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Brief Articles

Acute Cholecystitis Is a Common Complication after Allogeneic Stem Cell Transplantation and Is Associated with the Use of Total Parenteral Nutrition

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A B S T R A C T

The incidence and risk factors for acute cholecystitis after allogeneic hematopoietic stem cell transplantation (HSCT) are not well defined. Of 644 consecutive adult transplants performed at our institution between 2001 and 2011, acute cholecystitis occurred in the first year of transplant in 32 patients (5.0%). We conducted 2 retrospective case-control studies of this population to determine risk factors for cholecystitis after HSCT and to evaluate the performance of different methods of imaging to diagnosis cholecystitis in patients undergoing HSCT compared with non-HSCT patients. In the HSCT population, development of cholecystitis was associated with an increased 1-year overall mortality rate (62.5% versus 19.8%, $P < .001$). The risk of developing cholecystitis was higher in patients who received total parenteral nutrition (TPN) (adjusted odds ratio, 3.41; $P = .009$). There was a trend toward more equivocal abdominal ultrasound findings in HSCT recipients with acute cholecystitis compared with nontransplant patients (50.0% versus 30.6%, $P = .06$). However, hepatobiliary iminodiacetic acid (HIDA) scans were definitively positive for acute cholecystitis in most patients in both populations (80.0% of HSCT recipients versus 77.4% of control subjects, $P = .82$). In conclusion, acute cholecystitis is a common early complication of HSCT, the risk is increased in patients who receive TPN, and it is associated with high 1-year mortality. In HSCT recipients with findings suggestive of acute cholecystitis, especially those receiving TPN, early use of HIDA scan may be considered over ultrasound.

INTRODUCTION

Patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT) are susceptible to infections, leading to increased morbidity and mortality [1,2]. One infectious complication of HSCT is acute cholecystitis, a condition characterized by inflammation of the gallbladder with or without gallstone obstruction in the cystic duct [3]. Although biliary sludge formation [4-6] and cholelithiasis [5,7,8] are known to occur in HSCT patients, the incidence of acute cholecystitis and its risk factors in this population are not well described [9-12].

Prompt recognition of acute cholecystitis is critical in both immunocompetent and immunosuppressed patients. However, the diagnosis of acute cholecystitis is often delayed in the HSCT population, because transplant patients are prone to multiple hepatobiliary complications that have similar clinical presentations and the typical signs of inflammation/infection may be masked by immune and marrow suppression [5]. In the present study, we reviewed 644 consecutive patients undergoing HSCT to identify patients who experienced acute cholecystitis. We subsequently performed 2 separate retrospective case-control analyses: the first to define the risk factors for development of acute cholecystitis after HSCT and the second to determine the diagnostic utility of radiographic modalities at presentation of this disease in the transplant population.

METHODS

Study Population

Between January 2001 and December 2011, 644 patients underwent allogeneic HSCT at the Hospital of the University of Pennsylvania. Medical records of these patients were screened for International Classification of

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Table 1
Baseline Demographic and Clinical Characteristics

Demographic Characteristic	HSCT Acute Cholecystitis Patients (n = 32)	HSCT Non-Cholecystitis Control Subjects (n = 96)	Non-HSCT Cholecystitis Control Subjects (n = 96)	*P*
Median age at HSCT, yr (range)	52.2 (24-75)	52.0 (20-76)	52.5 (18-78)	
Men	21 (65.6)	63 (65.6)	63 (65.6)	
Women	11 (34.3)	33 (34.4)	33 (34.4)	
Underlying disease				
ALL	5 (15.6)	11 (11.5)		.971
AML	13 (40.6)	39 (40.6)		.442
CLL/lymphoma	4 (12.5)	16 (16.7)		1
MDS	3 (9.4)	11 (11.5)		.532
MM	2 (6.3)	8 (8.3)		.420
PMF	3 (9.4)	3 (3.1)		1
CML	2 (6.3)	4 (4.2)		.144
Other	0	4 (4.2)		.926
Graft source				
Bone marrow	6 (18.8)	28 (29.2)		.283
Peripheral blood	26 (81.2)	68 (70.8)		
Sibling donor	15 (46.9)	53 (55.2)		.414
Conditioning regimen				
TBI-containing	14 (43.8)	43 (44.8)		.918
Myeloablative	18 (56.2)	53 (55.2)		.919
Reduced intensity	14 (43.8)	43 (44.8)		
ABO compatible graft	21 (67.7)	46 (49.0)		.162
GVHD prophylaxis				
Tac containing	23 (71.9)	70 (72.9)		.909
Tac/MTX	19 (59.4)	57 (59.3)		
Tac/MTX/ maraviroc	4 (12.5)	13 (13.5)		
CsA/MTX	6 (18.8)	15 (15.6)		
CsA/steroids	1 (3.1)	3 (3.1)		
CsA/mycophenolate	1 (3.1)	7 (7.3)		
None	1 (3.1)	1 (1.0)		
TPN	20 (64.5)	37 (39.8)		.019
CMV reactivation	5 (15.6)	22 (23.3)		.371
Weight loss >10%	13 (46.4)	38 (42.3)		.489

