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Outcomes and timing of endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis

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ABSTRACT

Background: Indication of endoscopic retrograde cholangiopancreatography (ERCP) in acute biliary pancreatitis (ABP) is challenging.
Aims: In this retrospective study, we analyzed real-world data to understand the ERCP practice in ABP in Hungarian centers.
Methods: Clinical data on ABP patients (2013–2015) were extracted from our large multicentric database. Outcomes, quality indicators and the role of early timing of ERCP (<24 h from admission) were analyzed.
Results: There were 356 patients with ABP. ERCP was performed in 267 (75%). Performance indicators of ERCP proved to be suboptimal with a biliary cannulation rate of 84%. Successful vs unsuccessful cannulation of naïve papilla resulted in lower rates of local [22.9% vs 40.9%, (P = 0.012)] and systemic [4.9% vs 13.6%, (P = 0.042)] complications. Successful vs unsuccessful clearance resulted in lower rates of local complications [22.5% vs 40.8%, (P = 0.008)]. Successful cannulation and drainage correlated with less severe course of ABP [3.6% vs 15.9%, (P = 0.001) and 4.1% vs 12.2%, (P = 0.033)] respectively. A tendency of an increased rate of local complications was observed if ERCP was performed later [<24 h: 21.1% (35/166); between 24–48 h: 23.4% (11/47); >48h: 37.2% (16/43) (P = 0.088)].
Conclusion: Optimization of ERCP indication in ABP patients is critical as suboptimal ERCP practices in ABP without definitive stone detection are associated with poorer clinical outcomes.

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Core tip

The endoscopic management of acute biliary pancreatitis is still a controversial topic. In this prospectively collected cohort of patients in Hungary, we found that successful cannulation and clearance at the first attempt are associated with better outcomes and suboptimal ERCP practices may have a negative impact on the outcomes of the disease.

1. Introduction

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract requiring acute hospitalization; it is associated with significant morbidity and mortality worldwide with an increasing incidence of 5–100/100,000 cases per year [1]. Despite its importance, research on pancreatitis is continuously decreasing, suggesting that more attention should be paid to this disease [2].

One of the main etiological factors in the pathogenesis of AP is the obstruction of the ampulla of Vater by gallstones or sludge or by hypertrophy of papilla and bile reflux into the pancreatic duct, contributing to 35–60% of all AP cases. This subtype of AP is termed acute biliary or gallstone pancreatitis (ABP) [3]. Management of ABP requires two treatment strategies in most cases. The general, conservative medical treatment consists of appropriate fluid resuscitation (preferably lactated Ringer's solution) [4], pain management, and enteral nutrition in some cases [5]. The use of the interventional strategy in ABP to achieve biliary decompression is still uncertain. In cases of concomitant acute cholangitis, the need for urgent (<24 h) endoscopic retrograde cholangiopancreatography (ERCP) is recommended. There is also a clear indication of ERCP in cases of obstruction where biliary drainage must be properly resolved in a short period of time [1,6–8]. On the other hand, without apparent signs of cholangitis or obstruction (manifest systemic inflammation, biliary stones or dilatation on imaging, and jaundice or abnormal liver function test), the indication of ERCP in the setting of ABP is still debated because of the lack of available evidence [1,6]. The data provided by meta-analyses of randomized controlled trials (RCTs), where the most recent ones analyzed 10 and 11 RCTs, demonstrated a significant decrease in complications, hospital stay, and cost in patients with ABP managed with early ERCP (within 72 h) compared to conservative management [9,10]. An ongoing RCT is organized by the Dutch Pancreatitis Study Group on this still controversial topic; the APEC trial is set to determine the role of early ERCP with biliary sphincterotomy in ABP without cholangitis [11]. Despite the studies noted above, optimal comprehensive management of ABP is still lacking clear evidence.

The Hungarian Pancreatic Study Group (HPSG) was created in 2011 to improve patient care in pancreatic diseases and within a short period; this organization has produced several pancreatic registries, trials and established guidelines [12–16]. One of its registries, concerning Acute Pancreatitis, has recorded data on AP cases from all participating centers throughout Hungary and now in more than a dozen countries [17].

