this study was G\*power version 3.1 (Universität Düsseldorf, Düsseldorf, Germany, RRID:SCR\_013726). The inclusion criteria for this study encompassed all PD patients treated at our facility between August 2019 and July 2021, aged 18 years and above. Exclusion criteria comprised medical records lacking albumin and platelet data and a history of albumin therapy within the past 2 years.

Table 1. Baseline characteristics of patients included in our study

Characteristics	Peritonitis (n = 20)	Non-peritonitis (n = 103)	p
Age (years)	$42.0 \pm 18.0$	*	
Male (n[%])	16 (80.0)	68 (66.0)	0.2260
BW (kg)	$59.1 \pm 18.3$	59.1 ± 11.9	1.0000
BH (cm)	$157.0 \pm 12.9$	$160.0 \pm 10.5$	0.2610
MUAC (cm)	$27.3 \pm 1.6$	$27.0 \pm 3.0$	0.6640
BMI (kg/m2)	$23.4 \pm 5.7$	$23.0 \pm 4.3$	0.7190
Nutritional status (BMI)			
Severe malnutrition (n[%])	3 (15.0)	3 (2.9)	0.0390
Malnutrition (n[%])	2 (10.0)	10 (9.7)	0.9680
Normal (n[%])	6 (30.0)	63 (61.2)	0.0140
Overweight (n[%])	4 (20.0)	14 (13.6)	0.4610
Obesity (n[%])	5 (25.0)	13 (12.6)	0.1600
Educational levels			
None (n[%])	1 (5.0)	3 (2.9)	0.6340
Elementary school (n[%])	8 (40.0)	14 (13.6)	0.0070
Junior high school (n[%])	4 (20.0)	17 (16.5)	0.7040
Senior high school (n[%])	6 (30.0)	45 (43.7)	0.2600
University (n[%])	1 (5.0)	24 (23.3)	0.0960
Smoking (n[%])	3 (15.0)	26 (25.2)	0.3300
Comorbidity			
Diabetes mellitus (n[%])	6 (30.0)	26 (25.2)	0.6580
Hypertension (n[%])	20 (100.0)	103 (100.0)	1.0000
Renal stone (n[%])	5 (25.0)	17 (16.5)	0.3680
Renal cyst (n[%])	2 (10.0)	5 (4.9)	0.3740
Chronic lung disease (n[%])	1 (5.0)	9 (8.7)	0.5810
Ischemic heart disease (n[%])	1 (5.0)	10 (9.7)	0.5080
Stroke (n[%])	0 (0.0)	4 (3.9)	0.6830
Laboratory findings			
Hemoglobin (gr/dl)	$8.8 \pm 1.5$	$8.7 \pm 1.4$	0.7730
Leukocyte (cells/µl)	$8156.3 \pm 2013.9$	$7982.9 \pm 2847.9$	0.7950
Hematocrit (%)	$27.7 \pm 7.2$	$25.1 \pm 5.2$	0.0560
Platelet (cells/µl)	$268100.0 \pm 84208.0$	$252456.0 \pm 80518.0$	0.4300
Neutrophile	$5615.5 \pm 1851.6$	$5767.3 \pm 2765.9$	0.8140
Lymphocyte	$1527.0 \pm 595.1$	$1285.5 \pm 462.7$	0.0420
NLR	$4.2 \pm 2.1$	$5.5 \pm 4.8$	0.2360
PLR	$192.2 \pm 80.8$	$220.6 \pm 104.9$	0.2520
Urea (mg/dl)	$94.4 \pm 37.2$	$112.4 \pm 56.9$	0.1750
Creatinine (mg/dl)	$9.5 \pm 3.7$	$12.5 \pm 11.3$	0.2410
Natrium (mmol/L)	$133.8 \pm 2.8$	$133.6 \pm 4.9$	0.8600
Kalium (mmol/L)	$3.7 \pm 0.6$	$4.0 \pm 1.0$	0.1950
Chloride (mmol/L)	$102.7 \pm 4.8$	$100.2 \pm 11.2$	0.3280

Note, data were presented in mean ± SD or n (%).

