

Retrospective Cohort Study

Elderly patients (≥ 80 years) with acute calculous cholangitis have similar outcomes as non-elderly patients (< 80 years): Propensity score-matched analysis

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Abstract**BACKGROUND**

Acute cholangitis (AC) is a disease spectrum with varying extent of severity. Age ≥ 75 years forms part of the criteria for moderate (Grade II) severity in both the Tokyo Guidelines (TG13 and TG18). Aging is associated with reduced physiological reserves, frailty, and sarcopenia. However, there is evidence that age itself is not the determinant of inferior outcomes in elective and emergency biliary diseases. There is a paucity of reports comparing clinical outcomes amongst elderly patients *vs* non-elderly patients with AC.

AIM

To investigate the effect of age (≥ 80 years) on AC's morbidity and mortality using propensity score matching (PSM).

METHODS

This is a single-center retrospective cohort study of all patients diagnosed with calculous AC (January 2016 to December 2016) and ≥ 80 years old (January 2012 to December 2016) at a tertiary university-affiliated teaching hospital. Inclusion criteria were patients who were treated for suspected or confirmed AC secondary to biliary stones. Patients with AC on a background of hepatobiliary malignancy, indwelling permanent metallic biliary stents, or concomitant pancreatitis were excluded. Elderly patients were defined as ≥ 80 years old in our study. A 1:1 PSM analysis was performed to reduce selection bias and address confounding factors.

Informed consent statement: This study was conducted using data collected from an institutional board approved standing database (National Healthcare Group Domain Specific Review Board, Ref No.: 2017/00200). Informed consent was hence not obtained from the included patients. Collected data were de-identified and were only accessible to members of the study team with no subsequent patient contact for data collection purposes. The study team made no attempts to access patients' medical records *via* the national electronic health record system.

Conflict-of-interest statement: All of the authors declare no conflicts of interest.

Data sharing statement: The data used in this study is not publicly available due to institutional policies. However, requests may be made to the corresponding author for access to de-identified data.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Study variables include comorbidities, vital parameters, laboratory and radiological investigations, and type of biliary decompression, including the time for endoscopic retrograde cholangiopancreatography (ERCP). Primary outcomes include in-hospital mortality, 30-d and 90-d mortality. Length of hospital stay (LOS) was the secondary outcome.

RESULTS

Four hundred fifty-seven patients with AC were included in this study (318 elderly, 139 non-elderly). PSM analysis resulted in a total of 224 patients (112 elderly, 112 non-elderly). The adoption of ERCP between elderly and non-elderly was similar in both the unmatched (elderly 64.8%, non-elderly 61.9%, $P = 0.551$) and matched cohorts (elderly 68.8% and non-elderly 58%, $P = 0.096$). The overall in-hospital mortality, 30-d mortality and 90-d mortality was 4.6%, 7.4% and 8.5% respectively, with no statistically significant differences between the elderly and non-elderly in both the unmatched and matched cohorts. LOS was longer in the unmatched cohort [elderly 8 d, interquartile range (IQR) 6-13, *vs* non-elderly 8 d, IQR 5-11, $P = 0.040$], but was comparable in the matched cohort (elderly 7.5 d, IQR 5-11, *vs* non-elderly 8 d, IQR 5-11, $P = 0.982$). Subgroup analysis of patients who underwent ERCP demonstrated the majority of the patients ($n = 159/292$, 54.5%) had delayed ERCP (> 72 h from presentation). There was no significant difference in LOS, 30-d mortality, 90-d mortality, and in-hospital mortality in patients who had delayed ERCP in both the unmatched and matched cohort (matched cohort: in-hospital mortality [$n = 1/42$ (2.4%) *vs* $1/26$ (3.8%), $P = 0.728$], 30-d mortality [$n = 2/42$ (4.8%) *vs* $2/26$ (7.7%), $P = 0.618$], 90-d mortality [$n = 2/42$ (4.8%) *vs* $2/26$ (7.7%), $P = 0.618$], and LOS (median 8.5 d, IQR 6-11.3, *vs* 8.5 d, IQR 6-15.3, $P = 0.929$).

CONCLUSION

Mortality is indifferent in the elderly (≥ 80 years old) and non-elderly patients (< 80 years old) with AC.

Key Words: Cholangitis; Choledocholithiasis; Cholelithiasis; Aged 80 and over; Geriatrics; Cholangiopancreatography; Endoscopic retrograde

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Core Tip: There is a paucity of data on mortality outcomes amongst elderly *vs* non-elderly patients with acute cholangitis. The overall in-hospital mortality, 30-d mortality and 90-d mortality was 4.6%, 7.4% and 8.5% respectively, with no significant differences in both the unmatched and matched cohorts. Mortality was comparable in patients with delayed endoscopic retrograde cholangiopancreatography.

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INTRODUCTION

Gallstones are widely prevalent in the community, and patients with gallstones are at risk of complications like acute cholecystitis, acute pancreatitis, and acute cholangitis (AC). AC results from an obstructed biliary system with sepsis, and resulting endotoxic shock is associated with a mortality risk of up to 20%^[1]. AC is a disease spectrum ranging from mild AC, which may respond to conservative management with medical therapy, to severe AC, which requires urgent biliary decompression in addition to fluid resuscitation and antibiotics^[2]. Tokyo Guidelines (TG13 and TG18) are widely accepted internationally and form the basis for diagnosis, severity

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stratification, and management of patients with AC^[3]. In AC, age determines the severity stratification, and age ≥ 75 years is a criterion for moderate (Grade II) severity in both the TG13 and TG18 guidelines^[3]. Aging is associated with reduced cardiac output, impaired gas exchange, reduction in vital capacity, decline in lean body mass, creatinine clearance reduction, hepatic drug metabolism impairment, frailty, and sarcopenia^[4]. Due to functional metabolic decline, multiple comorbidities, and atypical presentation with potential diagnostic delays, age contributes to inferior outcomes^[5]. Age is an independent predictor of mortality in lower respiratory tract infections, urinary tract infections, gastrointestinal infections and biliary infections^[5-8]. Age is also a predictor of disease severity with higher morbidity and mortality risk^[9].

However, there is evidence that age itself is not the determinant of inferior outcomes in elective and emergency biliary diseases^[10,11]. Endoscopic retrograde cholangiopancreatography (ERCP) have been demonstrated to be safe with good outcomes in elderly patients^[11,12]. In a study including 149 acute cholecystitis patients treated with emergency laparoscopic cholecystectomy (LC), Amirthalingam *et al*^[13] showed that patient comorbidities and not age determine outcomes. In a study reporting 85 patients with a median age of 83 years (interquartile range 80-89) and admitted to intensive care unit (ICU) with a diagnosis of AC, Novy *et al*^[14] reported malnutrition [odds ratio (OR) = 34.5, 95% confidence interval (CI): 1.4-817.9] and sequential organ failure assessment (SOFA) score at 48 h (OR by unit 0.7, 95% CI: 0.5-0.9) were associated with higher 6-mo mortality. Further, aging may impact other clinically relevant non-mortality outcomes such as length of hospital stay (LOS). In a prospective study including 124 patients with acute hepatobiliary sepsis and a median age of 64.5 years, Mak *et al*^[15] have reported that age predicts LOS. There is a paucity of comparative data reporting mortality and LOS amongst elderly and non-elderly patients with AC. Also, aging is associated with the confounding effect of comorbidity. This, along with heterogeneity of evidence reporting outcomes in patients with diverse etiology of AC, leaves a lacuna in the scientific literature on the real impact of age on patients with AC due to stone disease. Our hypothesis is, age ≥ 80 years old is associated with higher mortality in patients with AC. This propensity score-matched study aims to investigate if mortality is higher in the elderly (≥ 80 years old) patients with AC as compared to non-elderly (< 80 years old).

MATERIALS AND METHODS

This is a single-center retrospective cohort study of all patients diagnosed with calculous AC (January 2016 to December 2016) and ≥ 80 years old AC patients (January 2012 to December 2016) at a tertiary university-affiliated teaching hospital. We included patients treated for a suspected or confirmed AC diagnosis due to biliary stones^[16]. Patients with AC on a background of hepatobiliary malignancy, indwelling permanent metallic biliary stents, or concomitant pancreatitis were excluded. The severity grading of AC in the TG13 included age greater than 75 years as a risk factor, which was retained in TG18^[17]. Due to a higher sample of elderly patients, the overall cohort's median age was > 80 years, so we defined elderly as ≥ 80 years old. Non-elderly was defined as patients < 80 years old. Our local institutional review board (National Healthcare Group Domain Specific Review Board, No. 2017/00200) approved this study. This study's conduct is per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for retrospective cohort studies^[18].