This study aims to determine the role of ERCP and sphincterotomy and stone clearance in ABP and to provide an overview of the general use of ERCP in Hungary in this disease.

2. Materials and methods

2.1. Inclusion criteria

All patients with AP were enrolled, and their data were prospectively collected in the HPSG AP Registry, which has been approved by the Scientific and Research Ethics Committee of the Medical Research Council (TUKEB-22254-1/2012/EKU). All patients were informed about the data collection and signed the informed consent forms. An AP diagnosis was made according to the recommendations in the IAP/APA guidelines, with at least two of the following three criteria met: abdominal pain, pancreatic enzyme exceeding more than three times the upper normal level, and features of pancreatitis on imaging.

In this cohort study, we selected patients who fit the criteria previously laid down by the Dutch Pancreatic Study Group, which were used to determine biliary origin: (a) gallstones and/or sludge diagnosed on transabdominal ultrasound or computed tomography (CT) or (b) dilated CBD on ultrasound or CT (diameter: >8 mm for age ≤75 years and diameter: >10 mm for age>75 years) or (c) two of the following three laboratory abnormalities: (1) serum bilirubin level >1.3 mg/dL [>40 μmol/L]; (2) alanine aminotransferase (ALT) level >100 U/L with an ALAT level greater than the aspartate aminotransferase level; and (3) alkaline phosphatase level >195 U/L with a gamma-glutamyltransferase level >45 U/L. Other causes of AP, such as alcohol, hypertriglyceridemia, diet, drug-induced, trauma, viral infection, post-ERCP, and idiopathic AP had to be absent (Supplementary Table 1) [18].

691 patients with AP were enrolled in the AP registry between January 2013 and August 2015 from 14 centers. The manuscript was prepared in accordance with the STROBE statement [19].

2.2. Exclusion criteria

Patients under the age of 18 years and those with non-biliary pancreatitis were excluded from the analysis.

2.3. Data extraction

Data on demographics (sex and age), etiology, severity, and mortality of AP were extracted for all subjects with AP, and a descriptive statistical analysis was performed. The severity of AP was classified according to the revised Atlanta classification as mild, moderately severe, and severe [20]. Main outcomes were the severity of pancreatitis, local (peripancreatic fluid, pseudocyst, necrosis of pancreas on imaging, diabetes mellitus, and abdominal compartment syndrome) and systemic (transient or persistent organ failure based on the modified Marshall scoring system for organ dysfunction) complications, mortality, and length of hospital stay.

Detailed demographics, including body mass index, comorbidities, and data on outcomes for ERCP, were collected on patients with ABP, such as indication of ERCP, successful cannulation rate, management of CBD stones by sphincterotomy and duct clearance, biliary and pancreatic stenting, anatomy of the papilla (naïve/not naïve), and complication rates (bleeding and perforation). Timing of ERCP was calculated from admission. The outcomes for ABP (severity of pancreatitis, local and systemic complications, mortality, and length of hospital stay) were analyzed in relation to the timing of ERCP. No follow-up was carried out after hospital discharge.

2.4. Statistical analysis

Continuous measures are summarized and presented as means and standard deviations (SD) or as median and interquartile ranges (IQR). Categorical data are presented as observed and as percentages. To determine differences between continuous parameters, depending on the distribution of the data, we used the independent Student's t-test or the Mann–Whitney U test for two groups and one-way ANOVA with the Bonferroni post-hoc test or Kruskal–Wallis test in comparing more than two groups. We used the Chi-square test or Fisher's exact test to analyze the rela-

Table 1
General characteristics of the acute biliary pancreatitis cohort.

	All [n (%)]	Women [n (%)]	Men [n (%)]	P-value
Gender	356	204 (57.3%)	152 (42.7%)	–
Age	61.65 ± 17.32	61.3 ± 18.1	62.1 ± 16.1	NS
Prior cholecystectomy	35 (9.4%)	28 (13.9%)	7 (4.6%)	**0.004**
Previously documented pancreatitis	42 (11.8%)	26 (12.7%)	16 (10.5%)	NS
Diabetes mellitus	59 (16.6%)	26 (12.7%)	33 (21.7%)	**0.023**
Body mass index (available for 160 women and 123 men)	28.31 ± 6.1	28.24 ± 6.03	28.40 ± 6.22	NS
At least 2 co-morbidities	155 (43.5%)	85/204 (41.7%)	70/152 (46.1%)	NS

tions between the factors under examination. All analyses were performed with SPSS 24 statistical software (IBM Corporation).

