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Retrospective Cohort Study

Acute cholangitis: Does malignant biliary obstruction *vs* choledocholithiasis etiology change the clinical presentation and outcomes?

Tsou YK *et al*. AC of MBO *vs* CBDS

Yung-Kuan Tsou, Yi-Tse Su, Cheng-Hui Lin, Nai-Jen Liu

Abstract

BACKGROUND

Whether clinical outcomes of acute cholangitis (AC) vary by etiology is unclear.

AIM

To compare outcomes in AC caused by malignant biliary obstruction (MBO) and common bile duct stones (CBDS).

METHODS

This retrospective study included 516 patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) due to AC caused by MBO (MBO group, n = 56) and CBDS (CBDS group, n = 460). Clinical and laboratory parameters were compared between the groups. Propensity score matching (PSM) created 55 matched pairs. Confounders used in the PSM analysis were age, sex, time to ERCP, and technical success of ERCP. The primary outcome comparison was 30-d mortality. The secondary outcome comparisons were intensive care unit (ICU) admission rate, length of hospital stay (LOHS), and 30-d readmission rate.

RESULTS

Compared with the CBDS group, the MBO group had significantly lower body temperature, percentage of abnormal white blood cell counts, and serum levels of aspartate aminotransferase, alanine aminotransferase, and creatinine. Body temperature, percent abnormal white blood cell count, and

serum aspartate aminotransferase levels remained significantly lower in the MBO group in the PSM analysis. Platelet count, prothrombin time/international normalized ratio, and serum levels of alkaline phosphatase and total bilirubin were significantly higher in the NBO group. The MBO group had a significantly higher percentage of severe AC (33.9% *vs* 22.0%, P = 0.045) and received ERCP later (median, 92.5 h *vs* 47.4 h, P < 0.001). However, the two differences were not found in the PSM analysis. The 30-d mortality (5.4% *vs* 0.7%, P = 0.019), ICU admission rates (12.5% *vs* 4.8%, P = 0.028), 30-d readmission rates (23.2% *vs* 8.0%, P < 0.001), and LOHS (median, 16.5 d *vs* 7.0 d, P < 0.001) were significantly higher or longer in the MBO group. However, only LOHS remained significant in the PSM analysis. Multivariate analysis revealed that time to ERCP and multiple organ dysfunction were independent factors associated with 30-d mortality.

CONCLUSION

MBO patients underwent ERCP later and thus had a worse prognosis than CBDS patients. Therefore, clinicians should remain vigilant in MBO patients with clinically suspected AC, and perform ERCP for biliary drainage as soon as possible.

Key Words: Malignant biliary obstruction; Common bile duct stones; Endoscopic retrograde cholangiopancreatography; Acute cholangitis; Mortality; Etiology

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Core Tip: Our aim was to compare the outcomes of acute cholangitis (AC) with those of two common causes, malignant biliary obstruction (MBO) and common bile duct stones. We found that clinical manifestations such as body temperature, percentage of abnormal white blood cell count, and serum aspartate aminotransferase levels were significantly lower in the MBO group. The MBO group also had a significantly higher proportion of severe AC and a longer time to endoscopic retrograde cholangiopancreatography (ERCP). The 30-d mortality rate was significantly higher in the MBO group. Therefore, early recognition and early acceptance of ERCP are critical for MBO patients with AC.

INTRODUCTION

Acute cholangitis (AC) occurs clinically when bile duct obstruction results in a cholangiovenous or cholangiolymphatic reflux of pathogenic microorganisms or endotoxins[1,2]. The etiology of AC is diverse and includes common bile duct stones (CBDS), malignant biliary obstruction (MBO), benign biliary strictures, stent occlusion, *etc.* A Japan-Taiwan collaborative study that included 6063 patients showed that the most common etiology was

CBDS (60.3%), followed by MBO (15.6%) and stent obstruction (11.0%)[3]. Because of the variety of treatment options for malignancies in the current era, the number of MBO cases will inevitably increase even more[1,4].

