The Clinical Characteristics and Prognosis of Chinese Patients With Primary Light-Chain Amyloidosis: A Retrospective Multicenter Analysis

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Abstract

Objective To retrospectively identify the critical characteristics and prognostic factors of primary light-chain amyloidosis.

Patients and Methods: Data were collected and compared from 91 patients who were diagnosed with primary light-chain amyloidosis at four hospitals between January 2010 and November 2018. We analyzed the clinical characteristics and performed an overall survival (OS) analysis.

Results: Patients (median age, 60 years) were diagnosed with organ involvement of the kidney (91.2%), heart (56%), liver (14.3%), soft tissue (18.7%), or gastrointestinal tract (15.4%), and 68.1% of patients had more than two organs involved. Patients were most commonly treated with bortezomib-based regimens (56%), and only one patient had autologous stem cell transplantation (auto-ASCT). The median OS was 36.33 months and was affected by the ECOG score, renal involvement, cardiac involvement, hepatic involvement and negative immunofixation in the serum and urine after treatment. Multivariate analysis indicated that cardiac involvement and negative immunofixation in the serum and urine after treatment were independent prognostic factors for OS.

Conclusion: Cardiac involvement and the hematologic response to treatment were independent prognostic factors for OS in primary light-chain amyloidosis patients. The type and number of organs involved is more important than the number of organs involved for the OS.

Background

Primary light chain amyloidosis (pAL) is a disease derived from plasma cell clones, characterized by the extracellular deposition of N-terminally derived amorphous amyloid fibrils from a monoclonal light chain variable region. (1). Despite having a relatively small size, a clone can set off devastating multiorgan damage, which is caused by the monoclonal light chain. The incidence of primary systemic amyloidosis is estimated to be three to five patients per million per year(2),which is approximately one-fifth of that of multiple myeloma(3). The symptoms are often varied and nonspecific, so the diagnosis of pAL is often delayed. Many patients are diagnosed at an advanced stage, resulted in early mortality. The overall prognosis of pAL is poor, mainly because amyloid deposits in important organs such as the heart, liver and kidneys, and ultimately lead to organ failure and death. (4). In the last 15 years, substantial progress has been made in understanding the biology of the amyloid plasma cell clones and the mechanisms of organ damage; yet there are no specific treatments can be used to treat amyloidosis. Mishra et al found that human amyloidogenic light chain proteins directly cause cardiac dysfunction, so the circulating light chain can cause organ dysfunction(5). Treatment approaches for light-chain amyloidosis focus on suppressing the abnormal plasma cell clone, with the aim of reducing the production of amyloidogenic light chains. Stem cell transplantation is still available for treatment, but this only applies to a small number of patients. For patients who are not suitable for transplantation, the standard treatment regimen

is based on bortezomib treatment. For frail and older patients, oral treatment with melphalan and dexamethasone can be used. (6).

Many factors have been shown to be related to overall survival, such as the patient's age, nutrition status, bone marrow plasma cell infiltration and the severity of organ involvement. The accumulation of clinical data from around the world may help improve the diagnosis, prognostic assessment and treatment. At present, reports on the clinical characteristics and prognosis of pAL in China are rare. Thus, we performed a retrospective analysis of 91 pAL patients from four hospitals in China, try to find factors that affect the prognosis of pAL. This study may enrich the existing database and contribute to future meta-analysis.

Methods

We retrieved information on 91 patients who were diagnosed with pAL between January 2010 and November 2018 at the First Affiliated Hospital of Zhejiang University, Taizhou Hospital of Zhejiang Province, Shaoxing People's Hospital, and People's Hospital of Quzhou. (7)Amyloidosis was diagnosed according to consensus criteria, determined by the presence of Congo Red-positive fibril deposition and apple-green birefringence, as observed under polarized light. Immunohistochemistry was used to determine the kappa or lambda light chain specificity of the fiber. Immunofixation electrophoresis in serum or urine, serum-free light chain analysis or clonal plasma cell population in the bone marrow were required for the evaluation of clonality. Patients with a positive family history of amyloidosis or with amyloidosis of a secondary cause were excluded. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University, and was in accordance with the Declaration of Helsinki.

