A Retrospective Study into Etiology, Clinical Outcomes and Prognostic Factors of Severe Acute Liver Injury in Hong Kong

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ABSTRACT

Background: Severe Acute Liver Injury (ALI) contributes to significant morbidity and mortality in hospitalized patients. Early recognition, identification and treatment of the underlying cause are necessary for better outcome. This study aimed to investigate the common causes of severe elevation of Alanine Aminotransferase (ALT) in Chinese patients admitted to hospital in Hong Kong, and also to determine the clinical outcomes and prognostic factors associated with the ALI.

Methods: This was a retrospective, single center cohort study conducted in a regional hospital between January 2017 and December 2019. Patients' data admitted with ALT ≥ 1000 U/L were retrieved from the Department of Pathology data base. Their baseline clinical demographics, laboratory profiles and the etiology of ALI were analyzed. The primary outcome was all cause 30-day mortality. Independent predictors for mortality were also assessed.

Results: A total of 313 patients were analyzed. The most common causes of severe ALI in our study were ischemic hepatitis (52.1%), biliary pathology (19.2%), viral hepatitis (14.1%) and drug induced liver injury (6.4%). The overall 30-day mortality rate was 43.1%. Ischemic hepatitis (OR 40, 95% CL 5.1-315.2, p<0.001) and hepatitis due to infiltrative liver disease (OR 26, 95% CI 1.8 – 367.7, p=0.002) were associated with higher mortality. Each etiology shows a distinct clinical and biochemical profile.

Conclusion: Ischemic hepatitis was the leading cause of severe ALI and was associated with high mortality. Early diagnosis and prompt treatment would be essential. Biliary pathology was not an uncommon cause of marked ALT elevation in Hong Kong and should gain its recognition in the differential diagnosis.

Keywords: Acute liver injury; Prognostic factors

INTRODUCTION

Severe Acute Liver Injury (ALI) contributes to significant morbidity and mortality and is frequently seen especially in critical illness [1]. Early recognition, identification and treatment of the underlying cause are required for better clinical outcome. However, there have been limited studies 3-10 assessing the most common etiology of severe acute liver injury. Many of these publications involved small number of patients and their conclusions may not be applicable to our locality.

There are many causes for acute liver injury e.g. viral hepatitis, Drug Induced Hepatitis (DIH), ischemia and autoimmune etiology [2]. These conditions often lead to an increase in ALT level of two to five times of the upper limit of normal. Occasionally, we may see patients with more severe ALI with markedly elevated ALT levels and these conditions often warrants urgent hospital referral and management. The definition of severe ALT elevation has not been well defined but a few studies had used an ALT level ≥ 1000 U/L as the cut off for clinical evaluation [3,4,5]. The differential diagnoses often include ischemia, viral hepatitis and DILI [2]. However, some studies have shown that biliary obstruction is also one of the common causes of ALI despite it is classically associated with cholestatic pattern on biochemical profile [3-7]. Previous reports have also reported that patients with ALI had different outcomes depending on the etiology and also varied by geographical region and ethnicity [4,6,8]. The management plan can be very different with different causes and thus early recognition of the etiology and identification of any prognostic factors are important to achieve a better outcome. This study aimed to investigate the common causes of serum ALT ≥ 1000 U/L in patients admitted to a district hospital in Hong Kong, and also to determine the clinical outcomes and prognostic factors associated with mortality in severe acute liver injury.

METHODS

Study design

This was a retrospective, single center cohort study conducted in Tseung Kwan O Hospital, a regional hospital in HK, between Jan 2017–Dec 2019. Inclusion criteria included patients admitted with one or more episodes of ALT ≥ 1000 U/L. Exclusion criteria were (1) age under 18 years old, (2) non-ethnic-Chinese, (3) died or were discharged before evaluation of the cause of increased ALT.

Serum ALT data was identified through the Department of Pathology computerized biochemical database. Additional data were obtained from Electronic Medical Records (ePR) for analysis including patient demographics and co-morbidities (e.g. cirrhosis of any cause, Chronic Hepatitis B (CHB), Chronic Hepatitis C (CHC), alcoholic liver disease, Non-Alcoholic Fatty Liver Disease (NAFLD), heart failure, chronic kidney disease). Liver cirrhosis was diagnosed clinically or by the presence of cirrhotic features from imaging. The peak levels of alanine aminotransferase ALT were collected and other laboratory results (e.g. white cell count, platelet count, haemoglobin level, sodium, potassium, serum urea nitrogen, serum creatinine, serum albumin, bilirubin, alkaline phosphatase ALP, clotting profile, blood gas) were recorded at the time of peak ALT measurement or within the following 24 hrs whichever first was available. Primary outcome was 30-day all-cause mortality from the collection date of ALT ≥ 1000 U/L. Secondary outcomes included length of hospital stay, need of ICU admission and liver transplantation. Independent predictors for mortality were also evaluated. The causes of ALI were determined according to appropriate clinical setting and comparable clinical impression documented by the attending physicians after reviewing each clinical record. In cases where no documentation of the causes of ALI was made, an independent hepatologist reviewed the patient's medical record to determine the cause. It would be categorized as indeterminate if no identifiable etiology could be found after sufficient evaluation and ruling out common aetiologies.

The study protocol was reviewed and approved by the Research Ethics Committee (Kowloon East/Kowloon West).

Statistical analysis

Data analysis was performed using SPSS version 23.0 software. Continuous variables with normal distribution were expressed as means +/- standard deviation and compared using two-samplet test. Non-parametric variables were expressed as medians with interquartile range and compared using Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using Chi-square test or Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to identify risk factors associated with mortality. Variables with p<0.1 in the univariable analyses were used in the full multivariable analyses. A multivariable analysis with backward elimination method was also performed to select out most relevant variables for evaluation. All statistical tests were two sided and p valve<0.05 was considered statistically significant.

