

## Retrospective Study

## Timing of paracentesis and outcomes in hospitalized patients with decompensated cirrhosis

Cristina Tocia, Andrei Dumitru, Luana Alexandrescu, Razvan Popescu, Eugen Dumitru

**ORCID number:** Cristina Tocia 0000-0002-4857-0630; Andrei Dumitru 0000-0002-9550-3537; Luana Alexandrescu 0000-0002-0182-3549; Razvan Popescu 0000-0002-6436-9961; Eugen Dumitru 0000-0002-7268-3723.

**Author contributions:** Tocia C and Dumitru A contributed equally to this work; Tocia C and Dumitru A designed the study, performed the research, collected and analyzed the data, and wrote the manuscript; Dumitru E conceived and supervised the study and performed the critical review; Alexandrescu L and Popescu R performed the literature research and interpreted the data. All authors have read and approved the final manuscript.

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**Cristina Tocia, Andrei Dumitru, Luana Alexandrescu, Eugen Dumitru,** Department of Gastroenterology, Constanta County Clinical Emergency Hospital, Constanta 900647, Romania

**Razvan Popescu,** Department of General Surgery, Constanta County Clinical Emergency Hospital, Constanta 900647, Romania

**Corresponding author:** Andrei Dumitru, MD, Academic Fellow, Department of Gastroenterology, Constanta County Clinical Emergency Hospital, Bd Tomis no 145, Constanta 900647, Romania. [dr.andreidumitru@gmail.com](mailto:dr.andreidumitru@gmail.com)

## Abstract

## BACKGROUND

Ascites is one of the most common complications of cirrhosis, placing a significant burden on the healthcare system. Data regarding the optimal time of paracentesis and outcomes among patients with cirrhosis and ascites are scarce.

## AIM

To assess the outcomes of patients who underwent paracentesis within 12 h after admission compared to patients who underwent paracentesis later than 12 h.

## METHODS

The study included 185 patients with cirrhosis and ascites who underwent paracentesis. The early paracentesis group was defined as paracentesis performed < 12 h after admission (65 patients) and the delayed paracentesis group was defined as paracentesis performed > 12 h after admission (120 patients). New-onset complications of cirrhosis, length of hospital stay, weekday or weekend admission, in-hospital mortality rate, and 90-d readmission rates were assessed and compared between the groups.

## RESULTS

Significantly more patients in the delayed paracentesis group than in the early paracentesis group developed hepatic encephalopathy (45% vs 21.5%,  $P < 0.01$ ), hepato-renal syndrome (21.6% vs 9.2%,  $P = 0.03$ ) and infections (25% vs 10.7%,  $P = 0.02$ ) during hospitalization. There were no statistically significant differences in the occurrence of spontaneous bacterial peritonitis and upper gastrointestinal bleeding between the two groups. Length of stay was shorter in the early paracentesis group than in the delayed paracentesis group (6.7 d vs 12.2 d) and in-hospital mortality was lower among patients in the early paracentesis group.

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Patients in the delayed paracentesis group had a higher risk of developing complications during hospitalization.

## CONCLUSION

Early paracentesis (within 12 h after admission) could be a new inpatient quality metric among patients hospitalized with cirrhosis and ascites as it is associated with fewer complications of cirrhosis, lower in-hospital mortality and shorter length of stay.

**Key Words:** Cirrhosis; Ascites; Hepatic encephalopathy; Spontaneous bacterial peritonitis; Early paracentesis; Delayed paracentesis

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**Core Tip:** Data regarding the optimal time of paracentesis and outcomes among patients with cirrhosis and ascites are scarce. We evaluated the outcomes of 185 patients with cirrhosis and ascites who underwent paracentesis within 12 h after admission (65 patients) compared to patients who underwent paracentesis later than 12 h (120 patients) and we found that early paracentesis is associated with fewer complications, lower in-hospital mortality and shorter length of stay.

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## INTRODUCTION

Cirrhosis is a leading cause of death worldwide and is also associated with increased healthcare resource use<sup>[1]</sup>. Ascites is one of the most common complications of cirrhosis<sup>[2]</sup> and a common reason for admission to hospital, placing a significant burden on the healthcare system. Infected ascites leads to spontaneous bacterial peritonitis (SBP) which occurs in 10%-30% of patients with cirrhosis and is associated with high mortality<sup>[2-5]</sup>.