Statistical Analysis

The overall survival (OS) was calculated from diagnosis until death or the last follow-up. Survival analysis for various factors were performed using the Kaplan-Meier method, and survival curves among groups was compared by the log-rank test. The risk of the selected variables was calculated using the Cox proportional hazards regression model, and 95% confidence intervals were generated, with a hazard ratio < 1.0 indicating survival benefit. Univariate and multivariate analyses were carried out to examine the predictive factors for OS. A 2-tailed P value of less than 0.05 was defined as significant. All statistical analyses were performed by SPSS 18.0.

Results

Symptoms and Clinical Presentations

Ninety-seven patients were admitted to the three hospitals; 3 patients were lost to follow-up and 3 were excluded because the BMPC measurements at diagnosis were not available. A total of 91 patients were included in the analysis (Table 1). The median age at diagnosis was 60 years (41–82 years), and 56% of the patients were male. Edema and proteinuria were the two most common symptoms reported by patients at diagnosis, 62 (68.1%) and 42 (46.2%), respectively. Many patients reported both of these

symptoms. Nonspecific symptoms such as fatigue were present in 12.1% of the patients, and abdominal distention and abdominal pain were present in 6.6% of the patients. Only two patients presented with chest pain, one patient presented with poor appetite and one patient presented a cough (Figure 1). According to the Consensus Criteria, the kidney was involved in 83 patients (91.2%), the heart in 51 (56%), the liver in 13 (14.3%), the gastrointestinal tract in 14 (15.4%), the soft tissue in 17 (18.7%), the neurological system in 6 (6.6%) and the lung in 6 (6.6%). Among the patients, 29 (31.9%) had only one organ involved, 41 (45.1%) had two organs involved, and 21 (23%) had three or more organs involved.

Biopsy and Laboratory Findings

During the diagnostic workup, 80 patients (87.9%) underwent bone marrow (BM) biopsy, and 76 patients (83.5%) underwent kidney biopsy. However, only 8 (8.8%) patients underwent skin biopsies, 4 patients (4.4%) underwent a soft tissue biopsy. Liver and gastrointestinal tract biopsies were performed in 2 (2.2%) and 7 (7.7%) patients, respectively (Figure 2). All of the patients had immunohistochemical staining of amyloid deposits for the κ or λ light chains: 60 (65.9%) of the patients stained positively for λ and 31 (34.1%) for κ light chains. Overall, 82 patients (90.1%) had a monoclonal protein detected by serum or urine immunofixation. The immunoglobulin heavy chain was IgG in 21 (23.1%) patients and IgA in 20 (22%) patients; a single light chain was found in 50 (54.9%) patients. The median bone marrow plasma cell infiltration was 5%. Anemia was rare, with a median hemoglobin level of 125 g/L. Most patients (67%) had hypoproteinemia with serum albumin less than 30 g/L, and the median was 26.8 g/L. Renal impairment was not very common in with the patients, with a median creatinine level of 79μmol/L. In the cardiac assessment, the median level of the N-terminal pro-brain natriuretic peptide (NTproBNP) was 1195 pg/ml.

Treatment and Survival

Patients were treated with several different regimens (Table 1). Bortezomib-based regimens (VD/VCD = bortezomib + dexamethasone/bortezomib + cyclophosphamide + dexamethasone) were used as the primary treatment in most patients (56%); thalidomide-based regimens were used in 26.4% of patients, and 3.3% of patients received lenalidomide-based regimens. A melphalan-based regimen was used in 2 (2.2%) patients. 10 patients (11%) did not receive any treatment, and only1 patient (1.1%) received HDM-ASCT treatment. The median OS from diagnosis was 36.33 months (range, 0.1–77.5 months).

Univariate and Multivariate Analysis of OS

Table 2 summarizes the correlation between patient clinical characteristics and prognosis (OS). A univariate log-rank test showed that certain patient characteristics had a significant effect on OS (P value range < 0.001 to 0.008). An ECOG score > = 2 (12.53 months vs 72.33 months; P = 0.001, Figure 3A), renal involvement (7.3 months vs 52.97 months; P = 0.008, Figure 3B), cardiac involvement (23.9 months vs not reached; P = 0.001, Figure 3C), hepatic involvement (5.3 months vs 52.97 months; P = 0.007, Figure 3D), and a negative immunofixation result (26.46 months vs not reached; P<0.001, Figure 3E) were associated with inferior survival.

