

# Outcomes following cholecystectomy in human immunodeficiency virus-positive patients treated with antiretroviral therapy: A retrospective cohort study

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**Abstract:** The number of the human immunodeficiency virus (HIV)-positive patients are increasing worldwide, and more HIV-positive patients are undergoing urgent or elective cholecystectomy. There is still insufficient evidence on the relationship between surgical complications of cholecystectomy and antiviral status in HIV-positive patients. The purpose of the present study is to evaluate surgical outcomes after cholecystectomy in HIV-positive patients. Records of consecutive HIV-positive patients who underwent cholecystectomy between January 2010 and December 2020 were reviewed retrospectively. Patients were divided into urgent and elective surgery groups. Urgent surgery was defined as surgery within 48 hours of admission. Postoperative complications were evaluated according to the Clavien-Dindo classification. A total of 30 HIV-positive patients underwent urgent ( $n = 7$ ) or elective ( $n = 23$ ) cholecystectomy. Four complications (13.3%) occurred, and the rate was significantly higher in the urgent group than in the elective group ( $p = 0.008$ ). However, all complications were minor (3 cases of grade I and one case of grade II), and there were no severe postoperative complications. There was no significant difference in CD4+ lymphocyte status in all patients and between the 2 groups before and after surgery ( $p = 0.133$ ). No cases of postoperative deterioration in the control of HIV infection were observed. In conclusion, cholecystectomy in HIV-positive patients with controlled HIV under recent antiretroviral therapy may be performed safely even in an emergency situation.

**Keywords:** cholecystectomy, human immunodeficiency virus, surgical outcome

## Introduction

Globally, approximately 38 million people live with human immunodeficiency virus (HIV) (1). Advances in antiretroviral therapy (ART) have greatly improved the prognosis of HIV-positive patients (2). As a result, surgical interventions are being commonly applied in HIV-positive patients (3), and the number of surgeries performed for such patients is expected to increase. As HIV affects the host's immune system, there is concern about increased incidence of postoperative complications in HIV-positive patients (4).

Cholecystectomy is a common surgical procedure for cholelithiasis or gallbladder polyps, and is often performed urgently for acute cholecystitis (5,6). From the perspective of postoperative complications, urgent cholecystectomy, which is often performed for severe acute cholecystitis, has been reported to be associated with higher overall morbidity, surgical site infections, and serious morbidities such as bleeding requiring transfusion, sepsis, and other severe systemic

dysfunctions compared to elective cholecystectomy for symptomatic cholelithiasis and gallbladder polyps. With the increase in HIV-positive patients, the number of urgent cholecystectomies is also expected to increase. However, there are few reports on the postoperative outcomes of urgent and elective cholecystectomy in HIV-positive patients and its impact on subsequent HIV infection treatment after surgery.

The aim of the present single center's retrospective study was to evaluate surgical outcomes after cholecystectomy in HIV-positive patients, with special reference to the impact of surgery on HIV control and treatment.

## Patients and Methods

### Patients

Records of consecutive HIV-positive patients who underwent cholecystectomy between January 2010 and December 2020 were reviewed retrospectively at the

National Center for Global Health and Medicine, which has been designated as a clinical center for acquired immunodeficiency syndrome (AIDS) treatment. We performed a retrospective review of the medical records of these patients. Data were retrieved from prospectively maintained databases and included baseline patient characteristics (demographic data, preoperative risk factors, and comorbidities), type of antiretroviral drug being used, operative characteristics, and postoperative outcomes. All operations were performed after obtaining informed consent from each patient. This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The present study was approved by and satisfied the consensus of the National Center for Global Health and Medicine Research Ethics Committee/Institutional Review Board (ID: NCGM-G-004099-00).

