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Body mass index (BMI) and alpha-fetoprotein (AFP) level correlate with the severity of HCV-induced fibrosis in a cohort of Egyptian patients with chronic HCV

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Abstract

Background: Viral hepatitis is the seventh leading cause of mortality globally, and half of this mortality is attributed to hepatitis C virus (HCV). Egypt has the highest HCV prevalence worldwide, with an estimated 14.7% of the population being HCV-positive. HCV infection is the primary cause of liver fibrosis, cirrhosis, and hepatocellular carcinoma. Liver fibrosis varies in severity during chronic HCV infection, and 10–20% of chronic hepatitis C (CHC) patients with severe fibrosis develop cirrhosis. The goal of this work was to assess the clinico-demographic predictors of severity of HCV-induced fibrosis in a cohort of Egyptian patients.

Results: A cohort of Egyptian patients with chronic HCV genotype 4a infection showed significant association between severe fibrosis stages and obesity, represented by a higher body mass index (BMI), low albumin level, high alpha-fetoprotein (AFP) level, low thyroid-stimulating hormone (TSH) level, and high alkaline phosphatase (ALP) level. Multivariate analysis delineated BMI, TSH, and ALP as independent significant variables that could predict the risk of fibrosis severity in HCV infections.

Conclusion: This study argues in favor of using the biomarker profile of CHC patients infected with HCV genotype 4a to identify patients at higher risk of developing severe fibrosis, which is a necessary first step towards precision medicine via patient stratification.

Keywords: Liver, Hepatitis, Virology, Genetics, Multivariate

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Background

Viral hepatitis is the seventh leading cause of mortality globally [1], and half of this mortality is attributed to hepatitis C virus (HCV). Almost 71 million individuals are estimated to be infected worldwide, with ~750,000 new infections occurring annually [2]. HCV infection is the primary cause of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [3].

Egypt has the highest prevalence of HCV infection worldwide, with an estimated 14.7% of the population being HCV-positive [4, 5]. Genotype 4a is the most prevalent genotype in Egypt. The main cause of this endemic is attributed to mass parenteral antischistosomal therapy campaigns in the 60s to 80s of the twentieth century [6].

During the acute phase of HCV infection, defined as the first six months post-infection, only 20% of patients spontaneously clear the virus [7]. However, in 80% of cases, the immune system is unable to eradicate HCV during the acute phase and HCV persists, leading to chronic hepatitis C (CHC) infection [8], which may contribute to the development of liver fibrosis, cirrhosis, and HCC as complications [9]. Several factors influence the progression of liver diseases; the most important of which is the extent of intrahepatic inflammation caused by HCV [10].

Genetic diversity of the virus and its rapid mutation rate may allow HCV to escape immune recognition [11]. In case of CHC, most patients are asymptomatic and may have non-specific symptoms such as fatigue, arthralgia, or myalgia [12].

Most of HCV infection cases will have persistently elevated liver enzymes in further follow-up [13]. However, the transaminase level may even remain normal or moderately increased [14]. Their level may vary significantly over the natural history of CHC and most of the patients may have only slight elevation of transaminases [15, 16].

HCV infection can also cause liver cell failure or HCC (approximately 2 to 4% per year) [17]. However, there are a number of factors that affect liver disease progression, and it is important to understand the natural history of HCV to be able to take correct decisions to reduce disease progression rates [18].

Structural liver damage, also known as fibrosis, is variable in chronic HCV infection. In mild cases, fibrosis is limited to the portal and peripheral areas, whereas more advanced fibrosis extends from one portal area to cirrhosis, which develops in approximately 10–20% of CHC individuals over 20 years [19]. Patients with CHC infection display the typical natural history of liver fibrosis, starting from the early stages of fibrosis, and in severe cases ending in liver cirrhosis [20, 21]. Fibrosis is one of the main prognostic factors that is correlated with the risk of developing liver cirrhosis. The study of demographic data and common clinical parameters is considered a good tool to indicate the possibility of fibrosis severity without any invasive intervention.