RESULTS

There were 338 patients with one of more episodes of ALT ≥ 1000 U/L admitted to Tseung Kwan O Hospital between January 2017 and December 2019. A total of 313 patients were finally included in the study after excluding patients based on the exclusion criteria (12 patients died on arrival before further investigations could be made, 9 patients were non-Chinese and 4 patients were under 18 years old). Patient demographics

The baseline characteristics of patient with ALI were summarized in Table 1. The mean age of patients was 65.4 years and 58.5% were male. Sixty-one (19.5%) patients had concomitant chronic liver disease, including CHB (45, 14.4%), CHC (1, 0.3%), alcoholic liver disease (2, 0.6%), NAFLD (25, 8%) and liver cirrhosis (12, 3.8%). Patients who died were significantly older (p<0.001) with lower median platelet count (p<0.001), ALP (p=0.017), mean pH (p<0.001) and bicarbonate levels (p<0.001), and with higher median serum creatinine (p<0.001), ALT levels (p<0.001) and INR (p<0.001). The presence of diabetes mellitus (DM) (p=0.005), hypertension (HT) (p<0.001), Chronic Kidney Disease (CKD) (p<0.001), Ischemic Heart Disease (IHD) (p=0.02), Cardiovascular Accident (CVA) (p<0.001) and active cancer (p=0.008) were more common in patients who died. No statistical difference could be detected in other variables.

Etiology and outcome

The distribution of etiologies and survival outcome are shown in Figure 1. Among the 313 patients with ALT ≥ 1000 U/L, the most common causes of ALI included acute ischemia (163, 52.1%), biliary pathology (60, 19.2%), viral hepatitis (44, 14.1%) and DILI (20, 6.4%). Fourteen patients (4.5%) had no identifiable cause after reviewing the clinical history and excluding the common causes of ALI. In patients with a more extreme elevation of ALT ≥ 3000 U/L, ischemic hepatitis remained the leading cause (41, 70.1%), followed by viral hepatitis (9: 15.5%) and DILI (3:5.2%).

Table 1: Baseline characteristic of patients with ALT>/=1000 IU/L.

Demographics	Total (n=313)	Patients who survived (n= 178)	Patients who died (n=135)	p-value
Age (y), mean +/-SD	65.4+/-18.1	58.8+/-18.9	74.1+/-12.4	<0.001
Males, n (%)	183 (58.5)	96 (53.9)	87 (64.4)	0.06
Comorbidities				
CHB	45 (14.4)	32 (18)	13 (9.6)	0.05
Other liver disease*	25 (7.9)	17 (9.5)	8 (5.9)	0.1
Liver cirrhosis	12 (3.8)	6 (3.4)	6 (4.4)	0.77
DM	86 (27.5)	38 (21.3)	48 (35.6)	0.005
HT	155 (49.5)	67 (37.6)	88 (65.2)	<0.001
CKD	60 (19.2)	19 (10.7)	41 (30.4)	<0.001

IHD	64 (20.4)	28 (15.7)	36 (26.7)	0.02
CHF	60 (19.2)	29 (16.3)	31 (23)	0.14
CVA	35 (11.2)	10 (5.6)	25 (18.5)	<0.001
COPD	20 (6.4)	8 (4.5)	12 (8.9)	0.16
Asthma	3 (1)	1 (0.6)	2 (1.5)	0.58
History of cancer	48 (15.3)	21 (11.8)	27 (20)	0.05
Presence of active cancer	23 (7.3)	7 (3.9)	16 (11.9)	0.01
Biochemistry				
Platelet (10^9/L), median (IQR)	135 (73-195)	160 (110-220)	84 (46-155)	<0.001
Serum creatinine (umol/L), median (IQR)	158 (78-381)	85 (67-140)	381 (222-527)	<0.001
Albumin (g/L), mean +/-SD	27.7+/-8.2	31.5+/-7.1	22.7+/-6.8	<0.001
Bilirubin (umol/L), median (IQR)	52 (28-99)	55 (32-100)	43 (25-97)	0.09
ALP (IU/L), median (IQR)	193 (135-297)	210 (147-313)	175 (118-277)	0.017
ALT (IU/L), median (IQR)	1726 (1178-2519)	1378 (1115-2171)	2043 (1405-3247)	<0.001
INR, median (IQR)	1.8 (1.2-2.7)	1.3 (1.1-1.9)	2.6 (2.0-4.0)	<0.001
pH, mean +/-SD	7.20+/-0.22	7.36+/-0.09	7.09+/-0.21	<0.001
HCO_3 (mmol/L), mean +/-SD	16.1+/-7.3	20.7+/-6.6	12.8+/-5.8	<0.001

Note: Other liver disease included 1 chronic hepatitis C, 2 alcoholic liver disease and 25 non-alcoholic fatty liver disease

Data were expressed as mean +/-SD, median (IQR) or n (%).

