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Yara Al-Amouri

Damascus University

Kenan Alshawish

Damascus University

Ibraheem Alfrouh

`ibraheem.alfrouh@damascusuniversity.edu.sy`

Damascus University

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Hyponatremia as a prognostic indicator of mortality and complications in patients with cirrhosis: A Prospective Cross-Sectional Study

Yara Al-Amouri¹, Kenan Alshawish¹, Ibraheem Alfrouh¹

1 Internal medicine Department, Damascus University, Damascus, Syrian Arab Republic

Corresponding author:

Ibraheem Alfrouh

ibraheem.alfrouh@damascusuniversity.edu.sy

Tel: 0963988439490

ORCID Number: 0009-0002-7839-8752

Background: Hyponatremia frequently accompanies advanced cirrhosis and may reflect the severity of hepatic dysfunction and circulatory abnormalities. This study investigated whether serum sodium concentration was associated with disease severity, major complications, and in-hospital mortality among patients with cirrhosis.

Methods: A prospective cross-sectional study was conducted at Al-Mouassat and National University Hospitals in Damascus, Syria, between March 2022 and March 2023. The study enrolled 160 adult patients with documented cirrhosis. Disease severity was evaluated using the Child-Pugh classification and Model for End-Stage Liver Disease (MELD) score. Hyponatremia was defined as a serum sodium concentration ≤ 130 mEq/L. Associations between hyponatremia and cirrhosis severity, complications, and in-hospital mortality were assessed using the chi-square test, Student's t-test, and odds ratio (OR) estimation.

Results: Fifty-four patients (33.7%) had serum sodium concentrations ≤ 130 mEq/L. Hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome were more frequent in patients with hyponatremia than in those with higher sodium concentrations ($p=0.027$, $p=0.023$, and $p=0.012$, respectively). Patients with hyponatremia also had significantly higher mean MELD scores. Of the patients with hyponatremia, 49 (90.7%) were classified as Child-Pugh C. Hyponatremia was significantly associated with Child-Pugh C cirrhosis (OR 4.83; 95% CI 1.7–13.2; $p=0.002$). In addition, patients with hyponatremia had higher odds of in-hospital mortality (OR 2.46; 95% CI 1–6; $p=0.048$).

Conclusions: Serum sodium ≤ 130 mEq/L was associated with greater severity of cirrhosis, as reflected by higher MELD and Child-Pugh scores, as well as an increased frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Hyponatremia was

also associated with higher in-hospital mortality. These findings support the clinical value of serum sodium assessment as part of the evaluation of patients with cirrhosis.

Keywords: Cirrhosis, Hyponatremia, Child-Pugh score, Mortality, Prognosis.

1 Background

Cirrhosis is the common final histological stage of a variety of chronic liver diseases. Histologically, it is defined as widespread liver damage characterized by fibrosis and the transformation of the liver's normal structure into structurally abnormal nodules. This liver damage may progress to cirrhosis over a period ranging from weeks to years. For example, patients with hepatitis C may experience chronic hepatitis for up to 40 years before developing cirrhosis ^[1]. Cirrhosis is an increasing cause of morbidity and mortality in developed countries, ranking fourteenth globally as a cause of death among adults, fourth in Central Europe, and ninth in the United States ^[2]. Cirrhosis results in approximately 1.3 million deaths annually worldwide ^[3].

The clinical manifestations of cirrhosis result from changes in the pathophysiology and reflect disease severity regardless of the underlying cause. Portal hypertension is a major complication of cirrhosis, leading to the development of ascites and esophageal varices ^[3]. Other major complications include variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Electrolyte disturbances, such as hyponatremia and hypokalemia, are common in decompensated cirrhosis ^[4].

Hyponatremia is the most common electrolyte disorder in hospitalized patients ^[5]. In the context of cirrhosis, it is defined as a serum sodium level below 130 mEq/L ^[6]. A European study of outpatients and hospitalized cirrhosis patients showed that 21.6% had a sodium level below 130 mEq/L, 5.7% below 125 mEq/L, and 1.2% below 120 mEq/L ^[7].

