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Clinical analysis of 156 cases of multiple organ failure caused by fish bile



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ABSTRACT

Objective: To analyze the clinical features and prognosis of patients suffering from fish bile poisoning. *Methods*: A total of 156 multiple organ failure (MOF) patients caused by fish bile poisoning were hospitalized in our department over the past 28 years. The patients' symptoms, examination results, treatment and outcomes were collected and analyzed.

Results: All patients' first symptom was gastrointestinal discomfort, including unbearable nausea and intractable vomiting. The symptoms that followed were oliguria or anuria, edema, headache, fatigue, jaundice, palpitation, alimentary tract hemorrhage, gross hematuria, dyspnea, shock, tachycardia, bradycardia, arrhythmia, coma, and cardiac arrest. The symptom severity and cohort were different among different patients. Twenty-one cases received gastroscopy, which exhibited diffuse gastric mucosal bleeding. Twelve patients received renal biopsy, which exhibited focal necrosis of tubular epithelial cells. One patient received a liver biopsy, which exhibited extensive hepatocyte necrosis. All patients received blood purification therapy. Of the four patients who died, 4 out of 5 organs had failed. The general mortality rate was 2.6%.

Conclusions: Compared with the MOF caused by trauma and sepsis, the fish bile poisoning MOF has a much lower morality rate. However, patients with higher age, more underlying diseases, and more organ failure tended to have a worse prognosis.

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1. Introduction

Multiple organ failure (MOF) is a critical condition with a greater than 50% mortality rate [1,2]. Raw fish gallbladder with bile has long been used as a folk remedy in Asia, especially in China, to treat such symptoms as decreased visual acuity, asthma, and pain. Fish bile poisoning has been reported in many Asian countries; however, none of these reports contained more than 50 cases [3–8]. At present, as increasing numbers of Chinese settle all over the world, fish bile poisoning is beginning to occur in many different countries. Therefore, understanding the clinical features, diagnosis and therapy of fish bile poisoning is not only the Chinese or Asian doctor's duty but also the responsibility of doctors worldwide. We report a retrospective analysis of 156 MOF patients who suffered from fish

bile poisoning and were hospitalized in Xinqiao Hospital from 1st January 1985 to 31th December 2013.

2. Clinical data and methods

2.1. Patient data

The patient gender distribution: male 89 cases (57% of all patients), female 67 cases (43% of all patients). The patient age distribution: the youngest was 7 years old, while the oldest was 85 years old. The age range was 7–20 years old in 10 cases, 21–60 years old in 127 cases and 61–85 years old in 19 cases with a mean age of 44.8 ± 18.3 years. The patient occupation distribution was peasants (from the countryside), 120 cases, students (from the countryside), 21 cases, and workers (from a town), 15 cases.

2.2. Patient hospital admission after the ingestion of gallbladders

The shortest time was 10 h, while the longest was 12 days. The range was as follows: <1 day for 9 cases, 1–2 days for 41 cases, 2.1–4

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days for 81 cases and 4.1–12 days for 25 cases. The patients who came to our department with more than 2 days after the ingestion of gallbladders were all transferred from other hospitals or clinics.

2.3. Fish gallbladder

All gallbladders ingested by patients were from fresh-water fish including silver carp (89 cases), grass carp (41 cases), cyprinoid carp (16 cases), and black carp (10 cases). These fishes weighed between 0.5 kg and 20 kg. The amount of gallbladders which the patients ingested ranged was from 1 (large fish) to 4 (small fish). All patients swallowed the fresh gallbladders with the bile when the fish was butchered.

2.4. Examination

A detailed inquiry and physical examination were performed by doctors every day. The general auxiliary examination, such as X-ray sternite, abdominal ultrasonic check, and electrocardiogram (ECG), was performed upon patient admission, and these were rechecked when necessary. A number of patients received a special auxiliary examination, such as an echocardiology (56 cases), gastroscopy (21 cases), renal biopsy (12 cases), or liver biopsy (1 case). Patient blood, urine, and stool samples were collected every morning for routine testing and the blood gas, electrolytes, coagulation, glucose, renal and liver function, and myocardial enzyme activities were monitored until the relative item became normal for at least 2 days. After the year 2000, the serum cardiac troponin T (CTnT) was also measured. All patients' serum markers for hepatitis B and C, acquired immunodeficiency syndrome (AIDS), and syphilis were also measured at admission. All of these assays were performed in the central clinical laboratory of Xinqiao hospital.