In the present study, we aimed to evaluate and determine the potential association between patients' demographics and clinical parameters on the degree of fibrosis severity in a cohort of Egyptian patients.

Methods

Study cohort

Subjects

One hundred adult Egyptian patients, with laboratory-confirmed chronic infections with hepatitis C virus genotype 4, were enrolled in the present study. The 100 patients included 34 females and 66 males, aged 20–60 years.

Blood samples were collected from patients diagnosed at National Hepatology & Tropical Medicine Research Institute, Cairo, Egypt within the period from August 2017 until December 2017.

A written informed consent was obtained from each participant, and all patients were fully informed concerning the nature of the disease and the diagnostic procedures involved.

Inclusion criteria

Patients with the following characteristics were included in the study: adult, male or female (18–60 years old), chronic HCV infection (more than a 6-month duration), elevation of serum aminotransferases (AST and ALT) levels, evidence of chronic hepatitis in liver biopsy, not previously treated with any antiviral drugs, cessation of all immune modulating therapy, and HBsAg-negative.

Exclusion criteria

Patients with the following characteristics: co-infection with HBV, decompensated liver cirrhosis, autoimmune liver disease, chronic renal disease, ischemic cardiovascular disease, antiviral or immunosuppressive therapy within the last 6 months, pregnancy and/or breastfeeding, uncontrolled diabetes mellitus or hypertension, and alcoholism were excluded.

Groups

The patients were classified into two groups according to the stage of liver fibrosis identified by liver biopsy and FibroScan according to Ishak's scoring system [22]:

- Group 1 was defined as “mild fibrosis patients” (mild group): from F1–F3.
- Group 2 was defined as “severe fibrosis patients” (severe group): from F4–F6.

Blood sample collection

Five milliliters peripheral blood sample was withdrawn from patients. In each sample, two milliliters were withdrawn into an EDTA tube for later DNA extraction, while 3 mL was taken in a plain tube for serum

separation that was used to carry out all serological markers for HCV, HBV, and standard laboratory tests.

Standard laboratory tests

Liver function tests

Determination of prothrombin time and concentration, serum bilirubin (direct and total), serum albumin, aspartate transaminase (AST), alanine transaminase (ALT), alpha-fetoprotein (AFP), complete blood picture (CBC), and alkaline phosphatase (ALP) assay were performed on all samples.

Markers of hepatitis virus

HBsAg was detected using ELISA Murex HBsAg version 3 commercially available kit (Diasorin®, UK), and Anti-HCV was assessed by ELISA Murex Anti-HCV version 4 kit (Diasorin®, UK). All procedures were done according to manufacturer instructions.

HCV-RNA titer

HCV-RNA titer was measured by real-time PCR using (Stratagene, Model: MX 3000PTM) equipment.

Thyroid function tests

T3, T4, and TSH levels were determined using IMMULITE 1000 immunoassay system (Siemens® Healthineers) for all patients.

Random blood glucose level

It was determined using glucose assay kit (Abcam®, UK) for all patients.

Statistical analyses

All statistical analyses were performed in the SPSS Statistical software package (v. 20) for Windows (SPSS, Chicago, IL). The graphs were plotted by GraphPad Prism 7 (GraphPad Software, San Diego, CA).

Quantitative data were summarized as mean, standard deviation, median, minimum, and maximum. Frequency (count) and relative frequency (percentage) were used to summarize categorical data. Non-parametric quantitative variables were compared by the Mann-Whitney test. Parametric quantitative variables were compared by the Student *t* test. For interpretation of results, *p* values < 0.05 were considered statistically significant.

Univariate and multiple binary logistic regression analyses were completed to detect predictors associated with the risk of severe fibrosis. The significant data in the univariate analysis were further analyzed by multiple analysis to determine the independent variables that affected the fibrosis severity.

Results

Patient demographics and laboratory characteristics

Study cohort

The 100 adult liver fibrotic patients chronically infected with hepatitis C virus (HCV) were categorized into two groups: group 1, 59 HCV patients with mild stages of fibrosis (thereafter, indicated as the mild group), and group 2, 41 HCV patients with severe stages of fibrosis (thereafter, indicated as the severe group).

