Case discussion
acute liver failure and Illness Scripts

Acute liver failure
Causes and management

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Case 1:
故事發生在日本,2020年1月

A lean (BMI 13 kg/m2) 62-year-old Japanese man without known chronic disease was transferred to the emergency department of our hospital due to severe anemia and liver dysfunction.

He was confused (Glasgow Coma Scale: E4V4M6), and his laboratory tests showed extremely high CK values. He was a nonsmoker and nonalcoholic. He sometimes used Etizolam for panic disorder. His family history was unknown for any neuromuscular disorders or myopathies, he had never had a vaccination against SARS-CoV-2

現在病史中您要澄清那些事實要問一些什麼?

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- 病史中您要澄清那些事實要問一些什麼?

1.病人什麼時候開始變得很瘦, 有看醫生嗎,醫生怎麼說是什麼病呢.
2.病人有嚴重貧血何時開始的,有無心臟和肺部症狀, 如呼吸急促, 前胸部疼痛等
3.從前有肝病嗎?何時知道肝功能不正常, 醫師怎麼說是什麼樣的肝病
4.從前有沒有消化打到出血,黑便或血便?
5. 意識不清楚, 昏迷不清是多久的事?
6.發病過程中有沒有嘔吐, 有沒有發燒,
7.家庭中有沒有人有同樣的問題出現,
8.過去幾年中有沒有做過新冠肺炎的疫苗注射, 為什麼不去打疫苗呢?
9.過去有得過哪一些病呢, 有在吃什麼藥嗎
10.有沒有接觸過新冠病毒(Covid 19)感染的病人

- He had contacted a person with COVID-19 three days before and complained of **generalized fatigue, decreased appetite, and fever a** day before the transfer. He did not take any antipyretic analgesics

病人來診之前3天曾經接觸與一個發燒的病人被證實是新冠病毒感染.
病人在來診治前一天也有發燒,胃口不佳,人很疲倦
病人沒有打過新冠病毒疫苗,因為從前打流感疫苗發生嚴重的過敏現象
所以不敢打

Physical findings:

- His initial vital signs showed a blood pressure of 138/63 mm Hg, heart rate of 108 beats/minute, a temperature of 36.9 ◦C, a respiratory rate of 21 breaths/minute, and oxygen saturation of 98% on room air. A shock status or a hypotensive event was not documented throughout the transference. On physical examination, he had no tenderness over the major muscle group and no lymphadenopathy, and his liver and spleen were not palpable. No remarkable asterixis was observed.來診時並無休克的現象,也沒有發燒.

CBC			
WBC	12.2	(3.3–8.6)	$\times 10^3/\mu L$
Neut	91.4	(38.5–80.5)	%
Lymph	4.6	(16.5–49.5)	%
Mon	4	(2.0–10.0)	%
Eos	0	(0.0–8.5)	%
Bas	0	(0.0–2.5)	%
RBC	2.46	(3.86–4.92)	$\times 10^{4/}$ mL
Hb	3.4	(11.6–14.8)	g/dL
Hct	15.4	(35.1–44.4)	%
MCV	62.6	(83.6–98.2)	fL
MCH	13.8	(27.5–33.2)	%
MCHC	22.1	(31.7–35.3)	%
Platelet	18.9	(15.8–34.8)	$\times 10^4/\mu L$
Biochemistry			
Total protein	7.0	(6.6–8.1)	g/dL
Albumin	3.9	(4.1–5.1)	g/dL
Total bilirubin	2.2	(0.4–1.5)	mg/dL
Direct bilirubin	0.9	(≤0.4)	mg/dL
AST	5398	(13–30)	U/L
ALT	2197	(7–23)	U/L
ALP (IFCC)	99	(38–113)	U/L
GGT	55	(9–32)	U/L
LDH	4636	(124–222)	U/L
CK	9498	(41–153)	U/L
BUN	31.3	(8–20)	mg/dL
Creatinine	1.25	(0.46–0.79)	mg/dL

Laboratory findings:

CBC and Blood chemistry 的結果要怎麼判讀.

1, Microcystic anemia, severe
2. Leukocytosis, mild
3. Platelet count : normal
4, Mild jaundice
5. Very high AST and ALT, AST>>ALT
6. LDH : very high
7. CK : abnormally high
8. Cr : mildly abnormal.
9. Alk-P-tase: normal

And GGT : above upper limit

- Laboratory data 如何解釋,
- 要想哪些問題?

Severe anemia, probably due to chronic cause
Mild leukocytosis, related to infection or inflammation
Severe liver cell necrosis with mild hyperbilirubinemia
No evidence of biliary obstruction
LDH and CK value : high, probably due to muscle damage or liver cell necrosis.

怎樣敘述病人的問題:Major problem and problem list?

Serology			
anti-EBV VCA IgG	1:320	(+)	
anti-EBV VCA IgM	<1:10	(−)	
anti-CMV IgG	31.4	(+)	
anti-CMV IgM	0.32	(−)	
anti-HSV IgG	31.4	(+)	
anti-HSV IgM	0.32	(−)	
HBs Ag		(−)	
HBs Ab		(−)	
HCV Ab		(−)	
IgM-HA Ab		<1:40	
IgA-HEV Ab		(−)	
ANA		<1:40	
AMA-M2	<1.5	(−)	
Ig G	1493	(861–1747)	mg/dL
Ig G4	57	(11–121)	mg/dL
Ig M	37	(50–269)	mg/dL
SARS-CoV-2		(+)	
N (Ct)		25.1	
N (copies)		666,135.0	
N2 (Ct)		20.3	
N2 (copies)		2,420,950.0	
Coagulation			
PT (%)	26.2	(70–130)	%
PT(INR)	2.33	(0.80–1.27)	

CRP	2.73	(<0.15)	mg/dL	Plasma myoglobin	4366	(≤154.9)	ng/mL
NH3	159	(12–66)	μg/dL	Urine myoglobin	73,900	(≤2.0)	ng/mL

這一些結果你要怎樣解釋?
下一步要怎麼做?

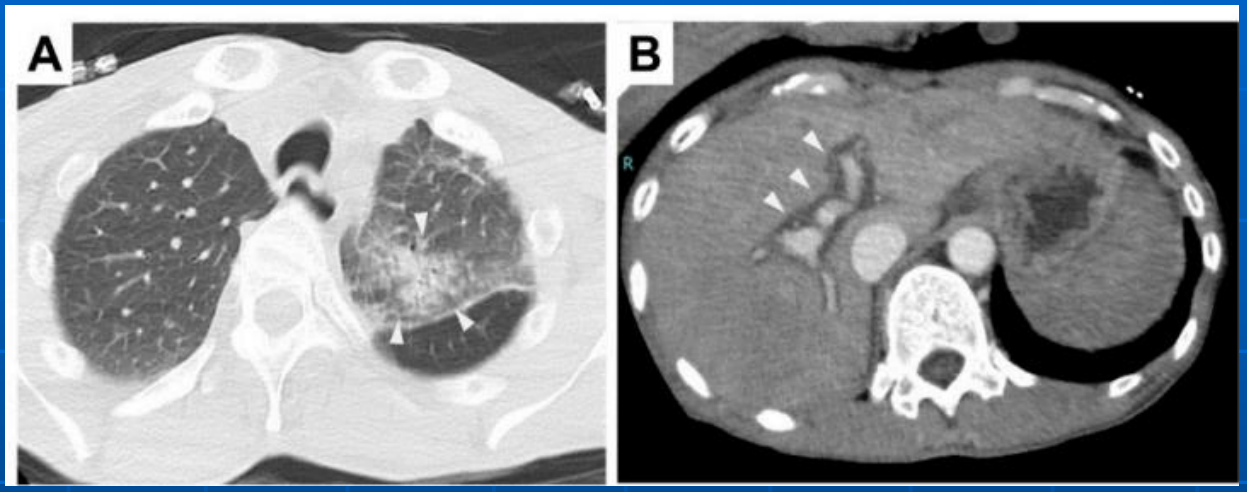
- A Focused Assessment with Sonography for Trauma (FAST) scan did not reveal any intra-abdominal echo-free space, ruling out the presence of abdominal bleeding.
- Further investigations, including nasogastric tube insertion and digital rectal examination, showed no signs of gastrointestinal bleeding.

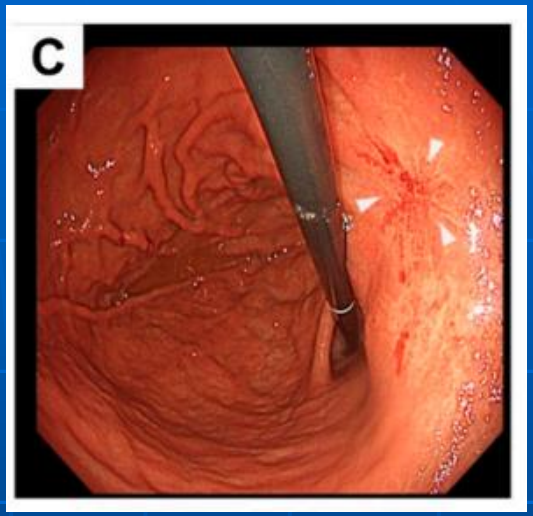
確認沒有intraabdominal injury-→internal bleeding
也沒有消化道出血.
何時開始貧血,也沒有注意

Major problems

- Hepatic coma
- Severe anemia
- Severe liver cell necrosis resulted in acute liver failure

Medical images





Chest-computed tomography (CT) imaging demonstrated bronchopneumonia in the left upper lobe of the lung (Figure 1A). Contrast-enhanced CT imaging demonstrated the presence of a periportal collar sign, suggesting the presence of acute hepatitis (Figure 1B). Hepatic congestion was not remarkable, and no indications of ischemic changes were observed in either the liver or skeletal muscles.
Gastroduodenal endoscopic examination unveiled a scar (S1 stage of Sakita–Miwa Classification) located at the lesser curvature of the stomach (Figure 1C).
The patient tested positive for Helicobacter pylori antibodies.
Fecal occult blood tests were negative on two occasions.
He declined to have a colonoscopy.