3. Results

3.1. General characteristics of the AP cohort

Biliary etiology was found in 356 (51.5%) patients, and 335 (48.5%) patients had other etiological factors (alcohol, hypertriglyceridemia, diet, drug-induced, trauma, viral infection, post-ERCP, and idiopathic AP). Among the subjects with ABP, there were more women, and they were older than patients with a different etiology [204/356 (57.3%) vs 106/335 (31.6%) (P < 0.001)] and mean age [61.5 ± 17.32 vs 51.47 ± 15.73 years (P < 0.001)]. The course of pancreatitis with biliary etiology was milder in contrast to non-ABP disease [mild ABP: 248/356 (69.7%) vs non-ABP: 183/335 (54.6%); moderately severe ABP: 86/356 (24.2%) vs non-ABP: 121/335 (36.1%); severe ABP: 22/356 (6.2%) vs non-ABP: 31/335 (9.2%) (P < 0.001)]. There was no difference in mortality between the two groups [ABP: 8/336 (2.4%) vs non-ABP: 13/322 (4.0%) (P = 0.242)].

3.2. Characteristics of the ABP cohort

A pancreatitis diagnosis was based on upper abdominal pain and elevated pancreatic enzymes in 327/356 (91.8%) of the patients.

ABP occurs more commonly in women [204/356 (57.3%) female vs 152/356 (42.7%) male]. In almost 10% of the cases, ABP developed after a cholecystectomy [35/356 (9.4%)] and more frequently in women [28/204 (13.9%) vs 7/152 (4.6%) (P = 0.004)].

Diabetes mellitus as a co-morbidity was found in 16.6% (59/356) of the patients, significantly more often in men [26/204 (12.7%) vs 33/152 (21.7%) (P = 0.023)].

Age, a previously documented episode of pancreatitis, body mass index (BMI), and co-morbidity were not different between the two sexes. A considerable number of ABP patients had more than two co-morbidities [43.5% (155/356)] (Table 1).

3.3. Indications for ERCP

Out of the 356 patients, 267 underwent ERCP (75.0%) for suspected cholangitis or cholestasis without cholangitis based on raised inflammatory markers with dilated biliary ducts and raised liver function tests. 89 patients in total did not undergo ERCP although it would have been indicated in 50 cases of suspected cholangitis (56.2%) ERCP was not performed in these cases due to an improving clinical picture, lack of consent from the patient, or rapid deterioration of multi-organ failure.

Endoscopic ultrasonography (EUS) was performed in only five patients, with bile duct stones being identified in two cases. MRCP was carried out in one patient, in which clear bile ducts were reported.

3.4. Quality indicators and findings of ERCP

The key performance indicators for ERCP met the criteria set out in the American Society of Gastrointestinal Endoscopy (ASGE) guidelines [21]. Successful biliary cannulation was achieved in 233 subjects with naïve papilla (90.7%), but the successful cannulation rate was 84.0% (216 procedures) at first attempt. In 80 subjects, extractions of stones smaller than 1 cm were successful in 93.7% of the cases. Stent implantation below the bifurcation was successfully carried out in all cases after successful deep biliary cannulation (33/33). Perforation occurred in 1/267 (0.4%) of the cases. Clinically significant bleeding requiring blood transfusion developed in 3/267 (1.2%) of the patients.

Common bile duct (CBD) stones, sludge, and/or dilation of the bile ducts were reported in 97 (36.3%), 91 (34.1%), and 124 (46.4%) cases, respectively. Spontaneous passage of a bile duct stone was suspected in 19.5% (52/267) of the patients during ERCP. In 30 cases (11.2%), no biliary pathology was found by ERCP. Endoscopic ultrasound was only carried out in five cases because of limited access at the time of data collection.

315 ERCPs were performed in 267 patients until completion or abandoning the intervention or treatment. 43 patients had two ERCPs, and five had three procedures.

