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Delayed cholecystectomy following endoscopic retrograde cholangio-pancreatography is not associated with worse surgical outcomes

Muhammad Abdalkoddus[1] · Joshua Franklyn[1] · Rashid Ibrahim[1] · Lu Yao[1] · Nur Zainudin[1] · Somaiah Aroori[1]

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Abstract

Background There is no universal consensus on the optimal timing of cholecystectomy following endoscopic retrograde cholangio-pancreatography (ERCP). This study aims to evaluate the effect of time delay and post-ERCP complications on cholecystectomy outcomes.

Materials and methods All patients who underwent pre-op ERCP for concurrent cholelithiasis and choledocholithiasis between January 2009 and August 2019 at University Hospitals Plymouth, UK, were included. Patients who underwent single-stage cholecystectomy and common bile duct exploration were excluded from the study. Based on the delay to cholecystectomy, the patients were divided into early (within 2 weeks), intermediate (2–6 weeks) and late (> 6 weeks) groups. The operative outcomes between the three groups were compared.

Results We included 444 patients in the study, with 62 (14%), 90 (20%) and 292 (66%) patients in the early, intermediate and late groups, respectively. The median duration from ERCP to cholecystectomy was 75 days. There was no statistically significant difference in the conversion-to-open rate, bile leak rate or retained stones between the three groups. The median post-operative hospital stay (PHS) was 2, 2 and 1 day ($P = 0.005$) in the early, intermediate and late groups, respectively. The readmission rate was significantly more in the delayed group (3.2%, 11.1% and 13.7%; $P = 0.05$). Patients who suffered post-ERCP complications had a significantly longer PHS (4 vs 1 day, $P = 0.001$) and had higher conversion-to-open rate (16 vs 4.5%, $P = 0.04$).

Conclusion Delayed cholecystectomy following ERCP is not associated with worse peri-operative outcomes and can facilitate more day-case surgery. However, early cholecystectomy can significantly reduce readmissions with gallstone-related symptoms and its associated hospital stay. Post-ERCP complications lead to a difficult cholecystectomy.

Keywords Delayed cholecystectomy · ERCP · Choledocholithiasis · Bile leak

✉ Somaiah Aroori
s.aroori@nhs.net

Muhammad Abdalkoddus
muhammad.abdalkoddus@nhs.net

Joshua Franklyn
joshua.franklyn@nhs.net

Rashid Ibrahim
rashid.ibrahim@nhs.net

Lu Yao
lucy.yao1@nhs.net

Nur Zainudin
nur.zainudin@nhs.net

[1] Peninsula HPB Unit, University Hospitals Plymouth NHS Trust, England, UK

The incidence of co-existing choledocholithiasis in patients with cholelithiasis is around 10–15% [1, 2]. A common method of treating concurrent common bile duct (CBD) stones is a two-staged approach, with pre-operative endoscopic retrograde cholangio-pancreatography (ERCP) and sphincterotomy followed by interval cholecystectomy [3]. It is hypothesised that subclinical inflammation induced by contrast injected during ERCP, the progression of acute cholecystitis and passage of more stones into the bile duct whilst waiting for cholecystectomy can make cholecystectomy technically difficult [4, 5].

There is no consensus on the optimal timing for cholecystectomy after ERCP. However, recent literature, including a systematic review has suggested that early cholecystectomy with an interval of 24–72 h has favourable operative

outcomes and should be considered the standard of care [6]. However, early cholecystectomy is not always feasible for many reasons, ranging from logistical delays to need-based clinical deferrals [7]. Population-based data from the UK and USA has suggested that over two-thirds of patients have a delayed cholecystectomy following gallstone-related acute hospital admissions, with a median wait of around 3 months [8, 9].

The purpose of this study is to evaluate the effect of the time delay between ERCP and cholecystectomy, and post-ERCP complications on peri-operative outcomes of cholecystectomy.