Patients who had been treated had a significantly longer OS than that of patients who did not receive any treatment (52.97 months vs 4.9 months; P = 0.002). Patients who received bortezomib-based treatment had a trend of favorable OS compared to those who received non-bortezomib-based treatments, although the difference was not statistically significant (72.33 months vs. 39.411 months; P = 0.108, Figure 4A). Although the overall number of organs involved was not related to OS, the number of organs that were involved among the heart, liver and kidney was. The involvement of one of these organs was associated with better OS than that in patients in whom two or three of these organs were involved (not reached vs 26.46 months vs 2.77 months; P = 0.0047; Figure 4B). Patients with cardiac involvement alone have shorter OS than those patients with renal alone. Patients with both cardiac and renal involvement had a better OS than that in the group with cardiac involvement but had a worse OS than that in the group with renal involvement (26.46 months vs 7.3 months VS not reached; P<0.001, Figure 4C).

Because the detection technology was limited in a few hospitals until 2017, only a small number of patients have detected the serum free light chain. Hence, we used the 2004 version of the Mayo staging system rather than the 2012 one. The results showed that the 2004 staging was not related to OS (not reached vs 23.9 months vs 10.57 months, P = 0.198, Figure 5A). Furthermore, the patient gender, age, eGFR, serum albumin level, light-chain type, and kidney stage were all independent predictors of OS (Figure 5B-F).

The multivariate analyses indicated that renal involvement, cardiac involvement, and hematologic response were independent prognostic factors for OS (P <0.05) (Table 3).

Discussion

Immunoglobulin light-chain amyloidosis is the most common form of amyloidosis, accounting for approximately 70% of all cases of these diseases(8). Immunoglobulin light-chain amyloidosis can be classified into two types: primary and secondary. pAL makes up a large proportion of the cases. The Medicare claims database showed that the median age at diagnosis for light-chain amyloidosis is 63 years, the incidence of 10–14 patients per million per year, and the prevalence higher in males than in females. The median age of the 91 patients in this study was 60-years-old, which is a little younger than that in Western countries. Because this disease can affect many organs and patients' symptoms are usually nonspecific, early and accurate diagnosis is usually not possible. An online survey of the Amyloid Research Consortium found that 37% of patients were diagnosed one year after the onset of initial symptoms and that an average of three doctors were seen before diagnosis. Among the patients we examined, edema and proteinuria were the two most common symptoms reported, and it is difficult for us to recognize this disease based on these symptoms. In this study, 68.1% (62 out of 91) of patients had more than two organs involved at diagnosis, which is similar to the rate of 65% (54 of 84) that was reported in South Korea(4), and higher than the rate of 60.3% (38 of 63) reported in Denmark(9). This result may be because some primary hospitals in China, physicians feel difficult to recognize the disease and its symptoms, thus delayed diagnosis. Therefore, efforts should be made to educate primary care physicians to have better awareness of the disease.

In our study, kidney involvement in almost all patients was confirmed by biopsy. In fact, an abdominal fat pad aspirate is a simple and minimally invasive procedure. In combination with the bone marrow biopsy, which was stained with Congo red, and/or the biopsy of a minor salivary gland, this procedure can yield a diagnostic sensitivity of approximately 90%; thus, removing the need for organ biopsies(10–12). Skin and soft tissue biopsies were only conducted in 18.7% (16/91) of the patients in these patients. We might try to avoid many invasive procedures in the future.

The patients who were diagnosed between 2004 and 2015 at the Pavia Amyloidosis Research and Treatment Center demonstrated that the heart is the most commonly affected organ, followed by the kidneys. We found that the kidney involvement rate in our analysis was 91.2%, which was higher than that in other published studies (71%–57%) (13). Another Chinese center even reported that 100% of patients had renal involvement (14). These differences may be because in China, those patients who do not have renal involvement have a higher missed diagnosis rate compared to patients who have renal involvement (for example, those who do not have renal injury are unlikely to undergo cardiac biopsy, cardiac MRI or liver puncture, and therefore, are more likely to have a missed diagnosis). Some studies have shown that renal insufficiency leads to unfavorable outcomes (15), but our results show that renal involvement was associated with better survival. This is consistent with the results from other studies, which showed that renal AL had a better 5-year survival rate, ranging from 60%–80%(16). This result is mainly due to the fact that the patients without renal involvement all had cardiac involvement. Patients with solely cardiac involvement are easily missed, so most of these patients have a higher cardiac stage at the time of diagnosis, and the prognosis is relatively poor.

