Serum Galactomannan Index for the Rapid Diagnosis of Fungal Peritonitis in Patients With Peritoneal Dialysis

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Received 8 July 2019; revised 22 November 2019; accepted 16 December 2019; published online 21 December 2019

Kidney Int Rep (2020) **5,** 530–534; https://doi.org/10.1016/j.ekir.2019.12.008

Fungal peritonitis, a relatively uncommon but serious complication of peritoneal dialysis (PD), is associated with high rates of technique failure (40%) and mortality (15%–50%).[1,2] Therefore, immediate PD catheter removal followed by antifungal agent administration for a minimum period of 2 weeks is strongly recommended by the International Society for Peritoneal Dialysis 2016 peritonitis guideline.[3] Despite treatment according to this guideline, only one-third of patients with fungal peritonitis are able to resume PD.[4] The poor treatment outcomes of fungal peritonitis are hampered by the lack of a sensitive biomarker that can facilitate timely diagnosis and treatment. Serum levels of the fungal cell wall component galactomannan (GM), which is shed by fungi during their growth and death,[5] may help address this gap in clinical care. This biomarker has been used to aid in the diagnosis of systemic and invasive fungal infections, as well as in monitoring the treatment response and relapse of fungal infections, particularly of the respiratory system.[5] A serum GM index (GMI) of ≥0.5 has previously been used to diagnose suspected fungal pulmonary infections.[6,7] As a proof of concept, the potential value of serum and PD effluent GMI in diagnosing and risk-stratifying patients with fungal peritonitis on PD was assessed in the present study.

RESULTS

Patient Demographics and Characteristics

Participant flow is shown in Figure 1. There were no significant differences among patients with fungal peritonitis (n = 23), bacterial peritonitis (n = 21), and no peritonitis (n = 19) with respect to age, sex, PD vintage, residual kidney function, and comorbidities (Table 1, Supplementary Table S1). As expected, controls without peritonitis had no peritonitis symptoms, higher serum albumin concentrations, and lower PD effluent cell counts than did the other groups. The most common fungal pathogen was *Candida* spp. followed by *Trichosporon* spp., *Aspergillus* spp., and *Fusarium* spp. (Table 2).