Methods

We retrospectively reviewed all patients who had successful pre-operative ERCP followed by cholecystectomy at University Hospitals Plymouth NHS Trust between January 2009 and August 2019. Patients with failed ERCP and those that underwent cholecystectomy with common bile duct exploration for bile duct stones were excluded from the study. The hospital audit department approved the study. The details of patients were obtained from electronic hospital records and a prospectively maintained ERCP database. The following data were collected for further analysis: patient demographics, ERCP details and complications, duration between the first successful ERCP and cholecystectomy, readmissions between ERCP and cholecystectomy, operative details of the cholecystectomy, intra- and post-operative complications and length of post-operative hospital stay (PHS). To account for the impact of delaying cholecystectomy, the total hospital stay (THS) (defined as the cumulative number of hospitalised days from all the readmissions for biliary complaints between ERCP and cholecystectomy plus PHS) was calculated. We also collected information on the incidence of retained stones. Retained stones were defined as imaging or intra-operatively identified choledocholithiasis within the period from the first successful ERCP until 2 years after the cholecystectomy [10]. Bile duct stones discovered beyond two years from the cholecystectomy were considered as primary bile duct stones and excluded from the analysis. Bile leak was defined as bile leakage from an abdominal drain/wound or identified following a radiological investigation [11]. Day-case cholecystectomy was referred to patients who were discharged on the same day as the operation and emergency cholecystectomy was defined as operations done following unplanned admission to the emergency department.

Patients were divided into three groups according to the duration from ERCP to cholecystectomy: early, intermediate and late groups, which correspond to zero to two weeks, two to 6 weeks and more than 6 weeks, respectively. The outcomes examined included operative difficulty (represented by operative time, rate of conversion to open cholecystectomy, and rate of subtotal cholecystectomy), intra- and post-operative complications, length of post-operative stay, the incidence of retained stones and readmission rates whilst waiting for the cholecystectomy. We also studied the impact of post-ERCP complications and the need for repeat ERCP/s on the above outcome variables.

Statistical analysis

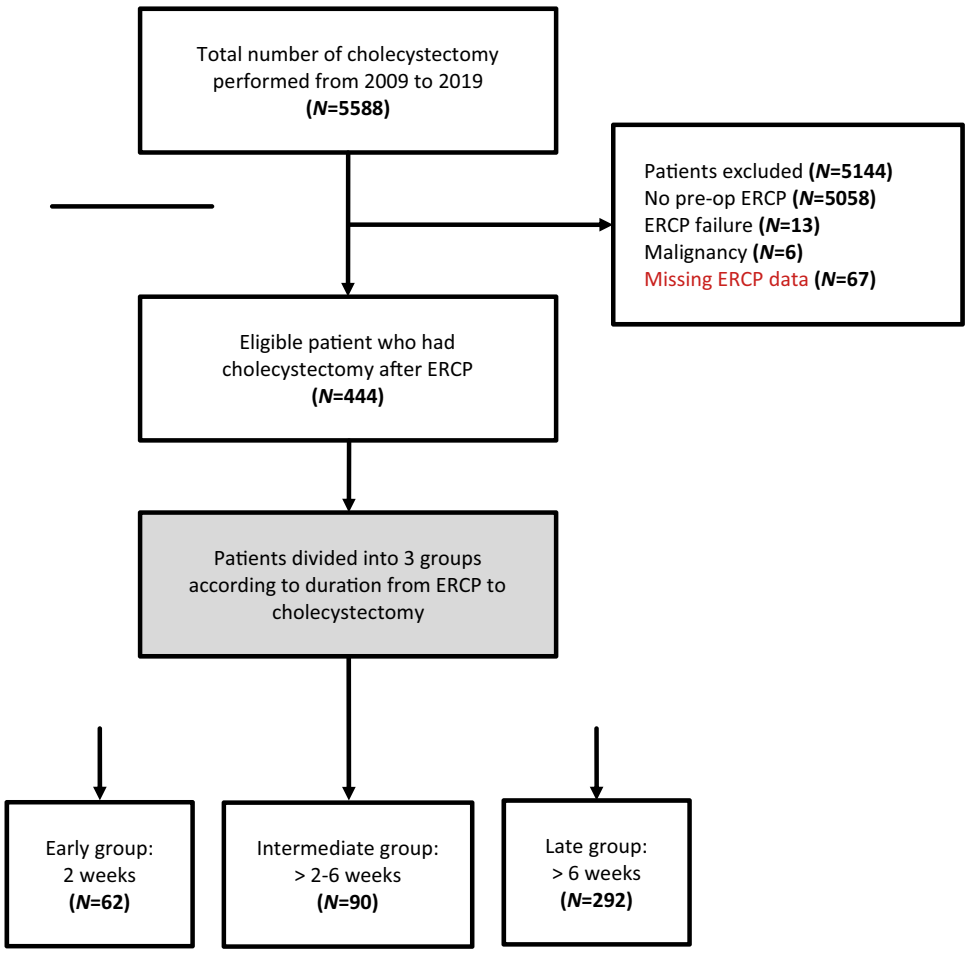
Categorical variables are presented as frequencies and percentages and were compared using Pearson's Chi-Square test or Fisher's exact test. We used the Shapiro–Wilk test to evaluate the normality of the numeric variable distribution. Numeric variables are presented as medians and interquartile range (IQR) and were compared using Spearman' correlation, Wilcoxon rank-sum test or Kruskal–Wallis test (with post hoc test to allocate significance and Bonferroni adjustment for multiple testing) as appropriate. The P-value less than or equal to 0.05 is considered as statistically significant. Statistical analysis was performed using R software (version 4.0.1, R Foundation for statistical computing, Vienna, Austria).