Abbreviations: CHB: Chronic Hepatitis B; DM: Diabetes Mellitus; HT: Hypertension; CKD: Chronic Kidney Disease; IHD: Ischemic Heart Disease; CHF: Congestive Heart Failure; CVA: Cardiovascular Accident; COPD: Chronic Obstructive Pulmonary Disease; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; INR: International Normalised Ratio; HCO_3: Bicarbonate.
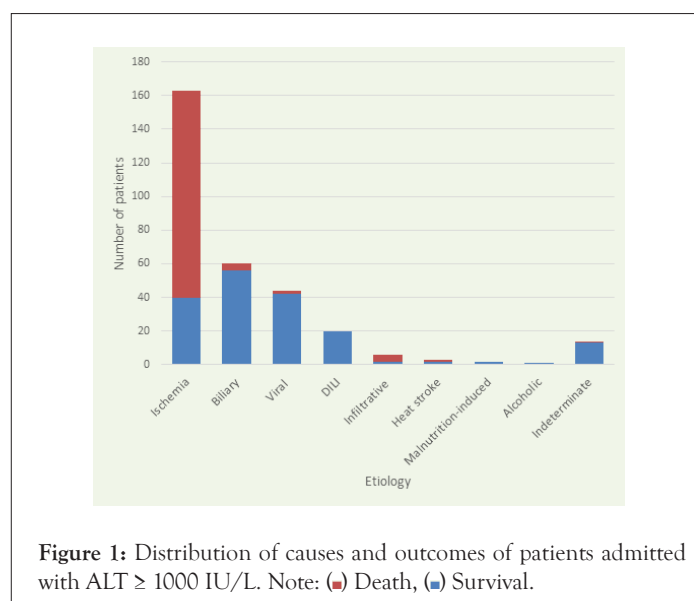

Figure 1: Distribution of causes and outcomes of patients admitted with ALT ≥ 1000 IU/L. Note: (■) Death, (■) Survival.

Ischemic hepatitis

Among the 163 patients with ischemic hepatitis, 86 (52.8%) of them were due to cardiogenic shock (34 cardiac arrest, 25 exacerbation of heart failure, 17 acute myocardial infarction, 7 arrhythmia, 2 PE, 1 myocarditis), 56 (34.4%) were due to septic shock (27 pneumonia, 3 urosepsis, 3 biliary sepsis, 6 other intra-abdominal sepsis, 1 CNS infection, 1 infective endocarditis, 15 unknown sources), 13 (8%) were due to hemorrhagic shock (6 gastrointestinal bleeding, 2 ruptured HCC, 2 rupture aneurysm, 3 other source of bleeding) and 8 (4.9%) were due to hypoxia resulting from respiratory failure.

Biliary pathology

Among the 60 patients with biliary cause, 31 (51.7%) were due to choledocholithiasis, 21 (35%) were due to acute cholangitis, 7 (11.7%) were due to acute cholecystitis and 1 due to pancreatic cancer with malignant obstruction.

Viral hepatitis

Among the 44 patients with viral hepatitis, 30 (68.2%) were due to HBV infection (5 acute HBV infection, 25 (56.8%) were due to acute flare of chronic HBV infection), 9 (20.5%) were due to HAV infection and 5 (11.4%) were due to HEV infection.

Drug Induced Liver Injury (DILI)

Among the 20 patients with DILI, 9 (45%) were due to herbal or traditional Chinese medications, 3 (15%) were due to amiodarone, 2 (10%) were due to paracetamol, 1 (5%) was due to anti-tuberculosis medication, 1 (5%) was due to acyclovir, 1 (5%) was due to azathioprine, 1 (5%) was due to NSAID and 2 (10%) with unknown medications.

Other causes

Among the remaining 12 patients with identifiable cause, 6 (50%)

were due to infiltrative disease (4 metastatic liver cancer, 2 HCC), 3 (25%) were due to heat stroke, 2 (16.7%) were due to anorexia nervosa and 1 (8.3%) was due to alcoholic hepatitis.

Clinical and biochemical characteristics

Among the top four common causes of severe ALI, a biochemical profile was conducted for each of the etiologies as shown in Table 2. Patients suffered from ischemic hepatitis were older, had lower platelet count, albumin, pH, serum bicarbonate and higher serum creatinine, INR when compared with other etiologies. Patients with biliary cause had higher ALP with lower ALT levels. Patients with viral hepatitis were younger and a higher median bilirubin level of 86.5 umol/L was observed.

Primary outcome

The overall 30-day mortality rate was 43.1% (135 patients). Most of them (123, 91.1%) suffered from ischemic hepatitis, followed by biliary pathology (4, 3%), infiltrative liver disease (4, 3%), viral hepatitis (2, 1.5%), heat stroke (1, 0.7%) and 1 patient (0.7%) suffered from an unknown cause of acute liver injury. Among the different causes of ALI, ischemic hepatitis (OR 40, 95% CL 5.1-315.2, p<0.001) and hepatitis due to infiltrative liver disease (OR 26, 95% CI 1.8 – 367.7, p=0.002) were found to be associated with higher mortality.

Secondary outcomes

A total of 71 (22.7%) patients in our study required ICU admission. Sixty-four (90%) of them had ischemic hepatitis, followed by 2 (2.8%) patients with biliary pathology, 2 (2.8%) patients with DILI and 2 (2.8%) patients with heat stroke. Ischemic hepatitis (OR 8.4, 95% CI 1.1-65.8, p=0.043) and heat stroke (OR 26, 95% CI 1.1-604.5, p=0.042) were associated with an increased likelihood of ICU admission. The median length of stay (LOS) was 6 (3-12) days for all the patients admitted in our study. Patients who survived had a longer median LOS than those who died (8 days [5-15] vs. 3 days [1-9], p<0.001). The median LOS among the top four common causes of ALI were 7 (4-10) days in the ischemic group, 7 (4-9) days in the biliary group, 5 (4-8) days in the viral hepatitis group and 9.5 (7-14) days in the DILI group. Liver transplantation was not performed in any of the patients in our study. One patient with hepatitis B flare and acute liver failure were transferred to liver transplant center but liver transplant was not performed due to a suspected underlying pancreatic cancer during liver transplant workup.