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; PMF, primary myelofibrosis; CML, chronic myelogenous leukemia; TBI, total body irradiation; tac, tacrolimus; MTX, methotrexate; CsA, cyclosporine.
Values are number of cases with percents in parentheses, unless otherwise indicated.

Diseases, 9th revision (ICD-9) diagnosis codes for "acute cholecystitis" and all conditions related to acute cholecystitis, including gallbladder calculus, bile duct calculus, chronic cholecystitis, perforation or obstruction of gallbladder, cholecystectomy, and cholecystostomy. Detection of 1 or more of these conditions after the date of transplantation triggered a manual chart review to confirm cases of acute cholecystitis in the first year after HSCT. Cases were defined as (1) having ≥1 imaging modality interpreted by a radiologist as definitively positive for acute cholecystitis, including abdominal ultrasound (US), abdominal computed tomography (CT), or hepatobiliary iminodiacetic acid (HIDA) scan, or (2) having surgical gallbladder pathology consistent with acute cholecystitis. Patients with an ICD-9 code related to acute cholecystitis but without 1 of the 2 above inclusion criteria were excluded. The institutional review board approved this study.

Data Collection and Study Design

To identify risk factors for development of acute cholecystitis, we conducted a nested case-control analysis with control subjects randomly selected through incidence density sampling of the institutional transplant cohort (N = 644) and assigned to cases at a rate of 3:1, matching for age and sex. We then evaluated multiple potential risk factors for the development of acute cholecystitis, including type of underlying hematologic malignancy, graft source, donor type, ABO incompatibility, conditioning intensity, conditioning regimen containing versus not containing total body irradiation, graft-versus-host disease (GVHD) prophylaxis regimen, weight loss >10% compared with day +0 body weight, any total parenteral nutrition (TPN) use, and cytomegalovirus (CMV) reactivation, the latter defined as serum PCR positivity. Cases were counted as having 1 of the above risk factors if present before diagnosis of acute cholecystitis, whereas control subjects were counted as having a risk factor if present within the first year of transplant. In an exploratory analysis, we also compared the 1-year survival rate of cases and control subjects using a chi-square test.

In a second, separate case-control analysis, we compared the radiographic findings of US, CT scan, and HIDA scan in HSCT recipients (n = 32) versus non-transplant control subjects (n = 96) diagnosed with acute cholecystitis at our institution. Nontransplant control subjects were randomly selected from our institution's medical record system by screening for ICD-9 diagnostic codes for 'acute cholecystitis' and all conditions related to acute cholecystitis, including gallbladder calculus, bile duct calculus, chronic cholecystitis, perforation or obstruction of gallbladder, cholecystectomy, and cholecystostomy, entered between 2001 and 2011. As in the first case-control study, cases of acute cholecystitis were confirmed through manual chart review. Control subjects were assigned to cases at a rate of 3:1 and matched for age and sex. In these 2 populations, we compared the number of abdominal US, CT, and HIDA scans performed and the proportion of these radiographic studies interpreted by an attending radiologist as positive, negative, or equivocal for acute cholecystitis. Positive studies were those in which acute cholecystitis was stated by the interpreting radiologist as the final diagnosis, and negative studies were those in which a normal gallbladder was seen or there were no radiographic findings of acute cholecystitis. Equivocal studies were those in which a definitive radiographic diagnosis was not made. In these equivocal studies, a differential diagnosis was provided with acute cholecystitis as one of several diagnostic considerations, or, alternatively, the radiologist stated that the diagnosis of acute cholecystitis was equivocal.