MBO usually presents with painless jaundice, pruritus, and infrequently fever and leukocytosis[5]. In contrast, although sometimes asymptomatic, patients with CBDS often present to the emergency department (ED) due to sudden or severe abdominal pain[6]. However, there is no gold standard for the diagnosis of AC. The Tokyo Guidelines (TG) were to define AC for performing evidence-based clinical research[2,7,8]. The diagnostic criteria of TG include systemic inflammation, cholestasis, and imaging findings. Since the TG18 guidelines adopt the TG13 criteria, it is called the TG18/TG13 diagnostic criteria[8]. From TG07 to TG18/TG13, the severity of AC is further stratified and clarified in more detail[2,7,8]. Endoscopic retrograde cholangiopancreatography (ERCP) is currently the recommended first-line treatment for AC because it is less invasive and has a lower risk of adverse events[8-10]. However, for patients with AC, different etiologies may have different clinical manifestations, and patients may receive different drainage methods and thus may respond differently to ERCP[11,12]. Therefore, it is necessary to consider differences in disease state according to etiology. However, to our knowledge, such studies are limited in the literature[3]. Most studies based their findings and conclusions on populations with heterogeneous etiologies of AC[13-15]. Therefore, based on the TG18/TG13 diagnostic criteria, we conducted this study to elucidate the differences between AC caused by the two main etiologies, MBO and CBDS.

MATERIALS AND METHODS

Study design and patients

The current study was a retrospective study from Chang Gung Memorial Hospital Linkou Center. The diagnostic criteria for a definite diagnosis of AC and the severity of AC were according to the TG18/TG13 diagnostic criteria[8]. Figure 1 shows the study flow chart. Between January 2016 and December 2017, 683 patients who presented to our ED, met the diagnostic criteria for definite AC, and received ERCP were collected retrospectively from the computer database of the Therapeutic Endoscopy Center in our center. The exclusion criteria were: (1) Causes of AC other than MBO or CBDS [previous indwelling biliary stent obstruction (n = 61), benign biliary stricture (n = 31), or other causes (n = 13)]; and (2) patients without a native papilla (n = 62). Patients with AC caused by malignant tumors were categorized into the MBO group; patients with AC caused by CBDS were categorized into the CBDS group. This study was reviewed and approved by the Ethics Committee of the Chang Gung Memorial Hospital (IRB No. 202201601B0). Since this was a retrospective study using routine clinical treatment or diagnostic medical records, the Chang Gung Medical Foundation Institutional Review Board approved the waiver of the participant's consent. All methods were carried out under relevant guidelines and regulations.

We reviewed the medical records of the two groups of patients and obtained the following data for comparison. Demographic data included age and sex. Vital signs included body temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate. Laboratory values included white blood cell (WBC) count, platelet count, prothrombin time–international

normalized ratio (PT-INR), serum levels of creatinine, total bilirubin, alkaline phosphatase (ALK-P), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Serum albumin level data were available for only 82 patients (15.9%) and were excluded from the analysis. Data were collected on patient symptoms, vital signs, and laboratory test results while the patient was in the ED. In the MBO group, the cancer type, stage, and location of biliary obstruction (distal extrahepatic bile duct or perihilar) were recorded for each patient.

Definitions

The definition of organ dysfunction was according to the TG18 criteria, and patients with organ dysfunction were identified on this basis[8]. Cardiovascular dysfunction was hypotension requiring dopamine ≥ 5 μg/kg per min or any dose of norepinephrine. Neurological dysfunction was the presence of conscious disturbance. Respiratory dysfunction was a PaO_2/FiO_2 ratio < 300. Renal dysfunction was serum creatinine > 2.0 mg/dL. Hepatic dysfunction was PT-INR > 1.5. Hematological dysfunction was a platelet count < 100 × 10^3/μL. Multiple organ dysfunction was the dysfunction of at least two organs. An abnormal WBC count was a WBC < 4000/μL or > 12000/μL. Time to ERCP was the time from the ED visit to the commencement of ERCP. Technical success of ERCP was the success of deep bile duct cannulation and subsequent treatments such as stone retrieval and stent insertion.

Outcome assessments

The primary outcome comparison was 30-d mortality. Secondary outcome comparisons included intensive care unit (ICU) admission rate, length of hospital stay (LOHS), and 30-d readmission rate.

Propensity score matching

Because this was a retrospective study without randomization, there was a potential confounding bias between the two groups, which could have affected the study results. Therefore, we performed propensity score matching (PSM) to compensate for the bias caused by the lack of randomization in the two groups of cases. We calculated propensity scores using a logistic regression model. Based on clinical judgment and previous reports[16], four potential confounders of outcome were used in the model: Age, sex, time to ERCP, and technical success of ERCP. We performed 1:1 nearest neighbor matching using a caliper set at 0.05.

