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Research paper

Clinical presentation and prognostic analysis of Chinese patients with systemic light chain amyloidosis with liver involvement

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ABSTRACT

To summarize the clinical characteristics and prognostic factors of Chinese patients with systemic light chain amyloidosis with liver involvement. We retrospectively analyzed the clinical features and natural history data of 102 patients diagnosed with systemic light chain amyloidosis with liver involvement at Peking Union Medical College Hospital between March 2007 and May 2018. More than 95% of patients showed the involvement of other organs. Kidney and heart were the most frequently involved organs, accounting for 71.6% and 68.6% of cases, respectively. Hepatomegaly was the most frequently observed physical sign, accounting for 67.6% of cases. Elevated levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) were frequently observed, accounting for 85.3% and 88.2% of cases, respectively. A significantly better prognosis was observed in patients with normal total bilirubin levels, as compared with those with elevated levels of total bilirubin. Patients in the normal total bilirubin group showed a significantly better progression-free survival (PFS) (38 months) as compared the elevated total bilirubin group (4 months; $P < 0.001$). The median overall survival (OS) in the normal total bilirubin group was not reached compared with the elevated total bilirubin group (4 months, $P < 0.001$). Notably, the early death rate was significantly lower in the normal total bilirubin group as compared to the elevated total bilirubin group (14.5% *vs* 48.5%, $P < 0.001$). In conclusion, the elevation of total bilirubin indicated an early death and worse PFS and OS. Early diagnosis is therefore essential, and requires appropriate treatment and intensive care.

1. Introduction

Systemic light-chain (AL) amyloidosis is a systemic disease caused by the deposition of misfolded monoclonal light chains secreted by underlying clonal plasma cells; this process leads to organ dysfunction. The most common organs affected by systemic AL amyloidosis are the heart, kidney, and peripheral nerves [1,2], although the liver is also a common site for amyloid deposition. In a previous series of autopsies [3], 70% of patients with systemic AL amyloidosis showed liver involvement. Hepatic systemic AL amyloidosis is caused by the excessive deposition of monoclonal globulin light chain, or fragments generated by this light chain, in the liver tissue, mostly in the parenchyma, along the sinusoids within the space of Disse, or in the walls of blood vessels. Hepatocytes are severely compressed when they contain an extensive accumulation of amyloid and are therefore likely to undergo atrophy or disappear [4,5]. Thus, patients often manifest with hepatomegaly and an increase in cholestatic enzyme. In some patients with advanced hepatic systemic AL amyloidosis, levels of total bilirubin (TBil) may also become elevated.

Previous studies suggested that patients with systemic AL amyloidosis, who had biopsy-proven liver involvement, also had a poor prognosis [6,7]; however, these results were limited by the lack of new drug regimens. In order to provide a more detailed understanding of hepatic systemic AL amyloidosis, and to explore the prognostic factors associated with this diseases in an era which features new drugs, we retrospectively reviewed the clinical features of patients with hepatic systemic AL amyloidosis in a single center and analyzed the outcomes of these patients.

2. Methods

2.1. Patients

Patients who were newly diagnosed with systemic AL amyloidosis at

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Peking Union Medical College Hospital (Peking China) between March 2007 and May 2018 were identified from our institutional database. The diagnosis of systemic AL amyloidosis was confirmed by the presence of Congo red-positive fibril deposition and the deposits were characterized as AL type by immunohistochemistry, immunofluorescence, or laser microdissection with mass-spectrometry-based proteomic analysis. Liver involvement was defined as a total liver span < 15 cm, as measured by liver ultrasonic examination or abdominal computer tomography in the absence of heart failure, or an alkaline phosphatase (ALP) < 1.5 times the institutional upper limit of normal, or Congo red-positive on liver tissue biopsy [8]. The study was approved by the Peking Union Medical College Hospital Ethic's Committee. The study was performed in accordance with the ethical standard laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2. The assessment of organ and hematological response

We used both the 2004 and 2012 criteria for Mayo Clinic staging [9,10]. The 2004 criteria included cardiac troponins (cTnI) and N-terminal fragment of the pro-brain natriuretic peptide (NT-ProBNP) in order to derive the prognosis of survival, while the 2012 criteria featured revisions of the staging system *via* incorporation of the difference between involved and uninvolved light chains (dFLC).