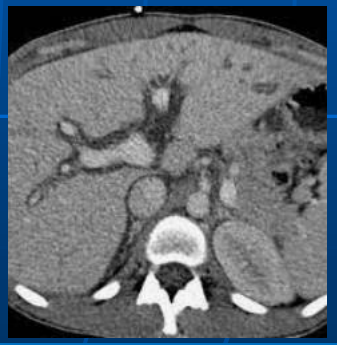
Dr: The severe anemia was attributed to a peptic ulcer

Periportal collar sign(CT)

- Periportal halo or periportal collar sign refers to a zone of low attenuation seen around the intrahepatic portal veins on contrast-enhanced d CT or hypoechogenicity on liver ultrasound. It likely represents **periportal edema**, which is often used as a synonymous term. Periportal haloes may occur around the central portal veins or their peripheral branches and occur on both sides of the portal triads.
- **Etiology**
- This sign is seen when there is fluid accumulation or dilatation of lymphatics in the loose areolar tissue around the portal triads. This sign is non-specific and can be seen in various conditions [1]:

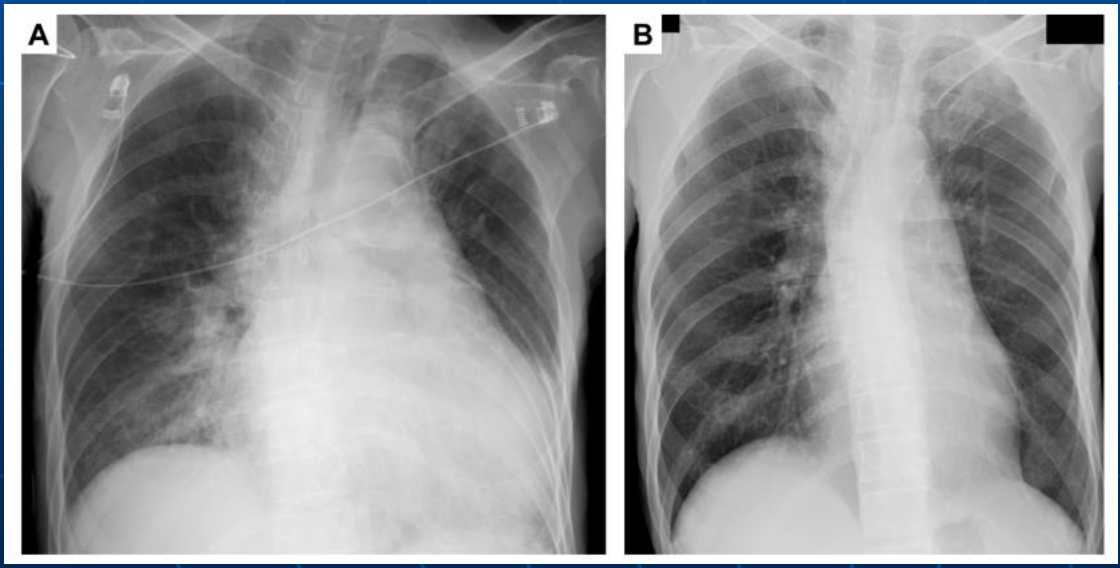
- congestive cardiac failure (CCF)
- secondary cardiac congestion
- acute hepatitis, particularly viral hepatitis
- lymphadenopathy at the porta hepatis causing lymphatic obstruction
- liver transplant and liver transplant rejection
- bone marrow transplantation (BMT)
- blunt hepatic trauma
- blunt abdominal trauma and aggressive fluid resuscitation

- .



Periportal edema due to intense hyperhydration in a septic patient

- A chest radiograph exhibited **a cardiothoracic ratio (CTR) of 67.6%** (Figure 2A), while brain natriuretic peptide (BNP) levels measured 2937 pg/mL. Electrocardiographic monitoring findings did not exhibit abnormalities such as ST elevation or negative T waves.
- Echocardiography demonstrated an enlarged left ventricle (LVDd 53.5 mm, LVDs 42.0 mm) and a ventricular ejection fraction (vEF) ranging from 20% to 25%. A severe reduction in wall motion was observed throughout the myocardium.
- The characteristic features of "takotsubo cardiomyopathy," including apical ballooning, symmetrical regional abnormalities in the form of a circumferential pattern, and left ventricular outflow tract obstruction, were absent in the observed case. Notably, there were no indications of cardiac valvular disease.



Chest radiograph findings: (A) CTR was 67.6% on the day of admission and (B) on the 28th day showed improvement in the CTR from 67.6% to 49.9%. (CTR, cardiothoracic ratio)

DX.

- Hear failure, cause to be determined.
- Acute liver failure, etiology ?

1. Cause of heart failure

- 1. type 2 myocardial infarction resulting
- from anemia was considered,
- 2.patient's heart failure was secondary to
- stress-induced myocardial injury,
- particularly in severe conditions such as
- anemia, liver failure, and rhabdomyolysis

the cardiologists ultimately determined that the patient's heart failure was secondary to stress-induced myocardial injury

-→ the patient received red blood cell transfusions to manage the underlying anemia.

2. ALF Dx. evidence

- Transaminases were extremely elevated, and the prothrombin time was prolonged and international normalized ratio (PT-INR) was 2.33. The patient was also diagnosed with ALF without hepatic coma, (according to the Japanese criteria for ALF)
- Why?→ SARS-CoV-2 infection

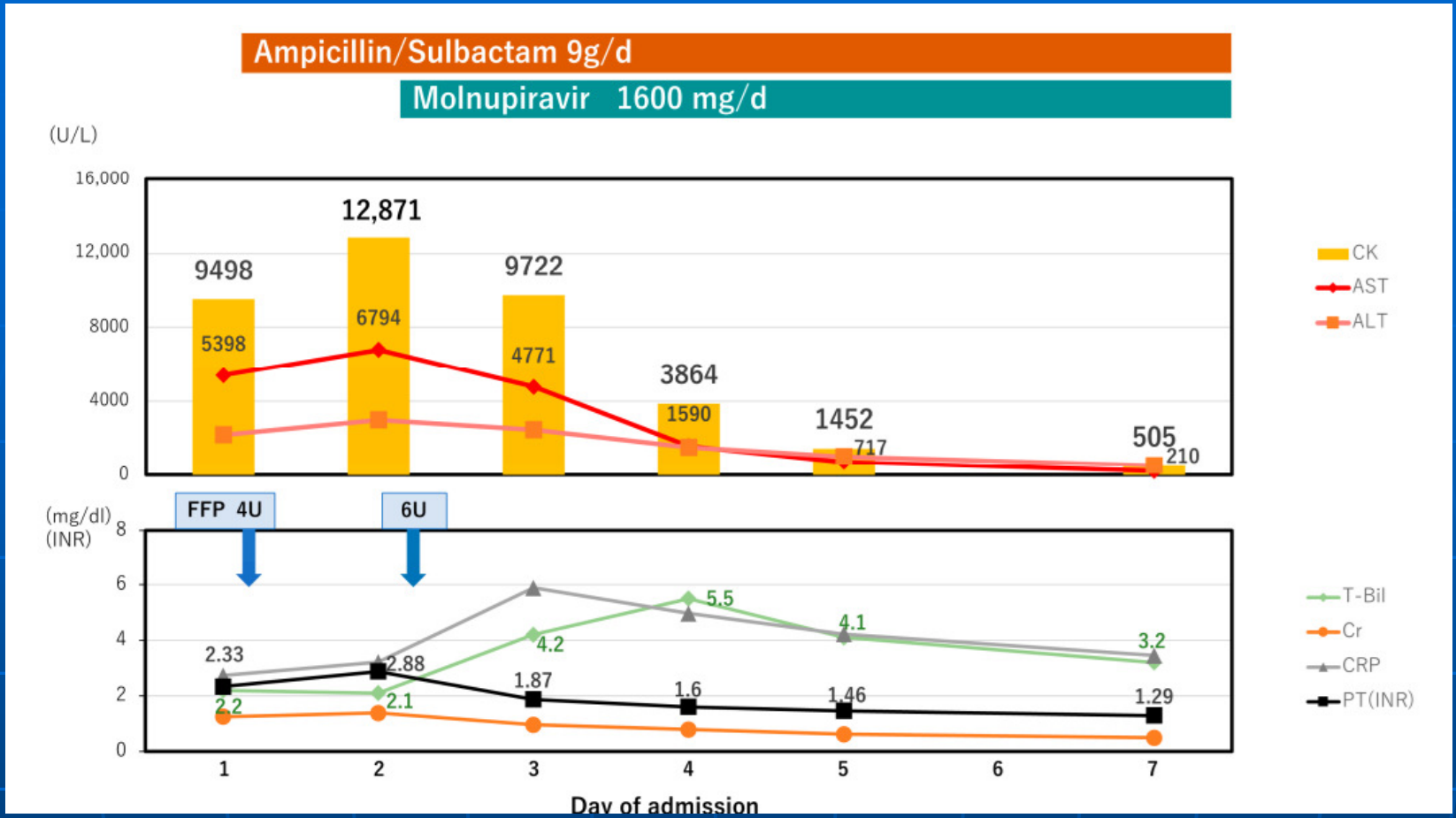
Clinical course--1

- Immediately, erythrocyte transfusion and cryoprecipitate were supplied.
- Lactulose and rifaximin were started to decrease ammonia, and antibiotics (Ampicillin Sodium/Sulbactam 9 g/day) were also started for bronchopneumonia.
- On the next day following admission, **AST, LDH, and CK were still elevated. The plasma myoglobin was 4300 ng/mL and myoglobin in the urine was 73,900 ng/mL.** The patient was further complicated with rhabdomyolysis.

Another Dx : rhabdomyolysis

Clinical course—2 about covid 19 infection.

- Consultation took place with infectious disease specialists, and 1600 mg/d of molnupiravir was started.
- Transaminases and CK were decreased from the third day and total bilirubin was elevated to 5.5 mg/dL on the fourth day.
- It finally recovered to the normal level two months later. Renal function was not affected throughout the clinical course.
- Prothrombin time was recovered by over 40% (below INR 1.5) on the fourth day.
- The SARS-CoV-2 was finally undetectable on the 26th day.
- The patient's hemoglobin recovered to 12.5 g/dL on the 46th day (Figure 3) and the CTR decreased to normal (Figure 2B)



Clinical course. Antibiotics (Ampicillin Sodium/Sulbactam 9 g/day) was started for bronchopneumonia. A total of 10 units of FFP were administered to address acute liver failure. Further elevations in AST, LDH, and CK levels were observed on the second day. Elevated levels of blood myoglobin and urinary myoglobin indicated the presence of rhabdomyolysis, leading to the initiation of monnupilavir treatment. By the third day, liver enzyme levels and CK began to decrease. Although there was a tendency for bilirubin to increase, it subsequently decreased by the fifth day. (FFP, fresh frozen plasma; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; Cre, creatinine; CK, creatine kinase; CRP, c-reactive protein; T-bil, total bilirubin)

The first documented case of the simultaneous occurrence of rhabdomyolysis and ALF associated with SARS-CoV-2 infection

- Several reports have highlighted the occurrence of liver enzyme abnormalities, acute hepatitis, and an ALF associated with SARS-CoV-2 infection [26–43]. It has been documented that approximately 76.3% to 82.5% of COVID-19 cases display abnormal liver test results [35,37]. Medetalibeyoglu et al. further demonstrated that elevated levels of AST and ALT, along with an AST/ALT ratio greater than 1, indicated a more severe disease course and increased mortality in COVID-19 patients [26]. However, their study reported maximum AST and ALT values of 421 IU/L and 610 IU/L, respectively. In contrast, our case exhibited significantly higher levels, with an AST/ALT ratio of 2.45. Moreover,
- Sobotka et al. indicated that severe acute liver injury (ALI) was infrequent, occurring in 0.1% of patients upon admission and 2% during hospitalization, with no ALF observed among a cohort of 1555 patients [30]. The available literature on ALF in the context of COVID-19 remains limited, with only a handful of reports documenting such cases [39– 43]. The reports on ALF cases are provided in Table 2, with the main findings summarized

Table 2. Published reports of acute liver failure associated with COVID-19.