Paracentesis is a procedure commonly performed in patients with decompensated cirrhosis. Guidelines recommend that diagnostic paracentesis should be performed in all patients who are hospitalized with cirrhosis and new onset grade 2 or 3 ascites, or in those hospitalized due to worsening of ascites or any complication of cirrhosis, to evaluate the presence or absence of SBP<sup>[2,4]</sup>. Rapid diagnosis of SBP by early paracentesis is very important for the outcome of patients even in the absence of symptoms given the fact that SBP usually has a subtle presentation or is asymptomatic. Patients with untreated SBP are at high risk of sepsis and early diagnostic paracentesis allows the initiation of rapid specific treatment with potentially better outcomes of the disease. Despite this, the adherence rate in clinical practice may be unsatisfactory<sup>[6,7]</sup>. Data regarding the optimal time of paracentesis and outcomes among patients with cirrhosis and ascites are scarce. The aim of this study was to assess the outcomes of patients with cirrhosis and ascites who underwent paracentesis within 12 h after admission compared to patients who underwent paracentesis later than 12 h.

## MATERIALS AND METHODS

### Data source and study sample

The retrospective study included 307 patients with cirrhosis and ascites admitted to the Department of Gastroenterology, Constanta County Clinical Emergency Hospital, between January 1, 2018 and December 31, 2019.

Information was collected from the digital database of the hospital (each electronic medical file contains demographic data including date of admission, Child-Pugh classification or MELD-Na score, all diagnoses and procedures performed, length of stay (LOS) and data regarding discharge or in-hospital death) and medical files of the patients (to assess the time of paracentesis and to classify ascites according to clinical and ultrasound criteria).

International Classification of Diseases, 10<sup>th</sup> revision, version 2015<sup>[6]</sup> (ICD-10) codes were used to identify patients with primary or secondary diagnoses of cirrhosis (K70.0, K70.2, K70.3, K70.9, K71.0 – K71.9, K74.6), ascites (R18.8) and/or SBP (K65.2). Also, the search engine included the procedure code for paracentesis (30406-00).

Inclusion criteria: Patients with cirrhosis of any etiology and one of the following three conditions: (1) New onset grade 2 or 3 ascites, (2) Ascites which has worsened recently, or (3) Ascites associated with a complication of cirrhosis, who underwent paracentesis during hospitalization.

Exclusion criteria: Patients with cirrhosis but without ascites or with grade 1 ascites (small amount of ascites detectable only on ultrasound studies), patients who did not undergo paracentesis, and patients with other etiologies of ascites (cancer, heart failure, tuberculosis).

Following the electronic search, medical files from the hospital's archive of selected patients were manually checked to assess the time of paracentesis since admission and to assess the occurrence of complications during hospitalization.

Ascites was documented by physical exam and detectable on imaging studies (ultrasound, magnetic resonance imaging, or computed tomography scan). Time to paracentesis after admission was assessed and early paracentesis (EP) was defined as paracentesis performed < 12 h after admission and delayed paracentesis (DP) was defined as paracentesis performed > 12 h after admission.

Of 307 patients with cirrhosis and ascites, after careful application of these criteria, 122 (39.7%) patients were excluded (79 patients who did not undergo paracentesis during hospitalization, 13 patients with grade 1 ascites, and 30 patients with stable ascites and no complications of cirrhosis) and 185 (60.3%) patients met the inclusion criteria. Sixty-five (35.1%) patients were assigned to the EP group and 120 (64.9%) to the DP group. In the case of patients who had multiple hospitalizations during the study period, only the first hospitalization was chosen as the index for analysis.

### **Variables and outcomes**

Demographic data, Child-Pugh classification (A, B, and C) and MELD-Na score were recorded in each group. New-onset complications of cirrhosis (developed after admission, during the index hospitalization) such as SBP, hepatic encephalopathy, hepato-renal syndrome, upper gastrointestinal bleeding, and various infections (urinary, pulmonary, *Clostridium difficile* infections), LOS in days, weekday or weekend admission, the in-hospital mortality rate during the same admission, and 90-d readmission rates were assessed and compared between the groups; the primary reason for readmission was identified using the ICD-10 codes for continuous hospitalization.