Statistical analysis

In the text and tables, data for continuous variables are expressed as medians and interquartile ranges (IQRs); categorical variables are expressed as numbers and percentages. For comparisons, the Mann-Whitney U test was used for continuous variable data, and Pearson's chi-square test or Fisher's exact test was used for suitable categorical variables. Logistic regression analysis was performed to identify factors associated with 30-d mortality. Only variables with a p value < 0.05 in the univariate analysis were included in the multivariate analysis. The results of the univariate and multivariate analyses were expressed as odds ratios (OR) and 95% confidence intervals

(CI). Two-tailed *P* values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (version 22.0; SPSS, Inc., Chicago, IL, United States).

RESULTS

A total of 516 patients were included in this study, including 56 (10.9%) in the MBO group and 460 (89.1%) in the CBDS group. PSM created 55 matched pairs (shown in Figure 1).

Characteristics of MBO

Table 1 Lists the etiology of MBO, tumor stage, and location of obstruction in the MBO group. All MBO patients were pathologically confirmed to be malignant. Pancreatic cancer was the most common etiology (42.9%), followed by ampullary tumor (23.2%), CBD cancer (10.7%), metastasis (10.7%), perihilar cholangiocarcinoma (5.4%), gallbladder cancer (3.6%), and hepatocellular carcinoma (3.6%). AC mostly occurred in advanced pancreatic cancer, perihilar cholangiocarcinoma, and gallbladder cancer, while it could occur in early ampullary tumors (including 2 adenomas) and CBD cancer. Regarding the location of the obstruction, most occurred in the distal EHD (82.1%), followed by the perihilar area (17.9%). Of the perihilar obstructions, 40% were Bismuth-Corlette type I, and 60% were Bismuth–Corlette type II.

Patient characteristics, laboratory values, and clinical outcomes

Table 2 summarizes the clinical and laboratory findings of the patients.

Demographic data

In the overall population, the median ages of the patients in the MBO and CBDS groups were 69 and 66 years, respectively. The proportions of men in both groups were 62.5% and 57.2%. There were no significant differences in age or sex between the two groups. Differences in demographic data were also not significant in the PSM analysis.

Laboratory values

In the overall population, body temperature (median, 36.9 °C *vs* 37.4 °C, *P* = 0.001), percent abnormal WBC counts (41.1% *vs* 60.9%, *P* = 0.004), and serum levels of AST (median, 109 U/L *vs* 167 U/L, *P* = 0.014), ALT (median, 103 U/L *vs* 189 U/L, *P* = 0.001), and creatinine (median, 0.8 mg/dL *vs* 1.0 mg/dL, *P* = 0.004) were significantly lower in the MBO group. However, platelet count (median, 237/μL *vs* 197.5/μL, *P* = 0.011), prothrombin time (international normalized ratio, median, 1.2 *vs* 1.1, *P* = 0.028), and serum levels of ALK-P (median, 357 mg/dL *vs* 181.5 mg/dL, *P* < 0.001) and total bilirubin (median, 8.2 mg/dL *vs* 3.7 mg/dL, *P* < 0.001) were significantly higher in the MBO group. In the PSM analysis, body temperature, percent abnormal white blood cell count, and serum AST levels remained significantly lower in the MBO group, while platelet counts and serum ALK-P and total bilirubin levels remained significantly higher in the MBO group.

Organ dysfunction and severity of AC

The percentages of organ dysfunction in the MBO and CBDS groups were as follows: 0% and 4.3% for cardiovascular dysfunction (*P* = 0.15), 10.7% and

5.2% for neurological dysfunction (P = 0.122), 7.1% and 7.0% for respiratory dysfunction (P = 1), 7.1% and 8.0% for renal dysfunction (P = 1), 7.1% and 2.2% for hepatic dysfunction (P = 0.063), and 8.9% and 5.9% for hematological dysfunction (P = 0.372), respectively. The differences in the percent of patients with dysfunction by organ were also not significant in the PSM analysis.

In the MBO and CBDS groups, regarding AC severity, 37.5% and 50.2% were mild AC (P = 0.072), 28.6% and 27.8% were moderate AC (P = 0.907), and 33.9% and 22.0% were severe AC (P = 0.045), respectively. However, in the PSM analysis, no significant differences were found regarding the severity of AC.

