Original Article

Prevalence of Fatty Liver and Clinical Implications in Patients with Chronic Hepatitis B Infection

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Background: Both CHB and fatty liver are common problems, and some patients may have both diseases together. The interaction between these two diseases is still not clear in relation to its effect on liver disease severity and hepatitis B treatment efficacy.

Objective: To study the prevalence of fatty liver in patients with chronic hepatitis B infection and identify factors associated with this condition including host factors, viral factors, and associations with liver disease severity.

Materials and Methods: Data were collected retrospectively from patients with chronic Hepatitis B between 2014 and 2017 in Rajavithi Hospital, Bangkok, Thailand. Demographic information, was recorded including physical examination data, biochemical data and HBV DNA levels, transient elastography and fat content in liver assessed by the controlled attenuation parameter technique (CAP). Data analysis was performed to assess the prevalence of fatty liver and clinical correlations between fatty liver and patient parameters, viral parameters and liver status.

Results: Of the 206 patients included, 86 patients (41.7%) were men; the mean body mass index (BMI) was 23.92±3.88 kg/m^2; 7.8% were obese (BMI >30 kg/m^2); and the mean age was 50.01±12.39 years. Most patients (81.6%) were aged less than 40 years; 73.3% had ALT <40 IU/ml; 83% had HBeAg negative; and 57.3% had HBV DNA level of more than 1,999 IU/ml. The prevalence of fatty liver in patients with chronic hepatitis B infection was 57.8%, and 10.2% had severe fatty liver (S3). Fatty liver in CHB infection was associated with male gender (p = 0.032), high BMI (p<0.001), high ALT level (p = 0.003) and high AST level (p = 0.020), but was not correlated with HBV DNA viral load, HBeAg status or liver stiffness. Multivariate analysis found that male gender and high BMI were associated with fatty liver in CHB infection with OR = 2.28, 95% CI: 1.21 to 4.30, p = 0.010 and OR = 2.28, 95% CI: 1.21 to 4.30, p = 0.010, respectively.

Conclusion: Fatty liver is common in patients with CHB infection and is related to male gender and high BMI. Liver fibrosis and cirrhosis were found in a significant portion of patients but were not related to fatty liver. Viral factors, rather than fatty liver itself, play a major role in liver necroinflammation and fibrosis.

Keywords: Chronic hepatitis B (CHB), HBeAg, HBV DNA level, AST, ALT, Fatty liver, Body mass index (BMI), Transient elastography (Fibroscan), Liver Stiffness measurement (LSM), Controlled attenuation parameter technique (CAP)

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Chronic hepatitis B (CHB), chronic liver inflammation caused by the hepatitis B virus is a major world public health problem and causes complications from cirrhosis and liver cell carcinoma. More than 240 million people worldwide are infected with this disease, and one million patients die per year from it[1]. The prevalence of chronic hepatitis B infection in Thailand, since the introduction of universal vaccination in neonates, has decreased from 10% to 5% in the present time, but it is still a major health problem due to the high rates of morbidity and mortality (15 to 40%) resulting from the disease[2].

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Fatty liver is another common public health problem[3]. The prevalence of fatty liver globally is about 25.2 %: it is highest in the Middle East, lowest in Africa and at about 27.3% in Asian countries[4]. The incidence of fatty liver is increasing and is usually associated with obesity and metabolic syndromes together with increased risk of cirrhosis with complications and hepatocellular carcinoma. Diagnosis of fatty liver can be performed using many modalities such as ultrasonography, computed tomography, magnetic resonance imaging, histologic examination and transient elastography (Fibroscan)[5].

Ultrasonography in fatty liver shows hepatomegaly, increased liver echogenicity, and blurring of vascular structures in the liver. Ultrasonography is easy to perform but has limitations in terms of accuracy, operator dependence and evaluation of fat content and severity of liver disease[5]. Liver biopsy is the standard modality for both diagnosis and assessment of disease severity, inflammation and fibrosis. Limitations of liver biopsy include

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accuracy problems due to uneven distribution of disease pathology, pathologist inexperience, contraindications (bleeding tendency, patient uncooperativeness) and complications (intra-abdominal bleeding, pneumothorax, infection and death)[6].