### **Ethics approval**

The study was conducted according to good laboratory practice and in concordance with national and international standards. The study protocol was approved by the Local Ethics Commission for the Approval of Clinical and Research Developmental Studies of the County Clinical Emergency Hospital of Constanta (approval No. 7/02.03.2020). This was a retrospective study; therefore, a consent form was not required.

### **Statistical analysis**

Statistical analysis was performed using the JASP 0.11.1 statistic software package. Descriptive statistics were used for demographic and baseline data: mean  $\pm$  standard deviation for continuous variables, absolute number and frequency for categorical variables. For comparison between variables in the EP and DP groups, a two-sample Student's *t*-test was used for continuous variables and the chi-square test or Fisher exact test were used for categorical variables. The association of each complication developed during hospitalization in each group was analyzed by calculating the odds ratio (OR) together with confidence intervals (CI). Results were considered statistically significant if the *P* value < 0.05.

## RESULTS

Demographic and baseline data of the 185 patients enrolled in the study are illustrated in [Table 1](#). Overall, there were no significant differences between the two groups. The mean age was  $63.7 \pm 10.2$  years in the EP group and  $62.5 \pm 11.1$  years in the DP group, and more than half of the patients from both groups were male. The most common etiology of cirrhosis in both groups was alcohol, followed by viral hepatitis B and/or C, mixed etiology (alcohol and viral hepatitis B and/or C) and other etiologies: Non-alcoholic, metabolic associated liver disease (9 patients), primary biliary cholangitis (2 patients), and autoimmune (1 patient). Most of the patients in each group had been classified as Child-Pugh C class. There were no statistically significant differences in the mean Child-Pugh scores and MELD-Na scores between the groups.

With regard to new-onset complications of cirrhosis (after admission, during hospitalization ([Table 2](#)), significantly more patients in the DP group than in the EP group developed hepatic encephalopathy (45% *vs* 21.5%,  $P < 0.01$ ) and hepato-renal syndrome (21.6% *vs* 9.2%,  $P = 0.03$ ). There were no statistically significant differences between the occurrence of SBP and upper gastrointestinal bleeding in the EP and DP group (15.3% *vs* 18.3%,  $P = 0.61$ , 30.5% *vs* 33.3%,  $P = 0.72$ , respectively). Hepatocellular carcinoma was present in both groups irrespective of time of paracentesis (18.4% in the EP group, 20.8% in the DP group,  $P = 0.70$ ). Other infections (urinary, pulmonary, and *Clostridium difficile* infections) occurred more frequently in the DP group than in the EP group (25%, *vs* 10.7%,  $P = 0.02$ ).

There was a significantly shorter LOS in the EP group compared to the DP group (6.7 *vs* 12.2 d,  $P = 0.01$ ) ([Table 3](#)).

Regarding the relationship between the time of paracentesis and the time of in-hospital admission, it was observed that more than three-quarters of the patients with early paracentesis (76.9%) were admitted during the weekdays, while most of those with delayed paracentesis (52.5%) were admitted during the weekend ( $P < 0.01$ ).

In-hospital mortality during the same admission was significantly lower among patients in the EP group than in the DP group (6.1% *vs* 17.5%,  $P = 0.03$ ).

Regarding 90-d readmission, from a total of 160 discharged patients (61 patients in the EP, and 99 patients in the DP), 45 (28.1%) patients were readmitted with complications. Among them, significantly more patients from the DP group than from the EP group were readmitted: 34.3% *vs* 18%,  $P = 0.03$ . The most common cause for readmission within 90-d in the EP group was upper gastrointestinal bleeding (45.4%), followed by ascites (27.3%), hepatic encephalopathy (18.3%), and in the DP group was ascites (47%), followed by hepatic encephalopathy (29.5%), and upper gastrointestinal bleeding (20.5%). Other causes were lower gastrointestinal bleeding in the EP group (1 patient) and hepato-renal syndrome in the DP group (1 patient).