Statistical Analysis

Cases and control subjects were compared with chi-square or Fisher's exact tests as appropriate. $P < .05$ was accepted as statistically significant. Logistic regression analysis was used to adjust for covariates when assessing risk factors for development of acute cholecystitis.

RESULTS

In our transplant cohort of 644 patients (630 first transplants, 13 second transplants, and 1 third transplant), 32 patients (5.0%) had radiographic and/or pathologic evidence of acute cholecystitis in the first year after HSCT and were counted as "case" patients. Baseline characteristics of these patients and each of the 2 control groups are listed in Table 1.

For each of these characteristics, data were successfully collected for all patients with the following exceptions: post-transplant weights were unavailable for 10 patients (4 cases, 6 control subjects), ABO incompatibility status was unavailable for 1 patient (case), CMV reactivation was unavailable for 1 patient (control), and TPN use was unavailable for 4 patients (1 case, 3 control subjects). Patients had a mean age of 52 years, and most (65.6%) were men. There were no significant baseline differences between cases and transplant control subjects with regard to underlying hematologic malignancy, graft source, donor type, conditioning regimen, ABO incompatibility, GHVD prophylaxis regimen, CMV reactivation, or weight loss after transplant.

Of those patients who developed acute cholecystitis in the first year after HSCT, the median time between day of transplantation and diagnosis of acute cholecystitis was 56.5 days (range, 6 to 342). Of note, 21 of 32 cases (65.6%) occurred within 90 days of transplant. Twelve patients (37.5%) were confirmed as having acute cholecystitis by positive imaging alone (none of these patients underwent cholecystectomy), 4 cases (12.5%) were confirmed by pathology but had negative or equivocal imaging studies (these patients ultimately went to surgery based on high clinical suspicion), and 16 (50%) had both imaging and pathology that were consistent with cholecystitis. As detected by pathology and/or imaging, 21 patients (65.6%) had acalculous cholecystitis, whereas the other 11 (34.4%) had evidence of cholelithiasis. Twenty cases of acute cholecystitis (62.5%) were treated with cholecystectomy, whereas 7 (21.9%) underwent cholecystostomy tube

placement and 5 (15.6%) were managed medically with antibiotics and supportive care.

Post-transplant cholecystitis was associated with poor survival outcomes. In an exploratory analysis, overall mortality at 1 year after HSCT was significantly higher in acute cholecystitis case patients compared with control subjects (62.5% versus 19.8%, $P < .001$). Of the 20 acute cholecystitis patients who died within 1 year of transplant, 3 (15.0%) died as a direct result of acute cholecystitis; septic shock was the immediate cause of death in all 3 cases. One of these patients developed acute cholecystitis and subsequent septic shock approximately 6 months after transplant in the setting of graft failure. The other 2 patients developed acute cholecystitis and septic shock before neutrophil engraftment. The time between diagnosis of acute cholecystitis and death for each of these patients was 6, 3, and 19 days, respectively. In all 3 patients who died, acute cholecystitis was managed by placement of a cholecystostomy tube.

Univariate analysis revealed that TPN use was significantly associated with the development of acute cholecystitis. A backward elimination model including all covariates used in the univariate analysis was created, but only TPN remained significant in the multivariate analysis (adjusted odds ratio, 3.41; $P = .009$). Among patients who were given TPN and developed acute cholecystitis, median time between last TPN use and diagnosis of cholecystitis was 3.5 days (range, 0 to 60) and median duration of TPN use was 7.5 days (range, 2 to 60). No significant associations were found with regard to underlying malignancy, graft source, donor type, ABO incompatibility, conditioning regimen, GVHD prophylaxis regimen, CMV reactivation, or weight loss.