Transient elastography (Fibroscan) uses high wave frequencies passing to the liver tissue to assess liver stiffness and fat content in the liver using the controlled attenuation parameter technique (CAP). This method has been shown to have high levels of accuracy and reliability, and it is easy to perform with low intra-operator variability in results[7].

Both CHB and fatty liver are common problems and some patients may have both diseases together. The interaction between these two diseases is still not clear in relation to its effect on liver disease severity and hepatitis B treatment efficacy. Patients with chronic hepatitis C infection with fatty liver are associated with severity of disease, fibrosis and poor treatment response, especially in genotype 3 when compared to other genotypes[8,9].

This research determined the prevalence of fatty liver in patients with chronic hepatitis B infection and identified factors associated with this condition including host factors, viral factors and associations with liver disease severity.

Materials and Methods

Patients

This retrospective study was conducted between 2014 and 2017 in Rajavithi Hospital, Bangkok, Thailand. CHB patients aged 18 to 65 years were included if they had had positive HBsAg in serum for at least 6 month and serum HBV DNA >2,000 IU/mL[10]. Exclusion criteria were patients with chronic alcoholism, decompensated cirrhosis, hepatocellular carcinoma, co-infection with chronic hepatitis C or HIV infection, previous history of hepatic surgery or liver transplantation, or incomplete data collection. Diagnosis of decompensated cirrhosis was based on clinical and laboratory findings such as anemia, jaundice, hepatic encephalopathy or portal hypertension (ascites, splenomegaly, superficial vein dilatation or esophageal varices). The laboratory results suggestive of decompensated cirrhosis are thrombocytopenia (platelets <100,000/mm^3), low serum albumin (<3.5 gram/dl) and prolonged prothrombin time (>13 seconds or INR >1.2)[11]. The present study protocol was reviewed and approved by the ethics committee of Rajavithi Hospital

Methods

Demographic information was collected, including physical examination data and biochemical results (complete blood count, liver function, and HBV DNA level, transient elastography and fat content in liver assessed by the controlled attenuation parameter technique (CAP). Data analysis was performed to assess the prevalence of fatty liver and clinical correlations between fatty liver and patient parameters, viral parameters and liver status.

Biochemical data

Hepatitis B serology (HBsAg, HBeAg, and anti-HBe) was tested using the enzyme-linked immunosorbent assay (ELISA). Serum HBV-DNA level was examined by the polymerase chain reaction technique (COBAS® TaqMan HBV Test, Roche Diagnostics, Basel, Switzerland) with the lower detection limit at 20 international unit (IU)/mL.

Liver stiffness measurement (LSM)[7]

Liver stiffness was evaluated by transient elastography (Fibroscan, Echosens, Paris, France) using a low-frequency and amplitude-vibration induced transducer. The waves propagate through the liver parenchyma, and the average speed of propagation of waves is measured; results are shown in kPa. The values for significant fibrosis (F $\geq$2) or cirrhosis (F4) depend on the cause of liver disease. Average values are >7 kPa for significant fibrosis (F2 to F4) and >11 for cirrhosis.

Controlled attenuation parameter (CAP)[12]

Controlled attenuation parameter (CAP) was assessed by transient elastography to measure backpropagated radiofrequency signals in order to detect and quantify fat in the liver. Results are shown in dB/m^2. From liver histopathology, fatty liver was categorized by the number of liver cells with fat content (steatosis) with S0 indicating steatosis less than 5% of hepatocytes; S1 denoting 5% to 33%; S2 indicating 34% to 66%; and S3 meaning 67% to 100% For sensitivity $\geq$90% of CAP for fatty liver detection, the CAP cut-offs were 215 dB m^{-1} for S $\geq$1, 252 dB m^{-1} for S $\geq$2, and 296 dB m^{-1} for S3.

Statistical analysis

Continuous variables of demographic data were presented as mean$\pm$SD in normal distribution data or median (min-max) in non-normal distribution data while categorical variables were given as number with percentage. Continuous variables were compared using t-test or the Mann-Whitney U test in non-normal distribution data, and categorical variables were compared using the Chi-square test or Fisher exact test. Multiple logistic regression analysis was used to determine the factors affecting the prevalence of fatty liver in CHB infection and liver stiffness. Results were described as Odds ratio (OR) with 95% confidence intervals, and a *p*-value of less than 0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistic version 22.0.