Study variables and outcomes

The patient demographics and clinical outcomes were studied. Patient demographics included age, gender, and comorbidities. Comorbidities included diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease, asthma, chronic renal failure, and biliary disease history. Previous history of biliary colic, acute cholecystitis, AC, and acute biliary pancreatitis were collectively defined as history of biliary disease. Presenting symptoms at admission included abdominal pain, fever, vomiting, jaundice, and hypotension. Hypotension was defined as admission systolic blood pressure < 90 mmHg. Laboratory data included white blood cell count, platelet count, creatinine, prothrombin time, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, gamma-glutamyl transferase, and total bilirubin levels. The shock index (SI) was defined as heart rate divided by the respective systolic blood pressure on arrival in triage^[19,20]. Abnormal SI was defined as SI < 0.5 or > 0.7 . In patients undergoing ERCP and cholecystectomy, procedure-related data and outcomes

were collected. Delayed ERCP was defined as ERCP > 72 h from admission. The primary outcomes of this study were in-hospital mortality, 30-d mortality and 90-d mortality. In-hospital mortality was defined as any deaths which occurred during the same hospital admission, regardless of the duration from admission. The 30-d and 90-d mortality were defined as any deaths (including both patients who were still inpatient and those who were discharged) within 30 d and 90 d from admission. The secondary clinical outcome was LOS.

Treatment protocol

Patients who presented with septic shock were managed according to the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock, 2012^[21]. The definite diagnosis of AC was based on the TG13 Guidelines, namely, evidence of systemic inflammation (fever, chills, or laboratory data), cholestasis (jaundice or laboratory data), and imaging of the biliary tree (dilatation, stricture, stone, or stent)^[16]. The severity was graded as mild, moderate, or severe as per TG13 guidelines^[16]. Out unit was involved in TG07 classification, and we were early adopters of the TG13 system. Thus, the majority of patients had TG13 stratification done prospectively. Patients that were included before the TG13 publication were retrospectively assigned TG13 diagnosis and severity stratification. Blood cultures were taken for all patients included in our study. Broad-spectrum empiric intravenous antibiotics were administered based on local antibiogram and in compliance with the World Society of Emergency Surgery guidelines for optimal and rational use of antibiotics in intra-abdominal sepsis^[22,23]. Patients with mild AC, patients who declined invasive intervention, and patients who were responsive to antibiotics alone were managed conservatively. Urgent biliary drainage was performed for patients with moderate and severe AC. The endoscopists' discretion and resources determined the timing of biliary drainage. ERCP was the first-line modality for biliary drainage. A diclofenac suppository is inserted routinely for post-ERCP acute pancreatitis prophylaxis. Percutaneous transhepatic biliary drainage (PTBD) was offered when ERCP was not feasible or contraindicated. Complete stone removal or temporary placement of biliary stents was performed at the endoscopists' discretion. Index admission cholecystectomy was reserved for patients with mild AC and subject to surgeon preference.

Statistical analysis

A 1:1 propensity score matching (PSM)^[24] was performed by the first author (Chan KS). PSM was performed at a ratio of 1:1 using a caliper width of 0.2 of the standard deviation of the logit of the propensity score^[25]. Patients were adjusted for 15 factors. Seven factors: clinical presentation (fever and hypotension) and laboratory investigations (white blood cell count, platelets, bilirubin, international normalized ratio, and albumin) impact clinical outcomes and thus were adjusted^[16,26]. Eight factors were statistically significant ($P < 0.1$) during comparison of the initial demographics between the elderly and non-elderly: gender, comorbidities (ischemic heart disease, chronic renal impairment, and history of biliary disease), clinical presentation (abdominal pain, jaundice), and laboratory investigations (gamma-glutamyl transferase and creatinine), and thus were adjusted. Standardized mean difference (SMD) and Hansen and Bowers were used to assess for covariate and global imbalance, respectively^[27].

Categorical values were described as percentages and analyzed by the chi-square test. Continuous variables were expressed as median (interquartile range, IQR) and analyzed by the Mann-Whitney *U* test, respectively. Statistical significance was determined by $P < 0.05$. All statistical analyses were performed with SPSS version 25.0 (SPSS Inc., Chicago, Ill., United States) and R software (R-3.3.3). The statistical review was performed by one of the co-authors qualified in biomedical statistics (Shelat VG).

RESULTS

Patient demographics and clinical profile

Five hundred fifty-six patients were managed for AC during the study period. Ninety-nine AC patients were excluded due to underlying malignancy. Four hundred fifty-seven patients met the inclusion: 318 (69.6%) elderly *vs* 139 (30.4%) non-elderly. The overall cohort's median age was 82.4 years (IQR 77.6-85.3), with female predominance ($n = 252/457$, 55.1%). About half ($n = 240/457$, 52.5%) of patients had a biliary disease history. One hundred and eighty (39.4%) patients had positive blood cultures, and

Escherichia coli was the most common pathogen ($n = 129/180$, 71.7%). **Figure 1** summarizes the microbiology of patients who had positive blood cultures. One hundred and ninety-eight (43.3%) and 126 (27.6%) patients had Grade II and Grade III AC, respectively. When the data of overall cohort was analyzed according to the timing of ERCP (≤ 72 h *vs* > 72 h from admission), there was no difference in the ERCP timing for patients with at least Grade II AC [≤ 72 h, $n = 88/201$ (43.8%) *vs* > 72 h, $n = 113/201$ (52.2%), $P = 0.368$].

PSM with a 1:1 ratio resulted in 224 patients (elderly 112, non-elderly 112). Before PSM, 5 of 15 unmatched variables had SMD > 0.25 ; following PSM, all of the variables reached an SMD < 0.25 (**Table 1** and **Figure 2**), suggesting an adequate and improved balance. Hansen and Bowers test for global significance also did not demonstrate statistical significance in the matched cohort (matched cohort: $\chi^2: 4.73$, $P = 0.994$; unmatched cohort: $\chi^2: 67.4$, $P < 0.001$). Baseline demographics in both the unmatched and matched cohorts are summarized in **Table 1**. The adoption of biliary drainage procedures was similar between elderly and non-elderly patients in the unmatched cohort. Eleven (3.5%) and 2 (1.4%) elderly and non-elderly respectively received urgent biliary drainage. However, in the matched cohort, elderly patients were more likely to undergo PTBD than non-elderly patients (11.6% *vs* 4.5%, OR 2.81, $P = 0.049$). Incidence of index admission cholecystectomy and interval cholecystectomy was also comparable between elderly and non-elderly patients in the unmatched cohort. However, in the matched cohort, elderly patients were less likely to undergo index admission cholecystectomy (1.8% *vs* 10.7%, OR 0.15, $P = 0.006$).

Clinical outcomes

The overall in-hospital mortality, 30-d mortality and 90-d mortality was 4.6%, 7.4% and 8.5% respectively; this was comparable between elderly *vs* non-elderly in both unmatched and matched cohorts. Peri-operative outcomes are summarized in **Table 2**. In the unmatched cohort, elderly patients had a statistically significant longer LOS (median 8 d, IQR 6-13 *vs* 8 d, IQR 5-11, $P = 0.040$). However, after matching, LOS was similar (median 7.5 d, IQR 5-11 *vs* 8 d, IQR 5-11, $P = 0.982$).

Table 3 summarizes the outcomes of patients who underwent ERCP. In the unmatched subgroup of patients who underwent ERCP and had delayed ERCP (> 72 h from admission) (elderly $n = 121$, non-elderly $n = 38$), the primary and secondary outcomes were indifferent between elderly and non-elderly patients respectively: in-hospital mortality [$n = 2/121$ (1.7%) *vs* $1/38$ (2.6%), $P = 0.699$], 30-d mortality [$n = 9/121$ (7.4%) *vs* $2/38$ (5.3%), $P = 0.645$], 90-d mortality [$n = 11/121$ (9.1%) *vs* $2/38$ (5.3%), $P = 0.453$], and LOS (median 10 d, IQR 7-15 *vs* 8 d, IQR 6-12, $P = 0.103$). These outcomes remain indifferent after PSM matching: in-hospital mortality [$n = 1/42$ (2.4%) *vs* $1/26$ (3.8%), $P = 0.728$], 30-d mortality [$n = 2/42$ (4.8%) *vs* $2/26$ (7.7%), $P = 0.618$], 90-d mortality [$n = 2/42$ (4.8%) *vs* $2/26$ (7.7%), $P = 0.618$], and LOS (median 8.5 d, IQR 6-11.3 *vs* 8.5 d, IQR 6-15.3, $P = 0.929$).

In the unmatched cohort, an abnormal SI was not associated with ERCP [abnormal SI: 178/282 (63.1%) *vs* normal SI: 114/175 (65.1%), $P = 0.662$]. This was observed in both the elderly [abnormal SI: 125/194 (64.4%) *vs* normal SI: 81/124 (65.3%), $P = 0.871$] and the non-elderly [abnormal SI: 53/88 (60.2%) *vs* normal SI: 33/51 (64.7%), $P = 0.600$]. There was no difference after PSM matching on the association of abnormal SI with ERCP: abnormal SI: 90/139 (64.7%) *vs* normal SI: 52/85 (61.2%), $P = 0.590$. This was true in both the elderly [abnormal SI: 48/66 (72.7%) *vs* normal SI: 29/46 (63%), $P = 0.277$] and the non-elderly [abnormal SI: 42/73 (57.5%) *vs* normal SI: 23/39 (59%), $P = 0.883$]. Subgroup analysis of patients with an abnormal SI on triage did not show any significant differences in outcomes between elderly and non-elderly patients (**Table 4**).