Timing and success rate of ERCP

The median time to ERCP was significantly longer in the MBO group than in the CBDS group (92.5 h *vs* 47.4 h, P < 0.001). When looking at the time to ERCP according to AC severity, patients with mild AC (median, 89.9 h *vs* 47.3 h, P = 0.026) and moderate AC (median, 113.1 h *vs* 44.5 h, P < 0.001) had a significantly longer time to ERCP in the MBO group than in the CBDS group. However, the time to ERCP was not significantly different between the two groups of patients with severe AC (median, 68.8 h *vs* 65.9 h, P = 0.133). However, in the PSM analysis, the time to ERCP did not differ significantly either in the overall population or according to AC severity.

The technical success rate of ERCP in the MBO group was significantly lower than that in the CBDS group (94.6% *vs* 99.1%, P = 0.031). The rate of stent insertion during initial ERCP was significantly higher in the MBO group than in the CBDS group (51/56 or 91.1% *vs* 42/460 or 9.1%, P < 0.001). The

type of stent insertion in the MBO group was as follows: 68.6% had plastic stents, and 31.4% had metal stents. In the PSM analysis, the technical success rate of ERCP was not significantly different between the two groups.

Primary and secondary outcomes

Table 3 shows the primary and secondary outcomes of the study. In the overall population, 30-d mortality was higher in the MBO group than in the CBDS group (5.4% vs 0.7%, $P = 0.019$). The ICU admission rate (12.5% vs 4.8%, $P = 0.028$) and the 30-d readmission rate (23.2% vs 8.0%, $P = 0.028$) were significantly higher in the MBO group. The LOHS was also significantly longer in the MBO group (median, 16.5 d vs 7 d, $P < 0.001$).

In the PSM analysis, there were no statistically significant differences in 30-d mortality, ICU admission, or 30-d readmission. The LOHS was still significantly longer in the MBO group than in the CBDS group (median, 16 d vs 8 d, $P < 0.001$).

Factors associated with 30-d mortality

The results of the univariate and multivariate analyses are listed in Table 4. The univariate analysis revealed that MBO (vs CBDS, OR: 8.623, 95%CI: 1.697-43.806, $P = 0.009$), time to ERCP (every 1-d delay, OR: 1.931, 95%CI: 1.210-3.081, $P = 0.006$), failure of ERCP (OR: 16.88, 95%CI: 1.696-166.389, $P = 0.016$), hepatic dysfunction (OR: 17.917, 95%CI: 2.986-107.492, $P = 0.00$), respiratory dysfunction (OR: 14.455, 95%CI: 2.807-74.421, $P = 0.001$), neurological dysfunction (OR: 17.889, 95%CI: 3.447-92.828, $P = 0.001$), cardiovascular dysfunction (OR: 29.600, 95%CI: 5.450-154.322, $P < 0.001$), multiple organ

dysfunction (OR: 33.172, 95%CI: 5.833-188.666, *P* < 0.001), severe AC (*vs* moderate AC + mild AC, OR: 17.174, 95%CI: 1.986-148.479, *P* = 0.010), and ICU admission (OR: 8.944, 95%CI: 1.568-51.014, *P* = 0.014) were associated with 30-d mortality. Not every single organ dysfunction variable associated with 30-d mortality was included in the multivariate analysis due to the use of multiple organ dysfunction in the multivariate analysis. The multivariate analysis revealed that time to ERCP (OR: 1.977, 95%CI: 1.027-3.807, *P* = 0.041) and multiple organ dysfunction (OR: 49.008, 95%CI: 1.692-1419.861, *P* = 0.023) were the two independent factors associated with 30-d mortality.

DISCUSSION

In the literature, few studies reported only MBO-associated AC[17], some gave an account of only CBDS-associated AC[11,18], and most reported mixed results for AC of different etiologies[3,13-15]. Although the etiology of AC varies, studies explicitly comparing the clinical presentations and outcomes of AC of distinct etiologies are rare. In the present study, we found that the clinical manifestations of AC in MBO patients were less conspicuous than those in CBDS patients, manifested by having lower body temperature, being less likely to have abnormal WBC counts, and by having lower serum levels of AST. These results remained verified in the PSM analysis. AC patients with poor systemic inflammation are difficult to diagnose according to the TG18/TG13 criteria[3]. Therefore, AC diagnosis might be delayed in our MBO patients, especially those with mild AC and moderate AC, which may explain the significantly later ERCP in MBO patients than in CBDS patients.