2.5. Diagnosis

Fish bile poisoning was diagnosed when the patient had the following two characteristics: (a) a history of swallowing fresh fish gallbladders with the bile. (b) The gastrointestinal symptom followed by other systemic symptoms after swallowing fish bile [9]. Acute renal failure (ARF, before 2005 year) or acute kidney injury (AKI, post 2005 year) were diagnosed when the patient had the following two characteristics: (a) oliguria or anuria with positive urine analysis. (b) Neodevelopment of azotemia (serum creatinine increased over 50%) [4,7,8,10]. The MOF was diagnosed when the patient had two or more dysfunctional organs [1,2,6].

2.6. Treatment

All patients received replacement therapy, including hemodialysis (HD), peritoneal dialysis (PD), or continuous renal replacement therapy (CRRT, post 2000 year). The patients whose circulation and respiration were stable received routine HD with 200-250 ml/min blood flow. The cellulose and hemophan membrane dialyzers were used for HD before the year 2000. The high-flux HD (HFHD) was performed using polysulfone membrane dialyzers after the year 2000. Unconscious patients and patients with unstable circulation and respiration conditions received peritoneal dialysis or CRRT (venous-venous hemofiltration, displacement liquid volume 2-3 L/h, post dilution). The patients with a hemorrhagic tendency received peritoneal dialysis. The exchange volume of the peritoneal dialysate was 8000-10000 ml/day. Furthermore, all patients received symptomatic and supporting therapy. A number of patients with severely elevated hepatic and myocardial enzyme activities or severe jaundice were given steroids (dexamethasone 10-20 mg/day for 1 week).

2.7. Statistics

The metrological data were expressed as the mean \pm SEM. The unpaired t test was performed with SPSS software, version 18.0 (IBM, Endicott, NY, USA). Values of P < 0.05 were considered statistically significant.

3. Results

3.1. History of chronic disease before ingestion of fish gallbladders

Thirteen patients were confirmed to be hepatitis B virus carriers by positive serum hepatitis B surface antigen (HBsAg). Twelve patients had a history of hypertension, seven had diabetes (type 2), and three had a chronic cough history. No evidence of coronary artery disease and chronic kidney disease (CKD) was discovered. The chronic disease distributed chiefly in patients over 60 years old (Table 1).

3.2. The symptoms

The time of the first symptom occurred after the ingestion of fish gallbladders: the earliest occurred in 0.5 h, while the latest occurred in 10 h. The range for symptom onset was <1 h for 36 cases, 1–2 h for 97 cases, 2.1–4 h for 15 cases and 4.1–10 h for 8 cases. All of the patients' first symptom was gastrointestinal discomfort, including unbearable nausea and intractable vomiting (at the beginning, the vomit contained the contents of the stomach and later only included watery dark green mucus), and a number of patients had abdominal pain and diarrhea (slight watery stool). The following symptoms included oliguria or anuria, edema, headache, fatigue, jaundice, palpitation, alimentary tract hemorrhage (tarry stool), gross hematuria, dyspnea, shock (hypotension), tachycardia, bradycardia, arrhythmia, coma, and cardiac arrest. The symptom severity and cohort were different in different patients (Table 2).

3.3. Examination results

All patients showed elevated serum creatinine (SCr), urea nitrogen (BUN), alanine transaminase (ALT), aspartic transaminase (AST), total bilirubin (TBil), and proteinuria (Table 3). A number of patients showed elevated serum potassium (K+), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), activated partial thromboplastin time (APTT), and CTnT. Some patients showed depressed serum bicarbonate anion (HCO₃⁻), hemoglobin (HGB), and platelets (PLT). Some patients had microscopic hematuria and fecal occult blood (Table 3). One hundred fifteen cases (74%) showed enlarged liver, and 107 cases (69%) showed enlarged kidneys under B-type abdominal ultrasonic check. Seventy four cases (47%) showed an abnormal ECG (Table 4). In 56 cases with echocardiolog, 31 cases (55.4%) showed enlarged left ventricle diastolic volume and/or depressed left ventricle ejection fraction. Of the 53 patients who had alimentary tract hemorrhage (tarry stool), 21 received a gastroscopy, and all of them showed diffuse gastric mucosal bleeding to some degree (Fig. 1). All 12 patients who received a renal biopsy had obvious hydropic or vacuolar degeneration and focal necrosis of the tubules, especially the proximal tubule epithelial cells (Fig. 2). One patient who had extremely elevated ALT, AST, and jaundice (who died later), as well as negative HBsAg received a liver biopsy and exhibited extensive hepatocyte necrosis, interstitial edema and destruction of the hepatic lobule (Fig. 3).