Case#	Age	Sex	Underlying Diseases	Highest AST (IU/L)	Highest ALT (IU/L)	T-bil (mg/dL)	PT-INR	CK	CRP (mg/dL)	Prognosis	Ref.
1	35	F	SLE	4202 (day 3)	5524 (day 3)	10.5 (day 3)	4.9	n/a	6.68	recovered	[39]
2	80	M	DM, HT, HLP, CAD, asthma,	>7000 * (day 5)	3737 (day 5)	8.4 (day 8)	8.94 (day 8)	n/a	n/a	died (day 9)	[40]
3	65	M	HT	746 (day 14)	467 (day 14)	22.2 (day 20)	2–3 ** (day 20)	n/a	n/a	n/a	[41]
4	53	M	CM	4735 (day 2)	1988 (day 2)	n/a	n/a	n/a	n/a	n/a	[42]
5	49	F	AD, HT, DA	950 (day 1)	1375 (day 1)	21.2 (day 6)	15.5 (day 4)	n/a	n/a	died (day 9)	[43]
6	62	M	PU, HF	6798 (day 2)	2987 (day 2)	6.0 (day 19)	2.88 (day 2)	12,871 (day 2)	5.89	recovered	Presentcase
summary	**Median 57.5**	**66.7% Male**		**Median 4469**	**Median 2488**	**Median 9.45**	**Median 4.9**				

AD, aortic dissection; AST, aspartate aminotransferase; ALF, acute liver failure; ALT, alanine aminotransferase; BPH, benign prostate hypertrophy; CM, cardiomyopathy; CK, creatine kinase; CKD, chronic kidney disease; CRP, c-reactive protein; DA, drug abuse; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IGT, impaired glucose tolerance; INR, international normalized ratio; LDH, lactate dehydrogenase; n/a, not available; OB, obesity; OSAS, obstructive sleep apnea syndrome; PT, prothrombin time; PU, peptic ulcer; SLE, systemic lupus erythematosus; T-bil, total bilirubin; n/a, not available.* calculate the median as 7000. ** Values are not indicated on the graph; therefore, calculate the median as 2.5.

Sobotka et al. indicated that severe acute liver injury (ALI) was infrequent, occurring in 0.1% of patients upon admission and 2% during hospitalization, with no ALF observed among a cohort of 1555 patients [30].

1. Among 1555 patients in the cohort, most (74%) had an elevated alanine aminotransferase (ALT) during hospitalization.
2. severe ALI (> 20 × upper limit of normal [ULN]) in 3%.
3 no patients in our cohort met formal criteria for ALF.
4. Elevated ALP and ALT were associated with longer LOS, admission to intensive care, mechanical ventilation, vasopressor use, and extracorporeal membrane oxygenation use ($p < 0.001$).

L.1113, Lindsay A Sobotka[1], et al **Acute Liver Injury in Patients Hospitalized with COVID-19.** Dig Dis Sci. 2022 Aug;67(8):4204-4214., Epub 2021 Sep 6

Acute liver injury in a COVID-19 infected woman in Taiwan

- A 60-year-old woman without medical history or chronic illness received three COVID-19 vaccinations since the start of the pandemic. The patient was infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and presented with mild symptoms on July 12th, 2022. Post-recovery, she underwent an examination at our hospital on August 30th, 2022. **AST and ALT levels in the liver function test were 207 U/L (normal value < 39, 5.3-fold increase) and 570 U/L (normal value < 52, 10.9-fold increase),** respectively. The patient was diagnosed with ALI, and no treatment was prescribed. The following week, blood tests showed a reduction in both levels (ALT 124 U/L, AST 318 U/L).
- Two weeks later, AST and ALT levels had
- decreased to near the expected upper
- limits (ALT 40 U/L, AST 76 U/L).

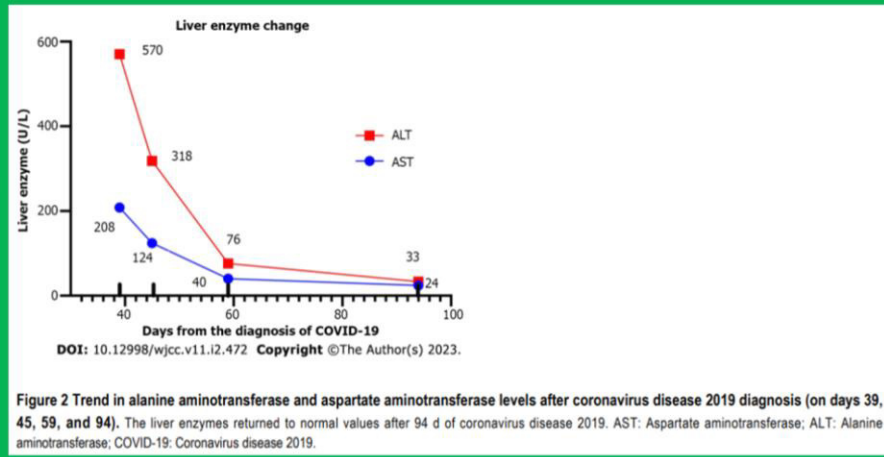


Figure 2 Trend in alanine aminotransferase and aspartate aminotransferase levels after coronavirus disease 2019 diagnosis (on days 39, 45, 59, and 94). The liver enzymes returned to normal values after 94 d of coronavirus disease 2019. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; COVID-19: Coronavirus disease 2019.

Pei-Hsuan Lai [1], Dah-Ching Ding [2] (L **Acute liver injury in a COVID-19 infected woman with mild symptoms: A case report歐(HLTC)** World J Clin Cases. 2023 Jan 16;11(2):472-478.(L1115)

F.Salık, O. Uzundere, M. Bıcak et al. ¸ Annals of Hepatology 26 (2021) 100553 (L1117,L1118)

- Among 533 cases admitted to ICU, mean age was 69.2 +/-14.8 years. 283 (53.1%) patients were male and 250 (46.9%) were female. In total, 401 (75.2%) patients had at least one comorbidity and the most common comorbidities were hypertension (218, 40.9%) and diabetes (151, 28.3%). Between the dates of the study, **353 of all patients died. The mortality rate was found to be 66.2%.** The average stay in the ICU was 11.3 § 10.7 days.

Table 3
Comparison of 7-day, 28-day and total mortality rates between groups.

	Total (n = 533)	Group 1 (n = 256)	Group 2 (n = 231)	Group 3 (n = 46)	p value
7-days mortality					0,001*
Yes	167 (31,3)	66 (25,8)	77 (33,3)	24 (52,2)	
No	366 (68,7)	190 (74,2)	154 (66,7)	22 (47,8)	
28-days mortality					0,003*
Yes	345 (64,7)	147 (57,4)	165 (71,4)	33 (71,7)	
No	188 (35,3)	109 (42,6)	66 (28,6)	13 (28,3)	
Total mortality					0,004*
Yes	353 (66,2)	152 (59,4)	165 (71,4)	36 (78,3)	
No	180 (33,8)	104 (40,6)	66 (28,6)	10 (21,7)	

* Statistically significant

Group 1 was formed of patients with normal liver biochemical parameters values;
Group 2 was formed of patients with liver biochemical parameters abnormality;
Group 3 was formed of patients with liver injury.

結論： 研究表明，肝功能障礙與較高的死亡率和較短的ICU佔用時間有關.

- The mechanism by which COVID-19 triggers acute hepatitis still remains unclear.
- Sun et al[10] suggested several possible explanations, such as the combination of the immune-mediated inflammatory response, direct cytotoxic injury due to viral replication, hypoxic hepatitis, drug-induced liver injury, or reactivation of pre-existing liver disease.

  ACE2 expression in the biliary and hepatic endothelial cells can explain the observed liver injury[16]. Hypoxia, drugs, or pre-existing liver disease were disregarded in our case because of the patient's narrative history.

Case 2,High fever

- A 26-year-old nonalcoholic female presented to the emergency department with a history of 4 days fever which was intermittent; the maximum temperature recorded was 102°F, associated with headache, retroorbital pain, and myalgia but without chills and rigor.

一個年輕的女性發高燒(high fever) 4天在病史上
你還想知道一些什麼來解決發燒的原因

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一個年輕的女性發高燒(high fever) 4天在病史上
你還想知道一些什麼來解決發燒的原因

1.There was no history of mucocutaneous bleeding or bruises.

- 2.There was a history of multiple episodes of nausea and vomiting along with diffuse abdominal pain and distension, loss of appetite, and the generalized weakness associated with acute shortness of breath.
- 3.There was no history of chest pain, palpitation, orthopnea, dizziness, loss of consciousness, abnormal body movements, or altered sensorium. There was no similar history in the past.
- 4. Gyn-Obs history---病人否認有任何性關係,LMP: 3天前OK
- 5.有沒有被蟲咬或被蚊子咬的病史.

Physical examination 要特別注意哪一些變化?

Physical examination 要特別注意哪一些變化?

- On examination, her blood pressure was 100/60 without a significant postural drop, pulse was 106 beats/min, oxygen saturation at room temperature was 98%, respiratory rate was 20/min, and the temperature was 101.4°F. **She was well-oriented to time, place, and person**. On abdominal examination, it was grossly distended with dull percussion with decreased bowel sound. There was the presence of crackles over the lower surface of both lung fields. Her heart sound was normal.

1.體溫與脈搏的變化有沒有相對性的脈搏緩慢(relative bradycardia)
2.有無皮膚出血的徵象破文整叮咬的傷口或紅腫
3.有無肺炎注意兩邊肺的呼吸聲.
4.血氧濃度:室溫氧飽和度為 98%，呼吸頻率為 20/分，
4.腹部檢查有無腹膜炎的徵象,特別注意疼痛的位置在何處確定是否需要找 婦科做內診

抽血檢查要特別注意哪一些事項?

Achhami et al. Annals of Medicine & Surgery (2023)

Table 1

Investigations done on the day of admission

Investigations	Results	Reference range
Total leukocyte count (cells/mm^3)	11 950	4000–11 000
Differential count (%)	Neutrophils: 60.90, lymphocytes: 34.30	Neutrophils: 40–70, lymphocytes: 20–45
Hemoglobin (g%)	12.4	11.9–14.6
Packed cell volume (%)	35.20	40–50
Platelets (cells/mm^3)	78 000	150 000–450 000
Alanine transaminase (U/l)	2202	9.0–52
Aspartate transaminase (U/l)	74 160	14–36
Total bilirubin (mg/dl)	4.70	0.2–1.3
Conjugated bilirubin (mg/dl)	1.40	0–0.3
Unconjugated bilirubin (mg/dl)	1.20	0.01
Alkaline phosphatase (U/l)	311	30–126
Prothrombin time (s)	19.50	11.0–16
Control (s)	14	
Random blood glucose (mg/dl)	60	80–140
C–reactive protein (mg/l)	87	0–10
Creatinine (mg/dl)	0.60	0.52–1.04
Urea (mg/dl)	19	15–45
Total protein, serum (g/dl)	5.30	6.3–8.2
Albumin, serum (g/dl)	2.20	3.5–5.0
Serum lactate (mmol/l)	5.1	0.7–2.0

請問血液檢查有什麼異常?