3.5. Outcomes for ABP in relation to success rates of ERCP

Data on cannulation success rate and clearance of the bile ducts were available in all cases. The success rate for bile duct cannulation in all patients was 83.5% (223/267) during the first ERCP, and any further endoscopic attempts resulted in a higher rate of success [90.6% (242/267)]. Successful cannulation was achieved in 84.0% (216/257) of patients with naïve papilla, and clearance of the bile duct was successful in 71.5% (191/267) at the first ERCP attempt. Endoscopic biliary sphincterotomy was done in 86.5% (231/267) of the ERCPs, whereas pancreatic sphincterotomy was only performed in 1.12% (3/267) of the cases. Biliary stents were placed in 12.36% (33/267) and pancreatic stents in 16.85% (45/267) of the cases. Successful cannulation was associated with significantly lower rates of local and systemic complications. Successful clearance was linked to lower rates of local complications. Successful cannulation and clearance both correlated with a less severe course of ABP and shorter hospitalization (Tables 2 and 3).

Complete failure of clearance and decompression of the bile ducts were related to higher frequency of local complications and a more severe course of ABP and longer hospital stay (Table 4).

3.6. Outcomes for ABP in relation to the timing of ERCP

ERCP was performed in 75% (267/356) of the cases, the majority of them during the first 24 h after admission.

Data on the timing of ERCP were available in 256 (95.9%) cases. ERCP was performed on 64.8% (166/256) of the patients within 24 h after admission, in 18.4% (47/256) of them between 24 and 48 h after admission, and in 16.8% (43/256) cases later than 48 h after admission. A tendency of an increased rate of local complications

Table 2
Successful cannulation versus failure to cannulate the common bile duct with the first endoscopic retrograde cholangiopancreatography in the acute biliary pancreatitis cohort.

	Successful bile duct cannulation with 1st ERCP [n (%)]	Failure to cannulate the bile duct with 1st ERCP [n (%)]	P-value
Total (n = 267)	**223 (83.5%)**	**44 (16.5%)**	–
Rates of severe disease	8 (3.6%)	7 (15.9%)	**0.001**
Local complications	51 (22.9%)	18 (40.9%)	**0.012**
Systemic complications	11 (4.9%)	6 (13.6%)	**0.042**
Mortality	4 (1.8%)	1 (2.3%)	NS
Hospital stay, median (IQR)	9 (6–13)	14 (8–21.5)	**0.00021**

Table 3
Successful clearance versus failure to achieve clearance of the common bile duct for all endoscopic retrograde cholangiopancreatographies in the acute biliary pancreatitis cohort.

	Successful bile duct clearance [n (%)]	Failure of clearance the bile duct [n (%)]	P-value
Total (n = 267)	**218 (81.6%)**	**49 (18.3%)**	–
Rates of severe disease	9 (4.1%)	6 (12.2%)	**0.033**
Local complications	49 (22.5%)	20 (40.8%)	**0.008**
Systemic complications	13 (6.0%)	4 (8.2%)	NS
Mortality	4 (1.8%)	1 (2.0%)	NS
Hospital stay, median (IQR)	9 (6–13)	11 (7–21)	**0.021**

Table 4
Successful clearance versus failure of clearance and decompression of common bile duct for all endoscopic retrograde cholangiopancreatographies in the acute biliary pancreatitis cohort.

	Successful clearance of bile duct [n (%)]	Unsuccessful clearance and decompression of bile duct [n (%)]	P-value
Total	**218/267 (81.6%)**	**32/250 (12.8%)**	–
Rates of severe disease	9 (4.1%)	6 (18.7%)	**0.001**
Local complications	49 (22.5%)	16 (50.0%)	**0.001**
Systemic complications	13 (6.0%)	4 (12.5%)	NS
Mortality	4 (1.8%)	1 (3.1%)	NS
Hospital stay median (IQR)	9 (6–13)	16 (8.5–24.5)	**0.001**

Table 5
Outcomes for acute biliary pancreatitis in relation to the timing of endoscopic retrograde cholangiopancreatography in all patients with acute biliary pancreatitis.