Table 1The chronic disease distribution among differentially aged patients.

Chronic disease	7–20 years Case (%)	21-60 years Case (%)	61–85 years Case (%)	Total Case (%)	Treatment and Control (%)
Case in age group	10	127	19	156	
Positive HBsAg	0(0)	11(8.7)	2(10.5)	13(8.3)	0(0)
Hypertension	0(0)	6(4.7)	6(31.6)	12(7.7)	5(41.7)
Diabetes (type 2)	0(0)	2(1.6)	5(26.3)	7(4.5)	5(71.4)
Chronic cough	0(0)	0(0)	3(15.8)	3(1.9)	0(0)

Table 2The symptoms and signs of patients after ingestion of fish gallbladders.

Symptoms and signs	Positive cases	Positive rate (%)	The earliest occurring time (days)	The longest persisting time (days)	Mean persisting time (days)
Nausea and vomiting	156	100	0.02	13	5.2 ± 1.4
Oliguria or anuria	156	100	0.5	49	11.3 ± 2.2
Jaundice	156	100	2	17	10.6 ± 2.5
Diarrhea	132	85	0.08	5	2.8 ± 1.1
Abdominal pain	119	76	0.04	4	2.3 ± 0.5
Fatigue	117	75	2	7	4.6 ± 1.0
Edema	96	62	2	5	4.1 ± 0.8
Hepatomegaly & knock pain	91	58	2	8	4.1 ± 1.3
Kidney knock pain	86	55	2	8	3.9 ± 1.4
Headache	81	52	2	5	2.5 ± 0.6
Tarry stool	53	34	3	7	3.5 ± 1.7
Palpitation	51	33	2	5	3.1 ± 1.0
Tachycardia (over 100 bpm)	28	18	1	3	1.3 ± 0.9
Arrhythmia	23	15	3	3	1.5 ± 1.1
Bradycardia (under 60 bpm)	19	12	3	2	1.2 ± 0.7
Dyspnea (mechanical ventilation)	17	11	6	1	0.5 ± 0.3
Acute heart failure	15	10	6	0.5	0.2 ± 0.1
Shock (Hypotension)	13	8	1	0.5	0.2 ± 0.1
Gross hematuria	11	7	1	9	4.2 ± 1.1
Coma	10	6	3	4	1.5 ± 1.8
Cardiac arrest	10	6	3		

Note: bpm means beats per minute.

Table 3The chemical examination data of patients after ingestion of fish gallbladders.

Examination item	Positive cases/checked cases	Positive rate (%)	Mean of peak value	Normal value	Mean recovered time of cured cases (day)
SCr(µmol/L)	156/156	100	563.4 ± 167.6	<115	18.5 ± 4.7
BUN(mmol/L)	156/156	100	26.7 ± 7.3	<6.3	18.9 ± 4.5
ALT(IU/L)	156/156	100	959.2 ± 270.6	<40	14.1 ± 3.3
AST(IU/L)	156/156	100	615.4 ± 203.5	<40	12.4 ± 3.0
TBil(μmol/L)	156/156	100	76.7 ± 10.5	<20	10.6 ± 2.5
Proteinuria(g/L)	156/156	100	1.3 ± 0.4	<0.1	23.7 ± 5.2
CTnT(µg/L)	35/35	100	15.5 ± 4.6	<0.15	10.0 ± 2.4
HCO ₃ -(mmol/L)	136/156	87	18.1 ± 2.4	22-28	5.2 ± 1.7
Microscopic hematuria	121/156	78	2.3 ± 0.3	0	20.3 ± 5.1
Fecal occult blood	119/156	76	3.1 ± 0.7	0	5.6 ± 1.4
LDH(IU/L)	109/156	70	905.5 ± 217.4	<60	8.4 ± 1.9
CPK((IU/L)	109/156	70	1895.7 ± 378.6	<200	9.0 ± 2.5
HGB(g/L)	42/156	27	98.2 ± 12.3	120-160	14.3 ± 3.9
K+(mmol/L)	30/156	19	6.7 ± 0.5	3.5-5.5	3.1 ± 0.7
APTT(ratio)	24/156	15	1.9 ± 0.4	0.8-1.2	4.5 ± 1.1
$PLT(\times 10^9/L)$	20/156	13	56.4 ± 10.7	100-300	7.2 ± 2.4

Note: For microscopic hematuria and fecal occult blood test, "-" = 0, "+" = 1, "+" = 2, "+++" = 3, "++++" = 4.