In the second case-control study, HSCT recipients with acute cholecystitis underwent abdominal US more frequently than nontransplant acute cholecystitis patients (93.8% versus 75.0%, $P = .02$). CT and HIDA scans were performed at similar rates in both populations (CT: 53.1% versus 55.2%, $P = .85$; HIDA: 46.9% versus 32.3%, $P = .14$). There was a trend toward a higher frequency of equivocal US studies (as opposed to definitively positive or negative for acute cholecystitis) in the HSCT population compared with the nontransplant control subjects (50.0% versus 30.6%, $P = .06$). CT was equivocal for acute cholecystitis in 47.1% of HSCT patients and in 37.7% of the general population control patients ($P = .37$). HIDA scans were not interpreted as equivocal in any patient in either population. In addition, HIDA was definitively positive for acute cholecystitis in a high proportion of patients in both populations (80.0% of HSCT recipients versus 77.4% of control patients, $P = .82$), whereas both US and CT were definitively positive only about half the time in both populations (US: 46.7% versus 56.9%, $P = .22$; CT: 41.2% versus 54.7%, $P = .24$).

DISCUSSION

In the general U.S. population, gallstones affect approximately 20 million patients annually. Of such patients, 1% to 4% annually become symptomatic with biliary colic, and acute cholecystitis eventually develops in about 20% of these symptomatic patients if left untreated [13]. The incidence of acute cholecystitis in our transplant cohort was much higher, with acute cholecystitis diagnosed in the first of year of transplant in 32 of 644 patients (5.0%) who underwent allogeneic HSCT. Patients who developed acute cholecystitis suffered from higher 1-year mortality after transplant, and 3 patients with acute cholecystitis died as a direct result of their gallbladder infections. We hypothesize that the observed association between acute cholecystitis and 1-year mortality may be related to the known correlation between acalculous cholecystitis and critical illness [14] as well as the need for TPN in patients with overall poorer nutritional and performance status after transplant [15].

To our knowledge, this is the only study in the last 15 years to examine the incidence and risk factors for acute cholecystitis with modern HSCT practices [9-12]. In our first case-control analysis, administration of TPN was the only identified risk factor for developing acute cholecystitis in the first year after HSCT. Given the retrospective nature of the study, we cannot prove causality with regard to the association between TPN use and acute cholecystitis. However, the observed temporal relationship between TPN use and diagnosis of acute cholecystitis is notable. Furthermore, hepatobiliary complications related to TPN have been widely reported in the general population [16-22], and multiple studies have demonstrated an increased risk of acute acalculous cholecystitis in patients receiving TPN [17-24]. The propensity to develop acalculous cholecystitis is thought to be related to TPN-induced bile stasis [19,22], which in turn increases the concentration of lysophosphatidyl choline in bile and promotes local injury of the gallbladder mucosa by disrupting normal water transport across gallbladder mucosa [25]. Although not recommended uniformly as prophylaxis against nutritional depletion in HSCT patients, a substantial proportion of HSCT patients ultimately require TPN during the peritransplant period [15]. In HSCT patients who require TPN, our data suggest that providers should have a high index of suspicion for acute cholecystitis in the setting of abdominal pain or abnormal liver function tests, even after TPN has been discontinued.

In addition to TPN, prior studies have suggested that the use of calcineurin inhibitors is associated with increased rates of gallstones and acute cholecystitis, although this has not been studied specifically in the HSCT population [26,27]. It is possible that the routine administration of calcineurin inhibitors may have contributed to the high rate of cholecystitis observed in our cohort. However, because only 2 patients (those who underwent T cell–depleted transplant) did not receive a calcineurin inhibitor for GVHD prophylaxis, we could not reliably evaluate calcineurin inhibitor use as a risk factor for developing acute cholecystitis.

Our second case-control study demonstrated a trend toward more equivocal US findings (as opposed to definitely positive or negative) for acute gallbladder inflammation in HSCT patients with acute cholecystitis compared with nontransplant patients with this condition. In the general population, a suspected diagnosis of acute cholecystitis can usually be confirmed with an abdominal US [28], as suggested in a 1994 systematic review reporting a sensitivity of 88% [29]. In the HSCT population, however, our data suggest that US may be less useful in making a prompt diagnosis of acute cholecystitis. The exact reasons for this discrepancy are unknown, although we hypothesize that sonographic findings dependent on the detection of acute inflammation, such as a positive "sonographic Murphy's sign," are less likely to be elicited in the immunosuppressed transplant population. This may result in the interpretation of fewer US studies as definitively positive for acute cholecystitis. Similarly, we hypothesize that transplant patients are also less likely to have US studies that are definitively negative for acute cholecystitis, because these patients often have subtle sonographic findings reminiscent of cholecystitis that are actually related to other conditions, such as gallbladder wall thickening and pericholecystic fluid secondary to hypoalbuminemia or volume overload.