Hematological response and organ response (OR) were routinely evaluated every 3 months after the completion of treatment. Complete response (CR) was defined as a normal serum dFLC with negative serum and urinary immunofixation electrophoresis (IFE), while a very good partial response (VGPR) was defined as a dFLC < 40 mg/L. A dFLC reduction of 50% or more defined a partial response (PR) while no response (NR) was defined as a response which was less than a PR. Disease progression was defined as any detectable monoclonal protein, or abnormal free light chain ratio, after CR, a serum immunoglobulin free light chain increase of 50% which must be to a level of greater than 100 mg/L after PR, or a 50% increase in serum M protein which must also be to a level greater than 5 g/L, or a 50% increase in urine M protein in urine M protein which also must be to a level greater than 200 mg/day [8].

Liver response was assessed according to consensus standards [2]: a 50% reduction in abnormal ALP value or a radiographic reduction in liver size of least 2 cm.

2.3. Follow-up

All patients were followed up at clinic or by telephone, and detailed follow-up data were recorded. The last follow-up was June 30, 2018. Early death was defined as death within 3 months of diagnosis. OS was defined as the time from diagnosis to death or last follow-up. PFS was calculated from the initiation of treatment to disease progression, relapse, or death from any cause.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. The χ^2 test, or Fishers exact test (where the number of cases was < 5) were used to compare categorical variables, while the Wilcoxon rank test was used for continuous variables. OS curves and PFS curves were estimated using the Kaplan-Meier Method. Analyses of the effects of potential risk factors on survival were performed with log-rank tests. Risk factors for survival were evaluated using Cox proportional hazards models and 95% confidence intervals (CIs) were calculated using multivariate Cox proportional hazards regression models. All statistical tests were two-sided, and $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

In total, 452 patients were newly diagnosed with systemic AL amyloidosis between March 2007 and May 2018; liver involvement was confirmed in 102 of these patients (22.6%). Of the 102 patients with hepatic systemic AL amyloidosis, 65 (63.7%) were male, and the median age was 55 years (range: 37–75 years). The median extent of liver enlargement for the 102 patients was 3.0 cm below the right costal margin (range: 0.0–17.0 cm), and hepatomegaly was found in 69 cases (67.6%). Eighty-seven patients (85.3%) showed initial elevated levels of ALP; the median concentration of ALP among patients with hepatic systemic AL amyloidosis was 224 U/L (range: 39–2637 U/L). Ninety (88.2%) patients had initial elevated levels of and gamma-glutamyl transferase (GGT), the median level of GGT was 216 U/L (range: 12–3606 U/L).

We divided the 102 patients into two groups, 69 (67.6%) patients had an initial normal concentration of TBil < 22.2 μmol/L, and 33 (32.4%) had elevated concentrations of TBil (≥ 22.2 μmol/L). The baseline demographics and clinical characteristics of the two groups are outlined in Table 1. There was no significant difference in median age at diagnosis and sex between the two groups. Patients in the normal TBil group showed a significantly lower concentration of ALP (200 U/L *vs* 253 U/L, P < 0.001) and significantly lower concentration of GGT (211 U/L *vs* 269 U/L, P = 0.014) compared to the elevated TBil group. We also found that the levels of aspartate aminotransferase (AST) were significantly higher in the elevated TBil group (49.5 U/L *vs* 39.0 U/L, P = 0.003). The concentrations of alanine aminotransferase (ALT), and albumin, did not differ significantly between the two groups. In addition, dFLC level was significantly higher in the elevated TBil group (324.4 mg/L *vs* 107.8 mg/L, P = 0.004). No significant difference was observed in the level of M protein or plasma cell count in the bone marrow when compared between the two groups.

3.2. Organ involvement

Of the 102 patients with hepatic systemic AL amyloidosis, the median number of involved organs was three (range: 1–5). Only 4 (3.9%) patients showed only liver involvement, twenty-six (25.5%) cases had 2 organs involved and 32 (31.4%) patients had three organs involved. The kidneys and heart were the most common organs involved, and the number of patients in which the heart or kidney were involved was 73 (71.6%) and 70 (68.6%), respectively.