The two groups were matched for the main demographic features, including gender and age distribution, since the gender distribution and the mean age were not significantly different between the two groups ($p > 0.05$) (Table 1).

The mean BMI of the mild group was 25.80 ± 9.03 kg/m² and that of the severe group was 31.78 ± 8.84 kg/m², with a significant difference between the two groups ($p < 0.001$) (Fig. 1).

Association between clinical parameters and severity of fibrosis:

Numerous clinical parameters were available for the patients in the study cohort. We performed statistical analysis to identify parameters that could be associated with the degree of fibrosis (Table 2).

Comparing the laboratory investigation results revealed a significant difference in the levels of serum albumin (AL) ($p = 0.008$), alpha-fetoprotein (AFP) ($p = 0.033$), thyroid-stimulating hormones (TSH) ($p = 0.022$), and alkaline phosphatase (ALP) ($p = 0.037$) between both groups (Fig. 2). No significant difference was found in the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL), blood glucose (BG), hemoglobin (Hb), creatinine (Cr), nor the platelet count and white blood cell (WBC) count ($p > 0.05$ for all parameters) between both groups.

Univariate and multivariate analyses for the parameters affecting fibrosis severity

Analysis of univariate and multivariate logistic regression were used to determine the factors that may be associated with severe fibrosis in CHC patients infected with HCV genotype 4a (Table 3). In the univariate analysis, BMI, albumin, TSH, and ALP were designated as significant predictors associated with the severe fibrosis in our study cohort. On conducting multivariate analysis, BMI, TSH, and ALP were designated as independent significant variables that could be used as predictors for the risk of fibrosis severity in HCV infections.

Discussion

Chronic HCV is a major cause of liver fibrosis leading to cirrhosis and hepatocellular carcinoma [23, 24]. The rate of progression of fibrosis is highly variable, where

Table 1 Patients' demographic characteristics

Demographic data	Mild group (N = 59) No.	Severe group (N = 41) No.	Test of sig.	<i>p</i> value
Gender				
Males	37	29	Chi-square test	0.405
Females	22	12		
Age (years)				
Mean ± SD	41.0 ± 8.0	38.95 ± 7.82	Student's <i>t</i> test	0.207

The *p* value for comparisons between mild and severe fibrosis groups

progression to cirrhosis ranges from 10 to 30 years [25, 26]. The prevalence of chronic HCV infection in Egypt is ~ 14.8% [2], underscoring importance to highlight various parameters associated with fibrosis severity in chronic HCV Egyptian patients. This study identified significant associations between severe fibrosis and high BMI, low albumin level, high AFP level, low TSH level, and high ALP level. Multivariate analysis revealed BMI, TSH, and ALP as independent significant variables associated with severe fibrosis in chronic infection with HCV genotype 4a.

Our results showed that obesity is a factor associated with increased risk of HCV-induced liver fibrosis. This finding agrees with several previous studies [27–32]. However, this BMI association with risk is not unchallenged, as a previous study reported no significant difference between BMI and severe fibrosis stages [33]. It is possible that, in the latter study, other confounding factors had major effects or that the number of subjects did not offer sufficient statistical power to resolve the BMI contribution [33].

Albumin is the main protein circulating in the blood, yet only formed by the liver [34]. The lower albumin level in patients with severe fibrosis is in accordance with several studies that reported similar results [35–39]. Our results revealed that with increasing HCV severity, the patients were at high risk for impairment in the thyroid function with decreasing in the activity of the thyroid gland (hypothyroidism), a finding that agrees with Metwalley et al. [40]. Similarly, Rodríguez-Torres et al. [41] and Chang et al. [42] reported that patients with severe fibrosis require thyroid treatment.

Serum AFP is a fetal glycoprotein. It is a widely used marker for HCC [43]. Our result was congruent with two published studies [44, 45], but not with Dayan et al. [46], who suggested there was no association between AFP level and HCV fibrosis progression. They thought that it was due to the limited number of patients.