Patients with cirrhosis may develop hyponatremia due to either hypovolemia (caused by extracellular fluid loss, such as from diuretic use) or hypervolemia (caused by increased extracellular fluid resulting from the kidneys' inability to excrete free water in proportion to intake). Hyponatremia is frequently observed in patients with decompensated cirrhosis, and its presence prior to liver transplantation may be an important prognostic indicator of post-transplant outcomes ^[8].

Although hyponatremia is a common disorder that physicians encounter in clinical practice, managing it in advanced cirrhosis can be challenging.

2 Methods

2.1 Study design, Setting and study period

A prospective observational study was conducted at Al-Mouassat and National University Hospitals, Damascus, Syria, during the period between March 2022 and March 2023

2.2 Sample size and Sampling Technique

The final research sample consisted of 160 patients, based on Richard Geiger's equation for calculating sample size:

$$n = \frac{\left(\frac{z}{d}\right)^2 \times (0.50)^2}{1 + \left(\frac{1}{N}\right) \times \left(\left(\frac{z}{d}\right)^2 \times (0.50)^2 - 1\right)}$$

Where:

n: sample size

N: Target population size (300)

Z: Standard score corresponding to a 95% confidence level (1.96)

d: margin of error (0.05)

2.3 Study Participants and Data Collection Procedures

The study was conducted at Al-Mowasat and National University Hospitals during the study period and included patients aged ≥ 18 years of either sex with cirrhosis of any etiology who consented to participate. Patients younger than 18 years, with renal or heart failure, hepatocellular carcinoma, severe extrahepatic disease or malignancy, hospital stay < 48 hours, or receiving medications known to affect serum sodium levels (e.g., thiazide diuretics, SSRIs, tricyclic antidepressants, or MAOIs) were excluded.

Cirrhosis was diagnosed by liver biopsy or a combination of clinical, biochemical, and radiological findings, including portal hypertension or esophageal varices. Hepatitis B and C were assessed using HBsAg and anti-HCV antibodies, respectively. Cirrhosis was classified as hepatitis B-, hepatitis C-, alcohol-, other-cause, or cryptogenic cirrhosis.

A detailed history and physical examination were performed, including assessment of demographic characteristics, medical and medication history, and cirrhosis-related complications. Hepatic encephalopathy was diagnosed based on behavioral or cognitive changes and asterixis. Hepatorenal syndrome was diagnosed according to International Club of Ascites criteria, while spontaneous bacterial peritonitis was defined by an ascitic fluid neutrophil count >250 cells/mm³ and/or positive bacterial culture after excluding other intra-abdominal infections.

Laboratory investigations at admission included serum sodium, AST, ALT, total bilirubin, albumin, PT/INR, and creatinine. Patients were categorized into hyponatremia (≤ 130 mEq/L) and non-hyponatremia (>130 mEq/L) groups. Liver disease severity was assessed using the Child-Pugh and MELD scores.

The primary outcomes were the associations of hyponatremia with liver disease severity, cirrhosis-related complications, and in-hospital mortality.

2.4 Statistical Analysis

Frequencies and percentages were used for categorical variables, while means and standard deviations (SD) were used for continuous variables. Chi-square and independent-samples t-tests were used for group comparisons. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association of hyponatremia with Child-Pugh class and mortality. Analyses were performed using IBM SPSS Statistics version 20.0, with $P < 0.05$ considered statistically significant.

3 Results

The study included 160 inpatients with liver cirrhosis, with a mean age of 57.9 ± 11 years; 103 (64.4%) were men. The most common etiologies were chronic hepatitis B (55%), idiopathic causes (20%), chronic hepatitis C (13.7%), alcohol-related liver disease (6.3%), and other causes (5%). The most frequent complications were ascites (76.8%), hepatic encephalopathy (31.3%), variceal hemorrhage (26.8%), spontaneous bacterial peritonitis (21.3%), and hepatorenal syndrome (7.5%).

Most patients had a MELD score >20 (71.8%) and Child-Pugh class C (75%). Mean serum sodium was 133.7 ± 5.7 mEq/L. Hyponatremia (≤ 130 mEq/L) was present in 54 patients (33.7%), while 106 (66.3%) had sodium levels >130 mEq/L (Table I).