With regard to CT, we observed that radiographic findings were definitively positive for acute cholecystitis in only about half of the HSCT cases. Although this was no different from the general population, the ability to definitively diagnose acute cholecystitis in a timely manner is likely more important in the HSCT population, becasue morbidity and mortality related to delayed diagnosis of intra-abdominal infection may be substantially higher [30,31]. With regard to nuclear imaging, HIDA scan was definitively positive for acute cholecystitis in 80% of the HSCT patients in our study. HIDA is indicated in the general population only when the diagnosis of acute cholecystitis remains uncertain after US. In the HSCT population, however, our data support the early use of HIDA when acute cholecystitis is suspected, because both US and CT are likely to yield equivocal results that may delay life-saving recognition and treatment of acute cholecystitis.

There are several limitations to our study. It was retrospective, and although we attempted to be inclusive in our screening for acute cholecystitis through ICD-9 codes, it is possible that we underestimated the incidence of acute cholecystitis with this method. In addition, because of the retrospective nature of the study, US, CT, and HIDA scans were read by several different radiologists, creating a potential for interobserver variability. However, studies across multiple centers have demonstrated consistently high sensitivity and specificity of all 3 imaging modalities for the detection of acute cholecystitis in the general population [29,32-37], which suggests significant disagreement among radiologists at our institution is unlikely.

In conclusion, this study demonstrates that acute cholecystitis is a common complication of allogeneic HSCT, especially in patients who receive TPN, and is associated with high 1-year mortality. Our data suggest that a high index of suspicion and early use of HIDA scan are required to make a prompt diagnosis of acute cholecystitis in HSCT patients. Additional prospective studies are needed to determine whether less TPN use decreases the incidence of acute cholecystitis. Early use of HIDA scan should be considered when there is clinical suspicion for this condition.

