ORIGINAL

Impact of pancreatic resection in patients with liver cirrhosis

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Abstract : Background : Several reports have shown a high mortality rate in patients with liver cirrhosis (LC) who undergo pancreaticoduodenectomy, however, there are few reports on its long-term prognosis. Methods : Twelve patients with LC who had undergone pancreatic resection were enrolled. To compare clinicopathological variables, 159 non-LC patients who had undergone resection for pancreatic cancer were enrolled. Results : Pancreaticoduodenectomy (PD) was performed in 5 LC patients and distal pancreatectomy (DP) was performed in 7 LC patients. Patients in the LC group had more co-morbidities, lower platelet counts and higher Fib4 index than the non-LC group. The postoperative complication rate was higher in the LC group (83.3% vs 47.8%). While the postoperative hospital stay and 30-day mortality rate were not different, the 90-day mortality rate was higher in the LC group (25.0% vs 2.5% ; p<0.01). Comparison by operative procedure showed no significant differences of postoperative outcomes in DP cases. However, in PD cases, postoperative complications were more frequent (100% vs 42.3%) and 90-day mortality was higher (40.0% vs 2.9% ; p<0.01) in the LC group. Conclusions : PD resulted in higher postoperative morbidity and mortality rates in patients with LC compared with non-LC patients. DP could be tolerated in the LC patients. J. Med. Invest. 70 : 189-194, February, 2023

Keywords **:** *liver cirrhosis, pancreaticoduodenectomy, pancreatectomy, pancreas, surgery*

INTRODUCTION

Liver cirrhosis (LC) is an important public health concern and a significant source of morbidity and mortality. LC is the 11th most common cause of death globally (1). Furthermore, the prevalence of LC in the United States is approximately 0.27% (2). Recently, the number of LC patients with a history of hepatitis B or C viral infection has decreased worldwide. In contrast, the worldwide population of LC patients has increased 13% since 2000 due to the increasing prevalence of metabolic syndrome and alcohol abuse (3).

The LC patients have an increased risk for postoperative morbidity and mortality, especially after major surgery, compared with patients with normal liver function (4, 5). The Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score have been widely used to evaluate chronic liver dysfunction and estimate perioperative risk in the LC patients (6-8). According to the Child–Pugh classification, mortality in major abdominal surgery is 10%, 30% and 76–82% for Child class A, B and C, respectively (9).

Pancreaticoduodenectomy (PD) is one of the most invasive abdominal surgical procedures. According to a study analyzing data from the Japanese National Clinical Database, the 30-day mortality and postoperative mortality after pancreaticoduodenectomy were 1.3% and 2.9%, respectively (10). Furthermore, high morbidity and mortality rates after PD in patients with LC have been reported. Futagawa *et al*. reported an in-hospital mortality rate of 5.9% after PD in 529 patients with chronic hepatic dysfunction, including 105 patients diagnosed with LC (6). Similarly, a meta-analysis of PD in the LC patients showed a 0-17 % mortality rate (8).

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Although it has been reported that PD in the LC patients has poor short-term results, the results of distal pancreatectomy (DP) in the LC patients has not been assessed. Futagawa *et al*. reported long-term outcomes in PD patients with LC, and the usefulness of the aspartate aminotransferase-platelet ratio index (APRI) (6). However, there are still few reports on the long-term prognosis after pancreatic resection for the LC patients. Therefore, we investigated the short- and long-term outcomes after pancreatic resection between 12 LC patients and 159 non-LC patients in this study.

PATIENTS AND METHODS

Patients

Twelve LC patients who underwent pancreatic resection at Tokushima University Hospital from 2004 to 2021 were retrospectively enrolled. LC was defined as a case in which intraoperative findings showed macroscopically obvious cirrhosis. Seven patients were pathologically diagnosed with pancreatic cancer, 2 patient were biliary cancer, 1 patient was duodenal cancer, and 2 patients were diagnosed with no malignancy. Pancreaticoduodenectomy (PD) was performed in 5 cases and distal pancreatectomy (DP) was performed in 7 cases. Frailty was assessed by the Clinical Frailty Scale (11).