Table I. Patient Characteristics

	(n=160)
Gender	n (%)
Male	103 (64.4%)
Age, mean (SD), years	57.9 (11)
Causes of cirrhosis	n (%)
B Hepatitis	88 (55%)
Idiopathic	32 (20%)
C hepatitis	22 (13.7%)
Alcohol	10 (6.3%)
Others causes	8 (5%)
Complications of cirrhosis	n (%)
Ascites	123 (76.8%)
Hepatic encephalopathy	50 (31.3%)
Variceal hemorrhages	43 (26.85)
SBP (spontaneous bacterial peritonitis)	34 (21.3%)
HRS (Hepatic renal syndrome)	12 (7.5%)
Severity of liver disease	

MELD score	n (%)
≤ 10	5 (3.2%)
11-20	40 (25%)
>20	115 (71.8%)
Child-Pugh score	n (%)
A	7 (4.3%)
B	33 (20.6%)
C	120 (75%)
Laboratories	mean (SD)
Total bilirubin, (mg/dl)	3.9 (2)
Direct bilirubin, (mg/dl)	1.8 (1.5)
AST, (IU/L)	74.7 (44.5)
ALT, (IU/L)	61 (28.4)
Serum albumin, (g/dl)	3.1 (0.71)
INR	1.6 (0.79)
Creatinine, (mg/dl)	1.12 (0.56)
Sodium (mEq/L)	133.7 (5.7)
Serum Sodium	n (%)
≤ 130 mEq/L	54 (33.7%)
>130 mEq/L	106 (66.3%)

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149 Patients were divided into hyponatremia (≤130 mEq/L, n=54) and non-hyponatremia (>130
150 mEq/L, n=106) groups. No significant differences were found in age, sex, or cirrhosis etiology.
151 Patients with hyponatremia had significantly higher direct bilirubin, AST, and INR levels and
152 lower albumin levels, while total bilirubin, ALT, and creatinine did not differ significantly.
153 Hepatic encephalopathy (42.6% vs. 25.5%, P=0.027), spontaneous bacterial peritonitis (31.5%
154 vs. 16%, P=0.023), and hepatorenal syndrome (14.8% vs. 3.8%, P=0.012) were significantly
155 more frequent in the hyponatremia group, whereas ascites and variceal hemorrhage showed no
156 significant differences (Table II).

157 Table II. Patient Characteristics According to Serum Sodium Level

Variable		Sodium level		Test	P-value
		≤ 130 mEq/L (54 patients)	>130 mEq/L (106 patients)		
Age		60 ± 10.8	57.2 ± 11.1	t-Test value = 1.522	0.129
Gender	Male	32 (50.3%)	71 (67%)	χ^2 -value = 0.93	0.334
	Female	22 (40.7%)	35 (33%)		
Cause of cirrhosis	B Hepatitis	27 (50%)	61 (57.5%)	χ^2 -value = 0.823	0.364
	C hepatitis	9 (16.7%)	13 (12.3%)	χ^2 -value = 0.585	0.44
	Alcohol	4 (7.4%)	6 (5.7%)	χ^2 -value = 0.186	0.666
	Others causes	14 (25.9%)	26 (24.5%)	χ^2 -value = 0.037	0.847
Laboratorie s	TB, (mg/dl)	4.2 ± 1.9	3.7 ± 2	t-Test value = 1.52	0.13
	DB, (mg/dl)	2.3 ± 1.5	1.5 ± 1.2	t-Test value = 3.65	0.0003
	AST, (IU/L)	82.1 ± 43	56 ± 45	t-Test value = 3.72	0.0002
	ALT, (IU/L)	64 ± 30	59 ± 27	t-Test value = 1.14	0.254
	AlB, (g/dl)	2.7 ± 0.7	3.6 ± 0.72	t-Test value = 7.99	0.0001
	INR	1.9 ± 0.8	1.6 ± 0.7	t-Test value = 2.62	0.009