DISCUSSION

In this single-center propensity score-matched study, patients ≥ 80 years old with AC due to biliary stone disease had similar mortality compared to patients < 80 years old. With an increase in life expectancy globally, the elderly population is also increasing. In the elderly population where there is an increased prevalence of gallstones in the elderly population, biliary events including AC are also more common. The elderly poses a unique challenge due to underlying comorbidity, frailty, sarcopenia, functional decline, cognitive decline, and diminished reserves to withstand stress^[4]. With diminished physiological reserves, sepsis resulting from AC poses a mortality risk, and our mortality outcomes are acceptable, considering mortality risk of up to 20% in patients with AC^[1]. Our reported mortality is comparable to mortality of less than 11%

Table 1 Patient demographics and clinical profile

	Overall cohort, <i>n</i> = 457				PSM cohort, <i>n</i> = 224			
	Elderly, <i>n</i> = 318	Non-elderly, <i>n</i> = 139	<i>P</i> value	SMD	Elderly, <i>n</i> = 112	Non-elderly, <i>n</i> = 112	<i>P</i> value	SMD
Age, yr	84.0 (82.1, 86.6)	67.9 (57.1, 77.2)	< 0.001		84.3 (82.1, 87.3)	66.6 (55.6, 76.4)	< 0.001	
Gender ¹ , male (%)	132 (41.5)	73 (52.5)	0.029	0.221	57 (50.9)	53 (47.3)	0.593	0.071
Co-morbidities, <i>n</i> (%)								
Diabetes mellitus	124 (39)	55 (39.6)	0.908		44 (39.3)	47 (42)	0.683	
Ischemic heart disease ¹	87 (27.4)	27 (19.4)	0.071	0.188	22 (19.6)	23 (20.5)	0.868	0.022
Chronic renal impairment ¹	61 (19.2)	17 (12.2)	0.069	0.191	17 (15.2)	14 (12.5)	0.562	0.077
COPD and/or asthma	18 (5.7)	4 (2.9)	0.201		8 (7.1)	3 (2.7)	0.122	
History of biliary disease ¹	182 (57.2)	58 (41.7)	0.002	0.313	50 (44.6)	53 (47.3)	0.688	0.054
Clinical presentation								
Abdominal pain ¹	197 (61.9)	109 (78.4)	0.001	0.365	85 (75.9)	85 (75.9)	1.000	< 0.001
Fever ¹	141 (44.3)	67 (48.2)	0.446	0.077	50 (44.6)	52 (46.4)	0.788	0.036
Vomiting	142 (44.7)	63 (45.3)	0.895		51 (45.5)	50 (44.6)	0.893	
Jaundice ¹	48 (15.1)	38 (27.3)	0.002	0.302	27 (24.1)	23 (20.5)	0.521	0.085
Hypotension ^{1,2}	18 (5.7)	12 (8.6)	0.238	0.115	10 (8.9)	6 (5.4)	0.299	0.138
Laboratory investigations								
WBC ¹ (10 ⁹ /L)	12.4 (8.9, 16.1)	12.1 (8.3, 15.9)	0.551	0.113	12.2 (8.6, 15.4)	12.1 (8.0, 16.2)	0.745	0.100
Platelets ¹ (10 ⁹ /L)	192 (150, 250)	216 (166, 280)	0.047	0.131	193 (160, 252)	209 (162, 280)	0.308	0.101
Creatinine ¹ (μmol/L)	103 (81, 138)	89 (68, 116)	< 0.001	0.094	103 (80, 136)	86 (67, 119)	0.003	0.088
Albumin ¹ (g/L)	32 (28, 35)	35 (29, 38)	< 0.001	0.396	33 (29, 36)	34 (29, 38)	0.186	0.150
Bilirubin ¹ (μmol/L)	54 (33, 84)	60 (34, 96)	0.226	0.096	65 (42, 93)	58 (33, 93)	0.287	0.104
ALT (IU/L)	133 (61, 247)	143 (68, 295)	0.330		142 (82, 244)	123 (59, 263)	0.294	
AST (IU/L)	160 (78, 366)	140 (72, 314)	0.165		176 (93, 365)	150 (74, 345)	0.149	
ALP (IU/L)	209 (130, 346)	188 (117, 314)	0.149		208 (137, 346)	184 (111, 291)	0.136	
GGT ¹ (IU/L)	242 (129, 435)	327 (158, 562)	0.006	0.292	286 (165, 504)	286 (133, 523)	0.591	0.022
INR ¹	1.13 (1.02, 1.30)	1.20 (1.10, 1.30)	0.890	0.112	1.15 (1.00, 1.30)	1.20 (1.10, 1.30)	0.506	0.038
Microbiology, positive (%)								
<i>Escherichia coli</i>	99 (75)	30 (62.5)	0.100		33 (75)	24 (66.7)	0.413	
<i>Klebsiella pneumoniae</i>	32 (24.2)	14 (29.2)	0.503		16 (36.4)	12 (33.3)	0.777	
<i>Enterobacter spp</i>	3 (2.3)	1 (2.1)	0.939		0 (0)	1 (2.8)	0.266	
<i>Pseudomonas aeruginosa</i>	1 (0.8)	0 (0)	0.550		0 (0)	0 (0)	-	
<i>Enterococcus spp</i>	1 (0.8)	1 (2.1)	0.453		1 (2.3)	1 (2.8)	0.886	
<i>Citrobacter spp</i>	1 (0.8)	0 (0)	0.545		1 (2.3)	0 (0)	0.357	
<i>Aeromonas spp</i>	1 (0.8)	0 (0)	0.545		0 (0)	0 (0)	-	
CT scan, <i>n</i> (%)	108 (34)	52 (37.4)	0.477		43 (38.4)	45 (40.2)	0.784	
Cholelithiasis	75 (69.4)	31 (59.6)	0.218		21 (48.8)	14 (31.1)	0.089	
Biliary dilation	47 (43.5)	18 (34.6)	0.283		30 (69.8)	26 (57.8)	0.243	
Choledocholithiasis	63 (58.3)	18 (34.6)	0.005		27 (62.8)	14 (31.1)	0.003	
MRCP, <i>n</i> (%)	157 (49.4)	73 (52.5)	0.536		61 (54.5)	55 (49.1)	0.422	

Cholelithiasis	113 (72)	38 (52.1)	0.003	37 (60.7)	35 (63.6)	0.741
Biliary dilation	93 (59.2)	50 (68.5)	0.178	41 (67.2)	26 (47.3)	0.030
Choledocholithiasis	103 (65.6)	39 (53.4)	0.077	41 (67.2)	23 (41.8)	0.006
Shock Index, abnormal ³	194 (61)	88 (63.3)	0.641	66 (58.9)	73 (65.2)	0.335
TG13 severity grading	2 (2, 3)	2 (1, 2)	< 0.001	2 (1, 3)	2 (1, 2)	0.016
Grade I	67 (21.1)	66 (47.5)		31 (27.7)	46 (41.1)	
Grade II	152 (47.8)	46 (33.1)		49 (43.8)	46 (41.1)	
Grade III	99 (31.1)	27 (19.4)		32 (28.6)	20 (17.9)	

All continuous variables were expressed as median (interquartile range) unless specified. All categorical variables were expressed as *n* (%) unless otherwise specified.

¹Propensity score matching was performed for these variables due to potential and/or significant effects on clinical outcomes, or due to significant differences in demographics between the two study groups.

²Hypotension was defined as systolic blood pressure of < 90 mmHg.

³Shock index was defined as heart rate divided by the respective systolic blood pressure during triage, where the normal range is 0.5 to 0.7 (inclusive).

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; GGT: Gamma-glutamyl transferase; INR: International normalized ratio; MRCP: Magnetic resonance cholangiopancreatography; PSM: Propensity score matching; SMD: Standardized mean difference; TG13: Tokyo Guidelines 2013; WBC: White blood cell.

Table 2 Clinical outcomes between elderly vs non-elderly patients

	Overall cohort, <i>n</i> = 457				PSM cohort, <i>n</i> = 224			
	Elderly, <i>n</i> = 318	Non-elderly, <i>n</i> = 139	OR, 95%CI	<i>P</i> value	Elderly, <i>n</i> = 112	Non-elderly, <i>n</i> = 112	OR, 95%CI	<i>P</i> value
Initial management								
ERCP	206 (64.8)	86 (61.9)	1.13 (0.75, 1.71)	0.551	77 (68.8)	65 (58)	1.59 (0.02, 2.75)	0.096
Percutaneous transhepatic biliary drainage	25 (7.9)	6 (4.3)	1.89 (0.76, 4.72)	0.166	13 (11.6)	5 (4.5)	2.81 (0.97, 8.17)	0.049
Conservative	98 (30.8)	49 (35.3)	0.82 (0.54, 1.25)	0.351	29 (25.9)	43 (38.4)	0.56 (0.32, 0.99)	0.045
Subsequent management								
Index admission cholecystectomy	16 (5.0)	13 (9.4)	0.51 (0.24, 1.10)	0.081	2 (1.8)	12 (10.7)	0.15 (0.03, 0.69)	0.006
Interval cholecystectomy	20 (6.3)	11 (7.9)	0.78 (0.36, 1.68)	0.525	7 (6.3)	10 (8.9)	0.68 (0.25, 1.86)	0.449
Length of hospital stay, days	8 (6, 13)	8 (5, 11)	-	0.040	7.5 (5, 11)	8 (5, 11)	-	0.982
In-hospital mortality	16 (5.0)	5 (3.6)	1.42 (0.51, 3.96)	0.500	6 (5.4)	5 (4.5)	1.21 (0.36, 4.09)	0.757
30-d mortality	27 (8.5)	7 (5)	1.75 (0.74, 4.12)	0.195	8 (7.1)	7 (6.3)	1.15 (0.40, 3.30)	0.789
90-d mortality	31 (9.7)	8 (5.8)	1.77 (0.79, 3.95)	0.160	8 (7.1)	8 (7.1)	1.00 (0.36, 2.77)	1.000