The ALP level decreased in the severe group, in agreement with Das et al. [47]; however, results reported by Ijaz et al. [48], Attallah et al. [49], and Wai et al. [50]

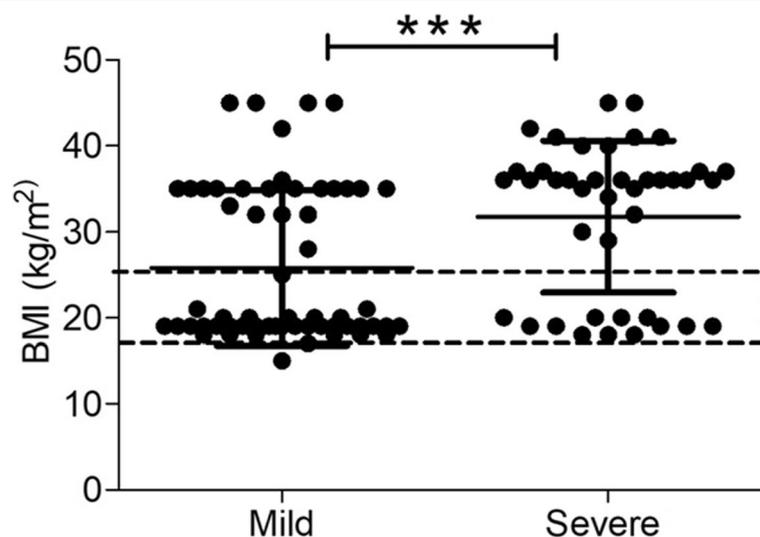


Fig. 1 Comparison of body mass index (BMI) between the two studied groups. BMI of patients from the mild group (N = 59) and severe group (N = 41). The median and interquartile range is shown with horizontal lines. The dashed box represents the normal range for BMI in healthy individual (18.9–25 kg/m²). ****p* < 0.001

Table 2 Results of laboratory investigations

Laboratory investigations	Mild group (N = 59) Mean ± SD	Severe group (N = 41) Mean ± SD	Chi-square p value
Albumin (g/dL)	3.96 ± 0.37	3.74 ± 0.42	0.008**
Alpha-fetoprotein (ng/ml)	13.05 ± 5.87	14.07 ± 18.34	0.033*
TSH (IU/L)	3.70 ± 0.71	3.34 ± 0.82	0.022*
ALP (IU/L)	136.44 ± 42.97	113.61 ± 53.61	0.037*
AST (IU/L)	86.63 ± 60.22	92.29 ± 53.72	0.334
ALT (IU/L)	75.85 ± 48.26	68.07 ± 33.47	0.725
Total Bilirubin (mg/dL)	1.07 ± 0.37	0.99 ± 0.46	0.125
Direct bilirubin (mg/dL)	0.24 ± 0.14	0.27 ± 0.22	0.478
Blood glucose (mg/dL)	98.92 ± 16.02	97.46 ± 16.43	0.660
Hemoglobin (Hb) (g/dL)	11.91 ± 1.75	11.55 ± 1.80	0.318
Creatinine (mg/dL)	0.97 ± 0.16	1.0 ± 0.19	0.847
Platelet (10 ³ /μL)	271.08 ± 69.61	286.41 ± 75.42	0.450
WBCs (cells/mm ³)	7938.59 ± 1696.06	7582.90 ± 1803.64	0.150

Chi-square p values for comparisons between mild and severe groups: *p < 0.05, **p < 0.01, and ***p < 0.001