The presence and severity of heart involvement is the most important prognostic determinant, and the main cause of early death(17). The rate of cardiac involvement in our study was similar to that in previous reports (15). A data from European reported that heart-involved patients had a survival rate less than 30% beyond 3 years, with a median survival of 7.1 months. Our study showed that the 3-year OS rate for patients with cardiac involvement was 36.4%, with a median survival of 23.9 months, which was similar to that in a previous Chinese study that reported a 40% 3-year OS and an 18-month median survival(14). A recent meta-analysis demonstrated that bortezomib treatment significantly improved the overall response rate (ORR), complete response, cardiac response rate, 2-year overall survival and the risk of neuropathy and reduced overall mortality compared to those in the controls without bortezomib therapy(18). Our results did not show a difference between the two groups, probably because the number of people in the two groups differed greatly.

Hepatic involvement is another poor prognostic factor, with a median OS of only 5.3 months in this study, which is much worse than that in the cardiac involvement group. Recently, a study from Italy compared the clinical presentation and outcome of 225 patients and 643 subjects without liver involvement from a series of 868 consecutive patients with light-chain amyloidosis who were diagnosed between 1986 and 2007. This study demonstrated that liver involvement was the hallmark of aggressive disease in light-chain amyloidosis(19).

Badar et al(20) found that the overall survival of the patients with concurrent cardiac and renal involvement was comparable to that of patients with cardiac involvement only but was worse than that of patients with renal involvement only. We found that the OS of the concurrent cardiac and renal group was better than that of the cardiac group but was worse than that of the renal group. We hypothesized that this result was observed because of the severity of the cardiac involvement in the concurrent cardiac and renal involvement group is lower than that of the cardiac only involvement group. Furthermore, the OS of the concurrent cardiac and hepatic groups was worse than that of either groups in which only one of the organs was involved. Therefore, hepatic involvement is the factor that is associated with the worst prognosis, although most of these patients were treated with a bortezomib-based regimen. The number of organs that are involved among the heart, kidney and liver is correlated with the prognosis.

Previous reports have claimed that the hematologic response is very important for evaluating the treatment efficacy and predicting survival. Because only a small number of patients have detected the serum free light chain, we were unable to accurately assess the hematological response. We found that the patients who achieved a negative immunofixation in the serum and urine after treatment had a longer OS than that of patients with positive immunofixation (not reached vs 26.46 months). We believe that as the technique improves and becomes more readily available, we will perform the test in a timely manner in prospective clinical work, and our future assessments will be more accurate.

It was reported that the Mayo stage and the level of pro-BNP/BNP were related to the prognosis of light chain patients(21–22). But our study shows that the Mayo stage 2004 does not correlate patient survival. Other studies have found that the number of organs involved (more organs were worse) was a poor prognostic factor, which was not proven in our study. In our data, the type of organ that is involved is more important than the number of organs involved, which affects the OS.

To date, only a few studies have focused on light-chain amyloidosis in China. The small number of studies could be because the incidence of light-chain amyloidosis is low, and only some large hospitals can make the diagnosis. The patients' status and treatment also vary across centers. Some patients did not receive therapy when the diagnosis was established, mainly due to financial concerns or the severity of the organ involvement. In this study, between 2010 and 2018, approximately 10% of patients did not receive any treatment. Those patients had a worse clinical outcome, with a median OS of 5.1 months, which was less than the OS that was reported previously, compared to that of patients who did receive treatment (23). In our study, 56% of patients received bortezomib-based regimens, such as VCD or VD, but only one patient received ASCT, which was mainly attributed to the patient status and cardiac involvement. ASCT can induce durable hematological and organ responses in systemic light-chain amyloidosis(24). However, because of the small number of patients who received ASCT in our study, we could not analyze this factor. In addition, we also found that albumin, a light-chain type, did not affect patient survival in this study. We did only few FISH tests for these patients, so this factor could not be used as a prognostic factor in our data.

Conclusions

This retrospective study reports the detailed clinical presentations of pAL patients and prognostic factors at four hospitals in China. Cardiac involvement and negative immunofixation in the serum and urine after treatment were independent prognostic factors for OS in pAL patients. The type and number of organs involved are more important than the number of organs involved and affects the OS. These results may help to improve the diagnosis, treatment, and patient care of pAL, as well as to provide data that will aid future meta-analysis.