All continuous variables were expressed as median (interquartile range) unless specified. All categorical variables were expressed as *n* (%) unless otherwise specified. ERCP: Endoscopic retrograde cholangiopancreatography; CI: Confidence interval; OR: Odds ratio; PSM: Propensity score matching.

cited in more recent studies^[28,29]. The higher mortality compared to some reports may be due to advanced age or co-morbidity associated with ageing^[30]. With regards to the exact cause of mortality, we did not collect separate data, and this remains a limitation of our study. However, locally, our institution tracks procedure-related mortality separately; ERCP-related mortality is < 1% locally. Further, it is difficult to distinguish ERCP-related complications such as post-ERCP cholangitis from the index-admission sepsis. Due to the retrospective nature of our study, it is difficult to establish a cause-

Table 3 Subgroup analysis of patients who had endoscopic retrograde cholangiopancreatography on outcomes in elderly vs and non-elderly patients

	Overall cohort, n = 292				PSM cohort, n = 142			
	Elderly, n = 206	Non-elderly, n = 86	OR, 95%CI	P value	Elderly, n = 77	Non-elderly, n = 65	OR, 95%CI	P value
Timing of ERCP from presentation				0.012			-	0.247
Within 24 h	15 (7.3)	16 (18.6)			9 (11.7)	12 (18.5)		
24-48 h	36 (17.5)	13 (15.1)			14 (18.2)	11 (16.9)		
48-72 h	34 (16.5)	19 (22.1)			12 (15.6)	16 (24.6)		
>72 h	121 (58.7)	38 (44.2)			42 (54.6)	26 (40)		
Stone(s) removed	102 (49.5)	44 (51.2)	0.94 (0.57, 1.55)	0.797	36 (46.8)	30 (46.2)	1.02 (0.53, 1.99)	0.943
Stent placed	89 (43.2)	38 (44.2)	0.96 (0.58, 1.60)	0.877	35 (45.5)	30 (46.2)	0.97 (0.50, 1.89)	0.934
Length of hospital stay, d	9 (7, 13)	8 (5, 11)	-	0.016	8 (5, 12)	8 (5, 12)	-	0.546
In-hospital mortality	2 (1)	1 (1.2)	0.83 (0.08, 9.31)	0.882	1 (1.3)	1 (1.5)	0.84 (0.05, 13.73)	0.904
30-d mortality	13 (6.3)	4 (4.7)	1.38 (0.44, 4.36)	0.581	3 (3.9)	4 (6.2)	0.62 (0.13, 2.87)	0.536
90-d mortality	16 (7.8)	4 (4.7)	1.73 (0.56, 5.32)	0.337	3 (3.9)	4 (6.2)	0.62 (0.13, 2.87)	0.536

All continuous variables were expressed as median (interquartile range) unless specified. All categorical variables were expressed as n (%) unless otherwise specified. ERCP: Endoscopic retrograde cholangiopancreatography; CI: Confidence interval; OR: Odds ratio; PSM: Propensity score matching.

Table 4 Subgroup analysis of patients who had abnormal shock index on triage on outcomes in elderly vs non-elderly patients

	Overall cohort, n = 282				PSM cohort, n = 139			
	Elderly, n = 194	Non-elderly, n = 88	OR, 95%CI	P value	Elderly, n = 66	Non-elderly, n = 73	OR, 95%CI	P value
Length of hospital stay, d	8 (6-13)	8 (6-10.8)		0.379	8 (5-12)	6 (5-10)		0.217
In-hospital mortality	10 (5.2)	3 (3.4)	1.54 (0.41, 5.74)	0.517	3 (4.5)	3 (4.1)	1.11 (0.22, 5.71)	0.900
30-d mortality	19 (9.8)	4 (4.5)	2.28 (0.75, 6.91)	0.136	5 (7.6)	4 (5.5)	1.41 (0.36, 5.50)	0.616
90-d mortality	20 (10.3)	5 (5.7)	1.91 (0.62, 5.26)	0.205	5 (7.6)	5 (6.8)	1.12 (0.31, 4.04)	0.869

All continuous variables were expressed as median (interquartile range) unless specified. All categorical variables were expressed as n (%) unless otherwise specified. CI: Confidence interval; OR: Odds ratio; PSM: Propensity score matching.

effect relationship.

The principles of management of AC are early diagnosis, resuscitation, risk stratification, compliance to sepsis bundle, and source control^[21]. Risk stratification is essential for resource allocation, patient and caregiver counselling, and timely proactive interventions. Source control is best achieved with endoscopic biliary decompression, *i.e.*, ERCP. The traditional systemic inflammatory response criteria lack specificity in hepatobiliary sepsis, and thus alternative indices are for risk stratification and prognostication of outcomes^[15]. The SI (heart rate/systolic blood pressure) is a validated tool^[19,31]. Yussuf *et al*^[31] demonstrated abnormal SI predicted mortality of severe sepsis in the emergency department. Our study however demonstrated that patients who had abnormal SI were equally likely to undergo

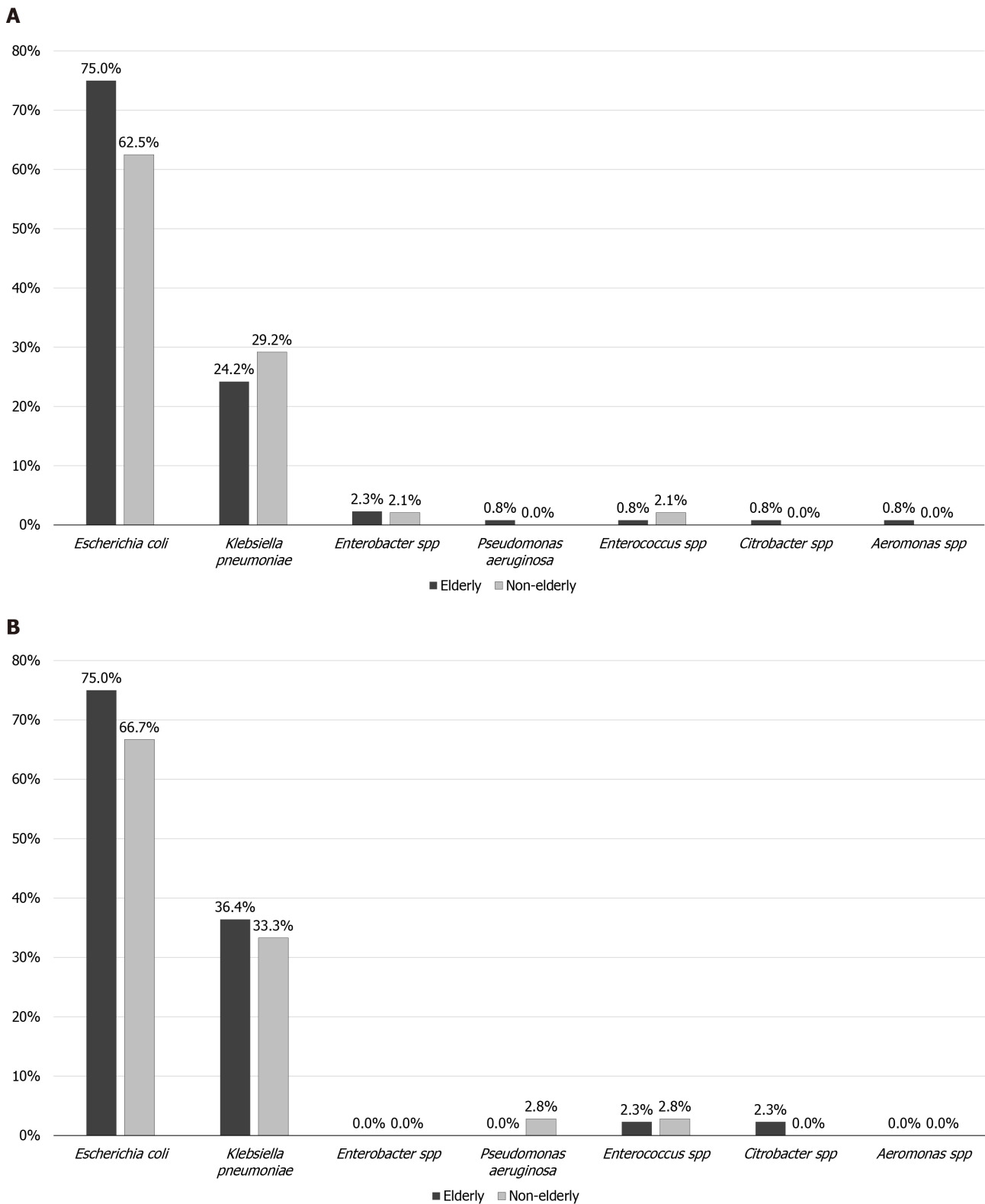


Figure 1 Microbiology of elderly and non-elderly patients who had positive blood cultures. A: Unmatched cohort; B: Matched cohort.