1.白血球增加
2.中性球增加
3.血小板明顯減少
4.AST很高
5.ALT很高
6. AST>>ALT
7.ALK-P-tase不正常
8.血膽色素不正常
9.非結合性膽色素很高
10. Prothrombin time 延長
11.血糖稍低
12. CRP明顯增高
13. Cr:正常
14.Serum Albumin很低
15. Serum lactate增高

這些結果代表什麼意義.

Achhami et al. Annals of Medicine & Surgery (2023)

Table 1

Investigations done on the day of admission

Investigations	Results	Reference range
Total leukocyte count (cells/mm^3)	11 950	4000–11 000
Differential count (%)	Neutrophils: 60.90, lymphocytes: 34.30	Neutrophils: 40–70, lymphocytes: 20–45
Hemoglobin (g%)	12.4	11.9–14.6
Packed cell volume (%)	35.20	40–50
Platelets (cells/mm^3)	78 000	150 000–450 000
Alanine transaminase (U/l)	2202	9.0–52
Aspartate transaminase (U/l)	74 160	14–36
Total bilirubin (mg/dl)	4.70	0.2–1.3
Conjugated bilirubin (mg/dl)	1.40	0–0.3
Unconjugated bilirubin (mg/dl)	1.20	0.01
Alkaline phosphatase (U/l)	311	30–126
Prothrombin time (s)	19.50	11.0–16
Control (s)	14	
Random blood glucose (mg/dl)	60	80–140
C–reactive protein (mg/l)	87	0–10
Creatinine (mg/dl)	0.60	0.52–1.04
Urea (mg/dl)	19	15–45
Total protein, serum (g/dl)	5.30	6.3–8.2
Albumin, serum (g/dl)	2.20	3.5–5.0
Serum lactate (mmol/l)	5.1	0.7–2.0

1.白血球增增加
2.中性球增加
3.血小板明顯減少
4.AST很高
5.ALT很高
6. AST>>ALT
7.ALK-P-tase不正常
8.血膽色素不正常
9.非結合性膽色素很高
10. Prothrombin time 延長
11.血糖稍低
12. CRP明顯增高
13. Cr:正常
14.Serum Albumin很低
15. Serum lactate增高

這些結果代表什麼意義.

1.感染發炎,
2.極嚴重肝細胞壞死
3.血清白蛋白偏低可能是肝功能萎縮造成
4.Metabolic acidosis.

Acute liver failure

Blood examination

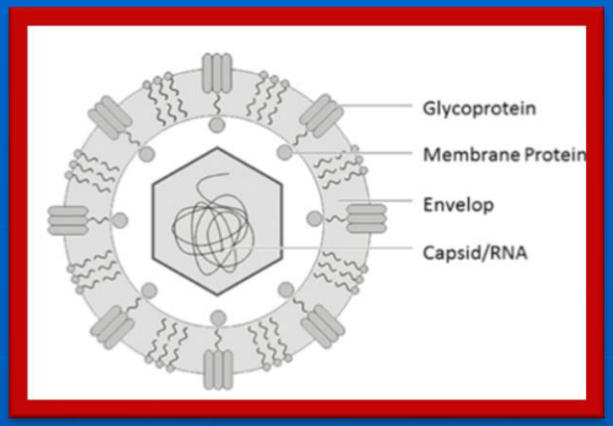
- 1.瘧疾、肝炎病毒、恙蟲病和鉤端螺旋體的血液檢查結果為
- 陰性。malaria, hepatitis viruses, scrub typhus, and leptospira were negative.
- 2,但在她的血液中檢測到登革熱病毒抗原非結構蛋白1
- dengue viral antigen nonstructural protein 1 was detected in her blood.

dengue viral antigen nonstructural protein 1,這是什麼?

Hong-Ru Chen, Yen-Chung Lai & Trai-Ming Yeh

Dengue virus non-structural protein 1: a pathogenic factor, therapeutic target, and vaccine candidate *Journal of Biomedical Science* *J Biomed Sci* **25**, 58 (2018).

Dengue virus (DENV) infection is the most common mosquito-transmitted viral infection. DENV infection can cause mild dengue fever or severe dengue hemorrhagic fever (DHF)/**dengue shock syndrome (DSS**). Hemorrhage and vascular leakage are two characteristic symptoms of DHF/DSS. However, due to the limited understanding of dengue pathogenesis, no satisfactory therapies to treat nor vaccine to prevent dengue infection are available, and the mortality of DHF/DSS is still high. **DENV nonstructural protein 1 (NS1),** which can be secreted in patients' sera, has been used as an early diagnostic marker for dengue infection for many years. However, the roles of NS1 in dengue-induced vascular leakage were described only recently. In this article, the pathogenic roles of DENV NS1 in hemorrhage and vascular leakage are reviewed, and the possibility of using NS1 as a therapeutic target and vaccine candidate is discussed.



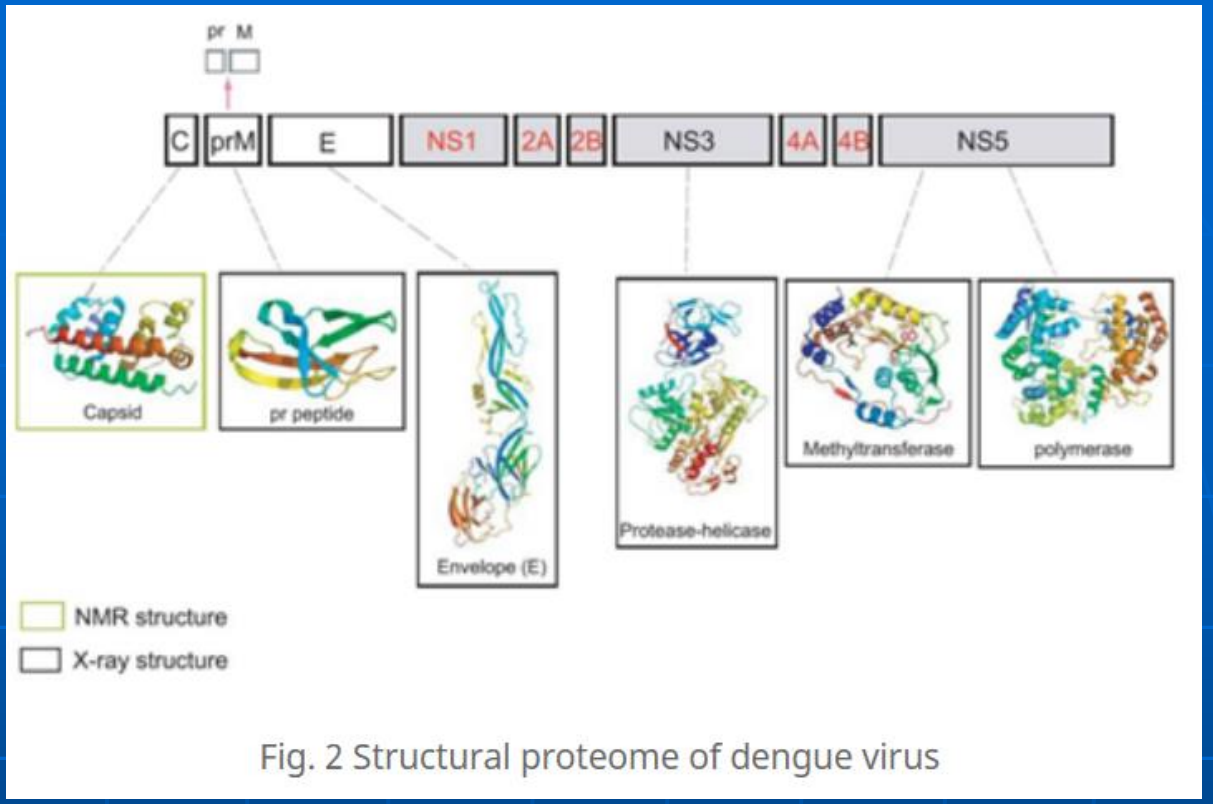


Fig. 2 Structural proteome of dengue virus

Dengue Fever virus is a RNA virus and homogeneous to West Nile virus, Japanese encephalitis virus and yellow fever virus. Genome of the dengue virus contains about 11,000 nucleotide bases, which code three different types of protein molecules (C, prM and E) that form the virus particle and seven other types of protein molecules that are found in infected host cells only and are required for life cycle of the virus.

1. **Capsid proteins (C)** Capsid protein (12 kDa) of mature DENV is highly basic
2. **Membrane protein (prM/M)** prM, also termed as precursor-membrane protein,
3. **Envelope protein (E)** Envelope protein is a glycoprotein belonging to class II viral membrane fusion protein
4. **Non-structural protein (NS)** The seven non-structural proteins include NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5. NS1 plays important role in structural stability and secretion of NS1 in dimeric form