### *Study variables*

We defined comorbidity as follows: chronic kidney disease was defined as decreased kidney function as evidenced by a glomerular filtration rate of less than 60 mL/min/1.73 m<sup>2</sup>, markers of kidney damage such as increased urine albumin-to-creatinine ratio or both of at least three months duration, regardless of the underlying cause (7). Diabetes mellitus, hypertension, hemophilia A, hepatitis B virus infection, and hepatitis C virus infection were already diagnosed at the time of admission and treated as appropriate. Alcohol use was defined as consuming more than 14 units of alcohol per week. One unit was defined as 10 mL or 8 g of pure alcohol (8). Smoking status was defined in patients who smoked before admission; past smokers were not included in the smoking group. Postoperative morbidity was graded based on the Clavien-Dindo classification (9). According to this grading, grade III, IV, and V complications were defined as "major complications"; grade I and II complications were described as "minor complications".

Patients were divided into the urgent surgery group and the elective surgery group. Urgent surgery was defined as surgery within 48 hours of admission. Urgent cholecystectomy was conducted for acute cholecystitis according to the Tokyo Guidelines 2018 (10). According to these guidelines, urgent cholecystectomy was indicated in the following conditions: severity grade I or higher, no negative predictive factors, favorable organ system failure conditions, and good performance status. The variables described above were compared between the groups.

### *Statistical Analysis*

Continuous variables were expressed as mean  $\pm$  standard deviation and were compared using the Student's *t*-test. Categorical variables were described as numbers (%) and were compared using the Pearson's chi-squared test.

A paired *t*-test was applied to the corresponding results that changed between before and after surgery. Statistical significance was set at  $p < 0.05$ . Statistical analysis was performed using JMP software (version 15.1.0; SAS Institute Inc., Cary, NC, USA).

## **Results**

### *Patient demographics*

A total of 30 HIV-positive patients were enrolled in this study. The patient characteristics are shown in Table 1. This study included cholecystectomy for cholelithiasis (16/30, 53.3%), cholecystitis (13/30, 43.3%), and gallbladder polyps (1/30, 3.3%) in HIV-positive patients. In 13 acute cholecystitis cases, 9 cases were calculous cholecystitis, and 4 cases were acalculous cholecystitis. Their mean age was  $47.3 \pm 8.7$  years. Of the 30 cases, 7 were urgent surgeries and 23 were elective surgeries. HIV transmission routes were homosexual contact (21/28, 75.0%), heterosexual contact (4/28, 14.2%), bisexual contact (2/28, 7.1%), and blood transfusion for hemophilia A (1/28, 3.5%); 2 patients were not analyzed in this regard. HIV RNA in serum was examined in 28 patients before surgery, and 14 patients showed detectable HIV RNA as follows:  $< 20$  copies/mL, 7/28 (25%); 20-40 copies/mL, 5/28 (17.8%); and  $> 40$  copies/mL, 2/28 (7.1%). The mean preoperative CD4+ lymphocyte count of all patients was  $551.0 \pm 253.1$  cells/ $\mu$ L, indicating that HIV infection in the patients included in this study was well controlled. None of the patients developed AIDS-related complexes at the time of surgery.

Baseline characteristics were compared between the urgent and elective surgery groups. Bivariate analysis revealed a significant difference in smoking status between the urgent and elective groups ( $p = 0.047$ ). However, other preoperative variables including HIV RNA and CD4+ lymphocyte status were not significantly different between the groups.

The preoperative laboratory examination results are summarized in Supplementary Table S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=59>). Bivariate analysis showed a significant difference in white blood cell count between the urgent and elective surgery groups ( $p < 0.001$ ).