ERCP, and outcomes were comparable between elderly and non-elderly patients. SI is not reflective of the severity of sepsis as it does not take into account tissue perfusion indices and altered mental state. The decision for ERCP at the time of admission was based on the severity of AC and resources. Thus, SI does not predict the need for ERCP. Also, ERCP may occasionally be delayed in patients with abnormal SI in an attempt to resuscitate first. ERCP is an invasive procedure with approximately 10% risk of complications. Elderly patients undergoing ERCP are at higher risk of complications such as pancreatitis, hemorrhage, perforation, cardiorespiratory

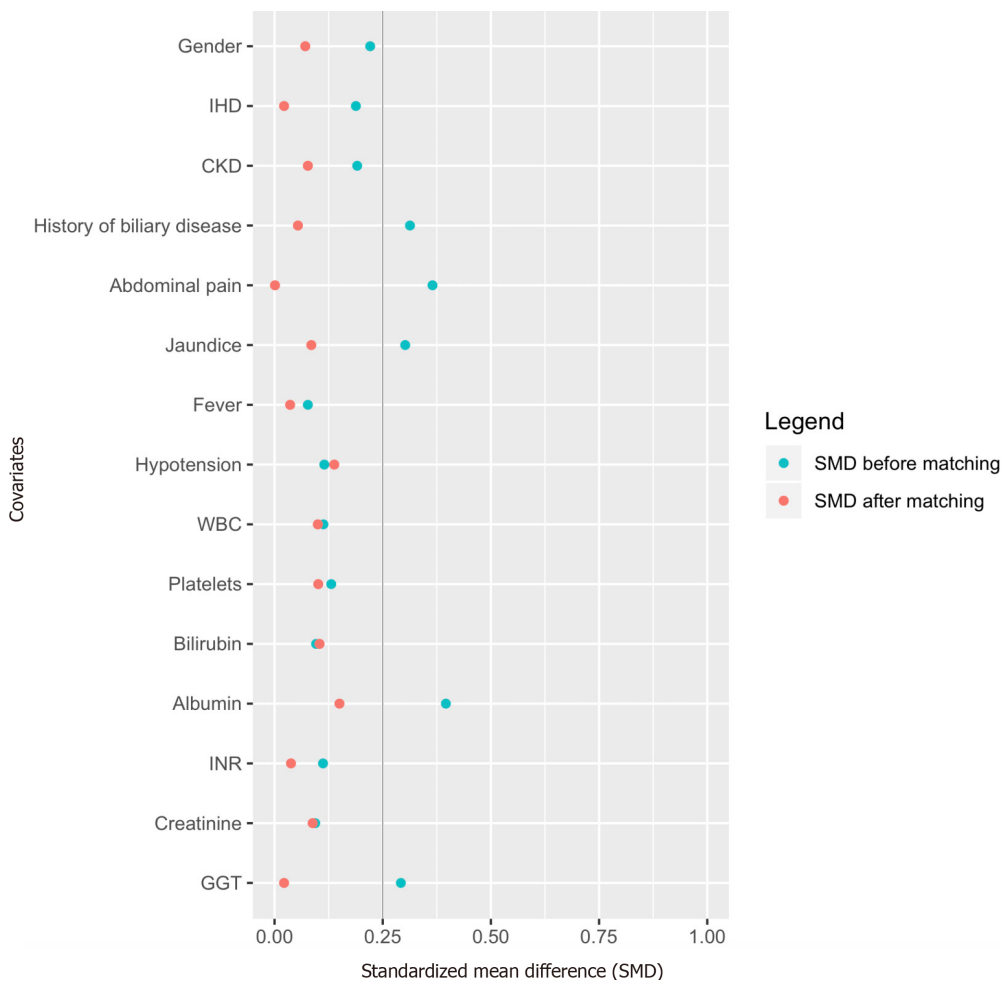


Figure 2 Plot of standardized mean difference in covariates: before propensity score matching (blue) and after propensity score matching (red). Standardized mean difference of < 0.25 indicates adequate balance. IHD: Ischemic heart disease; CKD: Chronic kidney disease; WBC: White blood cell; INR: International normalized ratio; GGT: Gamma-glutamyl transferase.

complications, and mortality^[32]. This increased morbidity and mortality are attributed to underlying comorbidity and lower physiological reserves of the elderly^[33].

However, several studies have shown no relationship between comorbidities and ERCP-related complications, except liver cirrhosis^[34]. Many authors have demonstrated the safety and efficacy of ERCP in elderly patients^[35,36]. In a single-center retrospective study reporting on efficacy and safety of ERCP in elderly patients with AC, Tohda *et al*^[37] reported that patients ≥ 80 years old were more likely to have periampullary diverticulum (24.5% *vs* 13.3%), but equal technical success rates (95.1% *vs* 95.2%) and frequency of ERCP-related complications (6.9% *vs* 6.7%) as compared to patients < 80 years age. The authors reported a lower rate of post-ERCP pancreatitis in the elderly than non-elderly (1.0% *vs* 3.8%). We used PSM analysis to reduce the confounding effect of comorbidities on mortality outcomes, thus reducing the selection bias. We did not specifically compare procedure-related morbidity between elderly *vs* non-elderly and showed comparable LOS and mortality in both the unmatched and matched cohorts between elderly and non-elderly patients. Our experience shows that both stent insertion for biliary decompression and definitive stone removal can be safely performed. In particular, patient physiology, coagulopathy, and endoscopist experience are determinants of ERCP outcomes. Regarding the timing of ERCP, most authors agree that urgent ERCP should be done at the next available opportunity, and in clinical practice, timing is determined by local resources as well as clinical status. The majority of authors recommend ERCP within 24-72 h of admission^[38]. Delay in ERCP in AC could influence patients' outcomes, and many authors define delay variably as the time to ERCP of more than 48-72 h since admission. Khashab *et al*^[39] defined delay in ERCP as > 72 h after admission and reported that it was associated with prolonged LOS (OR 19.8, 95%CI: 2.18-178, $P = 0.008$). Navaneethan *et al*^[40] defined delay in ERCP as > 48 h after admission and reported that it was associated with an increased risk of 30-d readmission. We defined delay as > 72 h after admission and did

not find any difference in clinical outcomes between elderly and non-elderly patients in both the unmatched and matched cohort. Khashab *et al*^[39] demonstrated that delayed ERCP and age are associated with worse composite clinical outcomes (death, persistent organ failure and admission to ICU). However, as our 90-d mortality only had thirteen patients with delayed ERCP, it was not possible to perform subgroup analysis of age on clinical outcomes. It is possible that worse outcomes are associated with delay in ERCP but independent of age.

In addition, it is essential for patients with haemodynamic instability to be adequately resuscitated with airway management, prompt administration of vasopressor after volume replacement, and early engagement of critical care specialist or anesthetist, followed by prompt and early biliary decompression^[41]. A recent study by Novy *et al*^[14] in 2020, which analyzed the outcomes of 85 patients ≥ 75 years old with severe AC and admitted to ICU, showed that the majority (76%) of the ICU patients had ERCP within 24 h, which was attributed to the ease of access to facilities. Institutions with availability of ERCP services should consider early ERCP synchronized with resuscitation measures as delaying ERCP is associated with poor clinical outcomes^[39]. Despite a policy for early ERCP, Novy *et al*^[14] reported ICU mortality of 18%. This highlights that there are other determinants of mortality in critically ill patients. It is important to note that there is an inherent selection bias for elderly patients included in the study; patients not eligible for ICU admission may have more inferior pre-morbid status and deemed not suitable based on medical futility, or may have had advanced care planning performed and decided that ICU admission is unlikely to provide benefit for the patient^[42]. Moreover, ICU admission implies the need for vasopressor therapy or intubation, which reflects the severity of the disease. We did not differentiate our patients based on their need for ICU admission or otherwise; or the use of vasopressor therapy. There is a paucity of data related to causative organisms and their impact on AC's clinical outcomes compared to other hepatobiliary diseases, such as acute cholecystitis or pyogenic liver abscesses^[43]. Microbiology of patients with AC was also consistent with existing studies, where *Escherichia coli* and *Klebsiella pneumoniae* were the most typical organisms^[44].

An alternative to biliary decompression is the use of PTBD. Our study demonstrated a significantly higher number of elderly patients who underwent PTBD compared to non-elderly patients [$n = 13$ (11.6%) *vs* $n = 5$ (4.5%), OR 2.81, $P = 0.049$] in the matched cohort. ERCP is traditionally the gold standard management for AC and has been proven to be safe and effective in the elderly population^[36,37]. PTBD is regarded as a second-line treatment for patients who failed ERCP, with altered biliary anatomy, or were contra-indicated for ERCP. However, unlike ERCP which requires the use of moderate sedation or general anaesthesia, PTBD only requires the use of local anaesthesia. Despite the safety of ERCP in elderly patients, elderly patients are at higher risk of complications from the use of sedation^[45]. Weighing the risks and benefits of endoscopic biliary decompression *vs* the use of sedation is also essential in the management of AC. Patient and/or family members may opt for PTBD which is deemed to be "less invasive" without the need for moderate sedation/general anaesthesia.