According to the OR calculation ([Table 4](#)), patients in the DP group were more likely to develop hepatic encephalopathy during hospitalization than patients in the EP group (OR = 2.98, 95%CI = 1.49-5.95,  $P < 0.01$ ). The same was true for hepato-renal syndrome (OR = 2.71, 95%CI = 1.05-7.00,  $P = 0.03$ ) and infections (OR = 2.76, 95%CI = 1.13-6.70,  $P = 0.02$ ). Also, weekend admission, LOS  $\geq 7$  d and in-hospital mortality were more likely to occur in the DP group ([Table 4](#)).

## DISCUSSION

In the present study, of 307 patients with cirrhosis and ascites, only 185 (60.3%) of these patients underwent paracentesis. In 43 (14.0%) patients there was no indication for paracentesis as the ascites had been classified as small (grade 1) or stable and without any complications of cirrhosis. However, in 79 (25.7%) patients no paracentesis was performed, although they had an indication for paracentesis, if we comply with the EASL guide of 2018 which states that a “diagnostic paracentesis is recommended in all patients with new-onset grade 2 or 3 ascites, or in those hospitalized for worsening of ascites or any complication of cirrhosis”<sup>[4]</sup>. Our findings are similar to previously published data<sup>[6,7,9]</sup>.

The time of paracentesis is of paramount importance for the outcome of hospitalized patients with cirrhosis and ascites<sup>[6]</sup>. In our study, only 35.1% of patients underwent paracentesis within 12 h after admission, and the remaining patients (64.9%) underwent paracentesis later than 12 h after admission. Literature is scarce regarding the optimal time for paracentesis.

Spontaneous bacterial peritonitis occurred in 15.3% of patients in the EP group and in 18.3% in the DP group. This finding is in concordance with the literature<sup>[10,11]</sup>. A

Table 1 Patients' demographics

	EP (n = 65)	DP (n = 120)	P value
Gender, n (%)			0.43
Male	34 (52.3)	70 (58.3)	
Female	31 (47.7)	50 (41.7)	
Age (yr)			
mean ± SD	63.7 ± 10.2	62.5 ± 11.1	0.80
Etiology, n (%)			
Viral	20 (30.7)	45 (37.5)	0.35
Alcohol	26 (40.0)	46 (38.3)	0.82
Mixed	12 (18.4)	24 (20.0)	0.80
Other	7 (10.9)	5 (4.2)	0.15
Child-Pugh, n (%)			
A	0	0	N/A
B	24 (36.9)	36 (30.0)	0.41
C	41 (63.1)	84 (70.0)	0.41
Child-Pugh score, mean ± SD	11.2 ± 2.9	11.9 ± 3	0.52
MELD-Na score, mean ± SD	21.4 ± 7.5	23.6 ± 8.8	0.28

EP: Early paracentesis group; DP: Delayed paracentesis group; SD: Standard deviation; N/A: Not applicable.

Table 2 Complications in the early paracentesis group and delayed paracentesis group

Complications, n (%)	EP (n = 65)	DP (n = 120)	P value
SBP	10 (15.3)	22 (18.3)	0.61
HE	14 (21.5)	54 (45.0)	< 0.01 <sup>a</sup>
HRS	6 (9.2)	26 (21.6)	0.03 <sup>a</sup>
UGIB	20 (30.5)	40 (33.3)	0.72
Infections	7 (10.7)	30 (25.0)	0.02 <sup>a</sup>

<sup>a</sup>P < 0.05. EP: Early paracentesis group.

DP: Delayed paracentesis group; SBP: Spontaneous bacterial peritonitis; HE: Hepatic encephalopathy; HRS: Hepato-renal syndrome; UGIB: Upper gastrointestinal bleeding.

study conducted by Garcia-Tsao *et al*<sup>[12]</sup> found SBP in 12% of patients admitted with cirrhosis and ascites. Interestingly, in our study, SBP was present in both groups irrespective of the timing of paracentesis, and there was no statistically significant difference between the two groups. We assume that in our group of patients, SBP was present on admission to the hospital, so there was no difference in the number of cases diagnosed by EP compared with those diagnosed by DP. However, early diagnosis may be important in the prognosis of the disease, as early diagnosis is followed by early treatment and this may influence the course of the disease.