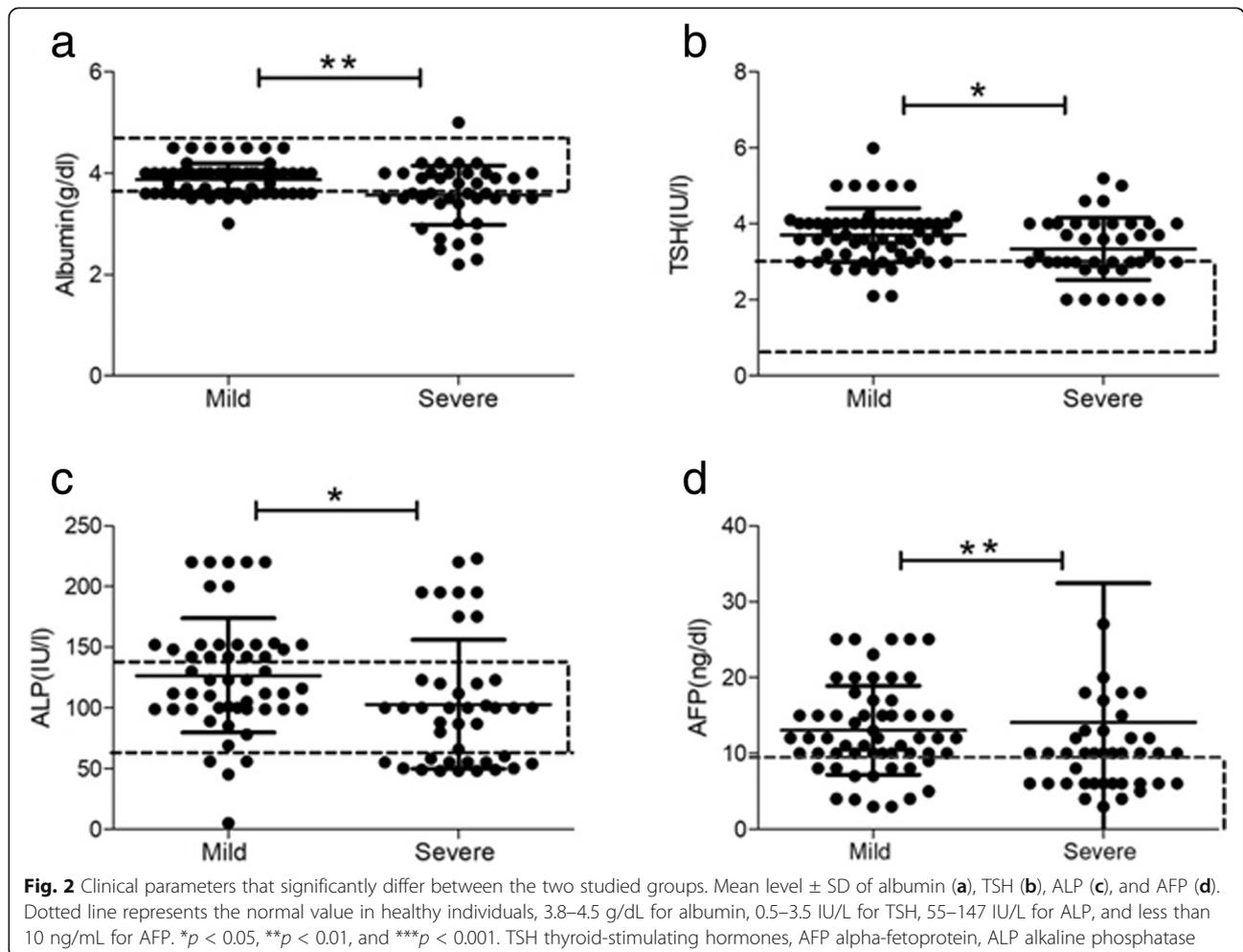


Table 3 Logistic regression analysis of clinical parameters associated with the degree of liver fibrosis in patients infected with HCV genotype 4a