Abbreviations

OS = overall survival

auto-ASCT = autologous stem cell transplantation

pAL = primary light chain amyloidosis

VD/VCD = bortezomib + dexamethasone/bortezomib + cyclophosphamide + dexamethasone

HDM = high dose melphalan

MRI = Magnetic Resonance Imaging

ORR = overall response rate

BNP = B-type natriuretic peptide

Declarations

Ethics, consent and permissions

The study was approved by the ethical committee of the First Affiliated Hospital, School of Medicine, Zhejiang University, and informed written consent was obtained from all of the patients before their participation in the study.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request

Competing interests

The authors have stated that they have no conflicts of interest.

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Authors' contributions

DHH and ZC designed the study. FSG, MLH, GFZ, PH, GW, XYH, WJW and YZ performed the data collection. MLH, FSG JSH and YY did the statistical analysis, DHH, MLH and ZC assessed the efficacy and wrote the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline demographic, clinical characteristics and treatment	
	Patients(n=91)
Median age, year(range)	60 (41-82)
Male, n (%)	51 (56)
ECOG 2 or more, n (%)	32 (35.2)
Organ involvement, n(%)	
Renal	83(91.2)
Cardiac	51(56)
Hepatic	13(14.3)
Gastrointestinal	14(15.4)
Soft tissue	17(18.7)
Peripheral neuropathy	6(6.6)
Lung	6(6.6)
Number of organ involved	
1, n (%)	29 (31.9)
2, n(%)	41 (45.1)
≥3, n(%)	21 (23)
Heavy chain	
IgG, n (%)	21 (23.1)
IgA, n (%)	20 (22.0)
Light chain, n (%)	50 (54.9)
Light-chain isotype	
Kappa, n (%)	31 (34.1)
Lambda, n (%)	60 (65.9)
Mayo Stage 2004, n (%)	
Stage I/II/III	19(20.9)/22(24.2)/14(15.4)

Missing	36(39.6)
Renal Stage, n (%)	
Stage I/II/III	33(36.3)/37(40.7)/9(9.9)
Missing	12(13.2)
BMPCs, median (range)	5(0-14)
Hb(g/L), median (range)	125 (79-190)
NTproBNP(pg/mL), median (range)	1195 (14-9000)
Serum albumin(g/L), median (range)	26.8 (10.5-47.4)
Creatinine(μmol/L), median (range)	79（29-579）
24 urine protein(g) , median (range)	
Treatment	
VD/VCD, n (%)	51(56.0)
TCD, n (%)	24(26.4)
MP, n (%)	2(2.2)
RD, n (%)	3(3.3)
Other (including no-treatment), n (%)	11(12.1)

Abbreviations: BMPCs = bone marrow plasma cells;

VD/VCD = Bortezomib + dexamethasone / Bortezomib + cyclophosphamide + dexamethasone; TCD = thalidomide + cyclophosphamide + dexamethasone ; MP = Melphalan + prednisone; RD = Lenalidamine + dexamethasone.

Table 2

Characteristic	HR	95% CI	p value
Age> 65 years	1.719	0.867-3.409	0.117
Sex (male)	1.171	0.624-2.197	0.623
ECOG ≥ 2	2.802	1.485-5.289	0.001
Renal involvement	0.320	0.132-0.774	0.008
Cardiac involvement	3.331	1.621-6.845	0.001
Hepatic involvement	2.828	1.290-6.201	0.007
3 or more organ involved	1.943	0.830-4.544	0.119
eGFR（<50mi/min/1.73m^2）	1.840	0.911-3.716	0.084
Serum albumin（<30g/L）	0.746	0.396-1.408	0.365
Bortizomib treatment	0.560	0.276-1.136	0.108
K light chain	1.179	0.615-2.261	0.62
Mayo Stage 2004(I vs II/III)	0.499	0.215-1.161	0.107
Hematologic response: Negative immunofixation	0.155	0.053-0.45	<0.001

Table 3

Characteristic	HR	95% CI	p value
ECOG ≥ 2	1.376	0.56-3.378	0.487
Renal involvement	0.41	0.146-1.148	0.09
Cardiac involvement	3.15	1.253-7.916	0.015
Hepatic involvement	3.026	0.83-11.033	0.093
Hematologic response: Negative immunofixation	3.15	1.253-7.916	<0.001