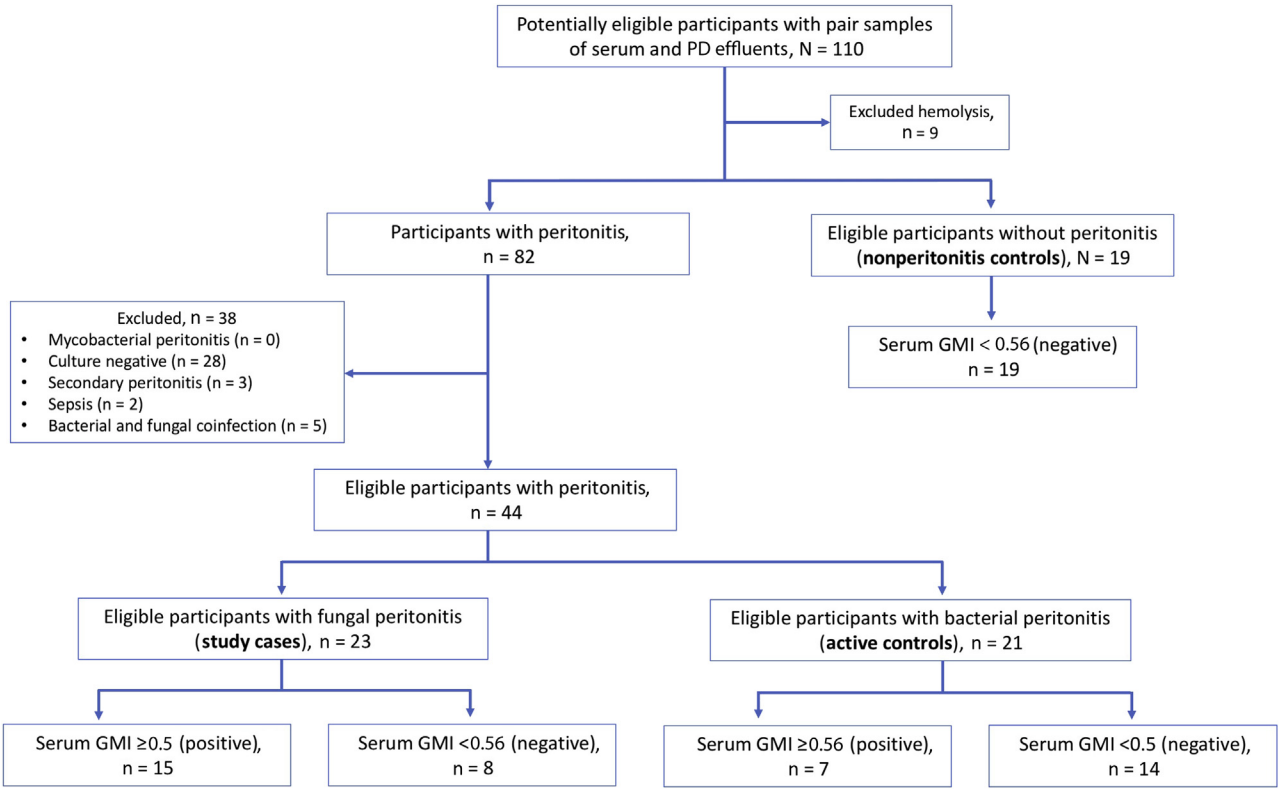

Figure 1. Patient enrollment and randomization flow diagram. GMI, galactomannan index; PD, peritoneal dialysis.

Serum GMI Values

Serum GMI in patients with fungal peritonitis was significantly higher than that in patients with bacterial peritonitis and controls without peritonitis (median, 0.85 [interquartile range, 0.43–1.75] vs 0.45 [interquartile range, 0.35–0.79] vs. 0.43 [interquartile range, 0.34–0.47], respectively; $P = 0.036$) (Figure 2a). To differentiate fungal peritonitis from non–fungal peritonitis (including bacterial peritonitis and nonperitonitis), a serum GMI cutoff value of ≥0.56 (Supplementary Table S2) provided the best diagnostic accuracy with 65.2% sensitivity, 85.0% specificity, 4.35 positive likelihood ratio, and 0.41 negative likelihood ratio. At this cutoff point, the calculated area under the curve from receiver operating characteristic curve analysis for serum GMI was 0.73 (95% confidence interval, 0.58–0.87) (Table 3 and Figure 2b).

Six patients with bacterial peritonitis (patients 2, 7, 13, 16, 19, and 20) had a positive GMI result. On the basis of polymerase chain reaction–based diagnosis of

Table 1. Clinical characteristics of patients on PD in this study

Characteristic	Fungal peritonitis (n = 23)	Bacterial peritonitis (n = 21)	Nonperitonitis (n = 19)
Male sex	10 (43)	10 (48)	11 (58)
Age (yr)	51.3 ± 13.3	55.4 ± 16.0	68.1 ± 7.1
Diabetes mellitus	12 (52)	9 (43)	10 (53)
Hypertension	18 (78)	17 (81)	14 (74)
Serum hemoglobin level (g/dl)	10.2 ± 3.2	10.7 ± 2.7	11.9 ± 1.3
Serum albumin level (g/dl)	2.7 ± 0.9	2.8 ± 0.5	3.4 ± 0.4
Serum potassium level (mEq/l)	3.4 ± 0.9	3.1 ± 0.9	3.5 ± 0.7
Urine volume (ml)	458.3 ± 264.4	283.3 ± 132.9	615.5 ± 418.4
Presentation			
Fever	1 (4)	2 (10)	0
Abdominal pain	5 (22)	12 (57)	0
Cloudy dialysate	18 (78)	15 (71)	0
PDE cell count (cells/μl)	2400 ± 4801	4732 ± 6783	7 ± 2
PDE neutrophil (%)	77 ± 18	85 ± 12	67 ± 11

PD, peritoneal dialysis; PDE, peritoneal dialysis effluent.
Data are mean ± SD or n (%).