Notably, patients in the normal TBil group showed significantly more frequent kidney involvement (78.3% *vs* 57.6%, P = 0.030), and the 24-h urine-protein was significantly higher in the normal TBil group (2.42 g *vs* 1.13 g, P = 0.032). There was no significant difference in estimated glomerular-filtration rate (eGFR) between the two groups. There was no significant difference between the two groups of patients with regards to the number with heart involvement, and the difference between the levels of cTnI and NT-proBNP.

Eighty-nine cases were eligible for Mayo clinic staging 2004; the number of patients in stage I, II, and III were 26 (29.2%), 31 (34.8%), and 32 (36.0%), respectively. Eighty-three patients were eligible for Mayo clinic staging 2012; the number of patients in stage 1, 2, 3, and 4 were 27 (32.5%), 19 (22.9%), 18(21.7%), and 19 (22.9%), respectively. Patients in the elevated TBil group showed no significant differences in either Mayo 2004 or Mayo 2012 staging when compared with patients in the normal TBil group.

3.3. Treatment

First-line treatment regimens applied to the 102 patients are presented in Table 1. Bortezomib-based treatment was the most frequently used first-line treatment; 43 patients accepted bortezomib-based

Table 1
Baseline characteristics of the patients (n = 102). dFLC, difference between involved and uninvolved free light chains; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; PN, peripheral nerves; GIT, gastrointestinal tract; ASCT, autologous stem cell transplantation.

Characteristics	All patients (N = 102)	Normal TBil group (N = 69)	Elevated TBil group (N = 33)	P value
Age at diagnosis,years,median (range)	55(37-75)	54(37-75)	56(37-75)	0.767
Male, n(%)	65(63.7%)	43(62.3%)	21(63.6%)	0.898
Time from onset of disease to diagnosis,months,median(range)	9.0(1.0-104.0)	10.0(1.0-104.0)	9.0(3.0-60.0)	0.348
Involved light chian,lamda,n(%)	47(46.1%)	33(47.8%)	14(45.2%)	0.669
dFLC,mg/L,median(range)	142.9(4.4-3411.2)	107.8(4.4-2056.1)	324.4(41.4-3411.2)	0.004
M protein,g/L,median(range)	0.0(0.0-26.3)	0.0(0.0-26.3)	0.0(0.0-7.8)	0.052
Bone marrow plasma cells count,%,median(range)	4.0(0.0-21.0)	4.5(0.0-21.0)	3.6(0.0-17.0)	0.998
Hepatic involvement				
ALP,U/L,median(range)	224(39-2637)	200(39-1546)	253(87-2637)	< 0.001
GGT,U/L,median(range)	216(12-3606)	211(12-1755)	269(59-3606)	0.014
ALT,U/L,median(range)	30(7-174)	29(7-174)	33(12-120)	0.240
AST,U/L,median(range)	40(13-308)	39(13-142)	49.5(20-308)	0.003
Alb,g/L,median(range)	34(13-53)	34(13-50)	33(14-53)	0.715
Heart involvement,n(%)	70(68.6%)	45(65.2%)	25(75.8%)	0.283
cTnI,ug/L,median(range)	0.06(0.00-11.80)	0.04(0.00-11.80)	0.14(0.00-0.99)	0.672
NT-proBNP,ng/L,median(range)	2093(32-103277)	1633(66-103277)	2899(32-64403)	0.649
Mayo Stage2004:n (%)				0.288
1	25/89(28.1)	19/61(31.1)	6/28(21.4)	
2	33/89(37.1)	24/61(39.3)	9/28(32.1)	
3	31/89(34.8)	18/61(29.6)	13/28(46.5)	
Mayo Stage2012:n(%)				0.310
1	27/84(32.1)	22/59(37.3)	5/25(20.0)	
2	19/84(22.6)	14/59(23.7)	5/25(20.0)	
3	19/84(22.6)	12/59(20.3)	7/25(28.0)	
4	19/84(22.6)	11/59(18.7)	8/25(32.0)	
Kidney involvement,n(%)	73(71.6)	54(78.3)	19(57.6)	0.030
sCr,μmol/l,median(range)	76(35-653)	77.0(35-584)	70(39-653)	0.588
eGFR,ml/min/1.73 m^2,median(range)	89(6-177)	86(17-177)	102(6-129)	0.161
24 h urine protein,g,median(range)	2.1(0.0-18.5)	2.4(0.0-18.5)	1.1(0.1-12.2)	0.032
PN involvement,n,%	7(6.9)	6(8.7)	1(3.03)	0.290
GIT involvement,n,%	13(12.7)	9(13.0)	4(12.1)	0.896
Number of organs involved,median(range)	3(1-5)	3(1-5)	3(1-4)	0.746
Treatment regimens				
ASCT,n,%	10(9.8)	9(13.1)	1(3.0)	0.122
Mephalan based,n,%	22(21.5)	16(23.2)	6(18.2)	0.565
Bortizomib based,n,%	43(42.2)	28(40.6)	15(45.4)	0.641
Immunomodulatory drugs based,n,%	10(9.8)	8(11.6)	2(6.1)	0.379
Best support,n,%	17(16.7)	9(13.1)	8(24.3)	0.156