Figures

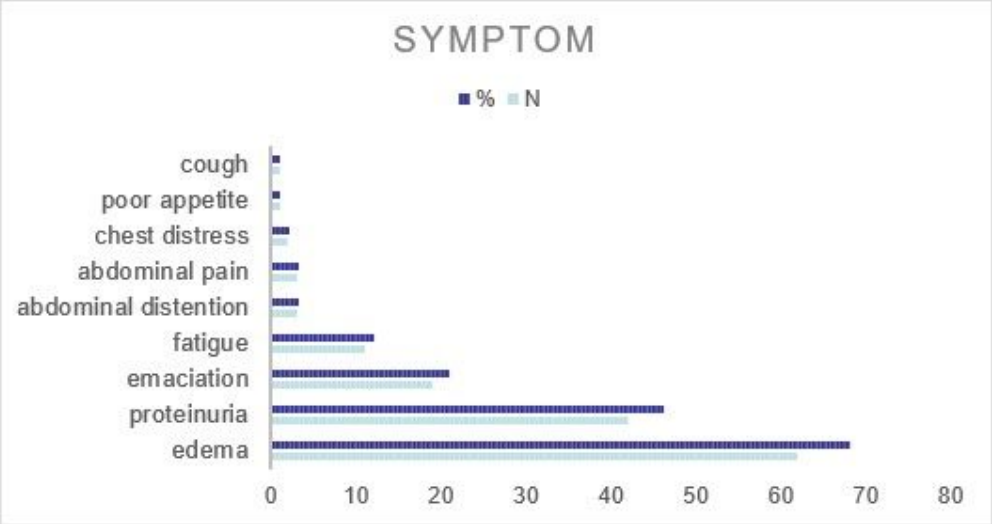

Figure 1

The incidence of symptoms at presentation.

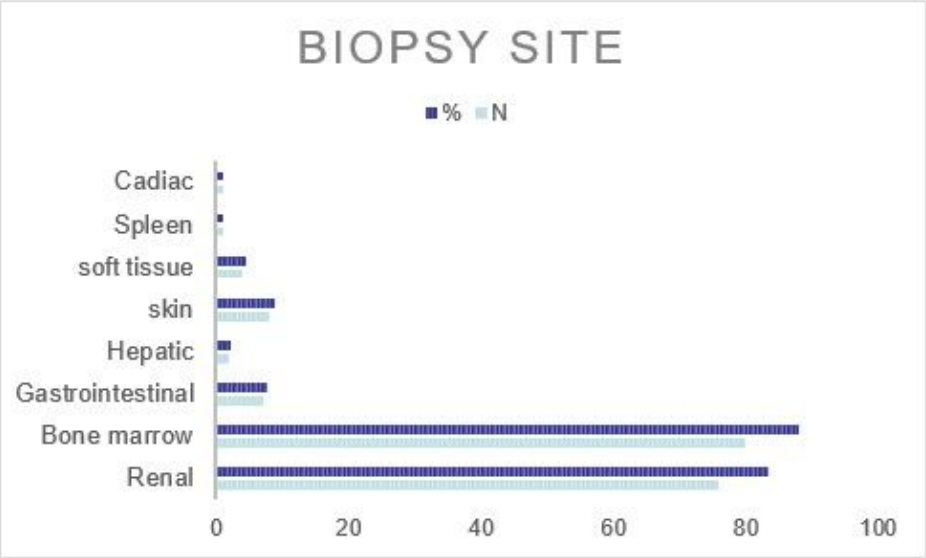

Figure 2

The biopsy site(s) of all patients.