In addition, significantly more patients in the DP group developed hepatic encephalopathy and hepato-renal syndrome. We can assume that this was due to DP and delayed treatment of SBP as untreated SBP has a worse prognosis and outcome. Also, other infections (urinary, pulmonary, *Clostridium difficile* infections) were more common in the DP group than in the EP group; this also suggests that EP facilitates the diagnosis of SBP and early treatment with antibiotics may also reduce the incidence of some other infections. Overall, patients who received EP had better outcomes and fewer complications in contrast to those who received DP. The relationship between EP and improved outcomes might be due to the rapid initiation of SBP treatment

**Table 3** Time of admission, length of stay, in-hospital mortality, and 90-d readmission rate in the early paracentesis group and delayed paracentesis group

	EP (n = 65)	DP (n = 120)	P value
Admission, n (%)			
Weekday	50 (76.9)	57 (47.5)	< 0.01 <sup>a</sup>
Weekend	15 (23.1)	63 (52.5)	
LOS (d)			
mean ± SD	6.7 ± 3.8	12.2 ± 4.5	0.01 <sup>a</sup>
In-hospital mortality, n (%)	4 (6.1)	21 (17.5)	0.03 <sup>a</sup>
90-d readmission, n (%)	11 (18.0)	34 (34.3)	0.03 <sup>a</sup>
Ascites	3 (27.3)	16 (47.0)	
UGIB	5 (45.4)	7 (20.5)	
HE	2 (18.3)	10 (29.5)	
Other	1 (9.0)	1 (3.0)	

<sup>a</sup>P < 0.05. EP: Early paracentesis group; DP: Delayed paracentesis group; LOS: Length of stay; UGIB: Upper gastrointestinal bleeding; HE: Hepatic encephalopathy; SD: Standard deviation.

**Table 4** The risk of complications developed during hospitalization in the early paracentesis group and delayed paracentesis group

Complication	Cases in the EP group, n (%)	Cases in the DP group, n (%)	OR	95%CI	P value
HE	14 (21.5)	54 (45)	2.98	1.49-5.95	< 0.01 <sup>a</sup>
HRS	6 (9.2)	26 (21.6)	2.71	1.05-7.00	0.03 <sup>a</sup>
Infections	7 (10.7)	30 (25.0)	2.76	1.13-6.70	0.02 <sup>a</sup>
LOS ≥ 7 d	25 (47.6)	88 (73.3)	3.01	1.60-5.67	< 0.01 <sup>a</sup>
In-hospital mortality	4 (6.1)	21 (17.5)	3.23	1.05-9.87	0.03 <sup>a</sup>
90 d readmission	11 (18.0)	34 (34.3)	1.94	0.90-4.15	0.08

<sup>a</sup>P < 0.05. EP: Early paracentesis group; DP: Delayed paracentesis group; HE: Hepatic encephalopathy; HRS: Hepato-renal syndrome; LOS: Length of stay; OR: Odds ratio; CI: Confidence interval.

based on antimicrobial therapy and albumin. As such, early detection and therapy of SBP are critical for improving favorable outcomes in patients with cirrhosis and ascites. Prior studies showed that paracentesis within one day of admission is associated with lower in-patient mortality and fewer readmissions<sup>[13]</sup>. Moreover, higher mortality was noted in patients with cirrhosis and ascites who did not undergo paracentesis compared to patients who did<sup>[6]</sup>.

Our study found that patients who received EP had a shorter LOS. A reason for this finding could be that rapid diagnosis of SBP or evacuation of tension ascites, and rapid initiation of antimicrobial treatment is effective and prevents the development of other complications leading to shorter hospitalization. On the other hand, patients in the DP group had more complications and this could explain the longer LOS in this group.

Patients were more likely to receive EP if admitted on a weekday compared to being admitted on a weekend and more than half of patients in the DP were admitted on the weekend. This could be explained by the low number of medical staff on call during weekends. Similar findings were noted in another study<sup>[14]</sup>.

According to the literature<sup>[15]</sup>, the time of paracentesis is associated with the risk of mortality. In a study conducted by O'Brien *et al*<sup>[16]</sup>, the majority of patients experienced DP and in-hospital mortality was higher in these patients. Similarly, in our study, patients who received EP had lower in-hospital mortality than patients who received DP (6.1% vs 17.5%, P < 0.05). Consistent with our findings, a recent study showed that patients who received DP had an increased risk of mortality<sup>[17]</sup>.