### *Risk factors for postoperative complications*

The intraoperative and postoperative outcomes are summarized in Table 2. The mean operation time and intraoperative bleeding volume were  $127.0 \pm 58.5$  minutes and  $8.0 \pm 19.8$  mL, respectively. Open cholecystectomy was performed in only 3 cases (3/30; 10.0%), all of which required urgent surgery. The mean postoperative CD4+ lymphocyte count of all the patients was  $532.5 \pm 235.5$  cells/ $\mu$ L. 4 complications occurred

**Table 1. Comparison of patient characteristics between the study groups before surgery**

Variables	All (n = 30) n (%) or mean ± SD	Urgent surgery (n = 7) n (%) or mean ± SD	Elective surgery (n = 23) n (%) or mean ± SD	p value
<b>Patient characteristics</b>				
Age, years	47.3 ± 8.7	49.4 ± 9.2	46.7 ± 8.8	0.062
Sex				
Male/Female	28/2	7/0	21/2	0.419
BMI, kg/m <sup>2</sup>	27.1 ± 3.93	25.8 ± 3.6	27.5 ± 4.0	0.297
Diagnosis				
Cholelithiasis	16 (53.3)	0 (0.0)	16 (53.3)	0.001
Cholecystitis	13 (43.3)	7 (23.3)	6 (20.0)	0.0005
Gallbladder polyps	1 (3.3)	0 (0.0)	1 (4.3)	0.574
Comorbidities				
CKD	3 (10.0)	2 (28.5)	1 (4.3)	0.061
Diabetes	3 (10.0)	0 (0.0)	3 (13.0)	0.313
Hypertension	3 (10.0)	2 (28.5)	1 (4.3)	0.061
Hemophilia A	1 (3.3)	1 (14.2)	0 (0.0)	0.065
HBV	1 (3.3)	0 (0.0)	1 (4.3)	0.574
HCV	3 (10.0)	1 (14.2)	2 (8.7)	0.666
Alcohol use	2 (6.8)	0 (0.0)	2 (9.0)	0.408
Smoking status	9 (30)	0 (0.0)	9 (39.1)	0.047
Previous abdominal surgery	3 (10.3)	0 (0.0)	3 (13.6)	0.302
HIV RNA, copies/mL				0.197
Not detectable	14 (50.0)	2 (7.1)	12 (42.8)	
< 20	7 (25.0)	3 (10.7)	4 (14.2)	
20–40	5 (17.8)	0 (0.0)	5 (17.8)	
> 40	2 (7.1)	1 (3.5)	1 (3.5)	
N/D	2 (7.1)	1 (3.5)	1 (3.5)	
CD4+ lymphocyte status				
Number, cells/μL	551.0 ± 253.1	468.3 ± 269.8	573.5 ± 250.1	0.416
Percentage, %	27.2 ± 9.3	27.2 ± 11.7	27.2 ± 8.8	0.996

Abbreviations: BMI, body mass index; CKD, Chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, Human immunodeficiency virus; N/D, no data; SD, standard deviation.

**Table 2. Surgical outcomes**

Variables	All (n = 30) n (%) or mean ± SD	Urgent surgery (n = 7) n (%) or mean ± SD	Elective surgery (n = 23) n (%) or mean ± SD	p value
Operation time, min	127.0 ± 58.5	110.8 ± 45.2	132.4 ± 62.0	0.331
Intraoperative bleeding, mL	8.0 ± 19.8	27.4 ± 30.6	2.1 ± 10.4	0.073
Open cholecystectomy	3 (10.0)	3 (42.8)	0 (0.0)	< 0.001
CD4+ lymphocyte status around POD 30				
Number, cells/μL	532.5 ± 235.5	523.1 ± 287.0	511.2 ± 251.7	0.929
Percentage, %	25.9 ± 8.8	26.1 ± 8.2	25.8 ± 9.2	0.935
Complications				
Major	0	0	0	-
Minor	4 (13.3)	3 (42.8)	1 (4.3)	0.008
PO hospital stay, days	5.7 ± 2.8	9.8 ± 2.4	4.5 ± 1.5	< 0.001

Abbreviations: PO, postoperative.; POD, postoperative day; SD, standard deviation.