Predictors of mortality

In univariable analysis, age>65 years (p<0.001), history of DM (p=0.006), HT (p<0.001), CKD (p<0.001), IHD (p=0.02), CVA (p<0.001), and presence of active cancer (p=0.009) were significantly associated with higher mortality. Regarding biochemical data, significant factors associated with high mortality include platelet count<160 × 10^9/L (p<0.001), serum creatinine>110 umol/L (p<0.001), albumin<34 g/L (p<0.001), ALT>3000 IU/L (p=0.002), INR ≥1.5 (p<0.001), pH<7.35 (p<0.001) and bicarbonate<22 mmol/L (p<0.001) as shown in Table 3.

Variables with p<0.1 in the univariable analysis were entered into the full multivariable analysis. Only INR ≥ 1.5 (aOR 7.43, 95% CI 1.95-28.22, p=0.003) and pH<7.35 (aOR 8.83, 95%CI 3.32-23.5, p<0.001) were strongly associated with mortality. Multivariable analysis using the backward elimination approach showed that apart from INR ≥ 1.5 and pH<7.35, serum creatinine>110 umol/L was also shown to be a significant predictor (aOR 5.81, 95% CI 1.87, p=0.002). Subgroup analysis was performed in patients with ischemic hepatitis which was the most common cause of severe ALI in this study and only pH<7.35 (aOR 7.79, 95% CI 2.86-21.23, p<0.001) were found to be significantly associated high mortality.

Table 2: Clinical and biochemical characteristics of each of the top four common causes of severe acute liver injury.

Clinical and biochemical profile	Ischemic	Biliary	Viral	DILI
Age				
mean +/- SD	73.8+/-12.9	64.2+/-18.5	49.2+/-15.0	58.4+/-17.7
p value		<0.001	<0.001	<0.001
Sex (male)				
Number (%)	106 (65%)	20 (33%)	32 (73%)	8 (40%)
p value		<0.001	0.34	0.03
Platelet (10^9/L)				
mean +/- SD	107.3+/-80.2	196.5+/-77.3	170.9+/-78.4	168.3+/-69.8
p value		<0.001	<0.001	0.007
Serum creatinine (umol/L)				
median (IQR)	315 (206-480)	76 (63-105)	79 (68-87)	69 (61-127)
p value		<0.001	<0.001	<0.001
Albumin (g/L)				
mean+/-SD	22.8+/-6.5	33.5+/-6.3	34.1+/-5.9	32.0+/-7.6
p value		<0.001	<0.001	<0.001
Bilirubin (umol/L)				
median (IQR)	42.5 (26.8-86.8)	55 (42-96)	86.5 (32.3-178.8)	73 (38.3-184)
p value		0.018	0.002	0.016

ALP (IU/L)			
median (IQR) 163.5 (117.8-249.5)	265 (171-360)	172 (145.3-231.3)	224.5 (126-327.3)
p value	<0.001	0.379	0.242

ALT (IU/L)			
median (IQR) 2089 (1402-3028)	1136 (1050-1314)	1834 (1173-2504)	1632 (1262-2061)
p value	<0.001	0.123	0.066

INR			
median (IQR) 2.5 (1.9-3.7)	1.2 (1.1-1.3)	1.3 (1.1-1.6)	1.2 (1.1-1.6)
p value	<0.001	<0.001	<0.001

pH			
mean+/-SD 7.14+/-0.21	7.37+/-0.11	7.4+/-0.06	7.38+/-0.22
p value	<0.001	<0.001	0.014

HCO_3 (mmol/L)			
mean+/-SD 13.4+/-6.1	22.7+/-4.3	26.1+/-3.0	19.6+/-7.5
p value	<0.001	<0.001	0.046

Note: All comparisons were made against the ischemic group.
Abbreviations: DILI: Drug Induced liver Injury; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; INR: International Normalised Ratio; HCO_3: Bicarbonate.

Table 3: Univariable and multivariable analyses of factors associated with mortality.

	Univariable analysis			Full multivariable analysis *			Multivariable analysis with backward elimination **		
	OR	95% CI	p-value	aOR	95% CI	p value	aOR	95%CI	p-value
Age>65 years	4.51	2.77-7.36	<0.001	1.07	0.43-2.7	0.88			
Male	1.55	0.98-2.45	0.06	1.08	0.46-2.49	0.87			
CHB	0.49	0.24-0.97	0.04	0.34	0.04-3.12	0.34			
ALD	1.32	0.08-21.31	0.84						
NAFLD	0.35	0.09-1.26	0.11						
Liver cirrhosis	1.33	0.42-4.23	0.63						
DM	2.03	1.23-3.36	0.006	0.63	0.26-1.52	0.3			
HT	3.1	1.95-4.94	<0.001	2.58	0.98-6.80	0.06			
CKD	3.65	2.00-6.66	<0.001	1.16	0.42-3.19	0.78			
IHD	1.95	1.12-3.39	0.02	0.42	0.17-1.07	0.07			
CHF	1.53	0.87-2.69	0.14						
CVA	3.82	1.77-8.26	0.001	1.43	0.40-5.11	0.58			
COPD	2.07	0.82-5.22	0.12						
Asthma	2.66	0.24-29.66	0.43						
History of cancer	1.87	1.01-3.48	0.05	0.58	0.13-2.52	0.47			
Presence of active cancer	3.41	1.36-8.55	0.009	2.8	0.34-22.88	0.34			
Platelet<160 × 10^9/L	3.43	2.09-5.64	<0.001	0.4	0.13-1.19	0.1			
Creatinine>110 umol/L	34.59	15.83-75.55	<0.001	3.32	0.88-12.5	0.08	5.81	1.87-18.08	0.002
Albumin<34 g/L	11.58	5.11-26.24	<0.001	0.87	0.15-5.16	0.88			
Bilirubin>22 umol/L	0.72	0.40-1.29	0.26						
ALP>120 U/L	0.36	0.19-0.66	0.001	1.24	0.48-3.25	0.66			
ALT>3000 U/L	2.58	1.43-4.64	0.002	0.79	0.31-2.03	0.63			
INR>/=1.5	25.31	11.61-55.20	<0.001	7.43	1.95-28.22	0.003	5.23	1.57-17.41	0.007
pH<7.35	20.28	9.78-42.08	<0.001	8.83	3.32-23.50	<0.001	10.15	4.27-24.1	<0.001
HCO_3<22 mmol/L	10	4.75-21.04	<0.001	1.36	0.41-4.50	0.61			