3.4. Clinical outcome

All 156 patients had ARF and hepatic failure. Thirty three patients had circulatory failure (15 patients had acute heart failure in which 3 patients had cardiac arrest, 13 patients had shock, of which 2 patients had cardiac arrest and 5 patients had cardiac arrest without any precursor). Seventeen patients had respiratory failure and needed mechanical ventilation. Ten patients had a coma. Of all patients, 152 were cured and discharged from the hospital with a mean hospitalization time of 20.3 ± 5.2 days. The general recovery rate was 97.4%. Four patients died. The general mortality rate was 2.6%. All patients that died had 4 of 5 organs failing and 2 patients

were over 60 years old. The outcome of patients with a different degree of MOF was shown in Table 5.

3.5. Replacement therapy style and outcome

The patients who received PD or CRRT were significantly older and in considerably more serious condition than those receiving HD. All serious patients with 3 or more failing organs were in the PD and CRRT groups. The PD group and the CRRT group both had 2 death cases. The chief clinical symptoms and chemical examination items of recovery time and hospitalization time of the PD and CRRT groups were much longer than that of the HD groups. There was no

Table 4 Analysis of abnormal ECG of patients after ingestion of fish gallbladders (n = 74).

Abnormal ECG type	Positive cases	Positive rate (%)	Recovered cases	Recovered rate (%)
Atrial premature beat	6	8.1	5	83.3
Junctional premature beat	1	1.4	1	100
Ventricular premature beat	7	9.5	5	71.4
Sinus tachycardia	13	17.6	13	100
Supraventricular tachycardia	1	1.4	1	100
Ventricular tachycardia	2	2.7	2	100
Sinus bradycardia	14	18.9	14	100
Atrioventricular block (I°)	11	14.9	7	63.6
Atrioventricular block (II°)	6	8.1	5	83.3
Atrioventricular block (III°)	3	4.1	3	100
ST–T changes	15	20.3	13	86.7
Fibrillation atrial	11	14.9	10	90.9
Fibrillation ventricular	4	5.4	3	75
Ventricular arrest	3	4.1	0	0

Table 5The amount of failing organs and outcome.

Failure organ amount	Positive cases	Positive rate (%)	Cured cases	Died cases	Mortality rate (%)
2	118	75.6	118	0	0
3	21	13.5	21	0	0
4	16	10.3	13	3	18.8
5	1	0.6	0	1	100

Table 6Patient condition and outcome after different replacement therapies.

Therapy style	Period	Cases	Mean age	Male	Male rate (%)	>3 organ failure cases	Dead cases	Mortality rate (%)
HD	1985-1999	75	40.9 ± 19.4	44	58.7	0	0	0
HFHD	2000-2008	43	41.5 ± 18.5	25	58.1	0	0	0
PD	1985-2008	18	$55.4 \pm 17.7^{*}$	9	50.0	18**	2	11.1**
CRRT	2000-2008	20	$56.9 \pm 17.5^{\circ}$	11	55.0	20**	2	10.0**

Compared with HD patients.

Table 7Recovery time of recovered patients after different replacement therapies.

Therapy style	Cases	Oliguria time (day)	SCr recovered time (day)	ALT recovered time (day)	Hospitalization time (day)
HD	75	9.9 ± 2.0	16.9 ± 3.9	12.9 ± 3.7	18.5 ± 4.1
HFHD	43	9.1 ± 1.9	16.4 ± 4.5	13.1 ± 3.3	17.9 ± 5.0
PD	16	$17.6 \pm 3.1^{***}$	$25.5 \pm 5.1^*$	$17.5 \pm 4.2^{*}$	$28.3 \pm 5.4^{**}$
CRRT	18	$16.7 \pm 2.7^{***}$	$24.1 \pm 5.3^{*}$	$18.4 \pm 4.0^{\circ}$	$26.6 \pm 4.9^{**}$

Compared with HD patients.

significant difference for patient gender in different therapy style groups. There was no significant difference in patient condition and outcome between the routine HD group and the HFHD group, and between the PD and CRRT group (Tables 6 and 7).