Cr, (mg/dl)	1.2 ± 0.6	1.09 ± 0.52	t-Test value =	0.197
			1.29	

Complications of cirrhosis	Ascites	44 (81.5%)	79 (74.5%)	χ^2 -value = 0.973	0.323
	Hepatic encephalopathy	23 (42.6%)	27 (25.5%)	χ^2 -value = 4.881	0.027
	Variceal hemorrhages	15 (27.8%)	28 (26.4%)	χ^2 -value = 0.034	0.853
	SBP	17 (31.5%)	17 (16%)	χ^2 -value = 5.099	0.023
	HRS	8 (14.8%)	4 (3.8%)	χ^2 -value = 6.287	0.012

TB: Total bilirubin, DB: Direct bilirubin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, Alb: Albumin, INR: International Normalized Ratio, Cr: Creatinine, SBP: spontaneous bacterial peritonitis, HRS: Hepatic renal syndrome.

158

159 Hyponatremia was significantly associated with higher MELD scores ($t=4.159$, $P=0.0001$).
 160 Among patients with hyponatremia, 90.7% were classified as Child-Pugh C compared with 67%
 161 of those without hyponatremia ($P=0.0028$). Hyponatremia was significantly associated with
 162 Child-Pugh C ($OR=4.83$, 95% CI: 1.7–13.2, $P=0.002$). In-hospital mortality was higher among
 163 patients with hyponatremia than those without (22.2% vs. 10.4%), with an increased risk of
 164 mortality ($RR=2.46$, 95% CI: 1–6, $P=0.048$).

165 4 Discussion

166 Low serum sodium levels (≤ 130 mEq/L) in patients with cirrhosis are considered hyponatremia
 167 ^[6]. Hyponatremia is common in cirrhosis and ascites and is associated with increased morbidity
 168 and mortality ^[7]. This study aimed to determine its prevalence and prognostic significance in
 169 hospitalized patients with cirrhosis, particularly its association with disease severity,
 170 complications, and in-hospital mortality.

The study included 160 patients hospitalized with cirrhosis; 64.4% were male, and 66.2% were in their sixth or seventh decades. Previous studies indicate that males are more likely to develop liver disease than females. Viral hepatitis was the most common cause of cirrhosis in our study, whereas alcoholism is the leading cause in the Western world and a major cause of mortality among men in the United States [9].

Hyponatremia (≤ 130 mEq/L) was observed in 54 patients (33.7%), a prevalence consistent with previous studies.

In a 2022 study by Chaudhary et al. [10] in Nepal involving 96 adults with chronic liver disease, hyponatremia was present in 32.2%. Similarly, Nareddy et al. [11] reported a prevalence of 34.7% among 95 hospitalized patients with cirrhosis in India in 2020.

Higher rates have also been reported. Elkady et al. [12], in a 2016 Egyptian study of 200 patients with cirrhosis, found that 43.5% had serum sodium ≤ 125 mEq/L.

Lower rates have been reported in other populations. Ennaifer et al. [13] found hyponatremia in 10.5% of 143 hospitalized patients with cirrhosis in Tunisia. In Japan, Umemura et al. [14] found that 15.2% of 171 patients had sodium below 135 mEq/L, while only 4.7% had levels ≤ 130 mEq/L. These differences may reflect variations in patient selection, sample size, or ethnicity.

Hepatic encephalopathy was more common among patients with hyponatremia. Hyponatremia may contribute to cerebral edema and exacerbate astrocyte swelling, thereby promoting hepatic encephalopathy [15]. This finding is consistent with Chaudhary et al. [10] and a Spanish study reporting hyponatremia as an independent predictor of hepatic encephalopathy (HR 8.36) [16]. Elkady et al. [12] reported hepatic encephalopathy in 91% of patients with sodium ≤ 125 mEq/L. However, Nareddy et al. [11] found no significant association, possibly due to their small sample size.

Low serum sodium was also significantly associated with hepatorenal syndrome, consistent with findings from Nareddy et al. [11] and Chaudhary et al. [10], although contrary to a previous study from South Korea [17]. Hyponatremia may be an early marker of impaired renal function and a precursor to hepatorenal syndrome [18]. Ascites, hyponatremia, and renal dysfunction are closely

198 interrelated, with factors such as spontaneous bacterial peritonitis, infection, gastrointestinal
199 bleeding, and diuretics potentially worsening renal function ^[19].