Table 2. Organisms cultured in cases of bacterial and fungal peritonitis in this study

Identified bacteria (21)	Identified fungi (23)
Pseudomonas aeruginosa (6)	*Candida* spp. (6)[a]
Escherichia coli (5)	*Trichosporon* spp. (3)[a]
CoNS (3)	*Aspergillus* spp. (3)
Streptococcus mitis (2)	*Fusarium* spp. (2)
Staphylococcus aureus (1)	Unidentified mold (2)
Enterobacter asburiae (1)	*Exophiala* spp. (1)[a]
Proteus mirabilis (1)	*Acremonium* spp. (1)
Stenotrophomonas maltophilia (1)	*Alternaria* spp. (1)
Bacillus spp. (1)[b]	*Paecilomyces* spp. (1)
	Penicillium spp. (1)
	Scedosporium spp. (1)
	Scopulariopsis spp. (1)

CoNS, coagulase-negative *Staphylococcus*.
[a]Yeast-form fungi (others are mold-form).
[b]Gram-positive bacteria (others are gram negative).
Number of cases is given in parentheses.

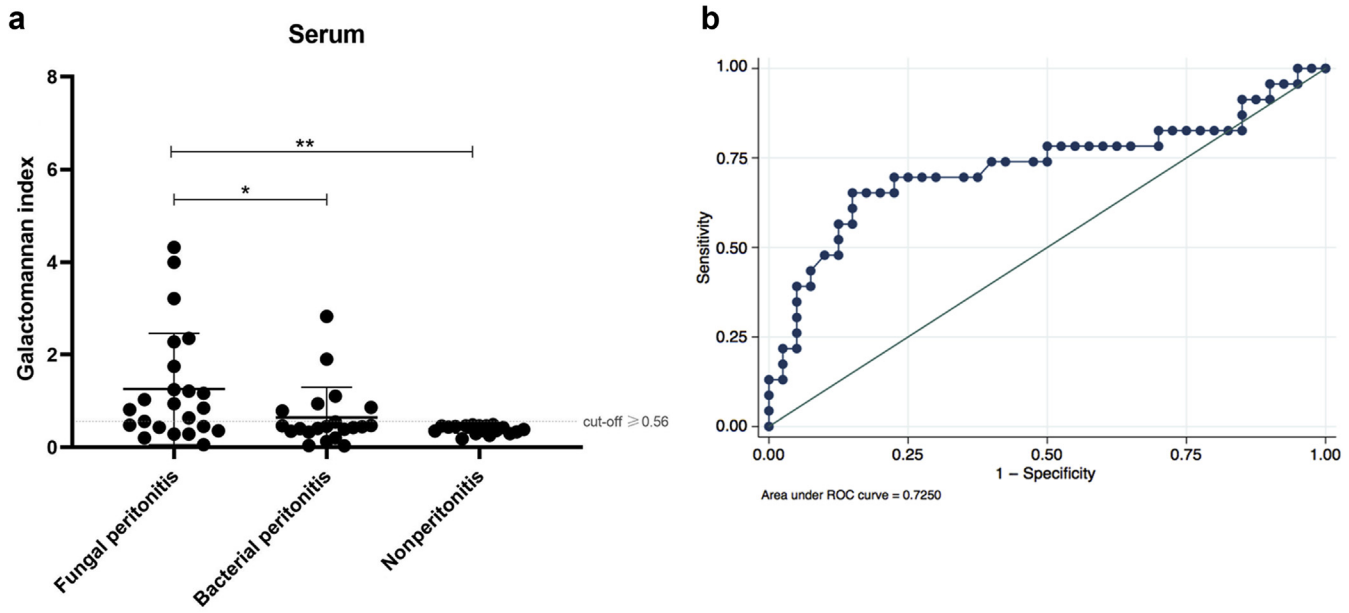

Figure 2. Serum galactomannan index measurements in patients with fungal peritonitis on peritoneal dialysis (study cases), patients with bacterial peritonitis on peritoneal dialysis (active controls), and controls without peritonitis (a). Receiver operating characteristic (ROC) curves of serum galactomannan assays for the diagnosis of fungal peritonitis (b). *$P < 0.01$, **$P < 0.001$.

fungal infections, 2 patients (patients 16 and 19) had a positive polymerase chain reaction result, indicating a true-positive GMI result. In other words, an occult infection with fungus likely explained the positive GMI result in these 2 cases of bacterial peritonitis. The results of the polymerase chain reaction of the remaining cases were negative, although 2 cases (patients 2 and 13) had positive serum dipstick test results for heme, suggesting a possible explanation for a false-positive GMI result. Of note, there were 2 cases (patients 7 and 20) in which the isolated organism, *Pseudomonas aeruginosa* (1 case) and *Escherichia coli* (1 case), was known to cause a false-positive GMI result.

In contrast, 8 patients with fungal peritonitis had a negative serum GMI, including patient 25 (*Candida parapsilosis*), patient 29 (*Exserohilum rostratum*), patient 30 (*Fusarium solani*), patient 31 (*Candida guilliermondii*), patient 33 (*Trichosporon* spp.), patient 38 (*Aspergillus flavus*), patient 42 (*Alternaria* spp.), and patient 43 (*Exophiala* spp.). Possible reasons for these false-negative serum GMI results were the presence of a serum inhibitor or a lack of peripheral blood translocation in either the fungal whole cell or the cell wall. Of note, the follow-up serum titer of patient 29 increased to a level above the cutoff value at 1.88 during amphotericin B treatment.