	<24 h[n (%)]	24–48 h[n (%)]	>48 h[n (%)]	P-value
Total (n = 256)	**166 (64.8%)**	**47 (18.36%)**	**43 (16.80%)**	–
Rates of severe disease	5 (3%)	3 (6.4%)	3 (7.0%)	NS
Local complications	35 (21.1%)	11(23.4%)	16 (37.2%)	**0.088**
Systemic complications	7 (4.2%)	4 (8.5%)	4 (9.3%)	N/A*
Mortality	2 (1.2%)	1 (2.1%)	0 (0%)	N/A*
Hospital stay, median (IQR)	8 (6–12)	10 (5.5–15)	13 (9.5–21)	**<0.001**

* Statistical analysis was not carried out in cases of systemic complications, mortality, and rates of severe disease due to low numbers of subjects.

was observed if ERCP was performed later [ERCP in 24 h: 21.1% (35/166); between 24 and 48 h: 23.4% (11/47); after 48 h: 37.2% (16/43) (P = 0.088)].

We note that only 1.1% (7/267) of the endoscopic interventions described signs of purulent cholangitis.

The length of hospitalization was significantly longer in all patients if ERCP was delayed (Table 5).

3.7. Other relevant findings

There was no statistically significant difference in the outcomes for ABP between the patients treated with or without ERCP. (Supplementary Table 2).

Use of antibiotics was a common practice. 87.6% (312/356) of all the patients received antibiotics, for which the indication was suspected cholangitis in 85.3% (266/312). They were administered to treat infections outside the biliary tree, such as pneumonia and urinary tract infections, in 11.9% (37/312) of the cases. The first choice among antibiotics for cholangitis was a combination of a cephalosporin and metronidazole.

4. Discussion

Prospectively collected, real-world data were analyzed in this multicenter study, and considerable coverage of Hungarian acute biliary pancreatitis cases is presented. Data shown above depict current management strategies used in Hungary.

Although a clear-cut diagnosis of definite cholangitis would have been desirable in our analysis, currently there is no validated definition of cholangitis in the setting of ABP. Simple AP can result in a transient and self-resolving biliary obstruction with deranged liver function tests and dilated biliary tree, which can mimic cholangitis with the raised inflammatory markers driven by pancreatitis. Thus the use of the definition of definite cholangitis as termed by the Tokyo criteria had to be avoided [18].

As described in other studies, we found that patients with ABP are older, and there are more women among them compared to AP of other etiologies [3]. In the Hungarian cohort, ABP tended to have a less severe natural course, but the mortality was the same as in other etiologies, as reported in a large study [2].

Previous cholecystectomy was relatively common and more so in women. This could be explained by the fact that biliary stone disease is more common in females and that stone disease of the

gallbladder increases the risk of ABP, most likely even after a previous cholecystectomy. A previously documented episode of AP occurred in more than 10% of the patients. Although data on the etiology of the previous attack was not available, we believe that the majority of the cases were likely driven by gallstone disease, similar to data reported by Godi et al. [12]. Diabetes is a known risk factor for AP, and significantly more men had diabetes in the Hungarian cohort, which was reported in AP with all etiologies [15].

ERCP was performed in 75% of the patients presenting with ABP. To our best knowledge, there are no previous cohort studies where the rate of ERCP was published and analyzed. We found that our ERCP practice in ABP is in line with the current guidelines; however, we must highlight that very limited access to urgent endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) resulted in a number of avoidable ERCPs. At the same time, a small proportion of the patients with suspected cholangitis were not amenable to ERCP. In summary, we believe that ERCP for ABP will be reduced as access to EUS and MRCP improves. In most cases, the indication was suspected cholangitis, and these are the patients who could have benefited most from additional diagnostic imaging [16,19,22].

Our results clearly demonstrated that the lack of access to additional diagnostic tools (EUS or MRCP) resulted in a high number of unnecessary and avoidable ERCPs, and this clinical practice needs to be improved.

Some of the key performance indicators describing the ERCP practices in this large cohort across many centers described suboptimal ERCP practices. Most importantly a success rate of 84% at first attempt (216 patients), which is below the quality benchmark of >90% recommended by ASGE. This may well be driven by the fact that some of the ERCPs were performed in low volume centers. It also reminds us that, if indicated, high-quality ERCP with maximal pancreas protection and high competence of alternative biliary access techniques should be mandatory.

