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To the Editor:

We read with interest the results of a large multicenter trial on risk factors for spontaneous bacterial peritonitis (SBP) by Terg *et al.* in the *Journal of Hepatology* [1]. In their analysis including 95 patients with SBP, neither proton pump inhibitor use nor the concentration of ascitic fluid (AF) protein could be confirmed as a risk factor for SBP.

Low AF protein has been reported to predispose to SBP in decompensated cirrhosis according to several studies [2–5] dating from 1986 to 1993. This association was attributed to a lack of opsonic factors, since AF protein correlates with peritoneal immunoglobulin concentration and complement activity [6,7]. During hospitalization, patients with AF protein $\leqslant$10 g/L developed SBP ten times more often than patients with higher AF protein concentrations in an analysis including 17 patients with SBP [2]. Two prospective studies comprising 127 patients (13 with SBP) [4] and 110 patients (28 with SBP) [5] confirmed low AF protein concentration as an independent predictor of SBP. In addition, AF protein $\leqslant$10 g/L was shown to predict the recurrence of SBP [3]. Thus, current guidelines recommend the measurement of AF protein to identify patients at high risk for SBP [8].

Given the discrepancies of available data, we here report the results of a *post-hoc* analysis from two prospectively collected registries of patients with cirrhosis and ascites undergoing paracentesis in two German tertiary centers comprising 683 patients, of whom 220 had SBP. Among 347 patients receiving paracentesis with AF protein measurement between 12/2007 and 07/2014 in the Jena University Hospital, 13 patients presented with a documented history of SBP more than 30 days before inclusion and 81 patients presented with SBP at baseline or during follow-up. In the Bonn University Hospital, 336 patients with liver cirrhosis received baseline paracentesis with AF protein measurement between 05/2006 and 09/2013. Of these patients, 51 had a history of SBP while 75 developed SBP at baseline paracentesis or during follow-up. In both cohorts, AF protein concentrations were similar for patients who never had SBP and patients who developed SBP (Table 1). When patients were stratified according to a cut-off of less than 10 g/L or less than 15 g/L AF total protein, frequencies were comparable between the SBP and non-SBP group.

In line with previous findings that AF protein does not change during and after SBP [9], restricting the analysis to patients without a history of SBP did not alter the results. AF protein in patients with SBP at baseline (Jena: 15 g/L, interquartiles: 9–20, $p = 0.33$; Bonn: 11 g/L, 8–20, $p = 0.86$) and AF protein in patients with a first episode of SBP during follow-up (Jena: 12 g/L, 8–20, $p = 0.93$; Bonn: 12 g/L, 7–23, $p = 0.54$) did not differ from patients who never had SBP (Jena: 12 g/L, 8–20; Bonn: 11 g/L, 7–18).

We can only speculate about the causes that underlie the failure to replicate the association between SBP and AF protein, which has been reported in several studies more than 20 years ago. Based on the data of the first report on low AF protein as a risk factor for SBP [2], the power to detect a significant difference between the groups exceeded 80% for each of our cohorts by far. It is probable that changed epidemiology and/or different treatments for cirrhosis play a major part. We can exclude the widespread use of antibiotic prophylaxis, since Terg *et al.* [1] did not include patients receiving antibiotic prophylaxis, only 2.3% of the patients in the Jena cohort and 1.5% of the patients in the Bonn cohort received long-term primary prophylaxis with quinolones or cotrimoxazol. Changes in diuretic therapy may also account for the discrepancies. Diuretics have been shown to improve AF opsonic activity to a greater degree than the protein concentration [10], which may reduce the correlation of AF protein with opsonic activity and therefore diminish its role as a

Table 1. Baseline clinical and laboratory findings in cirrhotic patients of both cohorts stratified for the occurrence of SBP.

	Jena University Hospital			Bonn University Hospital		
	Patients without SBP (N = 253)	Patients with SBP (N = 94)	*p* value[a]	Patients without SBP (N = 210)	Patients with SBP (N = 126)	*p* value[a]
Age at inclusion (yr)	60 (53-69)	58 (51-66)	0.21	62 (53-69)	58 (51-65)	0.03
Male sex	184 (73%)	68 (72%)	1.00	146 (70%)	90 (71%)	0.81
Alcoholic liver disease	198 (78%)	62 (66%)	0.03	151 (73%)	91 (72%)	0.90
Child-Pugh C	167 (66%)	75 (80%)	0.01	95 (46%)	65 (52%)	0.56
MELD score	16 (12-21)	20 (13-24)	0.03	16 (11-21)	17 (13-23)	0.01
Serum albumin (g/L)	24 (20-29)	23 (20-28)	0.13	28 (25-32)	27 (22-31)	0.01
Serum bilirubin (μmol/L)	40 (19-95)	48 (23-110)	0.39	35 (17-71)	35 (17-74)	0.94
Platelets (×10^9/L)	133 (90-189)	103 (77-161)	0.02	131 (92-198)	122 (73-178)	0.11
AF protein (g/L)	12.1 (8.0-19.5)	13.6 (8.0-19.7)	0.38	11.0 (7.0-18.0)	11.0 (7.0-19.0)	0.95
AF protein <15 g/L	164 (65%)	54 (57%)	0.21	139 (66%)	79 (63%)	0.55
AF protein <10 g/L	104 (41%)	35 (37%)	0.54	80 (38%)	52 (41%)	0.57

Median/Interquartiles and frequency/percentage are shown.
AF, ascitic fluid; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.
[a]*p* values from Mann-Whitney *U* test or Fisher's exact test as appropriate.

surrogate of peritoneal immune competence [6]. Indeed, in direct comparison, AF opsonic activity but not total AF protein was an independent predictor of SBP in a multivariate regression model [5]. Since differential effects of diuretic treatment and/or albumin use on sequential changes in AF protein and opsonic activity were not systematically assessed in our data sets, this hypothesis remains to be proven.

In summary, the study of Terg *et al.* [1] and the data presented herein fail to replicate an association of SBP with low total AF protein concentration in three large cohorts of hospitalized patients with decompensated cirrhosis. Although the underlying mechanisms remain elusive, our data have implications on the design of clinical studies and the identification of patients at highest risk for SBP, who might benefit from primary prophylaxis. Large prospective studies are needed to clarify the prognostic significance of low AF protein on the occurrence of SBP.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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