(4/30; 13.3%), 3 complications in the urgent surgery group, and one in the elective surgery group. The chest pain and fever were nonspecific, and the cause was never clearly determined. The overall mean duration of postoperative hospital stay was 5.7 ± 2.8 days; 9.8 ± 2.4 days in the urgent surgery group compared with 4.5 ± 1.5 days in the elective surgery group. Results of the bivariate analysis showed that for patients with cholecystectomy, complication rates were significantly higher in the urgent surgery group than in the elective

surgery group ( $p = 0.008$ ). Furthermore, open cholecystectomy and postoperative hospital stay duration were significantly associated with urgent surgery ( $p < 0.001$ ). The types of complications are listed in Table 3. Of the 4 complications, 3 were grade I, and one was grade II; all complications were minor. Only grade II complications occurred in the urgent surgery group. No major complications occurred in either the urgent or the elective surgery group. In addition, there were no significant differences between the open cholecystectomy

group and the laparoscopic cholecystectomy group in the postoperative complication rates ( $p = 0.341$ ).

### Effect on HIV treatment

All patients included in this study were treated with antiretroviral drugs at the time of surgery, and HIV infection in all patients was well controlled. Furthermore, all patients were restarted on oral antiretroviral drugs in the early postoperative period. No patients used other medications, such as intravenous infusions for HIV infection treatment. The antiretroviral drugs used for patients in this study are summarized in Supplementary Table S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=59>). The details of perioperative HIV infection status in the 4 patients who had postoperative complications are summarized in Table 4. All 4 patients had well-controlled HIV infections before surgery and no postoperative deterioration in HIV infection control. Bivariate analysis showed no significant difference in CD4+ lymphocyte status in all patients and between the urgent and elective groups before and after surgery ( $p = 0.133$ , paired  $t$ -test). Furthermore, there were no significant differences between the open cholecystectomy group and the laparoscopic cholecystectomy group in postoperative CD4+ lymphocyte status ( $p = 0.952$ ).

### Discussion

In the present study, the postoperative outcomes of cholecystectomy were investigated in HIV-positive patients. The incidence of postoperative complications after cholecystectomy in HIV-positive patients was

significantly higher in the urgent surgery group than in the elective surgery group. We also demonstrated that there was no significant difference in CD4+ lymphocyte status between the urgent and elective groups before and after surgery. A systematic literature search was conducted using the PubMed database on May 22, 2022, to identify published reports of cholecystectomy for HIV-positive patients. A combination of the following search terms was used: "cholecystectomy" AND "HIV". The literature search revealed 5 reports, including the surgical outcome of cholecystectomy for HIV-positive patients in the English-language medical literature (11-15). To the best of our knowledge, this is the first retrospective cohort study to analyze postoperative outcomes of cholecystectomy performed in HIV-positive patients divided into urgent and elective procedures.

The surgical outcomes for HIV-positive patients have changed over time. HIV infection was initially thought to be a fatal disease, and some reports revealed that the rate of postoperative complications was higher in HIV-positive patients than in HIV-negative patients (11,14,16-19). However, with advancements in ART, HIV infection is now becoming a controllable chronic disease (20,21). Some recent studies revealed that postoperative complication rates in patients with well-controlled HIV infections were comparable to those in HIV-negative patients (15,22-26). CD4+ lymphocyte status is one of the indicators of HIV infection status (27,28), and various reports have revealed that a low CD4+ lymphocyte count (especially  $< 200$  cells/ $\mu$ L) was associated with a significant increase in postoperative complications (12,29,30). Furthermore, Foschi *et al.* demonstrated that highly active antiretroviral therapy, low HIV RNA load ( $< 5,000$  copies/ml), and a high CD4+ lymphocyte count ( $> 200$  cells/ $\mu$ L) were associated with a significantly lower complication rate in cholecystectomy with HIV-positive patients (13). In the present study, postoperative complications were not common in either the elective or the urgent groups. The most likely explanation for this finding is that all patients in this study were treated with ART and had well-controlled HIV infections, which is consistent with previously reported results. Furthermore, bivariate analysis showed no significant difference in CD4+ lymphocyte status in all patients and between the