3.6. Patient age, underlying diseases and outcome

The death cases are listed in Table 8. Table 8 shows that most dead patients were old and had an underlying disease.

4. Discussion

This report included 156 patients with MOF caused by ingestion of fresh fish gallbladders. The amount of cases is the largest so far. Some clinical manifestations caused by fish gallbladders such as dyspnea (needed mechanical ventilation), acute heart failure, shock, gross hematuria, coma and cardiac arrest, were not apparent in previous references. Several new examinations that

have not been reported in fish bile poisoning, such as liver biopsy, gastroscopy, and CTnT, were carried out on some patients in our report. The renal biopsies on fish bile poisoning patients have been reported in only one reference [6]. In our report, 12 patients received renal biopsy. So, our report offers much new valuable information about fish bile poisoning.

The first symptom of the 156 patients' was gastrointestinal discomfort, followed by oliguria, ARF and hepatic failure, as corresponds to the references [4–8]. Some reports showed that every patient with fish bile poisoning was cured [9], which might be due to fewer cases. There were also some death cases related to fish bile poisoning [8]. There were 4 deaths in our report. The general mortality rate was 2.6%. The mortality rate was much lower than the general mortality rate of MOF patients caused by sepsis or trauma, which was approximately 50%, and nearly 100% when more than 4 organs failed [1,2]. In our 156 MOF patients, 118 cases had 2 failing organs, 21 cases had 3 failing organs, 16 cases had 4 failing organs, and 1 case had 5 failing organs; there were 17 cases that

^{*} p < 0.05.

^{**} p < 0.001.

^{*} p < 0.05.

^{**} p < 0.01.

^{***} p < 0.001.

Table 8The general condition of dead patients.

Patient number	Gender	Age	Underlying disease	Number of failing organs	Therapy style
1	Male	69	Hypertension Diabetes	4	CRRT
2	Male	19	Positive HBsAg	4	CRRT
3	Female	58	Positive HBsAgChronic cough	5	PD
4	Male	71	Hypertension Diabetes	4	PD



Fig. 1. A gastroscopic photo from a 34 year old male patient on the fifth day after swallowing a gallbladders from grass carp (fish weight approximately 3 kg), who presented with alimentary tract hemorrhage (tarry stool). The photo showed diffuse gastric mucosal bleeding.

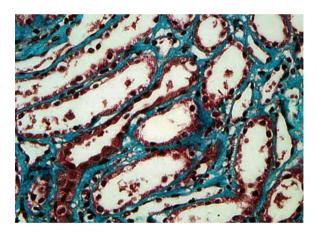


Fig. 2. Renal tissue from a 32 year old male patient on the ninth day after swallowing a gallbladder from silver carp (fish weight approximately $4 \, \mathrm{kg}$), who presented with obvious oliguria ARF and hepatic failure. The photo showed extensive tubular epithelial necrosis. PASM $400 \times$.

required mechanical ventilation, 15 cases had acute heart failure, 13 cases had shock, 10 cases had a coma, and 10 cases had cardiac arrest. These data showed the serious condition of our patients. What caused these problems? Most patients usually went to their nearby small-scale clinic or hospital for diagnosis and treatment. Only those serious cases that were difficult to address were transferred to our teaching hospital for treatment.

On one hand, this low mortality rate was connected with our elaborate observation and treatment; on the other hand, these findings suggested that the MOF caused by fish bile poisoning might have a better outcome than those caused by sepsis and trauma.

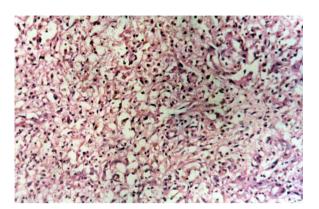


Fig. 3. The liver tissue from a 56 year old male patient on the fourth day after swallowing the gallbladder of a black carp (fish weight approximately 8 kg), who presented with extremely elevated ALT, AST, jaundice, and who died on the seventh day after poisoning due to MOF. His serum HBsAg was negative. The photo showed extensive hepatocyte necrosis, interstitial edema and destruction of the hepatic lobule. HE 200×.

There were 11 cases (7%) with gross hematuria; this clinical manifestation was not found in fish bile poisoning patients from previous studies. All of the 11 patients with gross hematuria had an obviously protracted APTT time. As such, gross hematuria might be due to severely damaged blood clotting function. All of these 11 patients with gross hematuria were cured. So, the gross hematuria in fish bile poisoning was not connected to patient severity.