Note: Variables with p<0.1 in the univariable analysis were entered into the full multivariable analysis,
Multivariable analysis using backward elimination (selection level of 0.05) to identify factors associated with mortality.
Abbreviations: CHB: Chronic Hepatitis B; ALD: Alcoholic Liver Disease; NAFLD: Non-Alcoholic Fatty Liver Disease; DM: Diabetes Mellitus; HT: Hyper tension; CKD: Chronic Kidney Disease; IHD: Ischemic Heart Disease; CHF: Congestive Heart Failure; CVA: Cardiovascular Accident; COPD: Chronic Obstructive Pulmonary Disease; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; INR: International Normalised Ratio; HCO_3: Bicarbonate.

DISCUSSION

Several studies [3-10] have been published in literature evaluating the etiologies and outcomes of severe acute liver injury but only a few studies focused on Chinese population [7,8,16,17]. To our knowledge, this is the first study evaluating the common etiologies and clinical outcomes of patients with ALT ≥ 1000 U/L in Hong Kong.

Our study confirmed that ischemic hepatitis was the most common cause of severe acute liver injury in Hong Kong. Over 50% of patients with ALT ≥ 1000 U/L and 70% of patient with ≥ 3000 U/L in our study were due to ischemic hepatitis which was consistent with findings from previous studies from other localities [3-10,16]. Although ischemic hepatitis is a potentially reversible condition, it is associated with high mortality and often requires ICU care. It has been reported that ischemic hepatitis was associated with>50% mortality and our study showed that 75% of patient with ischemic hepatitis died during their hospital stay [11-15]. The direct cause of death is usually due to the underlying illness, and not the liver injury itself. Early detection with prompt treatment aiming at correcting the underlying cause of hypoperfusion is therefore the key step to achieve a better patient outcome. In terms of clinical manifestation, ischemic hepatitis is usually preceded by an event of shock (e.g. cardiogenic shock, septic shock, hypovolemic shock) but it can also happen in other conditions such as hypoxemia (e.g. respiratory failure, carbon monoxide poisoning) and increased metabolic demand (e.g. sepsis). A systemic review showed that only half of the patients with ischemic hepatitis had documented episode of hypotension thus one should not rely on the presence of shock for the diagnosis of ischemic hepatitis [12].

Regarding the prognostic factors, our study found that renal impairment, a low pH and a high INR level were associated with higher mortality in patients with marked elevation of ALT. In subgroup analysis, only a low pH level was found to be statistically significant in patients with ischemic hepatitis. According to literature, several prognostics factors have been found which indicate a poor outcome in patients with ischemic hepatitis including duration of hypoxic hepatitis, INR, jaundice, low albumin level, presence of septic shock, Sequential Organ Failure Assessment Score (SOFA score), need for renal replacement and vasopressor therapy [14-17]. Our study was not designed to look specifically into ischemic hepatitis thus some of the parameters investigated in other studies were not included in this study. A possible reason for founding pH level as the only independent indicator in our study was that the patient population might be different from other studies. A large proportion of our ischemic patients with severe ALI were due to post cardiac arrest whereas septic shock was found to be a more common cause in other studies. Many elderly patients in our hospital would not be intubated and ventilated during cardiac arrest resulting in a lower pH level with poorer outcome [14-15]. We failed to demonstrate high bilirubin level as an indicator for poor prognosis in ischemic hepatitis. This could be because a lot of our patients died shortly after they developed ALI before any significant rise in serum bilirubin could be observed. Another reason could be the lack of serial blood monitoring in patient with poor prognosis once they developed ALI. Although we also failed to demonstrate INR and low albumin level as the prognostic factors for ischemic hepatitis, we found that the INR and albumin level tended to be lower in the ischemic hepatitis group compared to other causes of ALI in the biochemical profile. Low serum albumin level had been reported to be an independent

predictor in critical illnesses and in the study by Chang et al.; hypoalbuminemia was shown to be a strong predictor of mortality in hypoxic hepatitis [17]. Serum albumin plays an important role in maintaining colloid osmotic pressure, modulating inflammatory response and oxidative stress. Low serum albumin level is common in critical illnesses due to increased proteolysis and renal loss and decreased hepatic synthesis. Some studies have demonstrated some benefit of intravenous albumin infusion in critically ill patients, especially in patients with severe sepsis, possibly due to its effect in limiting oxidative damage [18-19]. However, its use has not been well established as other trials did not show a survival benefit. Therefore, further prospective studies are needed to confirm its benefit and evaluate the application in ischemic hepatitis.