Clinical course-1

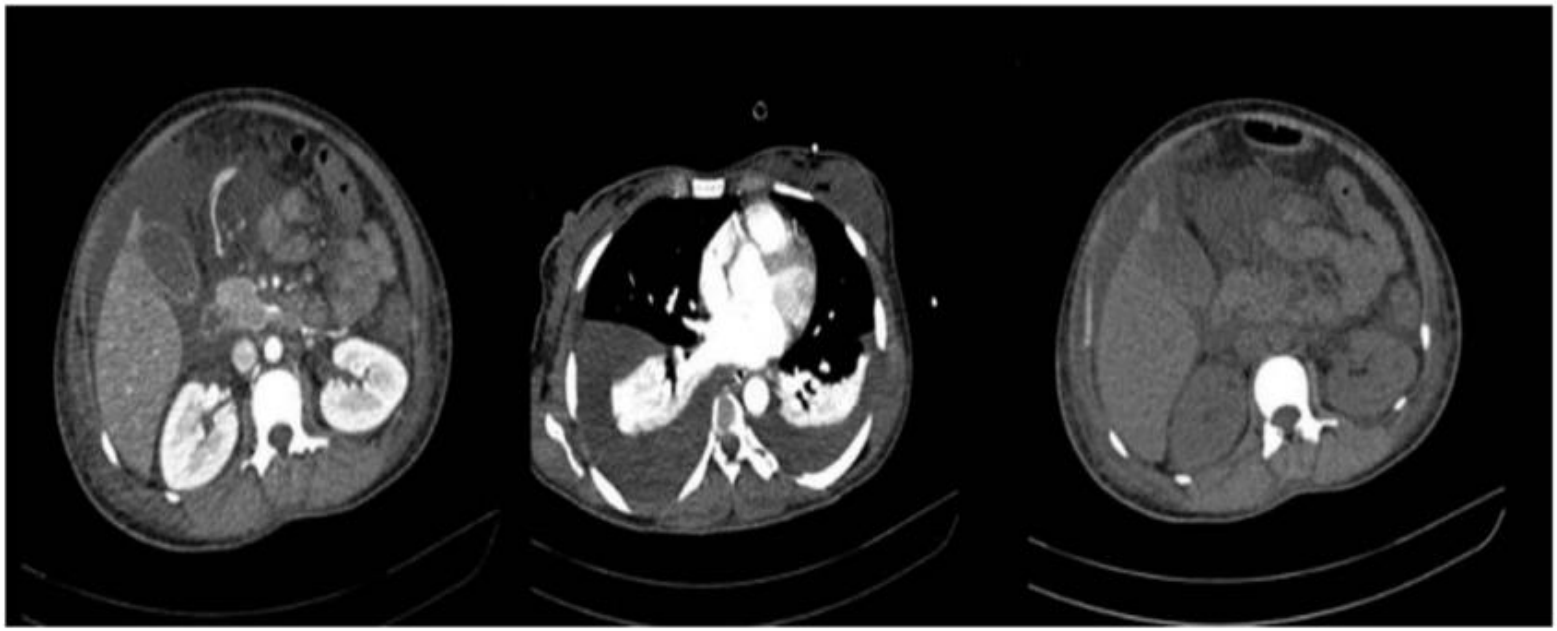


Figure 1. Computed tomography scan of whole abdomen: Gross ascites with large amount of bilateral pleural effusion with bilateral lower lobe atelectasis.

The ultrasound of the abdomen and pelvic done on the day of admission showed moderate ascites with bilateral pleural effusion. The following day after the admission, she had four to five episodes of nausea and vomiting, for which she was kept nil per oral. She was started on intravenous fluids and antiemetic due to worsening lactate levels and persistent tachycardia; later that day, she complained of severe abdominal pain and respiratory difficulty, for which she was shifted to the ICU.

Clinical course-2

- During the third day, her abdominal distension progressively increased, and she became tachypneic, confused, drowsy, and restless. She was subsequently **diagnosed with Dengue shock syndrome with ALF and grade III Hepatic Encephalopathy** evidenced by altered liver biochemistry with coagulopathy, severe lactic acidosis, and altered level of the sensorium.

Clinical course-3

- She was started on antibiotics, enema, diuretics, proton pump inhibitors, methylprednisolone, lactulose, 20% albumin infusion, N-acetylcysteine, and was kept on total parenteral nutrition. Hepatotoxic medications were avoided. She was intubated due to altered level of consciousness to protect her airway. The computed tomography scan of whole abdomen was done on the third day of hospital admission (Fig. 1). Therapeutic tapping of ascitic fluid was done to provide relief to the patient. Over time, her deranged transaminases (Fig. 2) level was improved. Her coagulopathy which was deranged (Fig. 3), was appropriately managed with fresh frozen plasma and vitamin K. Slowly her clinical status as well as biochemical profiles was improved.

Clinical course-4

- She was completely weaned off the ventilator on the fifth day of intubation. After 20 days, she was discharged from the hospital. Later during a follow-up visit, her transaminase levels were within normal range.

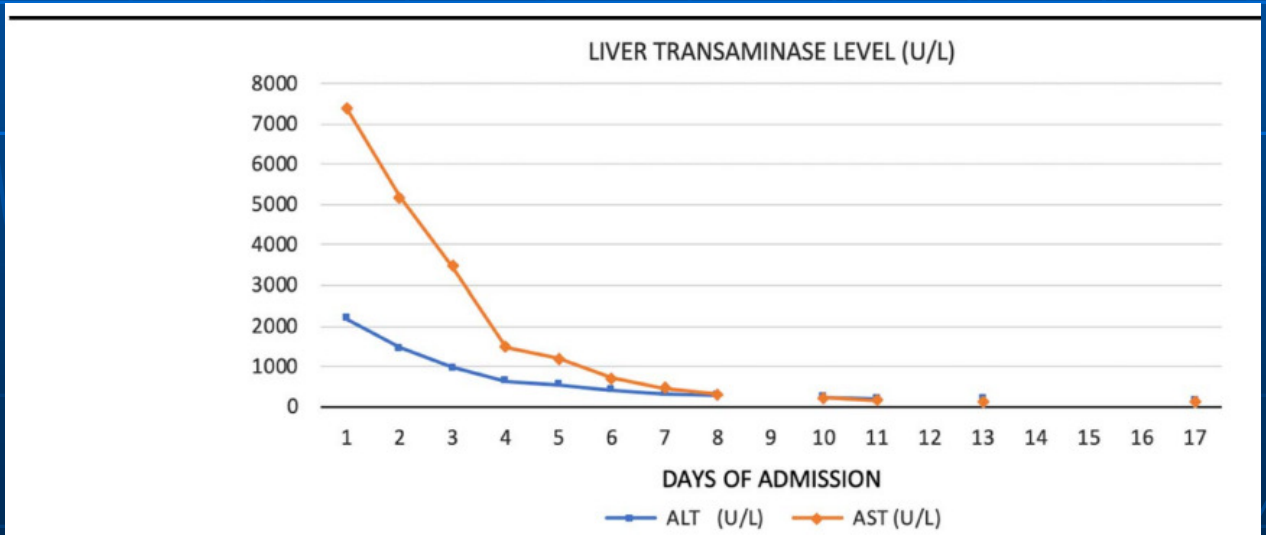


Figure 2. Liver transaminases level. ALT, alanine transaminase; AST, aspartate transaminase.

Dengue shock syndrome and ALF

- Dengue shock syndrome is the most severe form of dengue, which can affect several organs, including the liver, brain, and kidney, and result in fatal outcomes [Samanta and Sharma, 2015].
- Liver involvement in dengue is a crucial feature, and the effect ranges from an asymptomatic rise in liver enzymes to the development of ALF.

Samanta J, Sharma V. Dengue and its effects on liver. World J Clin Cases 2015;3:125. (Department of Gastro-enterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India.)

登革熱已成為一種重要的蟲媒病毒疾病，對熱帶國家人口的疾病負擔產生重大影響。登革熱通過伊蚊叮咬傳播。該病毒似乎具有一些肝毒性作用。肝功能檢查中紊亂形式的肝臟疾病很常見，可能包括血清膽紅素輕度升高、轉氨酶升高和血清白蛋白紊亂。雖然在大多數情況下無癥狀，但黃疸和急性肝衰竭（ALF）等臨床表現偶爾會使臨床表現複雜化。事實上，在流行國家，登革熱被認為是ALF的重要病因。

- ALF often results in multiorgan dysfunction including hemodynamic instability, renal failure, cerebral edema, and even death because of shock[4,12]. **Souza et al.[14] found that 74.2% of patients with serologically confirmed dengue had significantly elevated transaminase**. Many studies have point that the elevation of AST is more than alanine aminotransferase (ALT). The change in the ratio of aspartate aminotransferase (AST)/ALT is rarely observed in hepatitis A, B, or C viruses–induced acute hepatitis but only in Dengue fever[4]. Later Kuo et al.[15] and Nguyen et al.[16] found that the level of AST was higher than that of ALT.

如何去找引發急性肝衰竭之原因

- Infection?
- Dengue virus ?

找到登革熱病毒感染的證據就可以判斷這是急性肝衰竭的原因

Dengue fever with liver problems in Taiwan 3 cases died of acute liver failure.(1992) Total cases: 270

- 在1987年11月至1988年12月的疫情期間，通過生化測試對125名男性和145名女性患者進行了登革熱對肝功能的影響。天冬氨酸轉氨酶（AST）、丙氨酸轉氨酶（ALT）、膽紅素、鹼性磷酸酶、γ-谷氨醯轉肽酶（G-GT）水平分別為93.3%、82.2%、7.2%、16.3%和83.0%。在大多數情況下，轉氨酶的升高為輕度至中度，但在 11.1% 和 7.4% 的患者中，**轉氨酶的升高分別是 AST 和 ALT 正常上限的 10 倍**。最初，AST 水平高於 ALT，在癥狀出現後 9 天增加到最高水準，然後在兩周內降至正常水準。生化檢查結果在有和沒有乙型肝炎或丙型肝炎病毒感染的病例之間沒有顯著差異，但在出血發作的患者中觀察到 AST、ALT 和 G-GT 的升高顯著升高。2例患者的肝活檢顯示小葉性肝炎的特徵。**在五例死亡病例中，三例死於肝衰竭**。結論是，登革熱可能引起與常規病毒性肝炎患者相似的肝損傷和轉氨酶升高。在流行或流行地區，在肝炎的鑒別診斷中應考慮登革熱感染。

Chung-Huang Kuo et al (CGMH, Kaoshiung) 肝臟生化檢查和登革熱 . Kuo CH, Tai DI, Chang-Chien CS, et al. Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992;47:265–270 (L1127)

Abnormal liver functions in Dengue fever (Taiwan, 1992)

Liver functions)	% abnormality
天冬氨酸轉氨酶（AST）	93.
丙氨酸轉氨酶（ALT）	82,2
膽紅素	7.2
鹼性磷酸酶、	16.3
γ-谷氨醯轉肽酶（G-GT）	83.0

Remarks : 10-fold greater than the normal upper limit for AST and ALT in 11.1% and 7.4%

Acute liver failure---3 cases
Mortality--------5/270 ☹1.1%)

Chung-Huang Kuo et al (CGMH, Kaoshiung) Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992;47:265–270 (L1127)

Table 2. Characteristics of the analyzed dengue patients based on their critical outcomes.

Parameters	Critical Outcomes (n = 47)	Non-Critical Outcomes (n = 654)	OR (95% CI)	p Value
Group B *	45 (95.7)	500 (76.5)	76.92 (18.45–322.58)	<0.0001 [a]
Male	23 (48.9)	340 (52)	0.89 (0.49–1.60)	0.6859 [a]
Temperature ≥ 38.5 °C	10 (21.3)	329 (50.3)	0.27 (0.55–0.13)	0.0001 [a]
Tachypnea ≥ 20/min	35 (74.5)	408 (62.4)	1.76 (0.90–3.45)	0.0971 [a]
Tachycardia ≥ 120/min	6 (12.8)	85 (13)	0.98 (0.40–2.38)	0.9637 [a]
DBP < 60 mmHg	8 (17)	23 (3.5)	5.63 (2.36–13.39)	0.0005 [b]
Platelet count < 100,000/μL	29 (61.7)	154 (23.6)	5.23 (2.83–9.68)	<0.0001 [a]
aPTT ≥ 50 s	17 (36.2)	24 (3.7)	14.88 (7.23–30.58)	<0.0001 [b]
ALT or AST ≥ 200 U/L	12 (25.5)	29 (4.4)	7.39 (3.5–15.7)	<0.0001 [b]

* Group B was characterized by any of the following: aged 65 years and older and any of the warning signs (nausea, vomiting, hematuria, epistaxis, tarry stool, vaginal bleeding, abdominal pain, weakness, and poor appetite) or dengue-related underlying diseases, including DM, CKD, ESRD, liver cirrhosis, COPD, CHF, and neoplasms. The reference group here is Group A; OR: odds ratio; [a] chi-square test; [b] Fisher's exact test.