Table 3. Performance of serum GMI for differentiating fungal peritonitis from nonfungal peritonitis (bacterial peritonitis and nonperitonitis)

	GM testing	Fungal culture			
		Positive	Negative	LR+	4.35
				LR−	0.41
GMI cutoff value ≥0.56 in serum	Positive	15	6	Sensitivity	65.2%
	Negative	8	34	Specificity	85.0%
	PPV, 71.4%; NPV, 81.0%			Accuracy	77.8%

GM, galactomannan; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

DISCUSSION

Our case-cohort study demonstrated that serum GMI may be useful for the timely diagnosis of fungal peritonitis. Because GMI measurement is less time-consuming than the conventional culture method (6 hours vs. 3–6 days), the more rapid diagnosis of fungal peritonitis by GMI offers a potential clinical advantage to patients on PD. The International Society for Peritoneal Dialysis 2016 peritonitis guideline recommended that an immediate catheter removal should be considered when fungi are identified in PD effluent. Earlier catheter removal is associated with improved outcomes, including mortality.[3]

Optimal serum GMI cutoff values ≥0.5 have been used for the diagnosis of invasive fungal infections.[8,9,S1] However, in the present study, a slight increase in the cutoff to ≥0.56 provided the most optimal diagnostic accuracy for fungal peritonitis. This finding implies that there is a translocation of GM from the peritoneal fluid into the circulation in patients with fungal peritonitis. We demonstrated that serum GMI could be used for the diagnosis of fungal peritonitis with >65% sensitivity and 83% specificity. After excluding false positive from hemolytic serum (2 cases) and true positive from occult

fungal infection (2 cases), there were 2 cases (10%) with bacterial peritonitis and false-positive serum GMI above the 0.56 cutoff. These cases involved specific bacterial pathogens known to produce false-positive GMI results, namely, *Pseudomonas aeruginosa* (1 case) and *Escherichia coli* (1 case). The false positivity in these cases possibly occurred because of (i) the high concentration of these organisms in the blood, causing a cross-reactivity in the Platelia Aspergillus enzyme immunoassay (Bio-Rad, Marnes-la-Coquette, France),[9] and (ii) transient fungal antigenemia from cow's milk products[S2] or fungal overgrowth in the compromised gut during the episode of severe gram-negative peritonitis and prolonged antibiotic treatment.[S3] Dietary factors must therefore be taken into account when interpreting the cause of false-positive results in young children and patients with an impaired intestinal barrier.