The second most common cause of severe ALI was found to be biliary pathology which is contrary to the traditional teaching of differential diagnosis for ALI. Biliary obstruction is usually associated with cholestasis and less commonly presented with severe transaminitis. However, recent studies have reported biliary obstruction as being one of the most common causes of marked elevation of ALT in both the Western and Asian regions. The proposed mechanism of hepatocellular injury with biliary obstruction is due to an increase in biliary pressure resulting in retained bile salt which leads to bile salt induced hepatocyte necrosis or apoptosis. Apart from biliary obstruction, 7 patients in our study with cholecystitis but without evidence of choledocholithiasis were also found to have marked elevation of ALT [20-22]. One postulation is that there could be small stones passing through the biliary duct with transient biliary obstruction and biochemical abnormality. By the time of investigation, these stones had already passed, and thus no evidence of Common Bile Duct (CBD) obstruction could be documented. Other proposed mechanisms suggested that the presence of free radical reactions in cholecystitis induces oxidative stress and liver injury. The inflammation in the gallbladder may also cause inflammation in the nearby liver tissue, resulting in ALI [23-24].

Despite the high levels of liver enzymes, it does not predict the severity of the underlying biliary pathology and is generally associated with a good outcome once the obstruction or inflammation has resolved. However, making the diagnosis is often challenging in this group of patients, particularly in patients with choledocholithiasis without sign of sepsis as their clinical manifestation are often confused with other more recognized cause of hepatitis such as viral hepatitis or DILI. In our study, 31 patients were diagnosed to have choledocholithiasis but one third of the diagnosis was actually made subsequently after the first admission. All of the patients had an abdominal ultrasound but many of them did not reveal any evidence of CBD stone. Some patients were initially suspected to have other cause of hepatitis such as viral hepatitis or DILI. Others were discharged as having an unknown cause of hepatitis with clinical improvement. Half of these patients with unknown initial cause of hepatitis required repeated admissions with various presentation of gallstone complications such as symptomatic gallstone, cholangitis or cholecystitis. This resulted in further admissions and longer hospital stay for further unnecessary evaluation of primary liver disease. Base on the finding from our study demonstrating that biliary pathology was a common cause for marked elevation of ALT, in patient with abdominal pain and marked elevated liver enzymes, biliary disease should always be one of the top differential diagnosis.

Ultrasound (USG) abdomen is often a good initial investigation

as it is non-invasive and readily available in our clinical setting. Nevertheless, the sensitivity of USG in detecting CBD stone has only been reported to be up to 55% and a negative finding from USG does not rule out the diagnosis of CBD stone [25]. In patient with suspected choledocholithiasis without evidence of CBD stone in USG, we should proceed to further investigation such as Magnetic Resonance Cholangiopancreatography (MRCP) or Endoscopic Ultra Sound (EUS) which both have a high accuracy in detecting CBD stone. Many studies have been performed in the past comparing the accuracy of EUS to MRCP in detecting choledocholithiasis. A meta-analysis from 2017 showed that EUS has a slightly better diagnostic accuracy with higher pooled sensitivity (97%) than MRCP (87%) and comparable pooled specificity (90% and 92% respectively). EUS is theoretically better in detecting smaller stones (<5 mm) particularly in the distal CBD whereas MRCP has the advantage of being non-invasive and suitable for frail patients [26]. As a result, choosing the different modality of imaging depends on a number of factors including patient's factors (e.g. safety to endoscopic procedure, any contraindication to MRI, presence of altered anatomy), availability of the investigation and cost. Most suspected cases with biliary stone in our study had MRCP done when the initial USG finding was negative despite a long waiting time for MRCP from 4 days to 1 year in our hospital. Only one patient had EUS performed. This was largely due to the limited availability of trained endosonographers and patient's preference for having a less invasive investigation. The balance of choosing MRCP *versus* EUS may be shifted in the future as more skilled endosonographers are available. This may potentially help in shortening the time for diagnosis and subsequent treatment thus preventing further gallstone complications.

Viral hepatitis was unsurprisingly found to be the third common cause of severe ALI and is consistent with previous studies. The type of viral hepatitis was however different from the Western countries. Hepatitis B Viral (HBV) infection is still prevalent in Hong Kong and was therefore the commonest cause of severe ALI in our patients whereas Hepatitis C Viral (HCV) infection is more commonly found in the Western population. A local study published in 2019 found that the prevalence of HBV in Hong Kong was 7.8% with 8.3% among Hong Kong-born participants prior to the availability of universal HBV vaccination *versus* 1.8% among those born after the commencement of universal vaccination. The prevalence of HCV was only 0.3% in Hong Kong [27].

The prognosis of viral hepatitis varies depending on the causative virus. Hepatitis A infection is usually self-limiting and severe complications such as fulminant hepatitis are rare. The reported mortality rate was about 0.1%, 0.3% and people who are infected acquire lifelong immunity [28]. Hong Kong is one of the intermediate endemicity for HAV with up to 3500 causes reported in 1992. However there has been a gradual decline in HAV. From 2009 to 2018, the annual reported incidence was 43 to 138 with mortality rates ranging from 0 to 0.15 per million populations in the last two decades. In our study, all of the patients with HAV had good outcome and complete recovery [29].