## Data collection

Data extraction was performed from the medical records of PD patients using a standardized pilot form adhering to established standards. The data retrieval encompassed PD patient records within the timeframe

of visits spanning from August 2019 to August 2021. Collected information for each patient comprised demographic factors such as age, gender, weight, height, mid-upper arm circumference (MUAC), body mass index (BMI), educational attainment, smoking habits including duration, presence of comorbidities (including diabetes mellitus, hypertension, kidney stones, kidney cysts, chronic obstructive pulmonary disease, ischemic heart disease, and stroke), duration of comorbidities, occurrences of PD peritonitis, and biochemical parameters encompassing hemoglobin levels, leukocyte count, hematocrit, platelet count, neutrophil count, lymphocyte count, urea, creatinine, sodium, potassium, chloride, and albumin levels.

#### **Covariates**

The predictor covariates investigated in the study included albumin levels and the platelet to albumin ratio. These parameters were scrutinized to assess their potential association with the primary outcome measure, which was the incidence of PD-related peritonitis.

## Statistical analysis

In assessing the normality of numeric covariates, the Kolmogorov-Smirnov test was utilized. A p-value exceeding 0.05 was interpreted as indicative of a normally distributed dataset. Following this, through multiple logistic regression analysis, we examined the uniformity of demographic, clinical, and laboratory data across distinct groups. A p-value surpassing 0.05 suggested a homogeneous distribution of data among these groups. Furthermore, multiple logistic regression was employed to investigate the association between albumin levels, the platelet to albumin ratio, and the risk of peritonitis related to PD. In our analysis, statistical significance was set at p<0.05. To determine effect estimates, odds ratios (OR) and 95% CI were calculated for categorical covariates, while the mean difference (MD) was determined for numeric covariates. Receiver Operating Characteristic (ROC) analysis was carried out to determine optimal thresholds for albumin levels and the platelet to albumin ratio, with the cut-off point corresponding to the highest Youden Index deemed optimal. Data analysis was conducted utilizing the Statistical Package for the Social Sciences 17.0 software (SPSS Inc., Chicago, IL).

Table 2. The summary of the association between albumin levels and platelet – to albumin ratio and the risk of peritonitis among patients with peritoneal dialysis

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Parameters	Peritonitis	Non-peritonitis	MD/OR	95%CI	p
	(n = 20)	(n = 103)			
Albumin (gr/dl)	$3.3 \pm 0.6$	$3.6 \pm 0.5$	[-0.30]	[-0.55] – [-0.05]	0.0180
Albumin $<3.8 \ vs. \ge 3.8 \ gr/dl$	16 [80]	68 [66]	2.06	0.64 - 6.63	0.2260
PAR	$85819.5 \pm 42497.9$	$71399.4 \pm 24869.4$	14420.10	832.08 - 28008.12	0.0380
$PAR > 75598 \ vs. \le 75598$	12 [60]	39 [38]	2.46	0.93 - 6.55	0.0710

Note, data were presented in mean ± SD or n (%); MD, mean difference; CI, confidence interval; PAR, Platelet to albumin ratio

# **RESULTS**

# Patient selection

A total of 239 patients undergoing PD were initially included in the study. However, subsequent exclusion of 116 individuals was necessary due to incomplete medical records, specifically the lack of albumin level assessments. This resulted in a final sample of 123 PD patients for analysis, among whom 20 individuals (16.3%) experienced peritonitis. Figure 1 illustrates the detailed procedural flowchart delineating the thorough patient selection process employed. Furthermore, Table 1 provides comprehensive details regarding the characteristics of the patients incorporated into our analytical framework.

The baseline characteristics in this study generally exhibited homogenous values between the PD patient groups with and without peritonitis. The context of homogeneity encompassed factors such as age, gender, body weight, height, MUAC, BMI, smoking history, comorbidities (diabetes mellitus, hypertension, kidney stones, kidney cysts, chronic obstructive pulmonary disease, ischemic heart disease, and stroke), and laboratory parameters (hemoglobin level, leukocyte count, hematocrit, platelet count, neutrophil count, lymphocyte count, urea, creatinine, sodium, potassium, and chloride). However, we identified two potential confounding factors in this study: severe malnutrition and low educational attainment.

# Association of albumin level and platelet to albumin ratio and the risk of PD-related peritonitis

Our findings indicated that among PD patients, those with lower albumin levels demonstrated an elevated risk of peritonitis (MD: [-0.30]; 95%CI: [-0.55] – [-0.05]). Additionally, an increased risk of peritonitis was observed in PD patients with a higher platelet to albumin ratio (MD: 14420.10; 95% CI: 832.08 - 28008.12). A comprehensive summary of the association between albumin levels and the Platelet to albumin ratio and the risk of PD-related peritonitis is provided in Table 2.