Following the acute management of AC, cholecystectomy should be offered to patients to prevent future recurrences. In our experience, non-elderly patients are more likely to undergo index admission LC (Matched cohort: $P = 0.006$). Five out of 12 patients in the non-elderly group who underwent index admission LC in the matched cohort did not receive ERCP. It is likely that in addition to age, underlying comorbidity and personal choices impact the decision for surgery. These findings are similar to a single-center retrospective study of Discolo *et al*^[46]. In an eight-year study including 151 cholecystectomies for AC, Discolo *et al*^[46] reported a more than 61% rate of index admission cholecystectomy, and patients with age > 75 years were more likely to receive delayed cholecystectomy (41.4% *vs* 21.5%, $P = 0.01$). The authors also showed that TG severity grading did not impact the decision for index admission cholecystectomy ($P = 0.46$). Furthermore, there was no difference in average operative time ($P = 0.36$), open conversion ($P = 0.34$), and intra-operative complications ($P = 0.28$) based on the timing of cholecystectomy. We did not perform subgroup analysis on postoperative outcomes in patients who underwent index admission cholecystectomy given the small sample size. In general, index admission cholecystectomy could reduce the risk of recurrent biliary events; however, more evidence is needed in patients with AC. We have previously reported our views on a policy of 'universal cholecystectomy', *i.e.*, patients with a diagnosis that requires cholecystectomy (*e.g.*, acute cholecystitis, AC, or acute biliary pancreatitis) procedure should receive index admission surgery unless contraindicated for general anaesthesia or patient refusal^[47].

The important issue that surfaces from our study is, if age should be considered as

part of a risk stratification tool for the severity of AC. Age is usually included in severity classifications as a surrogate marker for functional capacity and extent of comorbidities. The use of other surrogate markers such as the clinical frailty scale or Charlson co-morbidity index may be a better predictor of disease severity in AC^[48]. In reality however, age serves as a useful tool in view of its ease of use as well as age-associated reduced functional reserves that are not associated with any co-morbidity. While clinical outcomes are not determined by age in patients with AC in our study; based on available literature, we advocate that age should continue to remain as one of the component variables that determines disease severity in patients with AC.

There are several limitations of our study. A retrospective study is inherently prone to selection bias, and thus cause-effect cannot be established. PSM helps to reduce this bias, and such analysis ranks higher than traditional observational studies^[24]. To the best of our knowledge, this is the first study using PSM to compare outcomes of AC secondary to biliary stones between elderly and non-elderly patients. PSM analysis cannot account for unknown confounding variables, and only a randomized controlled trial can overcome this bias. Our study included patients treated in 2012, *i.e.*, before the TG13 guidelines, and we retrospectively assigned TG13 criteria with possible reporting bias. We did not study the effect of polypharmacy, frailty, and Charlson's comorbidity index on AC outcomes. In a large population study over a decade in the Korean general population, Min *et al*^[49] have reported that the use of proton pump inhibitor is associated with increased AC risk (hazard ratio 5.75, 95% CI: 4.39-7.54). We also did not evaluate comorbidities like cerebrovascular accident and liver cirrhosis, as data was not available for all the patients. Our study used the age of 80 years old as a cut-off compared to 75 years, used in TG13/18 guidelines. Existing studies evaluating the safety of ERCP in elderly patients have used a variety of cut-offs for age, ranging from 80 years old to 90 years old^[35-37]. In addition, use of 75 years as a cut-off will reduce our sample size and impact the statistical power of study (96 patients < 75 years and 361 patients ≥ 75 years compared to 139 patients < 80 years and 318 patients ≥ 80 years respectively). Nevertheless, this difference in age cut-off reduces our study's generalizability from being considered an accurate validation study of TG13/18 guidelines. We also did not categorize which patients with history of biliary disease had prior ERCP and papillotomy. It is possible that elderly patients were more likely to have prior ERCP and papillotomy, and this could impact results of our study. We also did not collect data on disease or procedure-related morbidity and causes of mortality.

CONCLUSION

Elderly patients (≥ 80 years old) with AC have similar outcomes as compared to non-elderly patients (< 80 years old). In a subgroup of patients who underwent ERCP or with delayed ERCP, clinical outcomes are comparable between the elderly and non-elderly. Age alone may not predict the outcomes of AC and its use in the Tokyo Guidelines should be re-evaluated.

ARTICLE HIGHLIGHTS

Research background

Acute cholangitis (AC) is a disease spectrum with varying extent of severity. Age ≥ 75 years forms part of the criteria for moderate (Grade II) severity in the Tokyo Guidelines (TG13 and TG18). Aging is associated with reduced physiological reserves, frailty, and sarcopenia. However, there is evidence that age itself is not the determinant of inferior outcomes in elective and emergency biliary diseases.

Research motivation

Endoscopic retrograde cholangiopancreatography is deemed to be safe in elderly patients with AC. There is paucity of data on outcome determinants in elderly patients with AC. This era of ageing population prompted our interest to study the impact of age alone on outcomes of AC through the use of propensity score matching.

Research objectives

Our primary outcomes are in-hospital mortality, 30-d mortality and 90-d mortality. Secondary outcome is morbidity (length of hospital stay).

Research methods

This is a single-center retrospective cohort study of all patients diagnosed with calculous AC (January 2016 to December 2016) and ≥ 80 years old (January 2012 to December 2016) at a tertiary university-affiliated teaching hospital. Elderly was defined as ≥ 80 years old while non-elderly was defined as < 80 years old.

Research results

Four hundred fifty-seven patients with AC were included in this study (318 elderly, 139 non-elderly). Propensity score matching analysis resulted in a total of 224 patients (112 elderly, 112 non-elderly). The overall in-hospital mortality, 30-d mortality and 90-d mortality were 4.6%, 7.4% and 8.5% respectively, with no statistically significant differences between the elderly and non-elderly in both the unmatched and matched cohorts. Length of hospital stay was longer in the unmatched cohort [elderly 8 d, interquartile range (IQR) 6-13 *vs* non-elderly 8 d, IQR 5-11, $P = 0.040$], but was comparable in the matched cohort (elderly 7.5 d, IQR 5-11 *vs* non-elderly 8 d, IQR 5-11, $P = 0.982$).

Research conclusions

Mortality is indifferent in the elderly (≥ 80 years old) and non-elderly patients (< 80 years old) with AC.

Research perspectives

Age alone may not predict the outcomes of AC and its use in the Tokyo Guidelines should be re-evaluated.

REFERENCES

- 1 **Salek J**, Livote E, Sideridis K, Bank S. Analysis of risk factors predictive of early mortality and urgent ERCP in acute cholangitis. *J Clin Gastroenterol* 2009; **43**: 171-175 [PMID: 18769362 DOI: 10.1097/MCG.0b013e318157e62c]
- 2 **Miura F**, Okamoto K, Takada T, Strasberg SM, Asbun HJ, Pitt HA, Gomi H, Solomkin JS, Schlossberg D, Han HS, Kim MH, Hwang TL, Chen MF, Huang WS, Kiriyama S, Itoi T, Garden OJ, Liao KH, Horiguchi A, Liu KH, Su CH, Gouma DJ, Belli G, Dervenis C, Jagannath P, Chan ACW, Lau WY, Endo I, Suzuki K, Yoon YS, de Santibañes E, Giménez ME, Jonas E, Singh H, Honda G, Asai K, Mori Y, Wada K, Higuchi R, Watanabe M, Rikiyama T, Sata N, Kano N, Umezawa A, Mukai S, Tokumura H, Hata J, Kozaka K, Iwashita Y, Hibi T, Yokoe M, Kimura T, Kitano S, Inomata M, Hirata K, Sumiyama Y, Inui K, Yamamoto M. Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. *J Hepatobiliary Pancreat Sci* 2018; **25**: 31-40 [PMID: 28941329 DOI: 10.1002/jhbp.509]
- 3 **Kiriyama S**, Kozaka K, Takada T, Strasberg SM, Pitt HA, Gabata T, Hata J, Liao KH, Miura F, Horiguchi A, Liu KH, Su CH, Wada K, Jagannath P, Itoi T, Gouma DJ, Mori Y, Mukai S, Giménez ME, Huang WS, Kim MH, Okamoto K, Belli G, Dervenis C, Chan ACW, Lau WY, Endo I, Gomi H, Yoshida M, Mayumi T, Baron TH, de Santibañes E, Teoh AYB, Hwang TL, Ker CG, Chen MF, Han HS, Yoon YS, Choi IS, Yoon DS, Higuchi R, Kitano S, Inomata M, Deziel DJ, Jonas E, Hirata K, Sumiyama Y, Inui K, Yamamoto M. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci* 2018; **25**: 17-30 [PMID: 29032610 DOI: 10.1002/jhbp.512]
- 4 **Mohan R**, Huey CWT, Junnarkar S, Low JK, Shelat VG. Prehabilitation in elderly patients scheduled for liver resection and protocol for Recovery of Surgery in Elderly. *Hepatoma Res* 2020; **6**: 13 [DOI: 10.20517/2394-5079.2019.53]
- 5 **Gavazzi G**, Krause KH. Ageing and infection. *Lancet Infect Dis* 2002; **2**: 659-666 [PMID: 12409046 DOI: 10.1016/s1473-3099(02)00437-1]
- 6 **Li W**, Ding C, Yin S. Severe pneumonia in the elderly: a multivariate analysis of risk factors. *Int J Clin Exp Med* 2015; **8**: 12463-12475 [PMID: 26550157]
- 7 **Tal S**, Guller V, Levi S, Bardenstein R, Berger D, Gurevich I, Gurevich A. Profile and prognosis of febrile elderly patients with bacteremic urinary tract infection. *J Infect* 2005; **50**: 296-305 [PMID: 15845427 DOI: 10.1016/j.jinf.2004.04.004]
- 8 **Ortega M**, Marco F, Soriano A, Almela M, Martínez JA, López J, Pitart C, Mensa J. Epidemiology and prognostic determinants of bacteraemic biliary tract infection. *J Antimicrob Chemother* 2012; **67**: 1508-1513 [PMID: 22408140 DOI: 10.1093/jac/dks062]
- 9 **Boey JH**, Way LW. Acute cholangitis. *Ann Surg* 1980; **191**: 264-270 [PMID: 7362292 DOI: 10.1097/0000658-198003000-00002]
- 10 **Shelat VG**, Chia VJ, Low J. Common bile duct exploration in an elderly Asian population. *Int Surg* 2015; **100**: 261-267 [PMID: 25692428 DOI: 10.9738/INTSURG-D-13-00168.1]
- 11 **Tabak F**, Wang HS, Li QP, Ge XX, Wang F, Ji GZ, Miao L. Endoscopic retrograde