Results

During the study period, 5588 patients underwent cholecystectomy. Of these, 530 patients had pre-operative ERCP. Further assessment excluded 86 patients as detailed in Fig. 1. Four hundred and forty-four patients were included in the study. The median age of patients was 63 years (IQR 46–72). There were 177 (40%) males and 267 (60%) females.

The median duration between the first successful ERCP and cholecystectomy was 75 days (IQR 30–147) with 23 (5%) having an operation within 72 h of having the ERCP. In total, 27 (6.1%) suffered ERCP-related complications, the details of these are depicted in Fig. 2. The demographics of the whole cohort and the outcomes of patients who underwent cholecystectomy after ERCP are presented in Table 1. The majority of cholecystectomies were performed in the elective setting (374, 84%) and laparoscopically (386, 87%). The laparoscopic to open conversion rate amongst laparoscopically attempted cases was 5.6% (23 cases). The median operative time was 73 min (IQR 53–95), which was significantly longer when performed in the emergency setting rather than as a planned procedure (89, IQR 62–112 vs 70, IQR 51–92, respectively; $P = 0.002$). The median PHS after cholecystectomy was one day (IQR 0–4). This was significantly longer for emergency operations [3.5 (IQR 1–9) vs 1 (IQR 0–3); $P < 0.001$] and shorter in laparoscopic cases compared to open and open-converted cholecystectomies

Fig. 1 Study design with patient groups



[0 (IQR 1–3) vs 1 (IQR 4–8) vs 3 (IQR 6–10), respectively; $P < 0.001$). Bile leak rate for the whole cohort was 2% (9 cases), and retained stones rate was 4.1% (18 cases) (Table 1). Fifty-two patients (11.7%) were readmitted to the hospital with gallstone-related symptoms after the ERCP whilst awaiting cholecystectomy.

When we compared the outcomes between the three groups, we found that the late group included significantly younger patients (median age 70 vs 65 vs 56 years, $P < 0.001$) and an equal number of male and female patients (Male-to-female ratio—1:3.1 vs 1:1.2 vs 1:1.4, $P = 0.02$) compared to early and intermediate groups. More day-case surgery was performed in the late group (27, 26 and 39% for the early, intermediate and late groups, respectively; $P = 0.03$). The early group included significantly more emergency cholecystectomy cases compared to the other two groups (56.5, 18 and 6.5% for the early, intermediate and delayed groups, respectively; $P < 0.001$). We observed no difference in the median operative time, conversion rate or sub-total cholecystectomy rate between the three groups. We also found no difference in the rate of bile leak or retained stones between the three groups. However, we observed a significant negative correlation between post-operative hospital stay and ERCP duration to cholecystectomy ($P < 0.001$). Analysed by group, the difference was only significant between early and late groups (median of 2 and 1 days, respectively, $P = 0.05$); and between intermediate and late groups (median of 2 and 1 days, respectively, $P = 0.02$) (Fig. 3). However, the difference in THS between groups was not statistically significant (median of 2, 2 and 1 days for the early, intermediate and late groups, respectively; $P = 0.08$). It was also noted that the longer the delay between ERCP and cholecystectomy, the higher the readmission rate (3.2% vs 11.1% vs 13.7%, $P = 0.05$) (Table 1). The details of demographics and comparison of outcomes between the three groups are illustrated in detail in Table 1.