In contrast, the false-negative GMI in 4 patients with *Candida parapsilosis*, *Candida guilliermondii*, *Trichosporon* spp., and *Alternaria* spp. might be related to fungal burden or the cell wall GM compositions of these fungi, leading to decreased sensitivity. GM detection is not possible in patients with *Pneumocystis jiroveci*, *Candida* spp. (some strains), and *Acremonium* spp. because of the absence of GM content in the cell walls of these fungi.[S4] Meanwhile, the false-negative GMI occurred only in the serum of 4 patients who were infected with *Aspergillus flavus*, *Exophiala* spp., *Exserohilum rostratum*, and *Fusarium solani*. It is possible that fungal pathogens in all these cases did not invade into the bloodstream.

This study has some limitations. First, the number of patients in our proof-of-concept study was relatively small, such that a much larger study would be required to confidently establish the utility of serum GMI as a diagnostic biomarker for fungal peritonitis. Second, the results of this study may not generalize to populations on PD outside Thailand in whom the incidence of fungal peritonitis is appreciably lower.

In conclusion, serum GMI is a promising biomarker for the diagnosis of fungal peritonitis in patients on PD, particularly in conjunction with other parameters such as potassium hydroxide stain, culture, and polymerase chain reaction.

APPENDIX

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DISCLOSURE

DWJ received lecture fees from Baxter Healthcare and Fresenius Medical Care and grant support from Baxter Healthcare. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

We acknowledge the contributions of the staffs, nurses, and all investigators who work at participating Thailand PD Outcomes and Practice Patterns Study (PDOPPS) centers, including King Chulalongkorn Memorial Hospital Sunpasitthiprasong Hospital, Phayao Hospital, Pranangklao Hospital, Siriraj Hospital, Nakhon Pathom Hospital, Bangkok Metropolitan Administration General Hospital, Chaopraya yomraj Hospital, Taksin Hospital, Udon Thani Hospital, Chaiyaphum Hospital, Mukdahan Hospital, Sukhothai Hospital, Nakornping Hospital, Sawanpracharak Hospital, Trang Hospital, Pong Hospital, Chaophraya Abhaibhubejhr Hospital, Trat Hospital, KhueangNai hospital, Amnatcharoen Hospital, and Songkhla Hospital. This study was supported by the Kidney Foundation of Thailand, Ratchadaphiseksomphot Endowment Fund (CU_GRS_61_06_30_01), Chulalongkorn University, the National Research Council of Thailand (156/2560), Thailand Research Foundation (IRG5780017), and the 90th Anniversary of Chulalongkorn University Fund (GCUGR1125594013D).

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary References.

Supplementary Methods.

Table S1. Patient characteristics, previous peritonitis, laboratories, and outcome.

Table S2. Accuracy of serum galactomannan index for differentiating fungal peritonitis at different cutoff points.

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Genetic Kidney Disease in Southern Tasmania

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Received 20 October 2019; revised 13 January 2020; accepted 20 January 2020; published online 30 January 2020

Kidney Int Rep (2020) **5,** 534–537; https://doi.org/10.1016/j.ekir.2020.01.015

Evidence suggests that 1.7 million persons (10% of the Australian adult population) are living with chronic kidney disease (CKD).[1] Within the Australian CKD population, around 10% of individuals are found to have a genetic cause for their kidney disease.[2] As genomic sequencing technology becomes more mainstreamed, the identification of genetic kidney disease (GKD) is expected to increase. The CKD population experiences an excess of