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REFERENCES

1. Leather HL, Wingard JR. Infections following hematopoietic stem cell transplantation. *Infect Dis Clin North Am*. 2001;15:483-520.
2. Pasquini M, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides. 2013. http://www.cibmtr.org/referencecenter/slidesreports/summaryslides/pages/index.aspx.
3. Longo D, Fauci A, Kasper D, et al. *Harrison's principles of internal medicine*. 18th ed. (Google eBook). New York: McGraw Hill Professional, 2011.
4. Frick MP, Snover DC, Feinberg SB, et al. Sonography of the gallbladder in bone marrow transplant patients. *Am J Gastroenterol*. 1984;79:122-127.
5. McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. *Hepatology*. 2010;51:1450-1460.
6. Teefey SA, Hollister MS, Lee SP, et al. Gallbladder sludge formation after bone marrow transplant: sonographic observations. *Abdom Imaging*. 1994;19:57-60.
7. Safford SD, Safford KM, Martin P, et al. Management of cholelithiasis in pediatric patients who undergo bone marrow transplantation. *J Pediatr Surg*. 2001;36:86-90.
8. Jacobson AF, Teefey SA, Lee SP, et al. Frequent occurrence of new hepatobiliary abnormalities after bone marrow transplantation: results of a prospective study using scintigraphy and sonography. *Am J Gastroenterol*. 1993;88:1044-1049.
9. Wiboltt KS, Jeffrey RB. Acalculous cholecystitis in patients undergoing bone marrow transplantation. *Eur J Surg*. 1997;163:519-524.
10. Jardines LA, O'Donnell MR, Johnson DL, et al. Acalculous cholecystitis in bone marrow transplant patients. *Cancer*. 1993;71:354-358.
11. Kuttah L, Weber F, Creger RJ, et al. Acute cholecystitis after autologous bone marrow transplantation for acute myeloid leukemia. *Ann Oncol*. 1995;6:302-304.
12. Pitkäranta P, Haapiainen R, Taavitsainen M, Elonen E. Acalculous cholecystitis after bone marrow transplantation in adults with acute leukaemia. Case report. *Eur J Surg*. 1991;157:361-364.
13. Strasberg SM. Clinical practice. Acute calculous cholecystitis. *N Engl J Med*. 2008;358:2804-2811.
14. Indar AA. Acute cholecystitis. *BMJ*. 2002;325:639-643.
15. Arfons LM, Lazarus HM. Total parenteral nutrition and hematopoietic stem cell transplantation: an expensive placebo? *Bone Marrow Transplant*. 2005;36:281-288.
16. Grau T, Bonet A, Rubio M, et al. Liver dysfunction associated with artificial nutrition in critically ill patients. *Crit Care*. 2007;11:R10.
17. Fleming CR. Hepatobiliary complications in adults receiving nutrition support. *Dig Dis*. 1994;12:191-198.
18. Quigley EM, Marsh MN, Shaffer JL, Markin RS. Hepatobiliary complications of total parenteral nutrition. *Gastroenterology*. 1993;104:286-301.
19. Roslyn JJ, Pitt HA, Mann LL, et al. Gallbladder disease in patients on long-term parenteral nutrition. *Gastroenterology*. 1983;84:148-154.
20. Bower R, Mrdeza MA, Block GE. Association of cholecystitis and parenteral nutrition. *Nutrition*. 1990;6:125-130.
21. Hatada T, Kobayashi H, Tanigawa A, et al. Acute acalculous cholecystitis in a patient on total parenteral nutrition: case report and review of the Japanese literature. *Hepatogastroenterology*. 1999;46:2208-2211.
22. Tomar BS. Hepatobiliary abnormalities and parenteral nutrition. *Indian J Pediatr*. 2000;67:695-701.
23. Roslyn JJ, Pitt HA, Mann L, et al. Parenteral nutrition-induced gallbladder disease: a reason for early cholecystectomy. *Am J Surg*. 1984;148:58-63.
24. Tucker RA, Jenkins HL. Acalculous cholecystitis and fever related to total parenteral nutrition. *Drug Intell Clin Pharm*. 1984;18:897-899.
25. Kouroumalis E, Hopwood D, Ross PE, et al. Gallbladder epithelial acid hydrolases in human cholecystitis. *J Pathol*. 1983;139:179-191.
26. Spes CH, Angermann CE, Beyer RW, et al. Increased incidence of cholelithiasis in heart transplant recipients receiving cyclosporine therapy. *J Heart Transplant*. 1990;9:404-407.
27. Stief J, Stempfle HU, Götzberger M, et al. Biliary diseases in heart transplanted patients: a comparison between cyclosporine A versus tacrolimus-based immunosuppression. *Eur J Med Res*. 2009;14:206-209.
28. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? *JAMA*. 2003;289:80-86.
29. Shea JA, Berlin JA, Escarce JJ, et al. Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. *Arch Intern Med*. 1994;154:2573-2581.
30. Safdar A, Armstrong D. Infectious morbidity in critically ill patients with cancer. *Crit Care Clin*. 2001;17:531-570. vii-viii.
31. Safdar A, Armstrong D. Infections in patients with hematologic neoplasms and hematopoietic stem cell transplantation: neutropenia, humoral, and splenic defects. *Clin Infect Dis*. 2011;53:798-806.
32. Ralls PW, Colletti PM, Lapin SA, et al. Real-time sonography in suspected acute cholecystitis. Prospective evaluation of primary and secondary signs. *Radiology*. 1985;155:767-771.
33. Cooperberg PL, Burhenne HJ. Real-time ultrasonography. Diagnostic technique of choice in calculous gallbladder disease. *N Engl J Med*. 1980;302:1277-1279.
34. Kiewiet JJS, Leeuwenburgh MMN, Bipat S, et al. A systematic review and meta-analysis of diagnostic performance of imaging in acute cholecystitis. *Radiology*. 2012;264:708-720.
35. Fink-Bennett D, Freitas JE, Ripley SD, Bree RL. The sensitivity of hepatobiliary imaging and real-time ultrasonography in the detection of acute cholecystitis. *Arch Surg*. 1985;120:904-906.
36. Paulson EK. Acute cholecystitis: CT findings. *Semin Ultrasound CT MR*. 2000;21:56-63.
37. Fidler J, Paulson EK, Layfield L. CT evaluation of acute cholecystitis: findings and usefulness in diagnosis. *AJR Am J Roentgenol*. 1996;166:1085-1088.