A sub-group analysis of patients with ERCP-related complications and their outcomes was also carried out. Patients who suffered post-ERCP complications had a significantly longer PHS (4 vs 1 day, $P = 0.001$) and had a higher

Table 1 Baseline demographics and outcomes of cholecystectomy after ERCP

	Total cohort ($N=444$)	Early ≤ 2 weeks ($N=62$)	Intermediate > 2–6 weeks ($N=90$)	Late > 6 weeks ($N=292$)	P-value
Baseline demographics					
Median age (years, IQR)	63 (46:72)	70 (60:75)	65 (57:74)	56 (40:70)	< 0.001
Sex (M:F)	2:3	1:3.1	1:1.2	1:1.4	0.02
Cholecystectomy details					
Emergency surgery	70 (15.8%)	35 (56.5%)	16 (18%)	19 (6.5%)	< 0.001
Elective surgery	374 (84.2%)	27 (43.5%)	74 (82%)	273 (93.5%)	< 0.001
Laparoscopic technique	386 (86.9%)	55 (88.7%)	80 (88.8)	251 (86%)	0.8
Open technique	35 (7.8%)	3 (4.8%)	7 (7.7%)	25 (8.6%)	0.8
Day-case surgery	154 (34.7%)	17 (27.4%)	23 (25.6%)	114 (39%)	0.03
Operative difficulty					
Lap-to-open conversion rate	5.6%	6.8%	3.6%	6%	0.7
Subtotal cholecystectomy	22 (5.0%)	3 (4.8%)	4 (4.5%)	15 (5.1%)	1
Median operative time (mins, IQR)	73 (53:95)	75 (55:95)	80 (55:103)	70 (50:93)	0.4
Clinical outcomes					
Rates of bile leak	9 (2.0%)	0 (0.0%)	2 (2.2%)	7 (2.4%)	0.7
Rates of retained stones	18 (4.1%)	2 (3.2%)	4 (4.5%)	12 (4.1%)	0.9
Readmission rate	52 (11.7%)	2 (3.2%)	10 (11.1%)	40 (13.7%)	0.05
Median hospital stay (days, IQR)	1 (0:4)	2 (0:6)	2 (1:4)	1 (0:3)	0.005
Median total hospital stay (days, IQR)	1 (0:5)	2 (1:6)	2 (1:5)	1 (0:5)	0.08

conversion rate (16 vs 4.5%, $P=0.04$) compared to the patients that did not suffer any ERCP-related complications. Furthermore, we also observed a non-significant increased retained bile duct stone rate in the group that suffered post-ERCP complications (7.4 vs 3.8%, $P=0.3$). The comparison of outcomes between the groups that developed post-ERCP complications against the group that did not develop any complications is described in Table 2.

Discussion

The two-stage approach is the most commonly used treatment method for managing concurrent CBD stones [12]. However, pre-op ERCP can make cholecystectomy difficult due to contrast-induced inflammation, biliary instrumentation and acute cholecystitis progression [13]. A recent systematic review of 14 studies by Friis et al. found that early cholecystectomy following ERCP is associated with a lower risk of conversion to an open operation and shorter hospital stay. They concluded that early cholecystectomy between 24 and 72 h following ERCP is the most suitable time and should be the standard of care. However, the studies included in this systematic review were small, with the biggest series having 308 patients. Furthermore, the study found that although the conversion rate was higher when cholecystectomy was delayed by more than 24 h after ERCP, it levelled off after two weeks of delay [7]. Our series has not found any difference in the conversion rate or overall peri-operative complications between the three groups. The conversion rate was 6.8% in the early group compared to 3.6% and 6% in the intermediate and late groups. The overall conversion rate was 5.6%. Unlike our results, a study by de Vries et al. observed that the conversion rate was higher in the delayed (31%) and late (16%) groups compared to the early group (4%). It is worth noting that the overall conversion rate was high in this study at 17% (much higher than 5.6% in our cohort). The reasons for high conversion rate in the study by de Vries et al. are not clear [14]. Importantly, we also noted that the bile leak rates were no different when the operation was delayed; this has been echoed by other large series [14, 15]. The overall peri-operative complications in our study were 11.1% in the group in whom surgery was delayed by more than six weeks, compared to 4.3% and 6.7% when surgery was delayed by 2 and 2–6 weeks, respectively; however, the difference was not statistically significant.