Hepatitis E infection, similar to HAV, is usually mild and has a self-limiting course. A small portion of patients may develop acute hepatic failure; particular in pregnant woman with a mortality rate reported up to 15%-25%.Apart from pregnancy, chronic HBV carriers with acute HEV might be associated with poor outcomes [30-32]. A 10-year retrospective study on acute HEV in local hospitals showed that chronic HBV carriers with acute HEV

infection were found to have higher liver failure rate, liver-related mortality and all-cause mortality, although the results did not reach statistical significance. In patients who are immune compromised (e.g. HIV patients), there is a risk of developing chronic HEV infection and is typically with HEV genotype 3 infections [33]. In Hong Kong, the annual reported cases of HEV ranged from 43-96 between 2014 and 2018 with a mortality rate of 0 to 0.44 per million populations in the past 20 years. There were only 4 HEV patients in our study over the three-year period and the number was slightly less than expected [29]. One explanation was that some HEV patients might have an ALT level<1000 U/L and they were not included in the study. Another possible reason was due to an under diagnosis of HEV in our study. Only half of the studied patients had a complete viral hepatitis workup as a large proportion of our patients suffered from ischemic hepatitis which was mostly diagnosed clinically without further blood tests to exclude other causes. Among the 4 patients with acute HEV, one of them was chronic HBV carrier and none of them were pregnant. They all had a mild course of disease with full recovery.

The clinical course of Hepatitis B is more complex and varies in both acute and chronic infection. Acute HBV usually present as a self-limiting disease but 0.1% to 0.5% of patients may develop fulminant hepatic failure. The likelihood of progression from acute to chronic infection depends on the age at infection. Approximately 90% of infant who are infected as new born and 20% of young children infected at age 1-5 years old go on to develop chronic infection. The rate is less than 5% in adult acquired infection. The sequaelae of chronic HBV infection varies from inactive carrier state to acute exacerbation of hepatitis, hepatic failure, cirrhosis and development of hepatocellular carcinoma. The reported cumulative incidence of spontaneous Acute Exacerbation (AE) of chronic HBV infection, defined as abrupt elevation of ALT more than five times the upper limit of normal, is approximately 10% to 30% every year. While most exacerbations are usually mild, Severe Exacerbation (SAE), defined as high levels of ALT with jaundice and/or coagulopathy, can occur in some patients with chronic HBV infection [34,35]. These patients may progress to fulminant hepatic failure with high mortality.

The prognostic factors of SAE of CHB have been evaluated in a local study in 2003. The following factors were found to be independently associated with adverse outcomes: pre-existing cirrhosis, long prothrombin time (PT) of>30s, low albumin level and high bilirubin level on admission, high peak bilirubin level, long peak PT, long duration to reach PT and the presence of encephalopathy and/or ascites [36]. Among the 25 patients who had acute exacerbation of HBV infection in our study, two of them developed fulminant hepatic failure and died eventually despite the commencement of antiviral and other supportive treatments. They both had a high bilirubin>200 umol/L, and long PT>30s on admission, with peak levels of bilirubin>600 umol/L and peak PT>60s during admission. Liver transplant was not performed in both of the patients due to their advance age and poor premorbid state. The role of antiviral in severe exacerbation of hepatitis B remains controversial. A meta-analysis published in 2013 showed that Nucleotide Analogue (NA) had no impact on short term survival in patients with AE of CHB [37]. On the other hand, one meta-analysis on patients with acute on chronic liver failure due to spontaneous reactivation of HBV showed that NA significantly improved 1-month, 3-month and 12-month survival. Studies by Chien et al and Sun et al showed that early treatment with lamivudine when the bilirubin score was

below 20 mg/dl and MELD score below 30 were associated with better survival outcomes [38]. Interestingly in our study, history of CHB was associated with lower mortality (OR 0.49, CI 0.24-0.97, p=0.04) [39,40]. This may be due to the early initiation of antiviral therapy in most of our hepatitis B flare patients leading to a better outcome. Therefore, it is recommended that NA should be started early without waiting for serum HBV DNA results. Liver transplant remains the definitive treatment when patients develop severe hepatic failure (e.g. MELD>30).

Hepatitis C infection is not prevalent in the general population in Hong Kong and only prevails in selected group of patients. It was reported that over 50% of HCV carriers were intravenous drug users, followed by 8.9% of patients with history of blood transfusion in a recent local surveillance report in 2018. Acute infection of HCV is usually asymptomatic and around 50%-85% of cases would develop chronic infection [29]. The clinical course of chronic HCV is usually indolent with slow progression to more advance stage of disease. Acute exacerbation of CHC can occur but this condition is less characterized than hepatitis B. A study from Italy in 2013 showed that patients with genotype 2 were more prone to AE and paired liver biopsies had shown that these patients were more likely to have a rapid progression to advance stage of disease. This suggests that early initiation of anti-viral treatment in this group of patients is needed to prevent further unfavourable outcome [41,42]. In Hong Kong, the most common HCV genotypes were found to be 1b and 6. This may explain the reason why AE of CHC is seldomly seen in our locality. In our study, only one patient was found to have chronic hepatitis C with genotype 6. She was initially suspected to have a hepatic flare of CHC with ALT up to 1700 IU/L but a liver biopsy later confirmed that it was more likely to be due to DILI and her liver function improved without any specific treatment.