Table 3. Indicators for predicting critical outcomes in dengue patients in backward stepwise regression.

Characteristic	Odds Ratio * (95% CI)	p	Coefficient †	Score
Group B	60.23 (14.11–257.05)	<0.0001	2.05	4
< 38.5 ◦C	2.68 (1.18–6.08)	0.0183	0.49	1
Lower DBP	3.14 (1.01–9.76)	0.0479	0.57	1
Prolonged aPTT	5.76 (2.30–14.42)	0.0002	0.88	2
Elevated liver enzyme	3.16 (1.10–9.07)	0.0327	0.57	1

Chia-Yu Chi [1,2] et al **Development and Utility of Practical Indicators of Critical Outcomes in Dengue Patients Presenting to Hospital: A Retrospective Cross-Sectional Study**

Conclusions by the authors

- Dengue fever has been a significant burden in countries with poor resources. Since most dengue cases are better with conservative treatment, few develop serious complications. **Although liver involvement is mild in many cases, there are ALF cases associated with high morbidity and mortality due to complications such as encephalopathy, severe bleeding, renal failure, and metabolic acidosis.** People infected more than one time with different serotypes increase the risk of severe complications and mortality. To accurately diagnose dengue and prevent misdiagnosis as viral hepatitis in dengue-endemic areas, clinicians must be aware of the need for early patient monitoring and measurement of suitable laboratory data. The afflicted patient's health, bleeding, and laboratory-determined markers such as complete blood count, serum transaminase levels, prothrombin time, and international normalized ratio should thus be constantly monitored while assuring adequate supportive care and treatment. Resource limited countries like many countries in South Asia are facing an increasing case of dengue fever with increasing serious complications.

Case 3,

- The patient was a woman in her 40 s in whom an abnormal thyroid function had been noted 2 years previously, before her referral to our hospital. She consulted a hospital complaining of fatigue and vomiting. At consultation, she also had consciousness disorder, tachycardia, thyromegaly, increased thyroid blood flow.
-

這樣的病史您想要如何釐清問題?

- 1.abnormal thyroid function:兩年前就有問題醫師怎麼說>? 臨床醫師怎麼說是甲狀腺機能亢進還是機能甲狀腺低落
- 2. About management of thyroid disease;醫師怎麼治療? 治療的後果怎麼樣有沒有改善.
- 3.Fatigue and vomiting 是多久以前的事情?醫師認為跟治療有沒有相關, 是藥物的副作用嗎?還是病情惡化引起
- 4. Conscious disorder: 是最近才有的嗎.
- 5. Gyn-Obs 病史有詳細詢問嘛? Menstruation規則? LMP是哪一天, 現在懷孕嗎

- and hyperthyroidism and was diagnosed with thyroid storm. She was referred to our hospital with administration of a β1-blocker and hydrocortisone.

ON arrival :

On arrival in the emergency department, a physical examination revealed the following: blood pressure, 110/80 mmHg; pulse, 220 beats per minute with atrial fibrillation; respiration, 60 breaths per minute; body temperature, 39.6 ˚C; and Glasgow Coma Scale (GCS), 9. Her blood pressure gradually declined, and she experienced cardiopulmonary arrest.

ECMO was initiated.

- After return of spontaneous circulation, an ultrasound cardiogram showed that the ejection fraction was 47%, the transtricuspid pressure gradient was 32 mmHg, and the diameter of the inferior vena cava during expiration and inspiration was 27 and 22 mm, respectively. Hemodynamics were not sustained, so venoarterial extracorporeal membrane oxygenation (ECMO) was initiated.

Laboratory-1

Hemogram : white cell count, 6400/μL; hemoglobin, 10.7 g/ dL; platelet count, 79,000/μL;

- total bilirubin, 8.4 mg/dL; direct bilirubin, 6.4 mg/dL; **aspartate aminotransferase, 145 U/L; alanine aminotransferase, 45 U/L;** alkaline phosphatase, 596 U/L; albumin, 2.9 mg/dL; prothrombin time (PT) (%), 30%;
- free triiodothyronine, 30.1 pg/ mL; free thyroxine>7.77 ng/dL; thyroid-stimulating hormone, < 0.0.005 μIU/mL; and anti-thyroid-stimulating hormone receptor antibodies, 29.8 IU/mL. Antithyroglobulin and antithyroid peroxidase antibodies were absent.
- The creatine kinase levels were not elevated.
- An arterial blood gas analysis on arrival revealed the following: pH, 7.275; pO2, 317 mmHg (fraction of inspiratory oxygen of 1.0); pCO2, 29.5 mmHg; HCO3−, 13.3 mmol/L; base excess, − 12.1 mmol/L; and lactate, 7.4 mmol/L.

Laboratory-2

- Serological tests for hepatitis A/B/C, antinuclear antibodies, anti-mitochondrial antibodies, anti-gliadin antibodies, and HIV were negative.

如何敘述她的問題如何做診斷

Diagnosis

- The diagnosis was **thyroid storm** due to Graves' disease and multi-organ dysfunction,
- acute liver failure,
- acute heart failure,
- acute respiratory failure,
- acute renal failure,
- disseminated intravascular coagulation, and disturbance of consciousness.

She was admitted to the intensive-care unit (ICU)

甲狀腺風暴是什麼意思?

甲狀腺風暴

- 「甲狀腺風暴」是一個罕見但致命的狀況。幸好，這並不是一個常見的狀況，通常出現在甲狀腺機能亢進但沒有接受治療的患者身上。
- 當患者進入甲狀腺風暴時，症狀與甲狀腺機能亢進非常類似，只是**發生過程更為地突然與嚴重**，患者會抱怨很熱並不停發汗，體溫升高至超過攝氏38.5度，覺得心臟跳動非常快速，量起來超過每分鐘140下，整個人坐立不安、無法專心、意識混亂，
- 到院時，甲狀腺風暴的患者有幾個特色，包括心跳速度很快，血壓量起來收縮壓很高，但舒張壓很低，體溫甚至到超過41度，身體檢查可能會看到脖子前的甲狀腺腫大，或詢問病史時發現患者過去曾患有甲狀腺機能亢進。
- 不典型的症狀則以橫紋肌溶解、肝衰竭、休克、癲癇、急性腹痛或多重器官衰竭做為臨床表現，

甲狀腺風暴的患者死亡率甚高必須妥善處裡.

Course and treatment-1

- The patient received an anti-thyroid drug and underwent therapeutic plasma exchange (TPE) under veno-arterial ECMO. The ECMO duration was 5 days. Although her thyroid function improved, **her serum total bilirubin level continued to increase to 38 mg/dl until 8 days after her admission**. At this timing, the liver transplant team intervened. Plasma exchange, which was performed twice, improved her bilirubin level, but after TPE it increased continuously to 30 mg/dl again.
- The patient underwent total thyroidectomy to manage her thyroid function. The operative time was 3 h 25 min. Blood loss was 1290 mL due to inflammation and coagulopathy. Intraoperative transfusion required 4 units of red blood cells, 8 units of fresh frozen plasma, and 10 units of platelets

Course and treatment-2
consider liver transplanation

- On postoperative day 3, cervical swelling appeared and hemostasis was needed. Thyroidectomy reduced her thyroid hormone levels, but her bilirubin level increased to 30 mg/dl and her PT was
- <40 %. While the patient was under intensive care for multi-organ failure caused by thyroid storm, and her circulation and respiration were gradually improving, liver failure was observed to be progressing. Although liver failure was considered a possible prognostic factor, liver transplantation was not considered feasible in the presence of multiple organ failure and DIC, even though the patient was improving. As a life-saving measure, it was considered important to perform liver transplantation without missing the timing when the conditions of multiple organ failure and DIC improved. Although brain-dead-donor liver transplantation was considered, it was difficult to register the patient when multiple organ dysfunction was present as well. We, therefore, planned to perform **LDLT** as soon as the patient's condition improved while conducting an evaluation of **her husband**, who was willing to become a donor, simultaneously with intensive care.

Course and treatment-3, improved much but ALF persisted

- Her respiration and circulation gradually stabilized under mechanical ventilation, sedation, and a low vasopressor dose. The symptoms were disturbance of consciousness, renal failure, and liver failure. Her consciousness level gradually improved to GCS 10 after tracheostomy. Tere were no fndings of post-resuscitation encephalopathy on magnetic resonance imaging or electroencephalography. Based on these objective fndings, the neurologists concluded that the patient's consciousness was reversible. Her renal failure was controlled stably under continuous hemodiafltration, and it was possible to switch to intermittent hemodialysis with the expectation of discontinuing dialysis. However, **the patient's liver failure deteriorated. Her Child–Pugh score was 11 with a classifcation of C, and her model for end-stage liver disease score was 38**.

Course and treatment-4, LDLT was done.

- We decided to perform LDLT as a life-saving treatment.
- The patient underwent LDLT with a partial liver graft from her husband, whose blood type was A (identical to her blood type) on day 31 of admission. Based on preoperative volumetry, a right lobe graft was transplanted. The weight of the graft was **766 g**. The graft weight/ recipient standard liver volume ratio was 60.6%. The cold ischemic time was 56 min, and the warm ischemic time was 4 min, with 43 min for anastomosis.

Right hemicolectomy was performed because of severe ischemia, after reconstruction of the hepatic artery. Considering the influence of further invasiveness on her general condition, we finished the operation without biliary reconstruction under open abdominal management.
Te total operative time was 767 min, and blood loss during the whole operation was 3875 g.

Course and treatment-5
Biliary reconstruction

- Bile duct reconstruction was performed on post-operative day (POD) 2 as a secondary procedure. Te extracted liver weighed 800 g and exhibited a difuse brown–green color change. A histological examination revealed acute chronic changes. Bile thrombi were found in the centrilobular bile canaliculi, and hepatocytes and Kupfer cells showed pigmentation with a high degree of hepatocyte necrosis and neutrophil infltration, indicating significant acute changes. In addition, there were chronic findings, such as enlargement of the bile canaliculi, fibrosis in the portal and periportal regions, enlargement of hepatocytes mainly in the peripheral region, and Mallory–Denk body formation, suggesting that the liver with thyroid hormone-induced chronic hepatitis and chronic bile congestion had changed acutely due to thyroid crisis. No evidence of liver cirrhosis was found.