**Table 3. Postoperative complications classified according to the Clavien-Dindo classification**

Complication	Urgent surgery ( $n = 7$ )	Elective surgery ( $n = 23$ )	Grade
Ascites	1 (14.3)	0 (0.0)	I
Chest pain	0 (0.0)	1 (4.3)	I
Fever	1 (14.3)	0 (0.0)	I
Hemorrhage	1 (14.3)	0 (0.0)	II

**Table 4. The details of perioperative HIV infection status in the cases with postoperative complications**

Case No.	HIV treatment	Complications	CD4+ lymphocyte status				HIV RNA	
			Pre op.		Post op.		Pre op. (copies/mL)	Post op. (copies/mL)
			Number (cells/ $\mu$ L)	Percentage (%)	Number (cells/ $\mu$ L)	Percentage (%)		
1	TAF/FTC, DTG	Ascites	370	23.9	362	25.3	N.D.	N.D.
2	ABC/3TC, DRV/r	Chest pain	344	30.8	532	30.0	$< 20$	39
3	ABC/3TC, DRV/r	Fever	300	20.0	329	21.7	N.D.	N.D.
4	ABC/3TC, DTG	Hemorrhage	566	32.3	518	25.0	N.D.	$< 20$

Abbreviations: ABC, abacavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; FTC, emtricitabine; N.D, not detectable; pre op, preoperation; post op, postoperation; TAF, tenofovir alafenamide; 3TC, lamivudine; HIV, human immunodeficiency virus.

urgent and elective groups before and after surgery. This theory is supported by recent reports revealing that major emergency abdominal surgery had no significant effect on CD4+ T cell counts (31). Thus, our study suggests that cholecystectomy may be performed safely in HIV-positive patients without deterioration of HIV control, provided that HIV is well controlled.

It has been reported that urgent and emergency surgery is associated with a higher morbidity and mortality rate than elective surgery in the field of abdominal surgery (32). From the perspective of cholecystectomy, Rice *et al.* demonstrated that the overall rate of complications after urgent cholecystectomy for acute cholecystitis in the general population was significantly higher than that after elective cholecystectomy (16.8% vs. 6.2%) (33). In laparoscopic surgery, the most common complications of urgent cholecystectomy were "minor complications" such as wound infection, port site hernia, chest infection, and urinary tract infection (34,35). In addition to these minor complications, bile leaks and bile duct injury were the two common serious complications of laparoscopic cholecystectomy, with a risk rate of 2.2% (36). On the other hand, urgent open cholecystectomy, which is often performed for severe cholecystitis, is known to be associated with serious morbidities such as bleeding requiring transfusion, sepsis, and other systemic severe dysfunctions (35). In contrast, elective cholecystectomy is a safe and well-established procedure. In laparoscopic cholecystectomy, which is performed in most elective surgeries, the incidence of serious postoperative complications involving bile leakage and postoperative hemorrhage was reported to be 0.59% (37). In the present study, the rate of postoperative complications in the urgent surgery group was 42.8% and that in the elective surgery group was 4.3%, with a significant difference between the groups. All complications in this study were minor, and there were no major complications. These results are compatible with previous reports on cholecystectomy in HIV-negative patients.

This study has some limitations. First, the retrospective nature of the study and the relatively small number of included patients could have weakened the analyses. Prospective studies with large cohorts are needed to analyze the actual surgical outcomes in HIV-positive patients. Furthermore, the current study does not include a cohort of individuals not affected by HIV to serve as a control group and help validate the surgical outcome. Further large-scale studies are required to validate the surgical outcomes in both HIV-positive and HIV-negative patients.

In conclusion, cholecystectomy in HIV-positive patients with controlled HIV under recent ART may be performed safely even in an emergency situation.

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