# The cut-off point for albumin levels and the platelet-to-albumin ratio and the risk of PD-related peritonitis

The ROC analysis in our study indicated that the optimal cutoff points for predicting PD-related peritonitis were albumin levels of 3.8 g/dl and a platelet-to-albumin ratio of 75598. Our findings suggested that among PD patients, individuals with albumin levels <3.8 g/dl and a platelet-to-albumin ratio >75598 had comparable risks of peritonitis to those with albumin levels  $\ge 3.8 \text{ g/dl}$  and a platelet-to-albumin ratio <75598. A summary of the optimal cutoff points for albumin and the platelet-to-albumin ratio in predicting the risk of PD-related peritonitis is outlined in Table 2.

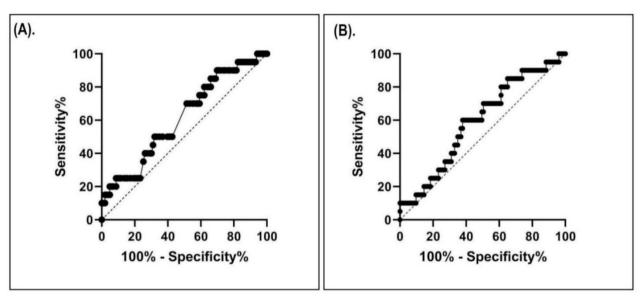


Figure 2. The ROC between albumin levels and platelet – to albumin ratio and the risk of peritonitis among patients with peritoneal dialysis. A). Albumin levels. B). Platelet – to albumin ratio.

## **DISCUSSION**

The findings of this study indicated a significant association between the occurrence of PD peritonitis and the concomitant decline in albumin levels, coupled with a notable increase in the platelet albumin ratio. In a broader context, these findings were found to be consistent with the conclusions drawn from various comprehensive literature reviews<sup>13,14</sup> and were further substantiated by empirical studies conducted in the field. 15-21 A plethora of study reports converged on the consensus that reduced albumin levels served as a robust predictor for the onset of PD peritonitis. Moreover, the pivotal role of albumin in the context of PD peritonitis had been consistently observed across a diverse array of geographical locations, including Turkey, 16,19 the United States, 20,21 Saudi Arabia, 15 China, 17 and Canada. 18 Notably, within the Indonesian context, study elucidating this phenomenon had been meticulously documented in Jogjakarta (unpublished data). Thus, our study outcomes not only contributed significantly to our understanding of the epidemiological landscape surrounding PD peritonitis but also underscored the indispensable role played by albumin in this condition, highlighting its clinical significance and offering invaluable insights for the development of effective patient care protocols and management strategies. However, our study failed to establish the role of albumin levels in the development of PD peritonitis when utilizing a designated cut-off threshold. Our results were indeed confounding and remained inadequately explained. Our findings aligned with prior study indicating that while previous study successfully demonstrated the significance of decreased albumin levels in triggering PD peritonitis, they encountered challenges in translating these observations into definitive cut-off values.<sup>18</sup>

The findings of this study revealed that PD patients with an elevated platelet to albumin ratio were at a heightened risk of experiencing peritonitis. Study assessing the role of the platelet to albumin ratio in the context of PD peritonitis had not been previously conducted, thus preventing a direct comparison of our findings with existing literature. Previous studies had investigated the role of the platelet to albumin ratio concerning the risk of PD catheter malfunction and mortality. They had shown that an increased platelet to albumin ratio contributed to elevated risks of PD catheter malfunction and mortality. Findings from earlier studies, though indirectly aligned with our study, underscored the significant contribution of the platelet to albumin ratio in precipitating adverse events in PD patients. Furthermore, beyond the realm of PD patients, the platelet to albumin ratio had been associated with various negative consequences of diseases such as peptic ulcer perforation, diffuse large B-cell lymphoma, postoperative heart transplant complications, acute kidney injury, and thrombocytopenia syndrome. Provided the role of the increased platelet to albumin ratio in various disease conditions' negative effects.