To compare clinicopathological variables between the LC and non-LC patients, 159 non-LC patients who underwent surgical resection for pancreatic cancer at Tokushima University Hospital from 2004 to 2021 were enrolled. In this study, we excluded the 4 patients in non-LC group with hemodialysis which was the strong factor affecting the surgical outcomes.

This study was approved by the Research Ethics Committee of Tokushima University Hospital (Approved number : 3215). Informed consent was obtained from all patients. Histopathological evaluation of hematoxylin and eosin stained sections was performed by the Pathology Department of Tokushima University Hospital.

Liver functional parameters

In this study, fibrosis 4 (Fib4) index (12), albumin-bilirubin (ALBI) score (13) and the aspartate aminotransferase-platelet ratio index (APLI) (6) which can be a useful marker of hepatic fibrosis were investigated as the liver functional parameters. This Fib4 score was calculated as the following formula : Fib 4 score = (Age ×AST(U/L)) / (Platelet count (10^9/L) × (square root of ALT(U/L))) ALBI was calculated as log 10 (total bilirubin (mg/dL) × 17.1) × 0.66) + (albumin (g/dL) × 10 × -0.085). ALBI grade was divided as follows : Grade1 ≦ -2.60, Grade2 : >-2.60 to ≦ -1.39, Grade3 : >-1.39). The aspartate aminotransferase-platelet ratio index (APRI) : aspartate aminotransferase (AST) level (IU/l)/AST (upper limit of normal ; set at 30 in the present study) (IU/l)/platelet count (10^9/L) × 100) was divided into 2 groups by less than 1 or more.

Statistical analysis

All statistical analyses of the data in this study were performed using JMP version 14 (SAS Institute, Cary, NC, USA). The $\chi 2$ test, Fisher's exact test, student t test and one-way analysis of variance were used to investigate the correlation of clinicopathological factors between the LC and non-LC patients. Survival curves were generated by the Kaplan–Meier method and differences were compared using the log-rank test. In this study, a p-value of <0.05 was considered to be significant.

RESULTS

Patient co-morbidities, clinicopathological variables and the clinical outcomes of pancreatic resection in the LC patients compared with non-LC patients

PD was performed in 5 LC patients and DP was performed in 7 LC patients. Clinical variables are shown in Table 1. Patients in the LC group had more co-morbidities (100% vs 45.9% ; p<0.01), more frailty (50.0% vs 20.1% ; p<0.05) and lower platelet counts ($13.5 \pm 2.9 \times 10^8$ vs $24.0 \pm 9.1 \times 10^8$) than patients in the non-LC group. Among the LC patients, the mean value of the indocyanine green retention test (ICG-R15) was 18.7 ± 5.7 minutes and the Fib4 index was 3.9 ± 1.5. The Fib4 index was significantly higher in the LC group (p<0.01). A total of 11 patients had a Model for End-Stage Liver Disease (MELD) score of less than 9. ALBI grade and APRI index were not different between the LC and non-LC groups (ALBI : p = 0.11, APRI index : p = 0.75). Postoperative complications were more frequent in the LC group (83.3% vs 47.8% ; p<0.05). Furthermore, while postoperative hospital stay and 30-day mortality were not different between the groups, the 90-day mortality rate was significantly higher in the LC group (25.0% vs 2.5% ; p<0.01).