One of our main findings is that failed cannulation and bile duct clearance are associated with a higher incidence of local complications and severity of ABP. This result can be interpreted in two ways. Firstly, successful clearance and decompression of the bile ducts can result in a quicker resolution of pancreatitis and less progression leading to complications. Secondly, it may be explained by the difficult access to the bile ducts in already complicated AP, driven by difficult intubation of the duodenum, poor visualization of the papilla, limited maneuverability of the duodenoscope, and challenging cannulation of the edematous papilla. ERCPs are therefore done for the indication of acute biliary pancreatitis classified as grade 3 difficulty on the modified Schutz grade, on a scale of 1–4, where 4 is the most difficult [23].

In this situation, high success rates can only be expected of competent, highly skilled endoscopists with substantial case numbers. This is how we explain the slightly suboptimal quality indicators (ASGE guideline) of ERCP in this cohort [19]. Cannulation of naïve papilla was successful at first attempt in 84.1% of all ERCPs (desired: 90%), perforation occurred in 0.4% (desired: $\leq$0.2%), and bleeding requiring transfusion resulted in 1.2% (desired: $\leq$1%). We note that this analysis contained data from 267 patients, hence the two latter measures. Quality indicators of stone extraction and stenting of obstructions below the level of bifurcation met the criteria for the guidelines.

We did not find a significant decrease in the rate of local complications and hospital stay in the cohort when ERCP was performed within two days. Evidence suggests that early ERCP in ABP with cholangitis is indicated [1,6–8], but our findings could not reinforce these previous data. In patients with a clear-cut diagnosis of acute cholangitis, ERCP should be considered as soon as possible to provide a better outcome [24].

Just like the need for ERCP, the high rate of antibiotic use reported in our study (87.6%) could possibly be reduced by better access to EUS and MRCP in the case of suspected cholangitis. However, cholangitis is one of the most feared sources of abdominal infection and can lead to sepsis, multiple organ failure, and death. Therefore, any strategy to delay or withhold antibiotics in the context of suspected cholangitis should be carefully assessed. Educational activities should be organized and materials disseminated to ensure strict adherence to international guidelines [1,6].

4.1. Strengths and weaknesses of the study

This cohort represents a general, diverse, multicenter (not only tertiary centers participated), acute biliary pancreatitis sample. For this reason, broader, more generalizable conclusions could be drawn. Limitations of this study are the relatively low case numbers in subgroups and the retrospective design with post-hoc question raising, which is susceptible to biases, thus limiting the conclusions considerably. Lastly, a large number of participating ERCP units without a structured approach to the timing of ERCP procedures in ABP limits the statistical conclusions on associations with the outcomes of pancreatitis.

5. Conclusion

The indication and benefit of ERCP in patients with ABP but without a clear-cut diagnosis, cholangitis remains a contentious issue. We recommend that the non-invasive diagnostic approach should be maximized to select the most suitable subgroup of these patients. As ERCP is difficult in ABP, quality indicators must be closely monitored, and procedures should be performed by experts in high-volume centers as suboptimal ERCP practices are likely to be associated with poorer outcomes of the acute biliary pancreatitis.

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Institutional review board statement

This study was approved by the Hungarian Scientific and Research Committee of Medical Research Council (MRC). All patients with acute pancreatitis were enrolled, and their data were prospectively collected in the Hungarian Pancreatic Study Group (HPSG) AP Registry, which has been approved by the Scientific and Research Ethics Committee of the Medical Research Council (TUKEB-22254-1/2012/EKU). All patients were informed about the data collection and signed the informed consent forms.

Conflict of interest

Adrienn Halász MD, Dániel Pécsi MD, Nelli Farkas MSc PhD, Ferenc Izbéki MD PhD, László Gajdán MD, Roland Fejes MD, József Hamvas MD, Tamás Takács MD PhD DSc, Zoltán Szepes MD PhD, László Czakó MD PhD DSc, Áron Vincze MD PhD DSc, Szilárd Gódi MD,

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.03.018.

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