Like other studies, we observed that the length of hospital stay following cholecystectomy is significantly shorter if surgery is delayed by more than six weeks [6]. In our cohort, the median hospital stay was 1 day when the operation was delayed by six weeks instead of 2 days if done earlier. This is most likely due to the subsidence of inflammation in and around the cysto-hepatic triangle, making cholecystectomy more straightforward, enhancing early discharge

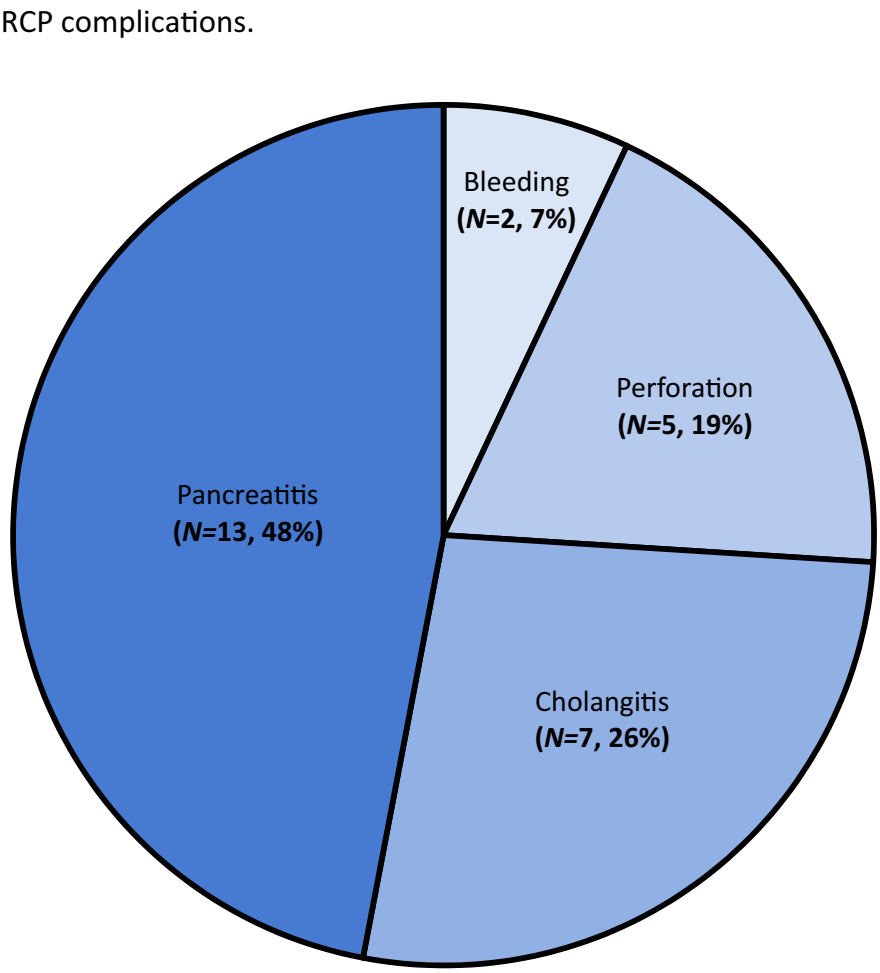


Fig. 2 Post-ERCP complications

Table 2 The outcomes of patients with ERCP-related complications and without ERCP-related complications