There were 119 cases (76.3%) with fecal occult blood and 53 cases (34%) with tarry stool, which corresponded with the gastroscopic findings of spotty bleeding. The gastroscopic results of fish bile poisoning have not been reported before. There were 24 cases (15%) with protracted APTT and a bleeding tendency; all of them had severely elevated ALT and AST and more than 3 failing organs, indicating that they had severe liver damage.

There were 20 cases (13%) with reduced PLT; when the ARF was cured, the PLT also returned to normal. This phenomenon suggested that these patients had bone marrow injury. It is not clear whether the bone marrow injury was induced by the bile or by uremic toxins.

All of the 35 cases that received a CTnT assessment had a significant increase in CTnT (100%). Only 109 cases (70%) had increased LDH and CPK, while 74 cases (47%) had abnormal ECG. All patients with cardiac symptoms showed an abnormal ECG. All patients with severe ECG abnormalities (3-degree A-V block in 3 cases, ventricular fibrillation in 4 cases) suffered from cardiac arrest. Some patients with severely abnormal ECG had a normal cardiac ultrasound. In 56 patients who received cardiac color Doppler ultrasound, only 31 cases (55.4%) showed abnormalities. All cases resulting in death had abnormal cardiac color Doppler ultrasound results. These data suggest that the fish bile could induce myocardial injury. The CTnT was a sensitive index of myocardial injury. As an indicator of myocardial injury, the sensitivity of LDH and CPK was lower than CTnT, but higher than ECG. The severe ECG abnormalities were connected to a poor prognosis. The cardiac color Doppler ultrasound was a poor indicator of myocardial injury, but once identified as abnormal, it indicating particularly serious myocardial damage and had important prognostic value.

Prognostic factors: (a) Fish bile: a number of patients who ingested very large fish gallbladders (for example, a 41-year-old man that ingested a gallbladder from a 20 kg grass carp was cured) had good outcomes, but a 63-year-old man who ingested 3 gallbladders from 0.5 kg grass carp died. This finding suggested that there was not a direct correlation between fish bile volume (over some amount) and prognosis. Our patients ingested fresh-water fish gallbladders from silver carp, grass carp, cyprinoid carp, and black carp, and there was no correlation between fish type and outcome. (b) Age: most patients were between 21 and 60 years old. Compared with patients older than 61, the patients had a relatively stable condition, fewer organ failures and less recovery time, suggesting the bad influence of old age in the prognosis of fish bile poisoning. This might be correlated with a weaker immune system, less effective recovery ability, and more underlying diseases in old patients. (c) Underlying disease: our data showed that some patients had underlying disease (such as positive HBsAg, hypertension, type 2 diabetes, and chronic cough), especially in older patients. Patients with underlying disease were much more difficult to address. The patients not only came to the hospital in a worse condition, but they also had more conflicts during treatment. All patients that died had certain underlying diseases which suggested that underlying disease could increase the morality rate of fish bile poisoning. (d) High potassium: in our patients, only 30 patients had high potassium (the mean peak value was $6.7 \pm 0.5 \, \text{mmol/L}$). In these high potassium patients, 3 cases had cardiac arrest; however, all of them were cured. Furthermore, very high potassium was a virulent condition and could induce sudden death; however, if normal and timely treatment (emergency dialysis and monitoring) was received, it did not increase mortality. (e) The number of failing organs: when multiple organs failed, the number of failing organs was the most important factor that influenced mortality. The more failing organs, the higher the mortality. In our report, all of the 4 patients that died had 4 or more failing organs. However, our morality rate (2.6%) was significantly lower than that of MOF caused by sepsis or trauma, suggesting that fish bile poisoning causing MOF could have a better outcome [11]. (f) Treatment

methods: patients with 2 failing organs received HD or HFHD. Their SCr, ALT, recovery time and hospitalization time was much shorter than those patients with 3 or more failing organs who received PD or CRRT. This difference was not attributable to the treatment style or a serious condition of sickness because the patients with a serious condition were usually selected to be treated with PD or CRRT. The effect of the replacement on fish bile induced MOF will depend on the results from prospective randomized-controlled trials.

Conflict of interest statement of all authors

All the authors (Fa-huan Yuan, Wei-ping Hou, Dai-hong Wang, Xiang Du, Li-xia Guang, Ying Zhang, Fang Pang) were in the department of Xinqiao hospital, and agree the ranking.

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