200 A clinically important finding was the association between hyponatremia and spontaneous
201 bacterial peritonitis, consistent with previous studies ^[11,18]. Hyponatremia is associated with
202 increased fluid retention and more frequent paracentesis, which may increase the risk of
203 spontaneous bacterial peritonitis ^[15].

204 No statistically significant association was found between hyponatremia and variceal bleeding,
205 consistent with previous studies ^[10,11,17]. Variceal formation is primarily related to portal
206 hypertension and vascular changes rather than excess body water. Further studies are needed to
207 clarify any potential relationship between hyponatremia and varices.

208 Patients with hyponatremia had significantly lower mean albumin levels and higher direct
209 bilirubin, AST, and INR levels ($P<0.05$). Similarly, Chaudhary et al. ^[10] found significantly
210 higher direct bilirubin, ALT, AST, and alkaline phosphatase levels in patients with
211 hyponatremia.

212 In contrast, Meganathan et al. ^[20] found no significant association between serum sodium and
213 ALT, AST, or alkaline phosphatase. Elkady et al. ^[12] likewise reported no significant association
214 between hyponatremia and alkaline phosphatase, AST, ALT, or bilirubin.

215 The mean MELD score was significantly higher in patients with hyponatremia. Moreover, 90.7%
216 of patients with hyponatremia were classified as Child-Pugh C compared with 67% of those
217 without hyponatremia ($P<0.05$). These findings are consistent with most previous studies linking
218 hyponatremia to more advanced cirrhosis.

219 Elkady et al. ^[12] reported differences in MELD scores according to sodium level and found that
220 61% of hyponatremic patients were Child-Pugh C. Nareddy et al. ^[11] similarly found Child-Pugh
221 C in 87.9% of patients with hyponatremia compared with 64.5% without hyponatremia.
222 Chaudhary et al. ^[10] also reported significantly higher MELD and Child-Pugh scores among
223 hyponatremic patients.

Conversely, a study from Bangladesh found no significant association between sodium levels and cirrhosis severity ^[21], possibly due to its small sample size. Our findings support the view that hyponatremia is a marker of advanced liver disease and is more prevalent in Child-Pugh C patients.

In-hospital mortality was significantly higher among patients with hyponatremia (OR 2.46, 95% CI: 1–6, P=0.048). Previous studies similarly identified hyponatremia as a predictor of both in-hospital and short-term mortality in cirrhosis.

Chaudhary et al. ^[10] reported in-hospital mortality of 25.9% among patients with hyponatremia versus 4.3% among those without. Cardenas et al. ^[22] found that hyponatremia nearly doubled 90-day mortality in patients without ACLF (RR 1.81), while the risk increased markedly in patients with both ACLF and hyponatremia (RR 6.85). Ennaifer et al. ^[13] also identified hyponatremia as a negative prognostic factor associated with increased 1-year mortality.

This study had several limitations. First, the sample size was relatively small. Second, patients were only followed during their hospital stay, and no longer-term follow-up was conducted. Third, changes in blood sodium levels were not monitored during the follow-up period, and the effect of this electrolyte imbalance on the outcomes was not investigated.

5 Conclusion

Hyponatremia occurred in 33.7% of hospitalized cirrhotic patients and was associated with more complications, advanced liver disease, and higher in-hospital mortality (RR=2.46, 95% CI: 1–6, P=0.048).

6 Declarations

6.1 Ethics approval and consent to participate

The study was approved by the Ethics Committee of Damascus University (Approval No. 1514; December 2, 2021) and was conducted in accordance with the ethical principles of the Declaration of

248 Helsinki. All participants provided written informed consent after receiving an explanation of the study.

249 No identifiable personal data were collected.

250 **6.2 Consent for publication**

251 Not applicable.

252 **6.3 Availability of data and materials**

253 The datasets generated and/or analyzed during the current study are available from the

254 corresponding author on reasonable request.