Clinical variables in the LC and non-LC patients parsed by operative procedure

Clinical variables in the LC and non-LC patients who

Table 1. Clinical variables between the LC and non-LC patients

Factors		LC (n = 12)	Non-LC (n = 159)	p-value
Age (years)	Mean ± SD	73.4 ± 7.59	69.1 ± 9.03	0.11
Gender	Male/Female	6 / 6	81 / 78	0.95
BMI	Mean ± SD	21.5 ± 2.4	22.0 ± 3.3	0.62
Frailty	Negative / Positive / N.A.	6 / 6 / 0	109 / 32 / 18	<0.05
Any co-morbidities	Negative / Positive	0 / 12 (100%)	86 / 73 (45.9%)	<0.01
Cause of LC	HBV / HCV / Alc	2 / 4 / 6	N.A	N.A
Platelet ($\times 10^4$)	Mean ± SD	13.5 ± 2.9	24.0 ± 9.1	<0.01
ICG R15 (min)	Mean ± SD	17.6 ± 6.2	N.A	N.A
Child-Pugh classification	A / B	10 / 2 (16.7%)	N.A	N.A
MELD score	<10 / 10≤	11 / 1 (9.1%)	N.A	N.A
Fib4 index	Median ± SD	3.9 ± 1.5	2.0 ± 1.5	<0.01
ALBI grade	1 / 2, 3	3 / 9 (75%)	77 / 82 (51.7%)	0.11
APRI index	<1 / 1≤	10 / 2 (16.7%)	132 / 20 (13.2%)	0.75
Diseases	Malignant / Benign	10 / 2 (16.7%)	159 / 0 (0%)	<0.01
Operative procedure	PD / DP / TP	5 / 7 / 0	104 / 50 / 5	0.15
Combined resection of PV	Negative / Positive	11 / 1 (8.3%)	135 / 24 (15.1%)	0.49
Op. time (minutes)	Mean ± SD	319.8 ± 97.4	431.9 ± 126.3	<0.01
Blood loss (ml)	Mean ± SD	270.9 ± 295.0	361.4 ± 442.7	0.49
Transfusion	Negative / Positive	10 / 2 (16.7%)	148 / 11 (6.9%)	0.28
Post-op. complications	Negative / Positive	2 / 10 (83.3%)	83 / 76 (47.8%)	<0.05
PF grade B≤	Negative / Positive	9 / 3 (25.0%)	133 / 26 (16.4%)	0.46
C-D grade IIIb≤	Negative / Positive	10 / 2 (16.7%)	151 / 8 (5.3%)	0.16
Post-op. stay (days)	Mean ± SD	34.6 ± 16.8	36.3 ± 28.2	0.84
30-day mortality	Alive / Dead	12 / 0 (0%)	159 / 0 (0%)	1.00
90-day mortality	Alive / Dead	9 / 3 (25.0%)	155 / 4 (2.5%)	<0.01

LC : liver cirrhosis, BMI : body mass index, ICG : indocyanine green, Fib4 : fibrosis 4, ALBI grade : albumin-bilirubin grade, APRI index : aspartate aminotransferase-platelet ratio index, PV : portal vein, PD : pancreaticoduodenectomy, DP : distal pancreatectomy, TP : total pancreatectomy, PF : pancreatic fistula, C-D : Clavien-Dindo

underwent PD are shown in Table 2. The LC group had more co-morbidities (100% vs 42.3% ; $p<0.01$) and lower platelet counts ($14.3 \pm 0.8 \times 10^8$ vs $25.3 \pm 9.3 \times 10^8$) than the non-LC group. The co-morbidities in the LC group included 5 cases of hypertension, 5 cases of type 2 diabetes mellitus, 5 cases of gastroesophageal varix, 3 cases of cardiovascular disease, and a case of amyotrophic lateral sclerosis (ALS). Although the operative time was significantly shorter in the LC group (358.2 ± 70.5 min. vs 487.4 ± 92.5 min.), postoperative complications were more frequent (100% vs 42.3% ; $p<0.01$). Furthermore, the rate of severe postoperative complications (Clavien-Dindo (C-D) classification grade 3 or higher) was 40.0% in the LC group and 4.8% in the non-LC group ($p<0.05$), and the 90-day mortality was higher (40.0% vs 2.9% ; $p<0.01$) in the LC patients compared with the non-LC patients.

Clinical variables in the LC and non-LC patients who underwent DP are shown in Table 3. Again, the LC group had more co-morbidities (100% vs 58.0% ; $p<0.01$) and lower platelet counts ($12.9 \pm 3.8 \times 10^8$ vs $21.1 \pm 7.3 \times 10^8$) than the non-LC group. Frail patients (Clinical Frailty Scale (CFS) scores 4 or more) were more frequent in the LC group ($p<0.05$). However, in the DP cases, there were no significant differences in the operative time, amount of blood loss, rate of postoperative complications or mortality rate between the LC and non-LC patients. While the 90-day mortality rate was higher in the LC group undergoing DP (14.3% vs 2.0%), this was not significant.

