LESS

Original Article

Laparosc Endosc Surg Sci 2020;27(4):220-228
DOI: 10.14744/less.2020.59354

Treatment of acute cholecystitis and risk factors for mortality in hemodialysis patients

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ABSTRACT

Introduction: There have been few studies on the treatment of acute cholecystitis (AC) in hemodialysis (HD) patients. The aim of this study was to investigate the risk factors for mortality in HD patients who developed AC, and to compare the results of treatment.

Materials and Methods: The records of HD patients who developed AC between 2009 and 2019 were analyzed retrospectively. The diagnosis and severity of AC was made according to Tokyo Guideline (TG) 18. The American Society of Anesthesiologists (ASA) scores were used for surgical risk. The Charlson comorbidity index (CCI) was used for comorbid conditions of patients. Risk factors were investigated for mortality. Medical treatment and cholecystectomy results were compared.

Results: Thirty-four patients were included in the study. Mortality occurred in six patients (17.6%). Age ≥65 years, an ASA IV score, a CCI ≥8, Tokyo Guideline 18 (TG 18) grade III, and blood urea nitrogen ≥60 mg/dL were increased those who died (p=0.03, p=0.001, p=0.02, p<0.001, p=0.03; respectively). According to TG 18, there was no difference between the medical treatment and cholecystectomy groups in terms of clinical success, readmission, and mortality rates (p=1.00, p=0.64, p=1.00; respectively). However, length of hospital stay was longer in the cholecystectomy group (p=0.01).

Conclusion: Despite the suggestions in the TG 18, medical treatment and in-hospital early cholecystectomy can be performed with similar clinical success, readmission, and mortality rates in HD patients who develop AC.

Keywords: Acute cholecystitis, end stage renal disease, outcomes, clinical success, medical treatment, cholecystectomy, death

Introduction

The incidence of end stage renal disease (ESRD) is gradually increasing. ESRD treatment is generally hemodialysis (HD) due to donor shortage.[1] The incidence of acute cholecystitis (AC) is higher in patients who are on HD than in the normal population.[2] Although cholecystectomy is generally the treatment of choice for AC in the normal population, there have been limited reports on AC treatment in patients who are on HD.[2-4] These patients have several comorbidities that could affect the treatment selection for AC, including hypertension, coronary artery disease (CAD), electrolyte imbalance, metabolic acidosis, congestive heart failure (CHF), anemia, tendency to bleed, and immunosuppression that causes infection.

Received: 03.12.2020 **Accepted:** 28.12.2020
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The aim of this study is to evaluate the operative and non-operative treatment outcomes, and the risk factors for mortality in HD patients with AC.

Materials and Methods

Medical records of AC patients who had received HD treatment between 2009 and 2019 were retrospectively scanned. Age, sex, presence of comorbidity, an American Anesthesiologists Association (ASA) scores, a Charlson comorbidity index (CCI), laboratory and imaging findings, treatment modality, post-treatment complications, readmission, length of hospital stay, and mortality were recorded. This retrospective study was approved by the local ethics committee (2018/8-17). Two centers were participated in the study. Informed consent was not obtained for the study. Patient follow-up was median 7 (0-86) months.

Definitions

The diagnosis of AC was made the characteristic patient's clinical presentation (pain in right upper quadran, fever, Murphy'ssign), laboratory findings (elevated white blood cell (WBC) count or C-reactive protein level (CRP)), and imaging findings (thickened gallbladder (GB) wall, pericholecystic fluid collection, enlarged GB)5. All patients were classified into three groups according to the severity grade of the Tokyo Guideline (TG) 18 for AC: grade I (mild), grade II (moderate), and grade III (severe).[5] An ASA score was used for surgical risk.[6] A CCI was used for comorbid conditions of patients. The treatment success was defined as resolution of symptoms and fever, and normalization of CRP levels and WBC counts. Complications were classified according to the Clavien-Dindo classification. Re-admission was defined as re-hospitalization within 30 days due to postoperative complications in patient who performed cholecystectomy or at any days after discharged recurrence of AC in patient who performed percutaneous cholecystostomy (PC). Mortality was defined as 30 days postoperatively for patients who performed cholecystectomy and as any day due to biliary complaints for patients who performed PC.