Results

Demographic data

Two hundred and six patients were included: 41.7% (86/206) were men; mean body mass index (BMI) was 23.92$\pm$3.88 kg/m^2; 7.8% were obese (BMI >30 kg/m^2); and the mean age was 50.01$\pm$12.39 years. Most patients (81.6%) were aged less than 40 years; 81.6% had AST <40 IU/ml; 73.3% had ALT <40 IU/ml; 83% had HBeAg negative; and 57.3% had HBV DNA level more than 1,999 IU/ml. Some patients had associated diseases: 8.3% had diabetic mellitus;

13.6% had hypertension; 8.7% had dyslipidemia; and 4.4% had chronic renal disease. The prevalence of fibrosis in patients with chronic hepatitis B infection was 27.7%, and 7.3% had cirrhosis. Baseline demographic and laboratory data are summarized in Table 1 and 2. The prevalence of fatty liver in patients with chronic hepatitis B infection was 57.8%, and 10.2% had severe fatty liver (S3) (Table 3).

Predictive factors for fatty liver in CHB infection

From the present study, fatty liver in CHB infection was associated with male gender ($p = 0.032$); high BMI ($p<0.001$); high ALT level ($p = 0.003$) and high AST level ($p = 0.020$). It was not correlated with HBV DNA viral load, HBeAg status, or liver stiffness (Table 4). Multivariate analysis found that male gender and high BMI were associated with fatty liver in CHB infection with OR = 2.28, 95% CI: 1.21 to 4.30, $p = 0.010$ and OR = 2.28, 95% CI: 1.21 to 4.30, $p = 0.010$ respectively. Other factors were not associated with fatty liver in CHB infection (Table 4).

Discussion

The prevalence of fatty liver is variable and associated with many factors such as geographic area, social community, gender, ethnicity, and age. It has increased due to the rising number of populations with obesity, diabetic mellitus and other metabolic syndromes[4]. The prevalence of fatty liver in patients with CHB infection in the present study was 57.8%, and 10.2% had severe fatty liver (S3). These results are comparable with many studies of Asian countries (42 to 60%) but higher than a recent study in Indonesia (29.9%)[13], and this may be due to differences in the ages of the populations (50.01±12.39 years in the present study vs. 40.8±11.0 years in the study in Indonesia).

The present study reviewed multiple factors associated with fatty liver in CHB infection, such as male

Table 1. Demographic data of patients with CHB infection (n = 206)

Factors	Number (%)
Age (years) (mean ± SD)	50.01±12.39
Min-max	20 to 78
Gender	
Male	86 (41.7)
Female	120 (58.3)
BMI (kg/m^2) (mean ± SD)	23.92±3.88
<18.5	11 (5.3)
18.5 to 24.9	129 (62.6)
25.0 to 29.9	50 (24.3)
≥30	16 (7.8)
DM	
No	189 (91.7)
Yes	17 (8.3)
HT	
No	178 (86.4)
Yes	28 (13.6)
DLP	
No	188 (91.3)
Yes	18 (8.7)
CKD	
No	197 (95.6)
Yes	9 (4.4)

BMI = body mass index (kg/m^2); DM = Diabetes mellitus; HT = Hypertension; DLP = Dyslipidemia; CKD = Chronic kidney disease

Table 2. Clinical data of patients with CHB infection (n = 206)