Kaplan-Meier curves of overall survival in the LC patients

The overall survival curve is shown in Figure 1. There was no difference in survival rate between the LC and non-LC groups ($p = 0.17$). Figure 2 shows the survival curve of the 10 LC patients with malignant cancer (7 cases of pancreatic cancer, 2 cases of distal bile duct cancer and 1 case of duodenal cancer) excluding the 2 patients with benign disease. The LC patients with malignant disease tended to have worse overall survival compared with the non-LC patients with pancreatic cancer ($p = 0.13$). Among the 10 LC patients with malignant disease, one patient died due to the bleeding from the pseudoaneurysm at the stump of gastroduodenal artery on postoperative day 43, one patient died due to refractory ascites and liver failure on postoperative day 50 and one patient suddenly died due to pneumonia and respiratory failure after charging hospital.

DISCUSSION

In this study, we compared the outcomes after pancreatic resection in 12 LC patients and 159 non-LC patients. The postoperative complication rate and 90-day mortality rate were higher in the LC group, compared with the non-LC group. However, when we parsed patients based on operative procedure, the DP cases showed no significant differences in postoperative complications

Table 2. Clinical variables between the LC and non-LC patients after PD

Factors		LC (n = 5)	Non-LC (n = 104)	p-value
Age (years)	Mean ± SD	72.4 ± 4.9	69.1 ± 9.2	0.43
Gender	Male / Female	3 / 2	46 / 58	0.49
BMI	Mean ± SD	21.2 ± 2.2	21.9 ± 3.3	0.67
Frailty	Negative / Positive / N.A.	3 / 2 / 0	69 / 23 / 12	0.48
Any co-morbidities	Negative / Positive	0 / 5 (100%)	60 / 44 (42.3%)	≤0.01
Cause of LC	HBV / HCV / Alc	1 / 0 / 4	N.A	N.A
Platelet ($\times 10^4$)	Mean ± SD	14.3 ± 0.8	25.3 ± 9.3	≤0.05
ICG R15 (min)	Mean ± SD	18.0 ± 3.2	N.A	N.A
Child-Pugh classification	A / B	4 / 1 (20.0%)	N.A	N.A
MELD score	<10 / 10≤	5 / 0 (0%)	N.A	N.A
Fib4 index	Mean ± SD	3.8 ± 0.9	2.0 ± 1.7	≤0.05
ALBI grade	1 / 2, 3	1 / 4 (80.0%)	40 / 64 (61.5%)	0.40
APRI index	<1 / 1≤	4 / 1 (20.0%)	84 / 20 (19.2%)	0.91
Diseases	Malignant / Benign	4 / 1 (20.0%)	104 / 0 (0%)	≤0.05
Combined resection of PV	Negative / Positive	4 / 1 (20.0%)	86 / 18 (17.3%)	0.88
Op. time (minutes)	Mean ± SD	388.2 ± 70.5	487.4 ± 92.5	≤0.05
Blood loss (ml)	Mean ± SD	312.8 ± 403.7	313.9 ± 270.8	0.99
Transfusion	Negative / Positive	3 / 2 (40.0%)	100 / 4 (3.9%)	≤0.05
Post-op. complications	Negative / Positive	0 / 5 (100%)	60 / 44 (42.3%)	≤0.01
PF grade B≤	Negative / Positive	4 / 1 (20.0%)	93 / 11 (10.6%)	0.55
C-D grade IIIb≤	Negative / Positive	3 / 2 (40.0%)	99 / 5 (4.8%)	≤0.05
Post-op. stay (days)	Mean ± SD	43.4 ± 15.0	33.9 ± 26	0.42
30-day mortality	Alive / Dead	5 / 0 (0%)	104/ 0 (0%)	1.00
90-day mortality	Alive / Dead	3 / 2 (40.0%)	101 / 3 (2.9%)	≤0.01

LC : iver cirrhosis, BMI : body mass index, ICG : indocyanine green, Fib4 : fibrosis 4, ALBI grade : albumin-bilirubin grade, APRI index : aspartate aminotransferase-platelet ratio index, PV : portal vein, PD : pancreaticoduodenectomy, DP : distal pancreatectomy, TP : total pancreatectomy, PF : pancreatic fistula, C-D : Clavien-Dindo