treatment, accounting for 42.2% of the study population. Mephalan-based therapy was used in 22 patients (21.5%) and autologous stem cell transplantation (ASCT) was administered to 10 patients, accounting for 9.8% of the study population. Immunomodulatory drugs, including thalidomide- and lenalidomide-based treatments, were used in 10 patients (9.8%). Seventeen patients (16.7%) chose only supportive treatment due to poor performance or economical reasons. There was no difference in chemotherapy dosing between normal TBil and elevated TBil groups. And no significant difference was observed in terms of treatment regimens when compared between these two groups.

3.4. Hematological and organ response

The best hematological response rates are listed in Table 2. Of the 66 patients which could be analyzed from this aspect, the overall hematological response rate was 78.8% (52 patients), including 15 patients with CR (22.7%), 24 patients with VGPR (36.4%), and 13 patients with PR (19.7%). Thirty-six patients could not be analyzed, including 19 patients who died in the first 3 months, 13 patients who were lost during follow-up, and 4 patients who were treated within 3 months. No significant difference was observed between the two groups in terms of CR or VGPR.

Sixty-five patients were evaluated for liver response. The median ALP dropped from 224 U/L (range: 109–1734 U/L) to 189 U/L (range: 63–1206 U/L) after treatment. Twenty cases (30.8%) achieved a liver response; 12 of these (60.0%) achieved hematological CR and 8 (40.0%) obtained VGPR. The median time to obtain the best hematological response was 4 months (range: 1–21) months, while the median time to hepatic response was 12 months (1–29 months). Notably, 18 patients manifested with an evident reduction in ALP concentration after treatment; the median initial concentration of ALP for these patients was 303 U/L (range: 127–1734 U/L) and dropped to 149 U/L (range: 74–396 U/L) when they achieved liver response. Furthermore, the other two patients manifested with a reduction in liver size of 3 cm and 4 cm, respectively. No significant difference in liver response was found between patients in the normal TBil and elevated TBil groups.

Table 2
Best hematological and organ responses of the patients evaluated. Data are shown as counts (% of n evaluated). CR, complete response; VGPR, very good partial response; PR, partial response.

Response	All patients	Normal TBil group	Elevated TBil group	P value
Best hematologic response,n(%)				
CR	15/66(22.7)	12/52(23.1)	3/14(21.4)	0.896
VGPR	24/66(36.4)	22/52(42.3)	2/14(14.3)	0.053
PR	13/66(19.7)	10/52(19.2)	3/14(21.4)	0.854
Liver response,n(%)	20/65(30.8)	17/51(33.3)	3/14(21.4)	0.393
Heart response,n(%)	18/38(47.4)	16/29(55.2)	2/9(22.2)	0.084
Kidney response,n(%)	23/45(51.1)	22/38(57.9)	1/7(14.3)	0.034