Fluid resuscitation was initiated in patients who diagnosed AC, and prophylactic antibiotics and analgesic were administered. Patients who also had acute cholangitis along with AC underwent endoscopic retrograde cholangiopancreatography (ERCP) following the medical treatment (MT), once the patients stabilized. Decision of treatment in patients with AC was made by the patient's responsible surgeon. If there is a suspicion of gallbladder perforation or signs of generalized peritonitis, cholecystectomy was performed directly. Cholecystectomy was performed by open technique within the first ten days after onset of AC symptom. Considering the clinical condition and comorbidities of the patients, if there was no findings of generalized peritonitis patients were administered MT that consisted of intravenous fluid, analgesics, and antibiotics treatment. PC or cholecystectomy was applied in some patients whose comorbid condition stabilized after MT. PC was performed by an interventional radiologist by ultrasonography and fluoroscopy through the transhepatic route. Patients who readmitted for new episode of AC during the follow-up period were evaluated for MT. Interval cholecystectomy was performed none of patients.

Statistical Analysis

The data from the centers that participated in the study were recorded in an Excel file. SPSS 22 (SPSS Inc. Chiacago, IL, USA) was used for statistical calculations. A Shapiro–Wilk test was used to test normality in statistical calculations. Fisher's chi-square, and Mann–Whitney U test were used for categorical and continuous variables. A p value <0.05 was considered statistically significant.

Results

Thirty-four patients with AC who had received HD treatment were included to study (Table 1). All patients had abdominal pain and half of the patients (17/34) had a fever of 38 °C higher. At the admission, 17 patients had elevation in liver function tests (alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin and one patient had elevation in amylase levels. Two patients had common bile duct stones in addition to AC. ERCP was performed to a patient in the MT group due to cholangitis. The other patient also had acute pancreatitis that improved with MT. Of the patients 29 received medical treatment, four received directly cholecystectomy due to the suspicious gallbladder perforation, and a 86-year-old patient underwent PC. Twenty of the patients who MT were discharged without receiving additional treatment. Of the five patients whose comorbid conditions stabilized after MT, cholecystectomy was performed in four and PC in one. All four patients underwent cholecystectomy had CAD, two had Type 2 Diabetes Mellitus (DM), two had CHF, and open cholecystectomy was performed to all of them. Three of the patients who underwent cholecystectomy showed recovery, and developed mortality in one of patient. PC patient who had a history of CAD, DM and CHF showed clinical improvement, the catheter was removed at second month, and no additional treatment was recommended. Seven patients were re-hospitalized, including six for AC recurrence and

Table 1. Patient demography

Patient	Gender (M, F)	Age	ASA Score	CCI (point)	HD duration (month)	Treatment type	LOS (day)	Mortality	Follow-up (month)
1	F	60	na	5	55	MT	5	No	1
2	F	50	3	3	41	MT	4	No	51
3	F	76	3	7	2	MT	30	No	35
4	M	66	4	8	56	MT, C	6	Yes	0
5	F	52	na	3	120	MT	5	No	28
6	F	55	na	3	147	MT	5	No	na
7	F	55	3	3	153	MT	7	No	1
8	F	71	3	5	60	C	8	No	86
9	F	68	3	5	144	MT	4	No	1
10	F	68	4	5	144	MT	13	Yes	0
11	F	60	3	6	12	MT	23	No	1
12	M	34	4	4	36	MT	19	Yes	0
13	F	62	na	4	144	MT	1	No	33
14	F	54	3	5	2	MT	9	No	44
15	F	54	3	5	2	MT	3	No	44
16	M	72	4	6	156	MT	2	Yes	0
17	F	73	3	5	57	MT	5	No	4
18	M	70	3	5	72	C	16	No	43
19	M	67	3	5	60	MT, C	9	No	na
20	F	64	3	6	1	MT	3	No	na
21	F	65	4	6	1	MT	2	Yes	0
22	F	60	na	5	38	MT	3	No	5
23	F	50	3	3	42	MT	5	No	51
24	M	71	na	5	120	MT	15	No	na
25	F	72	4	2	48	MT, C	14	No	2
26	F	64	3	6	12	MT	3	No	6
27	M	57	3	6	12	C	24	No	24
28	M	37	3	2	12	MT	9	No	8
29	F	77	4	6	12	MT, PC	18	No	1
30	M	71	3	9	8	MT	7	No	6
31	M	60	3	5	12	MT	12	No	na
32	M	60	3	5	12	MT, C	27	No	20
33	M	86	4	8	12	MT, PC	56	Yes	2
34	F	64	4	7	72	C	11	No	2