Consistent with a previous study, we observed a decreased percentage of patients with increased AC severity in the CBDS group but not in the MBO group[3]. Kiriyama et al[3] reported that 30-d mortality increased significantly with increasing AC severity (5.1%, 2.6%, and 1.2% in severe, moderate, and mild AC, respectively). However, this association was not present in their MBO patients. They suggested that the TG18/TG13 severity grading scale may have limited utility as a predictor of poor prognosis in AC caused by MBO.

In the overall population analysis, we found that MBO-associated AC had significantly higher 30-d mortality than CBDS-associated AC, which is consistent with previous studies[3,4]. Regardless of the etiology, time to ERCP has been reported to be a prognostic factor associated with 30-d mortality in AC patients[13,16,17]. In a study of distal MBO-associated AC, Park et al[17] reported that urgent ERCP (within 24 h of ED arrival) improved 30-d mortality in moderate-to-severe AC patients. In our study, in the overall population and in subgroup analyses of patients with mild and moderate AC, MBO patients had a longer time to ERCP than CBDS patients. Therefore, we performed a PSM analysis using a narrow caliper to minimize confounding variables, including time to ERCP[19]. We found no significant differences in AC severity or 30-d mortality between the two propensity-matched cohorts. Furthermore, we found that time to ERCP, but not MBO itself, was an independent factor associated with 30-d mortality in the multivariate analysis. Therefore, time to ERCP was an important factor associated with 30-d mortality in MBO patients[17]. Awareness and early recognition of MBO-

associated AC are paramount so that these patients can undergo ERCP earlier to improve outcomes.

The longer LOHS in patients with MBO-associated AC may be related to several factors. First, MBO is frequently associated with anatomical alterations, and this leads to a lower success rate of ERCP, as shown in this study[17]. Patients who fail ERCP require salvage therapy to relieve bile duct obstruction, thereby prolonging LOHS[20]. Second, following ERCP, MBO patients may require additional treatment for the underlying disease. Some studies reported that urgent or early ERCP can shorten LOHS[21,22]. However, in these studies, they did not mention the etiology of AC. Further studies are needed to clarify whether early ERCP can shorten the LOHS in patients with MBO-associated AC.

The 30-d readmission rate is frequently used as a quality measure, but only a few studies have reported readmission risk for AC patients[23,24]. Using the national readmission database, Parikh et al[23] reported a 30-d readmission rate of 21.5% for AC patients. They reported that pancreatic neoplasm-associated MBO was one of the factors associated with a high risk of 30-d readmission. However, in their study, the diagnosis, etiology, and severity of AC were unclear, and patients without ERCP were included. Navaneethan et al[24] reported a 30-d readmission rate of 22%. In their study, the diagnosis of AC was made according to the clinical manifestations and laboratory tests. Regarding the etiology of AC, 38.7% of the cases were CBDS, and MBO accounted for 16.7% of the cases. They reported that a non-CBDS etiology and a delay in performing ERCP (> 48 h) increased the risk of 30-d readmission. The 30-d readmission rate in our study was 9.7% in the overall population

and 23.2% in MBO patients. The 30-d readmission rate was higher in the MBO group than in the CBDS group, a finding presented in the overall population analysis but not in the PSM analysis, likely due to the removal of confounding factors for time to ERCP in the PSM analysis.

This study has several limitations. First, this was a retrospective study with the inherent drawback of selection bias. However, to reduce the effect of selection bias, we performed a PSM analysis between the two groups. Second, we only included AC patients presenting to the ED; AC patients on the ward might have been excluded from this study, especially those with MBO. Third, we only recruited patients with native papillae. As a result, MBO patients with previous indwelling biliary stents were excluded from the study. The above two reasons may explain the low proportion of MBO patients in this study.

CONCLUSION

In conclusion, 30-d mortality, ICU admission, and the 30-d readmission rates were significantly higher in MBO-associated AC patients in the overall population analysis but not in the PSM analysis. Time to ERCP was a paramount factor in this difference. Therefore, clinicians should remain vigilant in the care of MBO patients with clinically suspected AC and have to perform ERCP for biliary drainage as soon as possible.

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