- cholangiopancreatography in elderly patients: Difficult cannulation and adverse events. *World J Clin Cases* 2020; **8**: 2988-2999 [PMID: [32775380](#) DOI: [10.12998/wjcc.v8.i14.2988](#)]
- 12 **Agarwal N**, Sharma BC, Sarin SK. Endoscopic management of acute cholangitis in elderly patients. *World J Gastroenterol* 2006; **12**: 6551-6555 [PMID: [17072990](#) DOI: [10.3748/wjg.v12.i40.6551](#)]
 - 13 **Amirthalingam V**, Low JK, Woon W, Shelat V. Tokyo Guidelines 2013 may be too restrictive and patients with moderate and severe acute cholecystitis can be managed by early cholecystectomy too. *Surg Endosc* 2017; **31**: 2892-2900 [PMID: [27804044](#) DOI: [10.1007/s00464-016-5300-4](#)]
 - 14 **Novy E**, Carrara L, Remen T, Chevaux JB, Losser MR, Louis G, Guerci P. Prognostic factors associated with six month mortality of critically ill elderly patients admitted to the intensive care unit with severe acute cholangitis. *HPB (Oxford)* 2021; **23**: 459-467 [PMID: [32839088](#) DOI: [10.1016/j.hpb.2020.08.003](#)]
 - 15 **Mak MHW**, Low JK, Junnarkar SP, Huey TCW, Shelat VG. A prospective validation of Sepsis-3 guidelines in acute hepatobiliary sepsis: qSOFA lacks sensitivity and SIRS criteria lacks specificity (Cohort Study). *Int J Surg* 2019; **72**: 71-77 [PMID: [31678690](#) DOI: [10.1016/j.ijso.2019.10.022](#)]
 - 16 **Kiriyama S**, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, Gouma DJ, Garden OJ, Büchler MW, Yokoe M, Kimura Y, Tsuyuguchi T, Itoi T, Yoshida M, Miura F, Yamashita Y, Okamoto K, Gabata T, Hata J, Higuchi R, Windsor JA, Bornman PC, Fan ST, Singh H, de Santibanes E, Gomi H, Kusachi S, Murata A, Chen XP, Jagannath P, Lee S, Padbury R, Chen MF, Dervenis C, Chan AC, Supe AN, Liau KH, Kim MH, Kim SW; Tokyo Guidelines Revision Committee. TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci* 2013; **20**: 24-34 [PMID: [23307001](#) DOI: [10.1007/s00534-012-0561-3](#)]
 - 17 **Itoi T**, Tsuyuguchi T, Takada T, Strasberg SM, Pitt HA, Kim MH, Belli G, Mayumi T, Yoshida M, Miura F, Büchler MW, Gouma DJ, Garden OJ, Jagannath P, Gomi H, Kimura Y, Higuchi R; Tokyo Guideline Revision Committee. TG13 indications and techniques for biliary drainage in acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci* 2013; **20**: 71-80 [PMID: [23307008](#) DOI: [10.1007/s00534-012-0569-8](#)]
 - 18 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; **12**: 1495-1499 [PMID: [25046131](#) DOI: [10.1016/j.ijso.2014.07.013](#)]
 - 19 **Berger T**, Green J, Horeczko T, Hagar Y, Garg N, Suarez A, Panacek E, Shapiro N. Shock index and early recognition of sepsis in the emergency department: pilot study. *West J Emerg Med* 2013; **14**: 168-174 [PMID: [23599863](#) DOI: [10.5811/westjem.2012.8.11546](#)]
 - 20 **Birkhahn RH**, Gaeta TJ, Terry D, Bove JJ, Tloczkowski J. Shock index in diagnosing early acute hypovolemia. *Am J Emerg Med* 2005; **23**: 323-326 [PMID: [15915406](#) DOI: [10.1016/j.ajem.2005.02.029](#)]
 - 21 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165-228 [PMID: [23361625](#) DOI: [10.1007/s00134-012-2769-8](#)]
 - 22 **Sartelli M**, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, Ansaloni L, Bala M, Balogh ZJ, Beltrán MA, Ben-Ishay O, Biffl WL, Birindelli A, Cainzos MA, Catalini G, Ceresoli M, Che Jusoh A, Chiara O, Coccolini F, Coimbra R, Cortese F, Demetrashvili Z, Di Saverio S, Diaz JJ, Egiev VN, Ferrada P, Fraga GP, Ghnam WM, Lee JG, Gomes CA, Hecker A, Herzog T, Kim JI, Inaba K, Isik A, Karamarkovic A, Kashuk J, Khokha V, Kirkpatrick AW, Kluger Y, Koike K, Kong VY, Leppaniemi A, Machain GM, Maier RV, Marwah S, McFarlane ME, Montori G, Moore EE, Ngoi I, Olaoye I, Omari AH, Ordonez CA, Pereira BM, Pereira Júnior GA, Puppelis G, Reis T, Sakakhushev B, Sato N, Segovia Lohse HA, Shelat VG, Søreide K, Uhl W, Urych J, Van Goor H, Velmahos GC, Yuan KC, Wani I, Weber DG, Zachariah SK, Catena F. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. *World J Emerg Surg* 2017; **12**: 29 [PMID: [28702076](#) DOI: [10.1186/s13017-017-0141-6](#)]
 - 23 **Sartelli M**, Weber DG, Ruppé E, Bassetti M, Wright BJ, Ansaloni L, Catena F, Coccolini F, Abu-Zidan FM, Coimbra R, Moore EE, Moore FA, Maier RV, De Waele JJ, Kirkpatrick AW, Griffiths EA, Eckmann C, Brink AJ, Mazuski JE, May AK, Sawyer RG, Mertz D, Montravers P, Kumar A, Roberts JA, Vincent JL, Watkins RR, Lowman W, Spellberg B, Abbott IJ, Adesunkanmi AK, Al-Dahir S, Al-Hasan MN, Agresta F, Althani AA, Ansari S, Ansumana R, Augustin G, Bala M, Balogh ZJ, Baraket O, Bhangu A, Beltrán MA, Bernhard M, Biffl WL, Boermeester MA, Brecher SM, Cherry-Bukowiec JR, Buys OR, Cainzos MA, Cairns KA, Camacho-Ortiz A, Chandy SJ, Che Jusoh A, Chichom-Mefire A, Colijn C, Corcione F, Cui Y, Curcio D, Delibegovic S, Demetrashvili Z, De Simone B, Dhingra S, Diaz JJ, Di Carlo I, Dillip A, Di Saverio S, Doyle MP, Dorj G, Dogjani A, Dupont H, Eachempati SR, Enani MA, Egiev VN, Elmangory MM, Ferrada P, Fitchett JR, Fraga GP, Guesseend N, Giamarellou H, Ghnam W, Gkiokas G, Goldberg SR, Gomes CA, Gomi H, Guzmán-Blanco M, Haque M, Hansen S, Hecker A, Heizmann WR, Herzog T, Hodonou AM, Hong SK, Kafka-Ritsch R, Kaplan LJ, Kapoor G, Karamarkovic A, Kees MG, Kenig J, Kiguba R, Kim PK, Kluger Y, Khokha V, Koike K, Kok KY, Kong V, Knox MC, Inaba K, Isik A, Iskandar K, Ivatury RR, Labbate M, Labricciosa FM, Laterre PF, Latifi R, Lee JG, Lee YR, Leone M, Leppaniemi A, Li