Observing the collected data, we also suppose that DP may also have a negative

impact on healthcare utilization. Given that the patients who received DP developed more complications, and had longer LOS, we can expect increased use of medical resources by these patients.

Cirrhosis is one of the leading causes of morbidity, requires frequent hospitalizations and carries a high risk for readmission<sup>[7]</sup>. Studies show 30-d readmission rates between 20%-37%<sup>[18]</sup>, and a 90-d readmission rate of up to 53%<sup>[19]</sup>. In our study, the overall 90-d readmission rate was 28.1% and it was in concordance with the study published by Orman *et al*<sup>[20]</sup> and higher than the rate of 12.9% found by Tapper *et al*<sup>[21]</sup>. Another study by Volk *et al*<sup>[22]</sup> reported a 30-d readmission rate of 37%<sup>[22]</sup>. In the literature<sup>[22-24]</sup>, similar to our study, the most common reasons reported for readmission were complications of cirrhosis. Readmissions frequently occur among patients with advanced liver disease, with increased MELD score being associated with readmission in most studies<sup>[20]</sup>.

In our study, the majority of patients (75.5%) who were readmitted within 90 d with continuous hospitalization were from the DP group. Only 24.5% of them were from the EP group. Another study conducted by Sobotka *et al*<sup>[25]</sup> found that paracentesis was associated with increased 30-d readmission. Despite this finding, paracentesis is recommended by guidelines and it is a quality indicator in cirrhotic patients.

Given that most patients had advanced liver disease, the presence of coagulopathy could be a reason for not performing paracentesis or for performing DP, but there is also strong evidence supporting that paracentesis is a safe procedure even in patients with associated coagulopathy<sup>[26]</sup>. Kanwal *et al*<sup>[7]</sup> found that the quality of care regarding ascites was better among patients with worse liver disease.

A limitation of our study may be the lack of data regarding discharged patients as we could not assess the survival rates of the patients who were not readmitted to our hospital 90 d after discharge. Another limitation of our study is that it is a retrospective study conducted in a single center, and our results should be confirmed by prospective, multicenter studies on a larger number of patients.

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## CONCLUSION

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In light of the data provided, early paracentesis (within 12 h after admission) could be a new inpatient quality metric among patients hospitalized with cirrhosis and ascites as it is associated with fewer complications of cirrhosis, lower in-hospital mortality and shorter length of stay.

## ARTICLE HIGHLIGHTS

### **Research background**

Cirrhosis is a leading cause of death worldwide and ascites is one of the most common complications of cirrhosis. Patients are frequently admitted to hospital, placing significant burden on the healthcare system.

### **Research motivation**

Data regarding the optimal time of paracentesis and outcomes among patients with cirrhosis and ascites are scarce in the literature.

### **Research objectives**

The aim of this study was to assess the outcomes of patients with cirrhosis and ascites who underwent paracentesis within 12 h after admission compared to patients who underwent paracentesis later than 12 h.

### **Research methods**

This was a retrospective study of 185 patients with cirrhosis and ascites who underwent paracentesis. The early paracentesis group was defined as paracentesis performed < 12 h after admission (65 patients) and the delayed paracentesis group was defined as paracentesis performed > 12 h after admission (120 patients). Complications of cirrhosis occurring during hospitalization were assessed and compared between the groups.

### Research results

Significantly more patients in the delayed paracentesis group than in the early paracentesis group developed hepatic encephalopathy, hepato-renal syndrome and infections during hospitalization. There were no statistically significant differences in the occurrence of spontaneous bacterial peritonitis and upper gastrointestinal bleeding between the two groups. Length of stay was shorter and in-hospital mortality was lower in the early paracentesis group. Patients from the delayed paracentesis group had a higher risk of developing complications during hospitalization.

### Research conclusions

Early paracentesis (within 12 h after admission) is associated with fewer complications of cirrhosis, lower in-hospital mortality and shorter length of stay.

### Research perspectives

Early paracentesis could be a new inpatient quality metric among patients hospitalized with cirrhosis and ascites and deserves to be investigated further in larger studies.

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