Factors	Number (%)
WBC (cell/ml), mean ± SD	7,149.03±4,188.84
(min-max)	(2,700 to 59,000)
Hb (g/dl), mean ± SD	13.13±1.58
(min-max)	(7.2 to 16.6)
Hct (%), mean ± SD	40.86±5.52
(min-max)	(21.7 to 82.6)
Plt (cell*10^3), mean ± SD	233.42±65.35
(min-max)	(22 to 492)
HBeAg	
Negative	171 (83)
Positive	35 (17)
AST (IU/ml)	
<40	168 (81.6)
40 to 80	26 (12.6)
>80	12 (5.8)
ALT (IU/ml)	
<40	151 (73.3)
40 to 80	39 (18.9)
>80	16 (7.8)
Cr	
Normal (<1.2 mg/dl)	188 (91.3)
Abnormal (≥1.2 mg/dl)	18 (8.7)
HBV DNA level (IU/ml)	
Normal (<20 IU/ml)	29 (14.1)
Low viral load (20 to 1,999 IU/ml)	59 (28.6)
High viral load (>1,999 IU/ml)	118 (57.3)
Liver stiffness (kPa)	
No fibrosis (<7 kPa)	149 (72.3)
Fibrosis (≥7 kPa)	57 (27.7)
Liver cirrhosis	
No (<12 kPa)	191 (92.7)
Yes (≥12 kPa)	15 (7.3)

WBC = White blood cell; Cr = Creatinine; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; HBV DNA level = Hepatitis B virus DNA level

Table 3. Prevalence of fatty liver by liver in chronic hepatitis B patients assessed by the controlled attenuation parameter technique (CAP)

% of steatosis of hepatocytes	Number	%
No fatty liver: S0 (<5%)	87	42.2
Mild fatty liver: S1 (5% to 33%)	53	25.7
Moderate fatty liver: S2 (34% to 66%)	45	21.8
Severe fatty liver: S3 (67% to 100%)	21	10.2

Table 4. Factors associated with fatty liver in patients with CHB infection (n=206)

Factor	% of steatosis of hepatocytes				Total	*p*-value
	S0 (n = 87)	S1 (n = 53)	S2 (n = 45)	S3 (n = 21)		
Gender						0.032*
Male	26 (29.9)	27 (50.9)	23 (51.1)	10 (47.6)	86 (41.7)	
Female	61 (70.1)	26 (49.1)	22 (48.9)	11 (52.4)	120 (58.3)	
Age (mean ± SD)	49.13±13.36	51.72±13.39	49.42±10.35	50.67±9.60	50.01±12.39	0.661
BMI (kg/m^2)						<0.001*
<18.5	8 (9.2)	1 (1.9)	1 (2.2)	1 (4.8)	11 (5.3)	
18.5 to 24.9	67 (77.0)	13 (73.6)	19 (42.2)	4 (19.0)	129 (62.6)	
25.0 to 29.9	9 (10.3)	13 (24.5)	20 (44.5)	8 (38.1)	50 (24.3)	
≥30	3 (3.5)	0 (0.0)	5 (11.1)	8 (38.1)	16 (7.8)	
ALT (IU/ml)						0.003*
<40	69 (79.3)	39 (73.6)	33 (73.3)	10 (47.6)	151 (73.3)	
40 to 80	16 (18.4)	12 (22.6)	5 (11.1)	6 (28.6)	39 (18.9)	
>80	2 (2.3)	2 (3.8)	7 (15.6)	5 (23.8)	16 (7.8)	
AST (IU/ml)						0.020*
<40	73 (83.9)	43 (81.1)	41 (91.2)	11 (52.4)	168 (81.6)	
40 to 80	10 (11.5)	7 (13.2)	2 (4.4)	7 (33.3)	26 (12.6)	
>80	4 (4.6)	3 (5.7)	2 (4.4)	3 (14.3)	12 (5.8)	
HBV DNA level (IU/ml)						0.076
Normal (<20 IU/ml)	7 (8.0)	9 (17.0)	7 (15.6)	6 (28.6)	29 (14.1)	
Low viral load (20 to 1,999 IU/ml)	24 (27.6)	13 (24.5)	13 (28.9)	9 (42.8)	59 (28.6)	
High viral load (>1,999 IU/ml)	56 (64.4)	31 (58.5)	25 (55.5)	6 (28.6)	118 (57.3)	
HBeAg						0.232
Negative	67 (77.0)	45 (84.9)	40 (88.9)	19 (90.5)	171 (83.0)	
Positive	20 (23.0)	8 (15.1)	5 (11.1)	2 (9.5)	35 (17.0)	
Liver stiffness						0.129
No fibrosis (<7 kPa)	70 (80.5)	37 (69.8)	28 (62.2)	14 (66.7)	149 (72.3)	
Fibrosis (≥7 kPa)	17 (19.5)	16 (30.2)	17 (37.8)	7 (33.3)	57 (27.7)	