Table 3. Clinical variables between the LC and non-LC patients after DP

Factors		LC (n = 7)	Non-LC (n = 50)	p-value
Age (years)	Mean ± SD	74.1 ± 9.4	69.1 ± 8.2	0.14
Gender	Male / Female	3 / 4 (57.1%)	32 / 18 (36%)	0.29
BMI	Mean ± SD	21.8 ± 2.6	22.3 ± 3.2	0.69
Frailty	Negative / Positive / N.A.	3 / 4 / 0	38 / 7 / 5	<0.05
Any co-morbidities	Negative / Positive	0 / 7 (100%)	21 / 29 (58.0%)	<0.01
Cause of LC	HBV / HCV / Alc	1 / 4 / 2	N.A	N.A
Platelet ($\times 10^4$)	Mean ± SD	12.9 ± 3.8	21.1 ± 7.3	<0.01
ICG R15 (min)	Mean ± SD	19.1 ± 7.2	N.A	N.A
Child-Pugh classification	A / B	6 / 1 (16.7%)	N.A	N.A
MELD score	<10 / 10≤	6 / 1 (16.7%)	N.A	N.A
Fib4 index	Mean ± SD	4.0 ± 1.9	1.8 ± 1.0	<0.01
ALBI grade	1 / 2, 3	2 / 5 (71.4%)	33 / 17 (34%)	0.05
APRI index	<1 / 1≤	6 / 1 (16.7%)	47 / 3 (6%)	0.35
Diseases	Malignancy / Benign	6 / 1 (14.3%)	50 / 0 (0%)	<0.05
Combined resection of PV	Negative / Positive	7 / 0 (0%)	45 / 5 (10%)	0.24
Op. time (minutes)	Mean ± SD	271.0 ± 86.0	305.4 ± 91.0	0.35
Blood loss (ml)	Mean ± SD	241.0 ± 220.0	356.9 ± 422.9	0.48
Transfusion	Negative / Positive	7 / 0 (0%)	45 / 5 (10%)	0.24
Post-op. complications	Negative / Positive	2 / 5 (71.4%)	20 / 30 (60%)	0.55
PF grade B≤	Negative / Positive	3 / 4 (57.2%)	27 / 23 (46.0%)	0.58
C-D grade ≤IIIb	Negative / Positive	7 / 0 (0%)	48 / 2 (4%)	0.46
Post-op. stay (days)	Mean ± SD	28.3 ± 16	40.3 ± 32.7	0.35
30-day mortality	Alive / Dead	7 / 0 (0%)	50/ 0 (0%)	1.00
90-day mortality	Alive / Dead	6 / 1 (14.3%)	49 / 1 (2%)	0.18

LC : liver cirrhosis, BMI : body mass index, ICG : indocyanine green, Fib4 : fibrosis 4, ALBI grade : albumin-bilirubin grade, APRI index : aspartate aminotransferase-platelet ratio index, PV : portal vein, PD : pancreaticoduodenectomy, DP : distal pancreatectomy, TP : total pancreatectomy, PF : pancreatic fistula, C-D : Clavien-Dindo

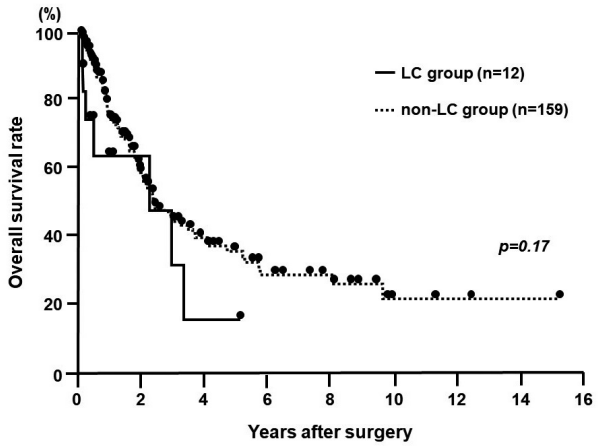

Figure 1. Kaplan–Meier curve of overall survival in the LC group and non-LC group.