Course and treatment-6,
complicated by acute cellular rejection

- The patient's condition was complicated by acute cellular rejection, intra-abdominal hemorrhaging, and colonic hemorrhaging. A sharp increase in liver enzymes was observed on POD 9, so a liver biopsy was performed with suspicion of rejection. A histological examination revealed a diagnosis of acute cellular rejection, and the patient was treated with steroid pulse therapy and a continuous infusion of the **tacrolimus**, resulting in improvement. The trough value of tacrolimus was controlled at around 15 ng/ml. At the time of the liver biopsy, the intercostal artery was injured, which was complicated by intra-abdominal bleeding on POD 15; therefore, **emergency laparotomy for hemostasis** was performed. Gastrointestinal hemorrhaging was observed on POD 23, and **ischemic colitis** was diagnosed via endoscopy.

Course and treatment-7, general condition gradually improved.

- After conservative treatment, the ischemic colitis improved, but bleeding occurred again on POD 53, and transcatheter arterial embolization of the inferior mesenteric artery was performed to achieve hemostasis. After these complications, the patient's liver function and general condition gradually improved.
- Two years after LDLT, other than the need for intermittent hemodialysis, the patient is in good condition with a normal liver function and lives her daily life. In addition, the donor's postoperative course was uneventful.

終於成功救回了她的命

醫療團隊非常認真而且執著努力不懈,用盡各種方法來處理問題解救病人的生命
---重點就是生命是無價的,應該盡可能努力做到醫治的目的.
好幾段時刻都是關鍵,如果放棄醫療命就沒了.

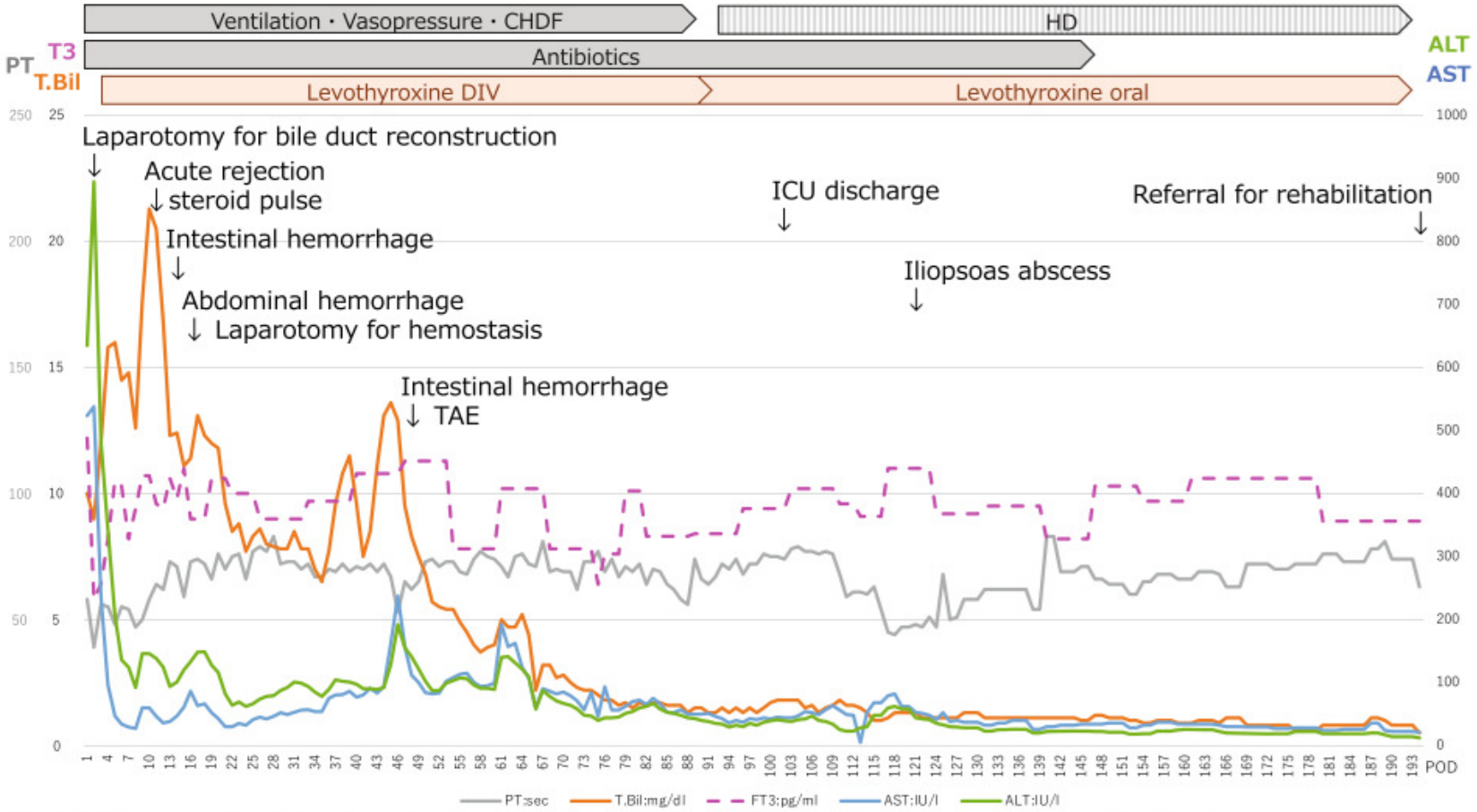


Fig. 2 Clinical course from living donor liver transplantation to discharge. CHDF: continuous hemodiafiltration; ICU: intensive care unit,

有好多因素導致急性肝衰竭.

- 有好多因素導致急性肝衰竭.
- 甲狀腺危象引起的肝損傷機制既有直接影響，也有間接影響。全身耗氧量增加導致的相對缺氧、
- 甲狀腺激素抑制肝臟內乳酸代謝、心力衰竭導致肝臟充血、
- 低血壓導致肝血流量減少等都會導致缺氧和肝臟缺血。
- 其他因素包括抗甲狀腺藥物引起的肝毒性、自身免疫性肝炎的誘發以及基礎肝臟疾病的加重。 抗甲狀腺藥物誘導的肝毒性發生率不到0.5%[12]，(more common with propylthiouracil than with methimazole.
- Methimazole-induced hepatotoxicity is typically cholestatic, while propylthiouracil-induced hepatotoxicity is typically hepatocellular. Methimazole 肝毒性通常是膽汁淤積性的，而propylthiouracil-induced hepatotoxicity is typically hepatocellular. 肝毒性通常是肝細胞性的。

Bilirubin value is reported to be an important indicator of liver necrosis and a prognostic factor.

- When the total bilirubin level is > 3.0 mg/dl, the mortality rate of thyroid storm associated with hyperbilirubinemia is reported to be 32.3%, and the bilirubin value is reported to be an important indicator of liver necrosis and a prognostic factor.

To date, only two cases of liver transplantation for liver failure following thyroid storm have been reported [9, 10]. Both were associated with hyperthyroidism in young women who underwent deceased donor liver transplantation with a high bilirubin level immediately before transplantation. In both cases, total thyroidectomy was performed prior to transplantation.

1.Hambleton C, Buell J, Saggi B, et al Thyroid storm complicated by fulminant hepatic failure: case report and literature review. *Ann Otol Rhinol Laryngol.* 2013;122(11):679–682. (22歳女性)

2. de Campos Mazo DF, de Vasconcelos GB, et al Clinical spectrum and therapeutic approach to hepatocellular injury in patients with hyperthyroidism. *Clin Exp Gastroenterol.* 2013;6:9–17. (19歳女性)

Case 4,

- A 27-year old male, obese, with a history of being men who have sex with men (MSM), who presented jaundice, choluria and abdominal pain with progressive loss of consciousness, and was later hospitalized. **He was diagnosed with ALF** with hemodynamic instability and grade III hepatic encephalopathy, requiring ventilatory support. T

如何判断引起急性肝衰竭的原因?

- The initial etiological study was negative for HBsAg, Anti-Hepatitis C virus and HIV. The serological laboratory showed: antiHBc-IgM (+), HBeAg (−), AntiHBe (+), AntiHBs (+) and low HBV viral load (Table 1a);

Table 1
Evolution of HBV serological markers before the Liver Transplant (LT) and first six months after LT, for both patients.

		Pre LT	1st week Post LT	2nd week Post LT	8th week Post LT	24thweek Post LT
Case 1(a)	HBsAg	–	UR	UR	UR	–
	Anti-HBs	+	+	+	UR	UR
	HBeAg	–	UR	UR	UR	UR
	Anti-HBe	+	UR	UR	UR	UR
	Anti-HBc IgM	+	UR	UR	UR	UR
	Viral load	1267 IU/ml	23 IU/ml	ND	UR	ND
	Anti-HBs titers	UR	31 mIU/ml	51 mIU/ml	4 mIU/ml	4 mIU/ml
		Pre LT	1st week Post LT	2nd week Post LT	8th week Post LT	24thweek Post LT

HBV 是肝衰竭的原因嗎?

- MSM→HBV infection
- **HBV** 是肝衰竭的原因
- Entecavir 1 mg/day was initiated, within the first 18 h of hospitalization and, the patient was transferred to a transplant center.
- In the following days, he had severe encephalopathy without cerebral edema nor focal lesions in the brain CT scan, but with a transcranial doppler ultrasonography measures suggesting of intracranial hypertension.

Hepatic encephalopathy 以後要怎麼辦?

The intracranial pressure (ICP) monitor, confirmed a 30 mmHg pressure with good response to the initial medical treatment.

Major treatment:
Liver trasnplantation

- The LT was performed 72 h after the introduction of antiviral treatment. Immunosuppression induction therapy was with basiliximab, methylprednisolone and later treatment with tacrolimus, mycophenolate, and prednisone. **Biopsy of explanted liver showed acute lobular hepatitis, with extensive necrosis of the parenchyma and 70% of macro and microvesicular steatosis.** Fourteen days after transplantation, the patient had an **acute hepatic cellular rejection** with a satisfactory response to standard therapy.
- At the time of discharge,the patient maintained treatment with entecavir indefinitely

Follow up.

- Six months after transplantation, the patient presented HBsAg (−), HBV viral load (−), Anti-HBs titers below 10 IU/L and normal liver function (Fig. 1 and Fig. 2)

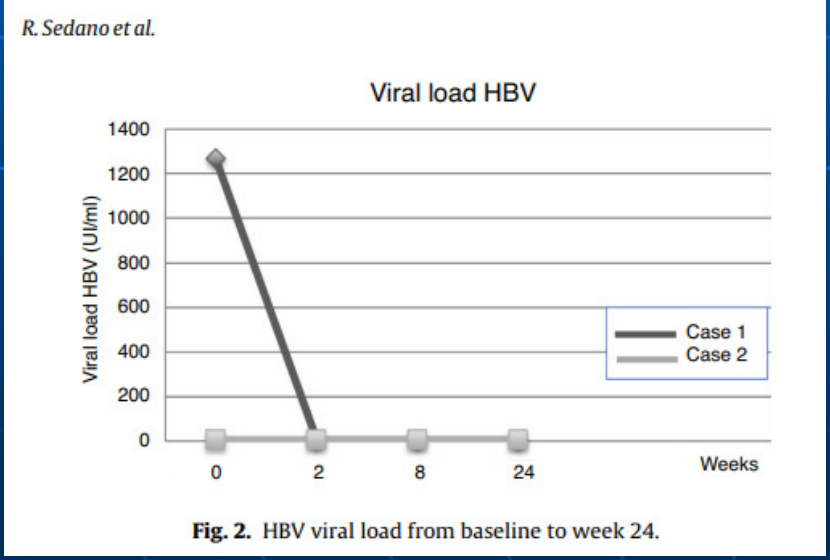


Fig. 2. HBV viral load from baseline to week 24.