M: Male; F: Female; ASA: American Society of Anesthesiologists; CCI: Charlson comorbidity index; HD: Hemodialysis; LOS: Lenght of hospital stay; MT: Medical treatment; PC: Percutaneous cholecystostomy; C: Cholecystectomy.

one patient for wound infection. MT was performed in all six patients with AC recurrence. Antibiotics treatment was given to patient with wound infection. Mortality was developed in six patients (17.6%). Four of the six mortalities were in the MT group, one in the cholecystectomy group, and one in the PC group. In one AC patient who had a history of CAD, DM and hypertension, and a finding compatible with acute cholecystitis in intraoperative exploration, mortality developed due to cardiovascular reasons on the first postoperative day. Mortality developed due to multi-organ dysfunction in two patients in the MT group, CHF and respiratory failure in two patients, and CHF and pulmonary edema in one patient in the PC group.

Table 2 shows the factors affecting mortality in patient who treated for acute cholecystitis. Age ≥65 (p=0.03), ASA

Table 2. Factors affecting mortality in hemodialysis patients who treated for acute cholecystitis

Parameters	Mortality n=6		No-mortality n=28		p
	n	%	n	%	
Age (years)					
≥65	5	83.3	10	35.7	0.03
<65	1	16.7	18	64.3	
Gender					
Male	4	66.7	8	28.6	0.08
Female	2	33.3	20	71.4	
Comorbidity					
Congestive heart failure	2	33.3	7	25.0	0.86
Hypertension	6	100.0	28	100.0	0.25
Type 2 Diabetes mellitus	4	66.7	9	32.1	0.15
Coronary artery disease	3	50.0	9	32.1	0.57
Cerebrovascular accident	0	0	3	10.7	0.42
Atrial fibrillation	1	16.7	2	7.1	0.62
ESRD duration (year) (median (min-max))	11 (3-13)		8 (1-30)		0.63
HD duration (month) (median (min-max))	46 (1-156)		42 (1-153)		0.75
ASA Score					
III	0	0	19	67.9	
IV	6	100	3	10.7	0.001
na	0	0	6	21.4	
CCI (point)					
<8	4	66.7	27	96.4	0.02
≥8	2	33.3	1	3.6	
Labaratory values (median (min-max))					
Alanine aminotransferase (U/L)	15 (4-54)		40 (3-903)		0.09
Aspartate aminotransferase (U/L)	29 (13-82)		44 (12-2104)		0.25
Total bilirubin (mg/dL)	1.2 (0.4-22.4)		0.8 (0.3-6.3)		0.51
Alkaline phosphatase (U/L)	136 (107-175)		175 (46-1593)		0.56
Gamma-glutamyl transferase (mg/dL)	67 (25-107)		89 (20-568)		0.22
C-reactive protein (mg/L)	10.4 (6.2-34.8)		4.7 (0.3-32.0)		0.08
White blood count (x10^3/µl)	12.0 (9.4-15.8)		8.2 (4.3-22.6)		0.07
Blood urea nitrogen (mg/dL)					
≥60	4	66.7	6	21.4	0.03
<60	2	33.3	22	78.6	
Creatinine (mg/dL)					
≥5	3	50.0	15	53.6	0.88
<5	3	50.0	13	46.4	
Imaging findings					
Calculous cholecystitis	5	83.3	23	82.1	0.95
Choledocholithiasis	0	0	2	7.1	0.50
Cholangitis	0	0	1	3.6	0.64
Pancreatitis	0	0	1	3.6	1.00

Table 2. CONT.