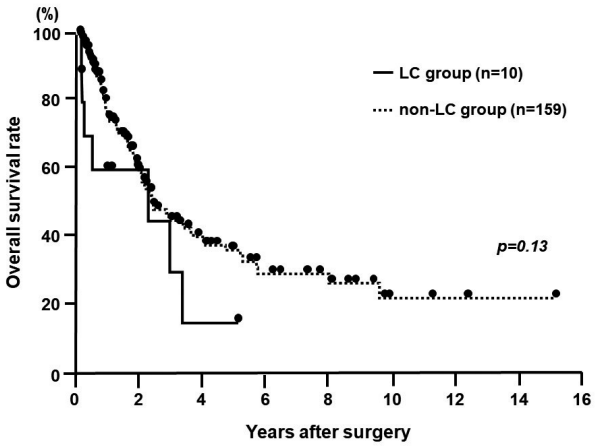

Figure 2. Kaplan–Meier curve of overall survival in the LC and non-LC patients with malignant disease.

or mortality rate. Our results suggest that PD in the LC patients has high morbidity and mortality rates, however DP could be a tolerated procedure, even in the LC patients.

There have been several published reports of PD in the LC patients, however, there are large differences in the survival rate and postoperative complication rate from report to report. One reason for this discrepancy is that the proportion of patients with malignant diseases or Child-Pugh class B/C was different in each report. Butler *et al*. (8) summarized the outcome of PD in patients with LC. In their meta-analysis, Busquets *et al*. (14), Fuks *et al*. (15), Sethi *et al*. (16), and Gil *et al*. (17) reported a 0% mortality rate after PD in patients with LC, however, almost all patients were Child-Pugh class A in these reports. On the other hand, El Nakeeb *et al*. (7), Regimbeau *et al*. (18) and Butler *et al*. (8) reported high in-hospital mortality (11.9-17.1%) after PD in the LC patients, including 10-20% Child-Pugh class B patients. Recently, Futagawa *et al*. (6) reported postoperative complications, in-hospital mortality and long-term survival according to Child-Pugh classification in a large retrospective study. The mortality rate according to Child-Pugh classification was 5.4% in Child-Pugh class A, 7.1% in Child-Pugh class B and 24% in Child-Pugh class C. To summarize these reports, PD seems to be a relatively safe and acceptable procedure in Child-Pugh A cirrhotic patients. Our study included 16.7% Child-Pugh class B patients and the 90-day mortality in our patient cohort was high (25.0%). These results are consistent with previous reports.

The MELD score has also been reported to be a useful method to estimate the mortality rate after PD in cirrhotic patients (6, 8, 16, 18). In fact, Butler *et al*. (8) showed that the MELD score is more useful to predict postoperative mortality than the Child-Pugh classification. In this study, 90% LC patients was MELD score less than 10, and MELD score could not classify for our dataset.

In this study, we investigated several fibrotic markers : Fib4 index (12), ALBI grade (13) and APRI index (6). These are all accepted markers of hepatic fibrosis or cirrhosis. In our patients, the Fib4 index was significantly higher in the LC group. However, the other markers were not significantly different between the LC and non-LC patients. One reason for this result may be that several of the PD patients had received preoperative biliary drainage. Some of these patients still had high bilirubin or AST before their surgery, therefore, these fibrotic markers could not accurately estimate fibrotic status. In contrast, Futagawa *et al*. (6) showed that the APRI index could correlate with prognosis in Child-Pugh class B patients. Hence, the APRI index might be more useful for fibrotic assessment in cirrhotic patients only, and may be less useful for comparing fibrosis in the LC and non-LC patients.

There have been no previous reports focusing on DP in the LC patients. DP is a less invasive procedure than PD. Therefore, DP is considered to be a more acceptable procedure than PD in patients with LC. In our study, 1 patient died within 90 days of their DP surgery, however, the mortality rate was not significantly different between the LC and non-LC patients. From our results, DP seems to be acceptable for cirrhotic patients, however, further large-scale studies are necessary to confirm this finding.

Limitations of this study include a small patient number in a single-center retrospective study where it was not possible to match the patients' clinical parameters between the LC and non-LC groups. Therefore, further studies are needed.

In conclusion, pancreatic surgery in patients with liver cirrhosis has higher postoperative morbidity and mortality and poorer long-term prognosis than pancreatic surgery in non-cirrhotic patients. PD has particularly high morbidity and mortality rates. DP could be more acceptable than PD, even in the LC patients.

INFORMED CONSENT

This study was approved by the Research Ethics Committee of Tokushima University Hospital (approved number : 3215) and written informed consent was obtained from all patients.

CONFLICT OF INTEREST

The authors declare no Conflict of Interests for this article.

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