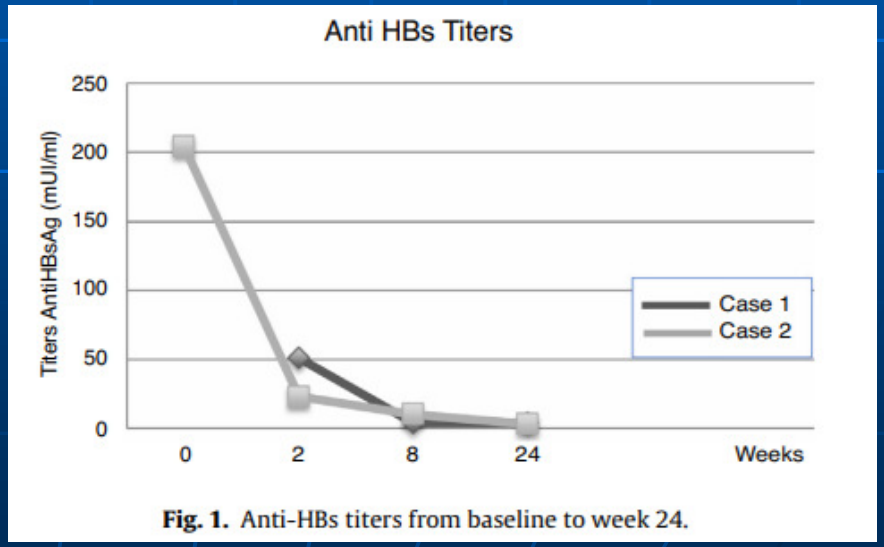


Fig. 1. Anti-HBs titers from baseline to week 24.

Diagnostic evidence of HBV related ALF

- The diagnosis of HBV-related ALF is characterized by
- 1. acute hepatitis, (from LFT)
- 2. associated with altered mental status
- 3. prolonged pro thrombin time, with INR > 1.5.
- 4. Typical serology findings are HBsAg (−), Anti-HBs (+),
- **Anti-HBc IgM (+),** HBeAg (−), Anti-HBe (+) and DNA
- HBV (−), as a consequence of the aggressive immune
- response against HBV

ALF in patients with HBV infection

- 1. Less than 4% of the acute hepatitis cases
- evolve with ALF [11].
- 2. Reactivation can occur in chronic HBV carriers
- with or without a positive HBsAg (being Anti-
- HBc positive)

Dx of reactivation of HBV

- Diagnosis criteria are:
- 1. detectable DNA viral load, whereas
- previously was undetectable,
- 2. a rise in DNA viral load compared to
- historic values
- 3. seroconversion from HBsAg negative/anti-HBc positive to HBsAg positive

Clinical presentation of ALF due to reactivation of HBV

- The clinical presentation depends on patient's
- comorbidities,
- use of immunosuppressive drugs,
- serological and immunological status, and
- Viral factors such as genotype, and presence of mutations.
- Reactivation of chronic hepatitis B infection needs treatment to reduce the risk of hepatic decompensation and eventually development to ALF which in these cases have higher mortality than de novo acute infections
- If acute on chronic liver failure (ACLF) develops, the prognosis is poor, with a 3 month-mortality without LT of 50–55%, going as high as 90%, in cases of MELD score >30

- Sedano et al. Annals of Hepatology 21 (2021) 100107 Viral load HBV 1400 1200 Viral load HBV (UI/ml) 1000 800 600 400 200 0 0 2 8 24 Weeks Case 1 Case 2 Fig. 2. HBV viral load from baseline to week 24. thrombin time, with INR > 1.5. Typical serology findings are HBsAg (−), Anti-HBs (+), Anti-HBc IgM (+), HBeAg (−), Anti-HBe (+) and DNA HBV (−), as a consequence ofthe

KCC for enlisting the patients of ALF for IT

- It is essential to enlist the patient for LT once the King's College's criteria (KCC) are fulfilled [2,22].

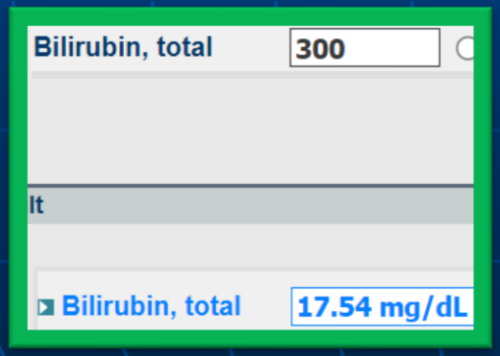
@Wai CT, FontanaRJ, Polson J, HussainM, ShakilAO, Han SH, et al., US Liver Failure Study Group. Clinical outcome and virological characteristics of hepatitis B related acute liver failure in the United States. J Viral Hepat 2005;12(2):192–8,

.

@Tillmann H, Patel K. Therapy of acute and fulminant Hepatitis B. Intervirology 2014;57:181–8, http://dx.doi.org/10.1159/000360939.

KCC

- **King's College Criteria:**
- INR >6.5 or 3 of the following 4 criteria:
- (1) patient age 40 years or more.
- (2) serum bilirubin >300 µmol/l,
- (3) time from onset of jaundice to the development
- of coma of >7 days,
- (4) INR >3.5



AASLD

TABLE 6

King's College Criteria

Acetaminophen	Non-acetaminophen
• Lactate >3.5	• INR > 6.5 with HE
or	or
• pH < 7.3 or lactate >3	• Any 3 of 5 with HE
or	– Age <10 or >40 yrs
• Grade III or IV HE and	– Bili > 300
– INR > 6.5	– Coag: INR > 3.5
– Creatinine > 300	– Duration jaundice to HE > 7 days
	– Etiology: Non A-E, other drug

King's College Criteria remain the most clinically useful with sensitivity of 68-69% and specificity of 82-92%

Lee WM, et al. AASLD Practice Guidelines. Hepatology 2011

Liver transplantation

- Transplantation has to take place before irreversible complications such as development of brain stem herniation, and further intervention would be futile. To prevent unnecessary delay, every patient with fulminant hepatitis should be referred to a specialized center for evaluation for liver transplantation.
- Transplantation is indicated in patients with an estimated mortality above 80%.
- Contraindications are **irreversible brain damage, uncontrolled sepsis, AIDS (as uncontrolled HIV infection opposed to controlled HIV infection), advanced comorbidities, or a malignant disease.** Patients with fulminant hepatitis have a higher priority for liver transplantation than those with chronic liver disease, resulting in short waiting periods of just a few days.

- 肝臟移植用於治療肝衰竭已有三十多年歷史，其成功率一年存活約百分之八十五、五年存活約百分之六十五。因全世界均有肝臟來源缺乏的問題，使得許多急待肝臟移植之成人及兒童因為等不到適合的肝臟而死亡。活體部分肝臟捐贈是解決肝臟來源缺乏的方法之一，可以增加救治肝衰竭病人的機會。(NTUH)

台大醫院
https://www.ntuh.gov.tw › ntuhtx

Accessed on 2024.01.07

Table 2 - Pre and post-LT survival time and hospitalization length for 25 patients.

Pre-LT hospitalization days, mean±SD	22 (±2.9)
Post-LT hospitalization days, median [$IQR_{p\ 25-75}$]	33 [$IQR_{p\ 25-75}$=21–45.5]
Post-LT survival 90 days	80%
Post-LT survival 01 year	76%
Post-LT survival 03 years	59.5%
Post-LT survival 05 years	54.1%
Post-LT survival 05 years	54.1%

LT: liver transplantation; SD: standard deviation; IQR: interquartile

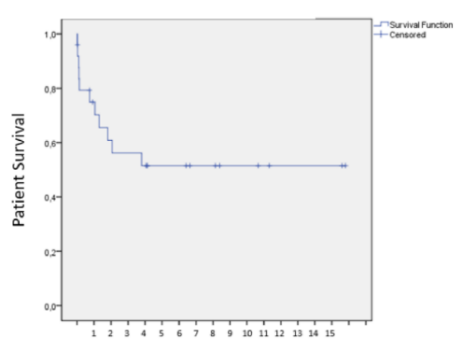


Figure 1 - Survival for 25 post-liver transplant patients in Acute-on-Chronic Liver Failure.

Post-LT survival:
One year survival rate : 76 %.

(L1141, L1142)

Jane Cronst [1] et al :
PROGNOSTIC FACTORS OF LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE. Arq Bras Cir Dig. 2023 Dec 8:36:e1779.

- LT promotes long-term survival for most ACLF transplanted patients, similar to what occurs to other patients for other indications. None of the analyzed variables in this study was shown to be a prognostic factor associated with post-LT survival in patients with ACLF. Aditional studies evaluating prognostic factors of larger cohorts are warranted to understand the factors related to the prognosis of ACLF patients undergoing LT for ACLF.

Jane Cronst [1] et al :
PROGNOSTIC FACTORS OF LIVER TRANSPLANTATION FOR ACUTE-ON-CHRONIC LIVER FAILURE. Arq Bras Cir Dig. 2023 Dec 8:36:e1779. (L1141,L1142)

Outcome for LT after ALF

- Patients listed for LT for ALF in the *ALFSG Registry between January 1998 and October 2018*
- _____
- 1.在 624 例列為 LT 的 ALF 患者中，398 例（64%）接受LT，
- 2, 100 例（16%）在沒有 LT 的情況下死亡，126 例 (20%）自發康復
- 3.在長期接受者中，病因包括
- 血清陰性/不確定（22%）、藥物性肝損傷（18%）、對乙醯氨基酚
- 過量（APAP;16%）和病毒性肝炎（15%）。
- 4. LT 后 1 年和 3 年患者生存率分別為91以及90%

_____

Constantine J Karvellas[1], et al
Outcomes of patients with acute liver failure listed for liver transplantation: A multicenter prospective cohort analysis Liver Transpl. 2023 Mar 1;29(3):318-330. Epub 2022 Sep 14.)L1143, 1144)

結論(2024.01.19)

1.急性肝衰竭是臨床的急症必須及早發現方能做適當的處理
2.急性肝衰竭自原因相當複雜必須判定,並排除後才能施行有效之治療
3.急性肝衰竭常伴隨合併症或其他器官衰竭也必須同時解決才能有較好之結果.
4.急性肝衰竭時最好成立多專長的治療團隊(MDT)
5. 肝移植是治療肝衰竭的最終手段.目前成功率相當高