- Y, Liang SY, Loho T, Maegele M, Malama S, Marei HE, Martin-Loeches I, Marwah S, Massele A, McFarlane M, Melo RB, Negoi I, Nicolau DP, Nord CE, Ofori-Asenso R, Omari AH, Ordonez CA, Ouadhi M, Pereira Júnior GA, Piazza D, Pupelis G, Rawson TM, Rems M, Rizoli S, Rocha C, Sakakushev B, Sanchez-Garcia M, Sato N, Segovia Lohse HA, Sganga G, Siribumrungwong B, Shelat VG, Soreide K, Soto R, Talving P, Tilsed JV, Timsit JF, Trueba G, Trung NT, Ulrych J, van Goor H, Vereczkei A, Vohra RS, Wani I, Uhl W, Xiao Y, Yuan KC, Zachariah SK, Zahar JR, Zakrisson TL, Corcione A, Melotti RM, Viscoli C, Viale P. Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). *World J Emerg Surg* 2016; **11**: 33 [PMID: 27429642 DOI: 10.1186/s13017-016-0089-y]
- 24 **Rosenbaum PR**, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**: 41-55 [DOI: 10.1093/biomet/70.1.41]
- 25 **Austin PC**. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; **10**: 150-161 [PMID: 20925139 DOI: 10.1002/pst.433]
- 26 **Tsuyuguchi T**, Sugiyama H, Sakai Y, Nishikawa T, Yokosuka O, Mayumi T, Kiriya S, Yokoe M, Takada T. Prognostic factors of acute cholangitis in cases managed using the Tokyo Guidelines. *J Hepatobiliary Pancreat Sci* 2012; **19**: 557-565 [PMID: 22825492 DOI: 10.1007/s00534-012-0538-2]
- 27 **Austin PC**. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28**: 3083-3107 [PMID: 19757444 DOI: 10.1002/sim.3697]
- 28 **Csendes A**, Diaz JC, Burdiles P, Maluenda F, Morales E. Risk factors and classification of acute suppurative cholangitis. *Br J Surg* 1992; **79**: 655-658 [PMID: 1643478 DOI: 10.1002/bjs.1800790720]
- 29 **Chijiwa K**, Kozaki N, Naito T, Kameoka N, Tanaka M. Treatment of choice for choledocholithiasis in patients with acute obstructive suppurative cholangitis and liver cirrhosis. *Am J Surg* 1995; **170**: 356-360 [PMID: 7573728 DOI: 10.1016/s0002-9610(99)80303-1]
- 30 **Kiriya S**, Takada T, Hwang TL, Akazawa K, Miura F, Gomi H, Mori R, Endo I, Itoi T, Yokoe M, Chen MF, Jan YY, Ker CG, Wang HP, Wada K, Yamaue H, Miyazaki M, Yamamoto M. Clinical application and verification of the TG13 diagnostic and severity grading criteria for acute cholangitis: an international multicenter observational study. *J Hepatobiliary Pancreat Sci* 2017; **24**: 329-337 [PMID: 28419764 DOI: 10.1002/jhbp.458]
- 31 **Yusoff SJ**, Zakaria MI, Mohamed FL, Bujang MA, Lakshmanan S, Asaari AH. Value of Shock Index in prognosticating the short-term outcome of death for patients presenting with severe sepsis and septic shock in the emergency department. *Med J Malaysia* 2012; **67**: 406-411 [PMID: 23082451]
- 32 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/j.1572-0241.2007.01279.x]
- 33 **Lai EC**, Mok FP, Tan ES, Lo CM, Fan ST, You KT, Wong J. Endoscopic biliary drainage for severe acute cholangitis. *N Engl J Med* 1992; **326**: 1582-1586 [PMID: 1584258 DOI: 10.1056/NEJM199206113262401]
- 34 **Freeman ML**. Complications of endoscopic biliary sphincterotomy: a review. *Endoscopy* 1997; **29**: 288-297 [PMID: 9255535 DOI: 10.1055/s-2007-1004193]
- 35 **Mitchell RM**, O'Connor F, Dickey W. Endoscopic retrograde cholangiopancreatography is safe and effective in patients 90 years of age and older. *J Clin Gastroenterol* 2003; **36**: 72-74 [PMID: 12488713 DOI: 10.1097/00004836-200301000-00019]
- 36 **Katsinelos P**, Paroutoglou G, Kountouras J, Zavos C, Beltsis A, Tzovaras G. Efficacy and safety of therapeutic ERCP in patients 90 years of age and older. *Gastrointest Endosc* 2006; **63**: 417-423 [PMID: 16500389 DOI: 10.1016/j.gie.2005.09.051]
- 37 **Tohda G**, Ohtani M, Dochin M. Efficacy and safety of emergency endoscopic retrograde cholangiopancreatography for acute cholangitis in the elderly. *World J Gastroenterol* 2016; **22**: 8382-8388 [PMID: 27729744 DOI: 10.3748/wjg.v22.i37.8382]
- 38 **Boender J**, Nix GA, de Ridder MA, Dees J, Schütte HE, van Buuren HR, van Blankenstein M. Endoscopic sphincterotomy and biliary drainage in patients with cholangitis due to common bile duct stones. *Am J Gastroenterol* 1995; **90**: 233-238 [PMID: 7847292]
- 39 **Khashab MA**, Tariq A, Tariq U, Kim K, Ponor L, Lennon AM, Canto MI, Gurakar A, Yu Q, Dunbar K, Hutfless S, Kalloo AN, Singh VK. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. *Clin Gastroenterol Hepatol* 2012; **10**: 1157-1161 [PMID: 22507875 DOI: 10.1016/j.cgh.2012.03.029]
- 40 **Navaneethan U**, Gutierrez NG, Jegadeesan R, Venkatesh PG, Butt M, Sanaka MR, Vargo JJ, Parsi MA. Delay in performing ERCP and adverse events increase the 30-day readmission risk in patients with acute cholangitis. *Gastrointest Endosc* 2013; **78**: 81-90 [PMID: 23528654 DOI: 10.1016/j.gie.2013.02.003]
- 41 **Wang Z**, Ahmed S, Shelat VG. Acute Cholangitis. In: Sartelli M, Bassetti M, Martin-Loeches I. Abdominal Sepsis. Hot Topics in Acute Care Surgery and Trauma. Cham: Springer, 2018: 65-81 [DOI: 10.1007/978-3-319-59704-1_7]
- 42 **Khandelwal N**, Kross EK, Engelberg RA, Coe NB, Long AC, Curtis JR. Estimating the effect of palliative care interventions and advance care planning on ICU utilization: a systematic review. *Crit Care Med* 2015; **43**: 1102-1111 [PMID: 25574794 DOI: 10.1097/CCM.0000000000000852]
- 43 **Teng TZJ**, Shelat VG. Biliary Candidiasis Caused by *Candida dubliniensis* Causing Perforated

- Cholecystitis. *Surg Infect (Larchmt)* 2020 [PMID: 32744926 DOI: 10.1089/sur.2020.261]
- 44 **Gomi H**, Takada T, Hwang TL, Akazawa K, Mori R, Endo I, Miura F, Kiriya S, Matsunaga N, Itoi T, Yokoe M, Chen MF, Jan YY, Ker CG, Wang HP, Wada K, Yamaue H, Miyazaki M, Yamamoto M. Updated comprehensive epidemiology, microbiology, and outcomes among patients with acute cholangitis. *J Hepatobiliary Pancreat Sci* 2017; **24**: 310-318 [PMID: 28371094 DOI: 10.1002/jhbp.452]
- 45 **Finkelmeier F**, Tal A, Ajouaou M, Filmann N, Zeuzem S, Waidmann O, Albert J. ERCP in elderly patients: increased risk of sedation adverse events but low frequency of post-ERCP pancreatitis. *Gastrointest Endosc* 2015; **82**: 1051-1059 [PMID: 26089104 DOI: 10.1016/j.gie.2015.04.032]
- 46 **Discolo A**, Reiter S, French B, Hayes D, Lucas G, Tan L, Scanlan J, Martinez R. Outcomes following early *vs* delayed cholecystectomy performed for acute cholangitis. *Surg Endosc* 2020; **34**: 3204-3210 [PMID: 31482348 DOI: 10.1007/s00464-019-07095-0]
- 47 **Yu H**, Chan EE, Lingam P, Lee J, Woon WWL, Low JK, Shelat VG. Index admission laparoscopic cholecystectomy for acute cholecystitis restores Gastrointestinal Quality of Life Index (GIQLI) score. *Ann Hepatobiliary Pancreat Surg* 2018; **22**: 58-65 [PMID: 29536057 DOI: 10.14701/ahbps.2018.22.1.58]
- 48 **Lee F**, Ohanian E, Rheem J, Laine L, Che K, Kim JJ. Delayed endoscopic retrograde cholangiopancreatography is associated with persistent organ failure in hospitalised patients with acute cholangitis. *Aliment Pharmacol Ther* 2015; **42**: 212-220 [PMID: 25997554 DOI: 10.1111/apt.13253]
- 49 **Min YW**, Kang D, Shin JY, Kang M, Park JK, Lee KH, Lee JK, Lee KT, Rhee PL, Kim JJ, Guallar E, Cho J, Lee H. Use of proton pump inhibitors and the risk of cholangitis: a nationwide cohort study. *Aliment Pharmacol Ther* 2019; **50**: 760-768 [PMID: 31448440 DOI: 10.1111/apt.15466]



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