The underlying theoretical basis for our findings regarding the role of low albumin levels and increased platelet to albumin ratio in triggering PD peritonitis remains incompletely understood. However, several pieces of literature suggest that increased platelet counts and low serum albumin levels may contribute to a pro-inflammatory state, thereby heightening the risk of peritonitis. Platelets are known to play crucial roles in infection, inflammation, and immune processes, and elevated levels may signify poor physical condition and chronic inflammation in patients.<sup>7</sup> Additionally, low serum albumin levels can lead to increased capillary permeability, allowing serum albumin to escape and expand the interstitial space, consequently elevating the risk of peritonitis.<sup>23</sup> Hypoalbuminemia may further exacerbate this risk by increasing capillary permeability and promoting the escape of serum albumin.<sup>6</sup> Inflammation, a common complication of PD, can also contribute to hypoalbuminemia by further increasing capillary permeability and reducing serum albumin levels in the bloodstream.<sup>6</sup> These elucidations may provide insight into the results obtained from our study regarding the role of hypoalbuminemia and increased platelet to albumin ratio in triggering PD peritonitis.

Our study enhanced the current academic comprehension regarding the role of hypoalbuminemia in triggering PD-related peritonitis. Additionally, our study represented the first exploration reporting on the involvement of the platelet to albumin ratio in cases of PD-related peritonitis. This underscored the pivotal nature of our study in advancing PD-related peritonitis study. The study enhanced comprehension regarding albumin levels and the platelet to albumin ratio as indicators of PD-related peritonitis, thereby aiding clinicians in prognostication and risk stratification for patients. By recognizing the contribution of low albumin levels and an increased platelet to albumin ratio to the risk of PD-related peritonitis, strategies for dietary management or medical interventions could be devised to mitigate this risk. Furthermore, the findings served as a foundation for further mechanistic exploration of the relationship between albumin levels, the platelet to albumin ratio, and PD-related peritonitis risk. Subsequent study endeavors could facilitate the identification of more targeted and efficacious intervention approaches to reduce the risk of peritonitis and enhance overall clinical outcomes for PD patients.

The findings of this study indicated the presence of confounding factors, including severe malnutrition and low educational attainment. First, malnutrition was known to elevate the risk of infection. Patients with malnutrition experienced an increase in the malnutrition-inflammation complex (MIC), characterized by reduced body protein stores or functional capacity imbalance. Second, lower educational levels acted as a risk factor for a lack of understanding of health status and maintenance. PD maintenance, requiring comprehension, perseverance, and hygiene, posed challenges for individuals with lower educational attainment. Consequently, this population may have been unable to effectively manage PD, indirectly increasing the risk of peritonitis. Therefore, the interpretation of our study findings warranted attention, recognizing that the role of albumin and the platelet-to-albumin ratio in PD-related peritonitis was not independent but also influenced by severe malnutrition and low educational levels.

This study was accompanied by several limitations that necessitated detailed consideration. First, the failure to evaluate relevant confounding factors such as patient hygiene, the presence of infections elsewhere, and catheter obstruction, which could have also impacted the occurrence of PD-related peritonitis, was noted. Second, concerns were raised regarding the relatively modest sample size and the disproportionate distribution between the case and control groups, potentially leading to spurious positive outcomes. Third, the retrospective study design yielded a lower level of evidence, prompting the need for a prospective study with a larger sample size to bolster evidentiary robustness. Fourth, the reliance on medical records for data retrieval introduced the possibility of information gaps, potentially compromising the accuracy of the study's conclusions.

#### CONCLUSION

Our study emphasizes the importance of incorporating albumin levels and the platelet to albumin ratio as crucial predictive factors in the onset of PD-related peritonitis. These results provide valuable insights into the prognostic outlook for PD patients, highlighting the need for additional exploration and validation across various clinical contexts.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study procedures were reviewed and approved by the local ethical committee. Participant consent was not required for this study as it involved retrospective data collection.

#### CONFLICTS OF INTEREST

We have no conflict of interest

#### **FUNDING SOURCES**

We have no source of funding

# **ACKNOWLEDGMENT**

None

## **AUTHOR CONTRIBUTION**

Conceptualization: MM, AR, AG; Data Curation: MM; Formal Analysis: MM; Investigation: MM, AR, AG; Project Administration: MM; Resources: MM; Methodology: MM, AR, AG; Software: MM; Visualization: MM, AR, AG; Supervision: AR, AG; Validation: MM, AR, AG; Writing – Original Draft Preparation: MM; Writing – Review & Editing: MM, AR, AG. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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