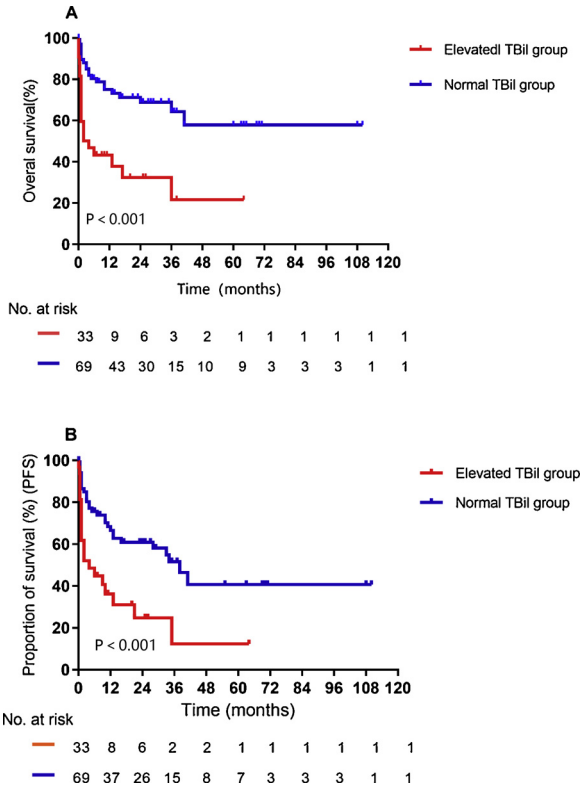

Fig. 1. Survival outcomes for patients in elevated TBil group and normal TBil group. (A) OS and (B) PFS.

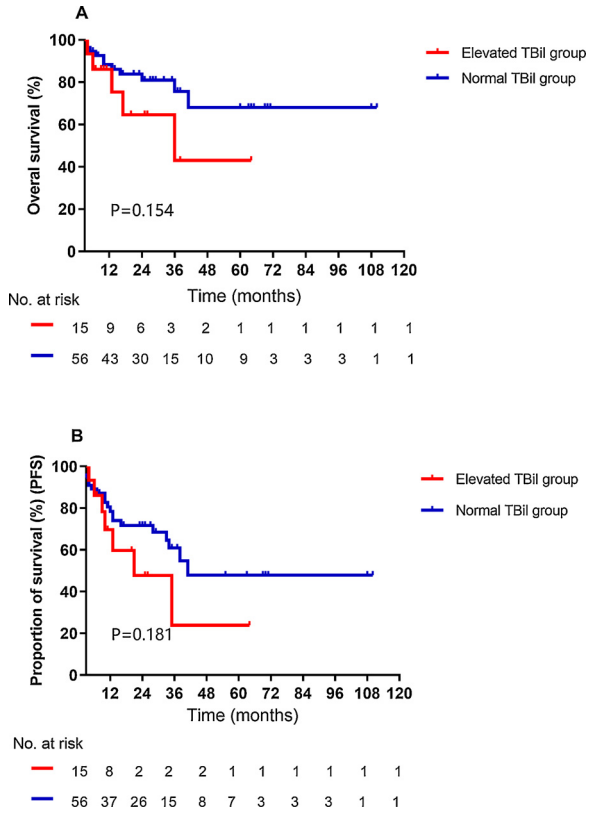

Fig. 2. Survival outcomes for patients without early death in elevated TBil group and normal TBil group. (A) OS and (B) PFS.

3.5. Survival outcome

The median follow-up time for this cohort was 36 months (range: 1–110) months. Forty-two patients died, including 23 (33.3%) in the normal TBil group and 19 (57.6%) in the elevated TBil group. The median OS of these 102 patients with hepatic systemic AL amyloidosis was 41 months. A significantly better prognosis was observed in patients with normal TBil as compared with those with elevated TBil group. The median OS in the normal TBil group was not reached compared with 4 months in the elevated TBil group ($P < 0.001$) (Fig.1A). The median PFS of these 102 hepatic systemic AL amyloidosis patients was 21 months. In addition, patients in the normal TBil group showed a better PFS; the median PFS in the elevated TBil group was 4 months as compared with 38 months in the normal TBil group ($P < 0.001$) (Fig.1B).

Early death events occurred in twenty-six patients (25.5%), with 16 in the elevated TBil group and 10 in the normal TBil group. The main causes of death in each group were multiple organs failure associated with disease progression. Patients in the elevated TBil group showed a significantly higher early death rate than patients in the normal TBil group (48.5% *vs* 14.5%, $P < 0.001$). We used 3 months as a landmark to calculate the OS and PFS for patients without early death in these two group and found no significant difference, in either OS or in PFS. However, patients in the normal TBil group tended to have longer OS as compared with patients in the elevated TBil group (not reached *vs* 32 m, $P = 0.154$) (Fig. 2A). In addition, PFS in the normal TBil group also tended to be longer than in the elevated TBil group (41 months *vs* 21 months, $P = 0.181$) (Fig. 2B).