Parameters	Mortality n=6		No-mortality n=28		p
	n	%	n	%	
Tokyo Guideline 18					
Grade I	0	0	12	42.9	
Grade II	0	0	13	46.4	<0.001
Grade III	6	100.0	3	10.7	
Treatment type					
Medical treatment	4	66.7	20	71.4	
Percutaneous cholecystostomy	1	16.7	1	3.6	0.45
Cholecystectomy	1	16.7	7	25.0	
LOS (day) (median (min-max))	10 (2-56)		8 (1-30)		0.93

ESRD: End stage renal disease; HD: Hemodialysis; ASA: American Society of Anesthesiologists; CCI: Charlson comorbidity index; LOS: Lenght of hospital stay.

IV score (p=0.001), CCI ≥8 (p=0.02), blood urea nitrogen (BUN) level ≥60 mg/dL (p=0.03), and TG 18 grade III AC (p<0.001) and were found as risk factors for mortality. Because of the small number of patients, PC treatment group was not included in the statistical comparison of the treatment types (Table 3). Plasma creatinine level (≥5.0 mg/dL) was higher in the MT group (p=0.04). Length of stay was longer in the cholecystectomy group (median 13 vs 5 days, p=0.01; respectively). However, there was no difference between the clinical success, readmission, and mortality rates of the both groups (p=1.00, p=0.64, p=1.00; respectively). No recurrence of AC was detected during follow-up in MT and PC group. None of the patients underwent elective cholecystectomy.

Discussion

AC is a common disease and the incidence of AC has been increasing in elderly patients in recent years. These patients often have comorbidities that increase the risk of perioperative complications associated with cholecystectomy, such as HD.[1,7-9] Dialysis patients have approximately six times higher incidence of AC than the normal population, and it is classified as patients with high surgical-risk due to comorbidities.[2] TG 18 recommends early laparoscopic cholecystectomy (LC) for grade I and grade II AC, PC or LC for grade III AC.[5,10] However, Harai et al. used MT only for patients with TG 13 grade I and II in the AC treatment. Clinical success rates were 100%, none of them underwent emergency or elective cholecystectomy, and no patient developed mortality.[11] A systematic review showed that MT is successful in 87 % of patients with AC who had 96% mild disease, and mortality rate is 0.8%.[12] As far as we know, there is no other study used MT in high-risk patients such as HD (Table 4). Although our study includes a small number of patients, we were showed that MT can also be used for AC treatment in patients with HD. In our study, the clinical success rate of MT for AC was 83.3% (20/24). According to TG 18, the clinical success rates of MT for AC were 100.0% (10/10) for grade I, 100.0% (8/8) for grade II, and 33.3% (2/6) for grade III. According to TG 18, the clinical success rates of early cholecystectomy for AC were 100.0% (2/2) for grade I, 100.0% (4/4) for grade II, and 50.0% (1/2) for grade III. There was no significant difference between the clinical success, readmission, and mortality rates of MT and cholecystectomy (83.3% vs 87.5%, p=1.00; 25.0% vs 12.5%, p=0.64; and 16.7% vs 12.5%, p=1.00; respectively).