	Univariate analysis		#Multivariate analysis	
	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)
Sex (male)	0.240	1.437 (0.785–2.630)		
Age (years)	0.074	0.967 (0.933–1.003)		
BMI (kg/m ²)	< 0.001***	1.074 (1.040–1.110)	< 0.001***	1.125 (1.070–1.183)
AST (IU/L)	0.493	1.002 (0.997–1.007)		
ALT (IU/L)	0.212	0.995 (0.988–1.0003)		
Albumin (g/dL)	< 0.001***	0.237 (0.107–0.523)	0.160	0.401 (0.112–1.436)
Total bilirubin (mg/dL)	0.184	0.614 (0.299–1.261)		
Direct bilirubin (mg/dL)	0.304	2.320 (0.467–11.537)		
Blood glucose (mg/dL)	0.530	0.994 (0.977–1.012)		
AFP (ng/mL)	0.573	1.006 (0.984–1.029)		
Hb (g/dL)	0.155	0.889 (0.756–1.045)		
Platelet (10 ³ /μL)	0.139	1.003 (0.999–1.007)		
WBCs (cells/mm ³)	0.155	1.000 (1.0–1.0)		
TSH (IU/L)	0.002**	0.523 (0.349–0.783)	0.005**	0.381 (0.193–0.751)
Creatinine (mg/dL)	0.371	2.114 (0.411–10.873)		
ALP (IU/L)	0.004**	0.990 (0.983–0.997)	< 0.001***	0.982 (0.974–0.991)

The *p* value of the comparison between mild and severe groups

#All variables with *p* < 0.05 were included in the multivariate analysis

p* < 0.05, *p* < 0.01, and ****p* < 0.001. All *p* values < 0.05 are shown in bold

were different. These studies suggested that lower viral load, higher bilirubin, and high levels of ALP and AST were associated with more severe fibrosis. They revealed that the higher levels of ALP are usually associated with liver metastasis, extra-hepatic bile obstruction, primary biliary cirrhosis, intrahepatic cholestasis, infiltrative liver disease, hepatitis, and cirrhosis.

Regarding age as a factor, our results agrees with several studies [51–54]. Massard et al. [30] reported that older age was associated with an increased risk of HCV-associated liver diseases. On another front, Gicquelais et al. [55], Espinosa et al. [56], and Prussing et al. [57] reported that HCV incidence has changed dramatically over the past years, with significant increase in the incidence of HCV among young people aged around 15–29 years.

Regarding the patients' gender, our results were in accordance with Narciso-Schiavon et al. [58]. However, there was a slight increase in the percentage of males especially in the severe group, in accordance with studies [30, 51, 52]. This issue remains controversial, as laboratory analysis showed no significant difference between the studied groups, in accordance with several studies [59–61], while other studies contradict our observations [62–65]. It is possible, though, that the overrepresentation of male subjects relates to HCV infection in general [52] and is not associated with a certain complication or its severity.

Conclusion

In conclusion, Egyptian patients with HCV type 4 infection showed significant association between severe fibrosis stages and high BMI (obesity), low albumin level, high AFP level, low TSH level, and high ALP level. In the univariate analysis, BMI, albumin, TSH, and ALP were designated as significant predictors associated with the severe fibrosis in HCV Egyptian patients. In the multivariate analysis, BMI, TSH, and ALP were designated as independent significant variables that could be used as predictors for the risk of fibrosis severity in HCV infections.

This study may direct practitioners and clinicians to determine the patient biomarker profiles which in turn defines who is at high risk for developing severe fibrosis and who is protecting from severe fibrosis. Such patient stratification step is pivotal to any attempt for adopting a precision medicine approach towards managing and prioritizing HCV cases.

Abbreviations

AFP: Alpha-fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CHC: Chronic hepatitis C; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; PAT: Parenteral antischistosomal therapy; TSH: Thyroid stimulating hormones; WBC: White blood cell

Acknowledgments

Not applicable

Authors' contributions

A.A.H., R.K.A., M.S.A., and M.A.T. conceived and designed the experiments. A.A.M. provided the samples and clinical information. A.A.H. performed the statistical analysis and prepared the figures. A.A.H., M.S.A., and M.A.T. wrote the manuscript, and R.K.A. critically read the manuscript. All authors read and approved the manuscript.

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Availability of data and materials

All data and materials are available upon request.

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee, Faculty of Pharmacy, Cairo University, Egypt (REC-FOPCU), under the protocol serial number: MI (2038).

A written informed consent was obtained from each participant, and all patients were fully informed concerning the nature of the disease and the diagnostic procedures involved.

Consent for publication

A consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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