Table 5. Multivariate analysis of factors associated with fatty liver in patients with CHB infection (n = 206)

Factors	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Male	2.39 (1.33 to 4.27)	0.003*	2.36 (1.24 to 4.47)	0.008*
BMI, kg/m^2: 18.5 to 24.9				
<18.5	0.41 (0.10 to 1.60)	0.197	0.46 (0.11 to 1.87)	0.279
25.0 to 29.9	4.92 (2.21 to 10.96)	<0.001*	4.57 (1.99 to 10.53)	<0.001*
≥30.0	4.68 (1.27 to 17.22)	0.020*	3.92 (0.97 to 15.88)	0.056
ALT, UL: <40				
40 to 80	1.21 (0.59 to 2.47)	0.601	1.03 (0.37 to 2.87)	0.962
>80	5.89 (1.29 to 26.82)	0.022*	6.12 (0.80 to 47.09)	0.082
AST (IU/ml)				
40 to 80	1.30 (0.53 to 2.87)	0.633	2.45 (0.37 to 16.17)	0.351
>80	1.54 (0.45 to 5.30)	0.496	1.37 (0.23 to 8.19)	0.730

ALT = Alanine aminotransferase; SVR = Sustained virological response; OR = Odds ratio; CI = Confidence interval values are presented as n (%); Median (min-max). * = Significant at $p<0.05$

gender ($p = 0.032$), high BMI ($p<0.001$), high ALT level ($p = 0.003$) and high AST level ($p = 0.020$); however, age, HBV DNA level, HBeAg status and liver stiffness were not associated factors (Table 5).

The prevalence of fatty liver in patients with CHB infection was higher in males than in females (69.8% and 49.8%, respectively, $p = 0.032$) and this is compatible with the findings of other research[14,15]. One study about fatty liver in women showed the incidence to be higher in women with menopausal and postmenopausal status than in those with premenopausal status[15]. Another study of 50 women with type 2 diabetes mellitus showed that low-dose estradiol and norethisterone improved liver enzymes levels significantly by reducing fat accumulation in the liver[16], suggesting that estrogens act as a protective factor against the development of fatty liver[17].

The prevalence of overweight and obese populations has increased globally, including in Asian regions, and varies between countries[18]; however, the prevalence of obesity in Asia is still lower than in Europe and the United States. The present study showed a strong association between the prevalence of fatty liver in patients with CHB infection with high BMI (BMI <18.5 kg/m^2 = 27.3%, BMI 18.5 to 24.9 kg/m^2 = 48.1%, BMI 25.0 to 29.9 kg/m^2 = 82%, BMI ≥30 kg/m^2 = 81.2% $p<0.001$), and this is compatible with the results of other studies of patients with CHB infection[19-21]. In a meta-analysis and systematic review by Machado M V et al, a strong association was found between body mass index (BMI) and fatty liver in patients with CHB infection, both in individual studies and pooled data (pooled SMD 2.17, 95% CI (1.23, 3.11), $p<0.001$) and a strong association between obesity and fatty liver with OR 6.59, 95% CI (3.51 to 12.25), $p = 0.003$[22]. Obesity, increased BMI and dyslipidemia showed associations with the presence of fatty liver in patients with CHB infection in the general population and may be related to metabolic syndrome[23].

Most patients in the present study had normal AST and ALT levels (81.6% with normal AST level and 73.3% with normal ALT level) and showed associations between fatty liver and high ALT ($p = 0.003$) and AST ($p = 0.020$) levels. Many studies have shown heterogenous associations between AST, ALT levels and the prevalence of fatty liver in patients with CHB infections[20,21,24,25], but a meta-analysis and systematic review by Machado MV et al showed no such association, with pooled SMD -0.37, 95% CI (-0.99, 0.24) $p = 0.236$ for AST level and pooled SMD -0.35, 95% CI (-0.88, 0.18), $p = 0.199$ for ALT level[22]. More studies of this association are needed. In CHB patients with non-detectable or low viral load, however, the common cause of elevated AST and ALT levels was fatty liver.