Drug induced liver injury was the fourth most common cause of severe ALI in this study. It was consistently found to be one of the top common causes reported in the literature. A retrospective study in China showed that DILI was the second most common cause of notably elevated ALT, following ischemic hepatitis, with a cut off of ALT 10 times above the Upper Limit of Normal (ULN). The type of causative drug seemed to be different between Western and Asian countries [7]. Antibiotics were shown to be the most common cause of DILI in United State and European countries whereas herbal medicine was the most common causative agent in Asian countries. Our study also shows a similar pattern with 9 out of 20 patients (45%) in the DILI group having a causative agent due to herbal medicine or traditional Chinese medication [42,43]. The identification of drug can be difficult as patients are often taking a number of medications at the same time. Two of our patients with DILI were labelled as having unknown medications. All of our patients in the study had complete recovery after the cessation of the causative drug. Despite the overall good prognosis in most DILI patients, a small group of patients may progress to liver failure resulting in mortality. A number of prognostic factors have been reported to be associated with poor outcomes. According to the Hy's rule, the combination of jaundice and high ALT, defined as bilirubin ≥ 2 times the ULN and ALT ≥ 3 times the ULN was associated with a mortality rate of more than 10% [44]. The presence of acute kidney injury and pre-existing liver disease were also shown to have a higher risk of death. There is generally no specific treatment for DILI apart from a selective group of drugs (e.g. N-acetylcysteine for paracetamol overdose), thus early

recognition is very important to prevent ongoing liver injury by the offending agent. Attention should be paid when obtaining a medication history in Chinese population as most of the DILI cases were found to be related to herbal medications. Use of any herbal or traditional Chinese medication would not be shown up in the medication record in the hospital authority system and patients may omit this part of the history during their first presentation.

Similar to the report by Con et al, our study also demonstrated that different etiology has a different clinical and biochemical profile [4]. Patients with ischemic hepatitis were older and were associated with more adverse laboratory results such as lower platelet count and albumin levels and higher creatinine, ALT and INR levels. This explained why it was associated with the poorest outcome and hence early diagnosis and treatment in this group of patients are essential. Patients with biliary pathology had lower ALT and higher ALP levels compared to other causes. These findings were not surprising as it was expected to be associated with more ductal injury resulting in higher elevation of ductal enzymes. Although patients with viral hepatitis was found to have high bilirubin and ALT levels, the overall outcome was good as most acute viral infections were self-limiting and most cases of hepatitis B flare were mild. DILI can present with different patterns of hepatic injury (e.g. hepatocellular, cholestatic or mixed type) thus the biochemical profile of the DILI group in our study cannot be generalised to all patients with DILI. Focus should be put on early detection of hepatotoxic drugs when approaching patients with any type of liver injury.

Apart from the common causes of ALI, malnutrition-induced hepatitis, which is a rare cause of marked elevation of ALT, was found in two anorexic patients in our study. In the era with a growing concern on metabolic associated fatty liver disease, malnutrition related liver complications are seldomly reported in literature. The diagnosis of our patients was made after excluding all the common causes of hepatitis, including a negative viral hepatitis serology, a negative autoimmune serology, no history of ischemic event, pre-exiting liver disease, intake of hepatotoxic drugs or alcohol consumption together with a compactable clinical presentation. Both of their ALT levels were>2000 U/L on admission and there was a gradual improvement of liver function with normalization achieved after three months from the initial presentation. The mechanism of the underlying liver injury in patients with Anorexia Nervosa (AN) is not yet fully understood. Studies have suggested that it is probably a complex and multifactorial process involving acute hypo perfusion, increase oxidative stress resulting from lower levels of glutathione and hepatocyte autophagy. It is a reversible condition with overall good prognosis but can occasionally lead to acute liver failure or fatal outcome. The main stay of treatment is a supervised increase in calorie intake and close monitoring of electrolytes to avoid re feeding syndrome [45,46]. A study published in 2019 showed that eating disorder is a growing psychiatric illness worldwide with a prevalence rate increasing from 3.5% to 7.8% between 2000-2018 globally. According to local statistics, 3.9% of adolescent boys and 6.5% of adolescent girls in Hong Kong were found to have eating disorders in a study in 2007 [47]. These numbers have doubled compared to the previous data in the last two decades [48]. This suggests that we may encounter more AN patient with liver complications in the future and we should be prepared to recognize these patients in order to initiate early and adequate feeding to avoid adverse outcomes.

There are several limitations in this study. First of all, it was a

single center study and therefore could be associated with a lack of external validity of the results. However, the findings from this study were generally consistent with previous publications, in particular with a multicenter study which involved three different hospital setting including a large tertiary liver transplant center, a community hospital, and a Veterans Affairs hospital. This may suggest the potential generalizability of the results. Secondly, it was retrospective in design and misclassification bias could have occurred. The diagnosis of ALI of each patient was made by reviewing the medical records and not all patients were given a full detailed investigation to exclude other possible causes of liver injury. In such cases the diagnosis mainly relied on the judgment by the attending doctors and an educational assumption would be needed. Thirdly, a small number of patients could only be included in a certain group of patients with less common etiologies of severe ALI over the three-year period. A longer period study may be helpful to recruit more patients for further evaluation of the clinical course and prognosis of each subgroup of patients.

CONCLUSION

In conclusion, the common causes of severe ALI in Hong Kong included ischemic hepatitis, biliary pathology, viral hepatitis and DILI. Ischemic hepatitis was associated with high mortality thus early recognition with treatment aiming at reperfusion would be vital. Biliary pathology, especially biliary obstruction due to choledocholithiasis has always been an under-recognized cause of ALI and physicians should have a higher clinical suspicion when encounter patient with abdominal pain and ALI. Viral hepatitis B remained the leading viral cause in Hong Kong and early initiation of antiviral is recommended to prevent adverse outcome. Diagnosis and identification of the causative drug in DILI can be challenging. Obtaining a detailed drug history, in particular the use of herbal medication is essential in Chinese population. Finally, we should be aware of other uncommon causes of severe ALI e.g. AN related hepatitis which is potentially reversibility once nutrition is restored. Prospective studies with larger sample size are warranted in the future to further evaluate the clinical characteristics of each subgroup of patients.

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