255 **6.4 Competing interests**

256 The authors declare that they have no competing interests.

257 **6.5 Funding**

258 None.

259 **6.6 Authors' contributions**

260 Yara Al-Amouri: conception and design of the study, data collection, and manuscript

261 preparation.

262 Kenan Alshawish: critical review and revision of the manuscript.

263 Ibraheem Alfrouh: manuscript editing and preparation of the final version for submission. All

264 authors reviewed and approved the final manuscript and agreed to be accountable for all aspects

265 of the work.

266 **6.7 Acknowledgements**

267 None.

268 **7 List of abbreviations**

269 **CLF:** Acute-on-Chronic Liver Failure

270 **Alb:** Albumin

271 **ALT:** Alanine Aminotransferase

272 **anti-HCV:** Hepatitis C Virus Antibody

273 **AST:** Aspartate Aminotransferase

274 **CI:** Confidence Interval

275 **Cr:** Creatinine

276 **DB:** Direct Bilirubin

277 **HBsAg:** Hepatitis B Surface Antigen

278 **HRS:** Hepatorenal Syndrome

279 **HR:** Hazard Ratio

280 **INR:** International Normalized Ratio

281 **MAOIs:** Monoamine Oxidase Inhibitors

282 **MELD:** Model for End-Stage Liver Disease

283 **OR:** Odds Ratio

284 **PT:** Prothrombin Time

285 **RR:** Relative Risk

286 **SBP:** Spontaneous Bacterial Peritonitis

287 **SD:** Standard Deviation

288 **SPSS:** Statistical Package for the Social Sciences

289 **SSRIs:** Selective Serotonin Reuptake Inhibitors

290 **TB:** Total Bilirubin

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9 Tables legends

	(n=160)
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365 **Table II. Patient Characteristics According to Serum Sodium Level**

Sodium level

Variable		≤ 130 mEq/L (54 patients)	>130 mEq/L (106 patients)	Test	P-value
Age		60 ± 10.8	57.2 ± 11.1	t-Test value = 1.522	0.129
Gender	Male	32 (50.3%)	71 (67%)	χ^2 -value = 0.93	0.334
	Female	22 (40.7%)	35 (33%)		
Cause of cirrhosis	B Hepatitis	27 (50%)	61 (57.5%)	χ^2 -value = 0.823	0.364
	C hepatitis	9 (16.7%)	13 (12.3%)	χ^2 -value = 0.585	0.44
	Alcohol	4 (7.4%)	6 (5.7%)	χ^2 -value = 0.186	0.666
	Others causes	14 (25.9%)	26 (24.5%)	χ^2 -value = 0.037	0.847
Laboratorie s	TB, (mg/dl)	4.2 ± 1.9	3.7 ± 2	t-Test value = 1.52	0.13
	DB, (mg/dl)	2.3 ± 1.5	1.5 ± 1.2	t-Test value = 3.65	0.0003
	AST, (IU/L)	82.1 ± 43	56 ± 45	t-Test value = 3.72	0.0002
	ALT, (IU/L)	64 ± 30	59 ± 27	t-Test value = 1.14	0.254
	AlB, (g/dl)	2.7 ± 0.7	3.6 ± 0.72	t-Test value = 7.99	0.0001
	INR	1.9 ± 0.8	1.6 ± 0.7	t-Test value = 2.62	0.009
	Cr, (mg/dl)	1.2 ± 0.6	1.09 ± 0.52	t-Test value = 1.29	0.197

Complications of cirrhosis	Ascites	44 (81.5%)	79 (74.5%)	χ^2 -value = 0.973	0.323
	Hepatic encephalopathy	23 (42.6%)	27 (25.5%)	χ^2 -value = 4.881	0.027
	Variceal hemorrhages	15 (27.8%)	28 (26.4%)	χ^2 -value = 0.034	0.853
	SBP	17 (31.5%)	17 (16%)	χ^2 -value = 5.099	0.023
	HRS	8 (14.8%)	4 (3.8%)	χ^2 -value = 6.287	0.012

TB: Total bilirubin, DB: Direct bilirubin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, AlB: Albumin, INR: International Normalized Ratio, Cr: Creatinine, SBP: spontaneous bacterial peritonitis, HRS: Hepatic renal syndrome.

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