The present study showed no association of fatty liver with age, HBV DNA level, HBeAg status or liver stiffness. The meta-analysis performed by Machado et al showed results similar to those of the present study regarding age as pooled data SMD 0.06, 95% CI (-0.17, 0.29), $p = 0.614$; and HBeAg status as pooled data: OR 0.89, 95% CI (0.73 to 1.79), $p = 0.227$; but it showed a negative relationship between HBV DNA level and fatty liver as pooled SMD -74.12, 95% CI (-82.93, -65.31), $p<0.001$[22]. Another study by Enomoto et al also found an inverted relationship between fatty liver and HBV-DNA level[26]. This finding may be due to the effect of increased serum adiponectin associated with CHB infection. Adiponectin regulates immunocytokines that cause liver injury, including tumor necrosis factor (TNF-α), and improves fatty liver and hepatitis via the inhibition of lipogenic factors and TNF-α[27,28]. More studies about the association of HBV infection and adiponectin are needed to confirm this hypothesis.

The present study showed that 27.7% and 7.3% of patients had significant fibrosis and cirrhosis respectively, but fatty liver is not associated with the degree of liver fibrosis or cirrhosis. A study by Peng et al also showed no association between stage of liver fibrosis and severity of hepatic steatosis in patients with CHB infection[24]. The meta-analysis performed by Machado et al showed no association between fatty liver and liver stiffness as pooled OR 0.69, 95% CI (0.35 to 1.39), $p = 0.305$ for necro-inflammatory activity and pooled SMD 0.22, 95% CI (-0.84, 0.41), $p = 0.495$ for

fibrosis[22]. This finding was different results found in patients with chronic hepatitis C infection, in which the hepatitis C virus causes fat infiltration in the liver and induces necroinflammation together, in contrast with CHB infection in which fatty liver may be related to the host factors[29-31]. The effects of fatty liver in patients with CHB infection on HBV seroconversion and response to treatment with pegylated interferon or oral medication are inconclusive[32-34]. Further studies of these areas are required.

In multivariate analysis, factors associated with fatty liver in patients with CHB infection were male gender and high BMI with OR = 2.28, 95% CI: 1.21 to 4.30, p = 0.010 and OR = 2.28, 95% CI: 1.21 to 4.30, p = 0.010, respectively. These results indicated that fatty liver in CHB infection was influenced by host factors other than viral factors and liver inflammation and fibrosis were mainly from viral factors.

The CAP method for evaluation of fatty liver is non-invasive and has good accuracy for evaluation of fat content in liver, but it has limitations in some conditions. The present study showed that CHB infection patients with fatty liver should be evaluated for other metabolic diseases such as obesity, diabetic mellitus or dyslipidemia rather than for CHB itself and may need treatment of the underlying causes of fatty liver disease.

The limitations of this study were its retrospective study design, small sample size, the limitations of transient elastrography and CAP methods for evaluation of liver stiffness and fatty liver in some conditions such as morbid obesity, narrow rib space, severe hepatitis, limitation of pathology for diagnosis of fatty liver, fibrosis and cirrhosis.

Conclusion

Fatty liver is common in patients with CHB infection and is related to male gender and high BMI. Liver fibrosis and cirrhosis were found in a quarter of patients and were not related to fatty liver. Viral factors play a major role in liver necro-inflammation and fibrosis rather than fatty liver itself. Further studies are required to investigate the role of fatty liver in liver disease progression and response to treatment for CHB infection.

What is already known on this topic?

Both CHB infection and fatty liver are common problems and some patients may have both diseases together. The interactions between these two diseases are still not clear in relation to their effect on liver disease severity and hepatitis B treatment efficacy. Patients with chronic hepatitis C infection with fatty liver are associated with severity, fibrosis and poor treatment response, especially in genotype 3.

What this study adds?

Fatty liver is common in patients with CHB infection and is related to male gender and high BMI. Liver fibrosis and cirrhosis were found in a quarter of patients and are not related to fatty liver. Viral factors, rather than fatty liver itself, may affect liver necro-inflammation and fibrosis. Estrogens and adiponectin may be protective factors against the development of fatty liver.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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