	ERCP-related complications ($N=27$)	No ERCP-related complications ($N=417$)	*P*-value
Baseline demographics			
Number of patients	27 (6.1%)	417 (93.9%)	–
Median age (years, IQR)	63.5 (35:71)	62 (46:72)	0.7
Operative difficulty			
Lap-to-open conversion rate	4 (16.0%)	19 (4.5%)	0.04
Subtotal cholecystectomy	2 (7.4%)	20 (4.8%)	0.4
Operative time (mins, IQR)	65 (58:90)	73 (52:95)	0.5
Clinical outcomes			
Rates of bile leak	0 (0.0%)	9 (2.2%)	1
Rates of retained stones	2 (7.4%)	16 (3.8%)	0.3
Rates of readmission	3 (11.1%)	60 (14.4%)	1
Median hospital stay (days, IQR)	4 (1:9)	1 (0:4)	0.001

and facilitating day-case surgery. On follow-up, the rates of retained stones in the CBD requiring post-operative stone extraction across the three groups were similar. Unfortunately, our study also revealed that 14% of patients who had delayed cholecystectomy have recurrent biliary symptoms warranting hospital admissions—besides the unknown number who had symptoms and managed the same at home. This finding has consistently been endorsed in literature with reports suggesting between 11 and 20% readmission rates when cholecystectomy is delayed [16, 17]. Our results

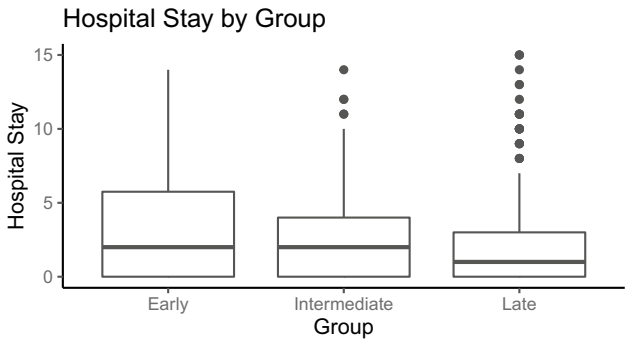


Fig. 3 Hospital stay by group

show that whilst delaying cholecystectomy facilitates day-case surgery, the aggregate hospitalisation (THS) increases due to readmissions for recurrent symptoms whilst waiting for elective cholecystectomy, thereby negating some of the benefit gained by delaying the operation (Table 1). Early cholecystectomy has the potential benefit of avoiding recurrent admissions, which will make a tangible difference to emergency and hospital services [18].

Early cholecystectomy, however, is not always clinically appropriate or logistically feasible in healthcare systems like the National health services (NHS). Only 5% of our study patients had a cholecystectomy within 72 h of having ERCP and bile duct stone clearance. This is all the more relevant during the COVID-19 pandemic as most benign procedures have been subject to further delays [19].

Interestingly, patients who had ERCP-related complications had a higher conversion to open surgery and longer post-operative hospital stay. This is an independent predictor of worse clinical outcomes; it can help in consenting patients and appropriate planning of operative listing. However, the literature regarding this assertion is scarce, and more data are necessary to establish causality. Our study is the largest series from the UK. Our findings are generalizable to most healthcare settings and help manage patients' and patients' expectations in the COVID and post-COVID era.

This study's primary limitation is the study's retrospective nature with its associated inherent limitations and biases. A large randomised controlled trial may be better suited to address these biases and can also provide more definitive answers. We acknowledge that there may be errors secondary to missing data, and inaccurately entered data. We have also used an arbitrary time interval to define early, intermediate and late groups; there is no standard definition. Different authors have used different periods, and this heterogeneity makes comparing outcomes difficult and speculative at times [6]. Despite these limitations, we have shown that delaying cholecystectomy does not increase complications and conversion rates. However, we still believe that early cholecystectomy should be offered to all patients whenever possible as it is safe and will reduce the readmission rate. If it is apparent that cholecystectomy is to be delayed for logistical or clinical reasons, then patients should be informed about potential recurrence of symptoms. This pragmatic approach may be the 'real world' solution to a common surgical condition.

Conclusion

Delayed Cholecystectomy following ERCP is clinically safe and not associated with higher bile leak, retained stones or conversion-to-open rates. On the contrary, it significantly increases day-case surgery rate and reduces post-cholecystectomy hospital stay. However, the total (aggregate) hospital stay is not significantly different due to higher readmissions with biliary complaints whilst awaiting surgery. ERCP-related complications increase hospitalisation duration following cholecystectomy with greater chances of conversion to open operation and can be used as a predictor of worse operative outcome.

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Declarations

Disclosures Drs. Muhammad Abdalkoddus, Joshua Franklyn, Rashid Ibrahim, Lu Yao, Nur Zainudin and Somaiah Aroori have no conflicts of interest or financial ties to disclose.

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