A systematic review showed that MT is mortality rate 0.8% in mild severity AC.[12] Gunay et al. found that the mortality rate of cholecystectomy is 15.7% in patients with AC who had treated HD.[1] The mortality rates in elderly and high ASA score patients who underwent cholecystectomy were found higher than MT.[13,14] In our study, the mortality rates were 16.7% (4/24) in MT, 12.5% (1/8) in cholecystectomy and 50.0% (1/2) in PC. According to our study, ≥65 years of age was found to be a risk factor for mortality (83.3% vs 16.7%, p=0.03). Yokoe et al. reported that the difference of mortality between TG 13 grades for AC was

Table 3. Comparison of medical treatment and cholecystectomy

Parameters	Medical treatment n=24		Cholecystectomy n=8		p
	n	%	n	%	
Age (years)					
≥65	8	33.3	5	62.5	0.15
<65	16	66.7	3	37.5	
Gender					
Male	8	33.3	5	62.5	0.053
Female	16	66.7	3	37.5	
ESRD duration (year) (median (min-max))	10 (1-30)		5 (4-15)		0.15
HD duration (month) (median (min-max))	38 (1-156)		58 (12-72)		0.57
Comorbidity					
Congestive heart failure	6	25.0	2	25.0	0.69
Hypertension	19	79.2	6	75.0	0.66
Type 2 Diabetes Mellitus	10	41.7	3	37.5	0.76
Coronary artery disease	8	33.3	5	62.5	0.83
Cerebrovascular accident	3	12.5	1	12.5	0.97
Atrial fibrillation	2	8.3	1	12.5	0.75
ASA score					
III	14	58.3	5	62.5	
IV	4	16.7	3	37.5	0.42
na	6	25.0	0	0	
CCI (point)					
≥8	1	4.2	1	12.5	0.40
<8	23	95.8	7	87.5	
Labaratoryvalues (median (min-max))					
Alanine aminotransferase (U/L)	26 (5-767)		65.5 (9-903)		0.37
Aspartate aminotransferase (U/L)	48 (13-1138)		35 (12-2104)		0.56
Total bilirubin (mg/dL)	0.8 (0.3-22.4)		0.8 (0.4-1.2)		0.57
Alkaline phosphatase (U/L)	198 (46-1593)		128 (59-315)		0.25
Gamma-glutamyl transferase (mg/dL)	73 (20-568)		89 (27-270)		1.00
C-reactive protein (mg/dL)	4.4 (0.3-34.8)		7.3 (1.7-28.7)		0.33
White blood count (x10^3/µl)	8.9 (4.3-22.6)		9.1 (4.4-19.2)		0.86
Blood urea nitrogen (mg/dL)					
≥60	7	29.2	2	25.0	0.82
<60	17	70.8	6	75.0	
Creatinine (mg/dL)					
≥5	16	66.7	2	25.0	0.04
<5	8	33.3	6	75.0	
TG 18					
Grade I	10	41.7	2	25.0	
Grade II	8	33.3	4	50.0	0.70
Grade III	6	25.0	2	25.0	

Table 3. CONT.

Parameters	Medical treatment n=24		Cholecystectomy n=8		p
	n	%	n	%	
Clinical success					
Total	20	83.3	7	87.5	1.00
TG 18 grade I	10	41.7	2	25.0	1.00
TG 18 grade II	8	33.3	4	50.0	1.00
TG 18 grade III	2	8.3	1	25.0	1.00
Re-admission					
Yes	6	25.0	1	12.5	0.64
No	18	75.0	7	87.5	
LOS (day) (median (min-max))	5 (1-30)		13 (6-27)		0.01
Mortality	4	16.7	1	12.5	1.00
Follow-up (month) (median (min-max))	6 (0-51)		20 (0-86)		0.58

ESRD: End-stage renal disease; HD: Hemodialysis; ASA: American Society of Anesthesiologists; CCI: Charlson comorbidity index; TG: Tokyo guideline; LOS: Lenght of hospital stay.