A multivariate model was constructed incorporating TBil, ALP, GGT, and Mayo 2004 staging. Multivariate analysis showed that elevated TBil was an independent predictor for survival ($P = 0.006$, HR: 2.424, 95% CI: 1.307–4.877). In addition, Mayo 2004 staging was also an independent risk factor for survival ($P < 0.001$, HR: 2.549, 95% CI: 1.573–4.129).

4. Discussion

Systemic AL amyloidosis is a systemic plasma cell disease with a poor prognosis, which can present with multi-systemic involvement, such as nephrotic syndrome, congestive heart failure, peripheral neuropathy and liver failure [8]. Patients with hepatic systemic AL amyloidosis may have mild symptoms such as abdominal distension, weight loss, early satiety, which can then be followed by hepatosplenomegaly, jaundice and ascites [6]. Hepatomegaly occurs in most patients with hepatic systemic AL amyloidosis; previous studies have reported that 80–90% of patients with systemic AL amyloidosis with liver involvement have hepatomegaly [11]. In our study, 67.6% of patients with hepatic systemic AL amyloidosis had hepatomegaly, which was lower than that reported previously. This may be related to the early recognition of hepatic systemic AL amyloidosis patients.

The long-term deposition of amyloid materials in the liver may lead to severe liver dysfunction, liver failure and even death [4]. These symptoms are easily misdiagnosed as viral hepatitis, alcoholic liver disease or autoimmune liver disease. In a previous study, laboratory examinations showed that the concentration of ALP was significantly increased, accompanied by an elevated concentration of GGT. The progressive elevation of ALP often indicates liver damage, and some patients may also have elevated bilirubin [4,6]. Our present results suggested that the concentration of ALP and GGT in patients with hepatic systemic AL amyloidosis patients were increased significantly, at 85.3% and 88.2%, respectively, which was consistent with previous reports.

Systemic AL amyloidosis is a systemic disease. Heart, kidney, and peripheral nerves are the organs that are most commonly involved [8]; hepatic systemic AL amyloidosis also presents with the involvement of multiple organs. In our present cohort of patients, we observed that the proportion of patients with single liver involvement was very low, only accounting for 3.9% of the study population. More than 95% of patients

with hepatic systemic AL amyloidosis showed the involvement of other organs, such as the heart, kidney, gastrointestinal tract, peripheral nerves or soft tissue. The kidney and heart were the most frequently involved organs. Generally, when patients are identified with unexplained hepatomegaly, an increased concentration of bile duct enzymes, with concurrent dysfunction in other organs, the possibility of hepatic systemic AL amyloidosis should be considered.

The prognosis of systemic AL amyloidosis is poor, and is closely related to the number of organs involved and the extent of involvement. Patients with liver involvement appear to have a poorer prognosis; previous research reported that the median overall survival time of patients with hepatic systemic AL amyloidosis was only 8.5 months [6]. Many reviews have reported that jaundice, or an elevated concentration of bilirubin, in patients with hepatic systemic AL amyloidosis often indicate a poor prognosis [12–14]. In our research, the OS of patients with hepatic systemic AL amyloidosis was 40 months; this was longer than that reported by previous reports. This may be related to early diagnosis and the development of new treatment strategies over the past ten years.

In addition, a significantly better prognosis was also observed in patients with a normal concentration of TBil as compared with those in the elevated TBil group; no significant difference was detected in terms of Mayo staging between these two groups. We confirmed that patients in the normal TBil group showed a better PFS (38 months) as compared with 4 months in the elevated TBil group ($P < 0.001$). The median OS in the normal TBil group was not reached, compared with 4 months in the elevated TBil group ($P < 0.001$). Furthermore, multivariate analysis showed that the elevation of TBil represents an independent risk factor for patients with hepatic systemic AL amyloidosis ($P = 0.006$, HR: 2.424, 95% CI: 1.307–4.877). Notably, in our present research, we found that early death occurred more frequently in the elevated TBil group (48.5% *vs* 14.5%, $P < 0.001$). Thus, the elevation of TBil could predict an early death in patients with hepatic systemic AL amyloidosis.

In conclusion, in the new drug era, patients with an elevated concentration of bilirubin are still associated with a poorer prognosis and are predicted to die early. As such, it is important to recognize cases of hepatic systemic AL amyloidosis early as this will allow the timely initiation of treatment.

Declaration of Competing Interest

No conflict of interest exits in the submission of this manuscript.

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