Table 4. The success rates of treatment types in hemodialysis patients with acute cholecystitis

Authors	Year	Patient number	High-risk patients	Clinical success rate (%)			Mortality
				MT	PC	C	
Toh Y4	1998	4	Yes	-	-	75.0	25.0
Gunay Y1	2013	47	Yes	-	66.7	92.3	23.4
Yang HC2	2015	1	Yes	-	100.0	-	0
Aktas A	2019	34	Yes	82.8	50.0	87.5	17.6

MT: Medical treatment; PC: Percutaneous Cholecystostomy; C: Cholecystectomy.

significant (p<0.001).[15] According to TG 18, all mortalities in AC patients were observed in TG 18 grade III patients in our study (0% grade I and II, 66.7% grade III; p<0.001). ASA score is higher in HD patients, and a reliable independent predictor of mortality following surgery.[16-18] In our study, nine patients were classified as ASA IV. PC was performed to two patients, and MT was given to four patients. Cholecystectomy was performed at the preference of the responsible surgeon in three patients who were not suitable for PC because the gallbladder was not hydropic. In our study, all mortalities were seen in ASA IV score (66.7% for ASA IV score vs 0% for ASA III score, p=0.001; respectively). Bekki et al. found that high CCI index in AC treatment is an independent risk factor for 30-day mortality.[19] In our study, CCI ≥8 was found to be a risk factor for mortality (p=0.02).

Controversy regarding the open or laparoscopic approach in the surgical treatment of acute cholecystitis have continued. TG 13 reported that laparoscopic approach may be preferred to open approach in patients with acute cholecystitis, while TG 18 reported that laparoscopic approach should be used as the first choice in suitable patients.[10,20] In a meta-analysis comparing open and laparoscopic approaches in patients with acute cholecystitis, it was reported that postoperative complications and lenght of hospital stay were less in laparoscopic approach, although it was not statistically significant. However, only three of the 10 studies included in the meta-analysis had high-risk patients (elderly and gangrenous cholecystitis).[21] In a retrospective study comparing open and laparoscopic cholecystectomy, overall complications, need for intensive care, and lenght of hospital stay were less in the

laparoscopy group. However, in this study, there were patients from all risk groups.[22] After the publication of TG 18, there are no studies comparing the open and laparoscopic cholecystectomy in patients with acute cholecystitis. However, compared to open cholecystectomy, laparoscopic cholecystectomy offers less pain, less lenght of hospital stay, faster recovery duration and better quality of life. Therefore, laparoscopic cholecystectomy is increasingly preferred in the treatment of acute cholecystitis.[10,23] Early cholecystectomy was performed to eight patients in our study. In our clinics, while early laparoscopic cholecystectomy was preferred in patients with high-risk acute cholecystitis, but the open cholecystectomy in the early period and laparoscopic cholecystectomy in the delayed period were preferred in hemodialysis patients with acute cholecystitis. With the increase of our laparoscopic experience since the last year, we have started to prefer early laparoscopic cholecystectomy in hemodialysis patients with acute cholecystitis.

This study had some limitations. It was retrospective and medical records might not be fully recorded. The sample size was small, so we couldn't do the subgroup and multivariate analysis. This study was conducted at two centers, and surgical experience, treatment and complication management might have differed among the centers. All these limitations might have affected our clinical outcomes.

Conclusion

Despite the recommendations in the TG 18, MT and in-hospital early cholecystectomy can be performed with a similar clinical success, readmission and mortality in patients with AC who HD. However, more studies are needed to recommend the use of MT in patients with AC who HD.

Disclosures

Ethichs Committee Approval: This retrospective study was approved by the local ethics committee (2018/8-17).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.A., C.K., S.T.; Design – A.A., C.K., M.U., A.B.C., M.S., K.S., S.T., F.S.; Supervision – C.K., S.T., F.S.; Materials – A.A., M.U.; Data collection and/or processing – A.A., M.U., C.K.; Analysis and interpretation of data – A.A., F.S., C.K.; Literature Search- A.A., C.K.; Writing – A.A., C.K., S.T., F.S.; Critical review – A.A., C.K., S.T., F.S.

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