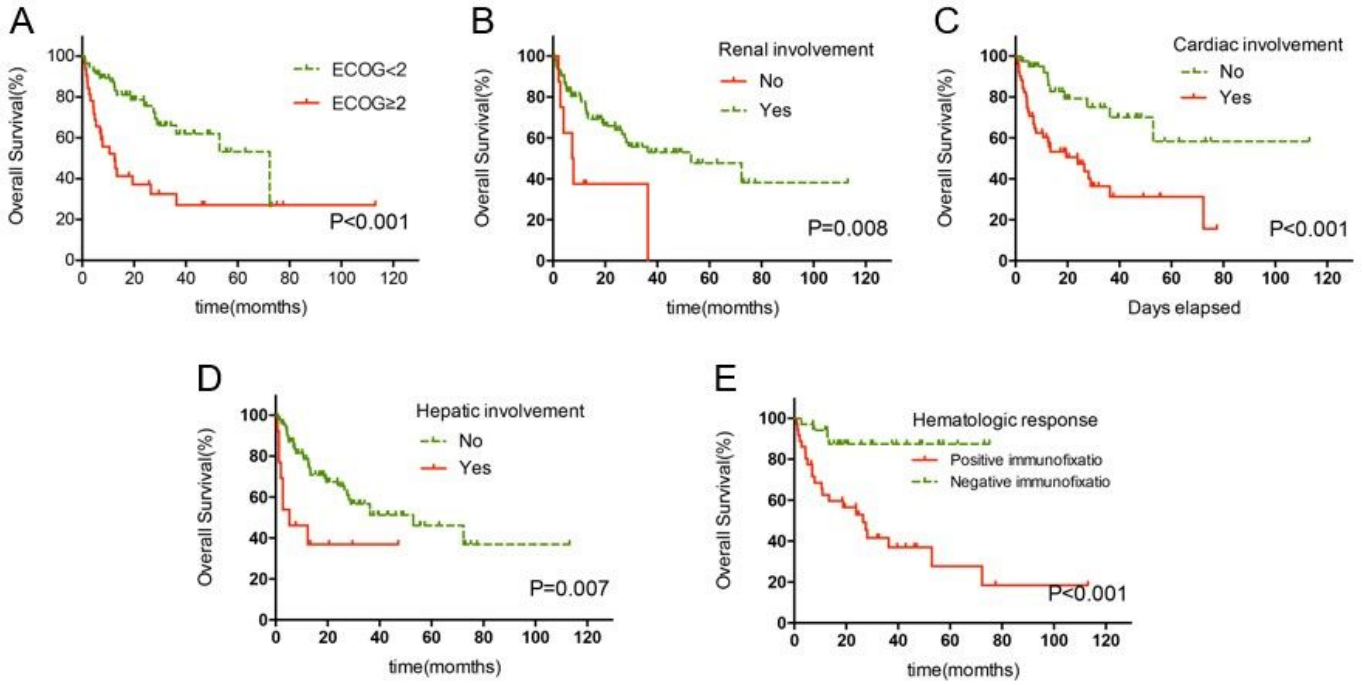

Figure 3

Kaplan-Meier curves demonstrating differences in overall survival. (A) Survival of patients according to ECOG: ECOG>=2 vs ECOG< 2 (P=0.002). (B) Survival of patients with and without renal involvement (P <0.001). (C) Survival of patients with and without hepatic involvement (P =0.002). (D) Survival of patients with and without cardiac involvement (P=0.032). (E) Survival of patients according to immunofixation results (P <0.001).

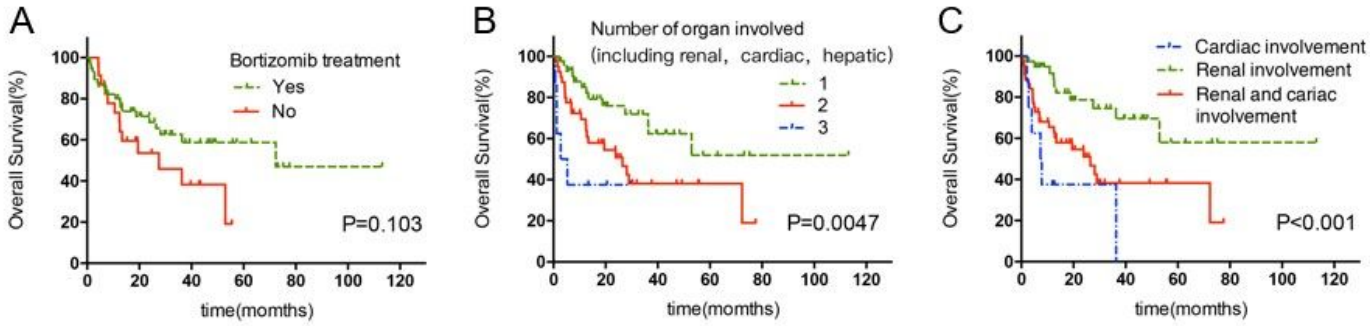

Figure 4

Overall survival according to the treatment group. (A) Survival of patients with and without bortezomib treatment (P =0.103). (B) Survival of patients who had different numbers of organ involved, including cardiac, renal and hepatic involvement (1 vs 2 P=0.017; 1 vs 3 P=0.002; 2 vs 3 P=0.172). (C) Survival of patients with renal involvement, cardiac involvement, concurrent renal and cardiac involvement (renal vs cardiac P=0.000; renal vs concurrent P=0.003; cardiac vs concurrent P=0.167).

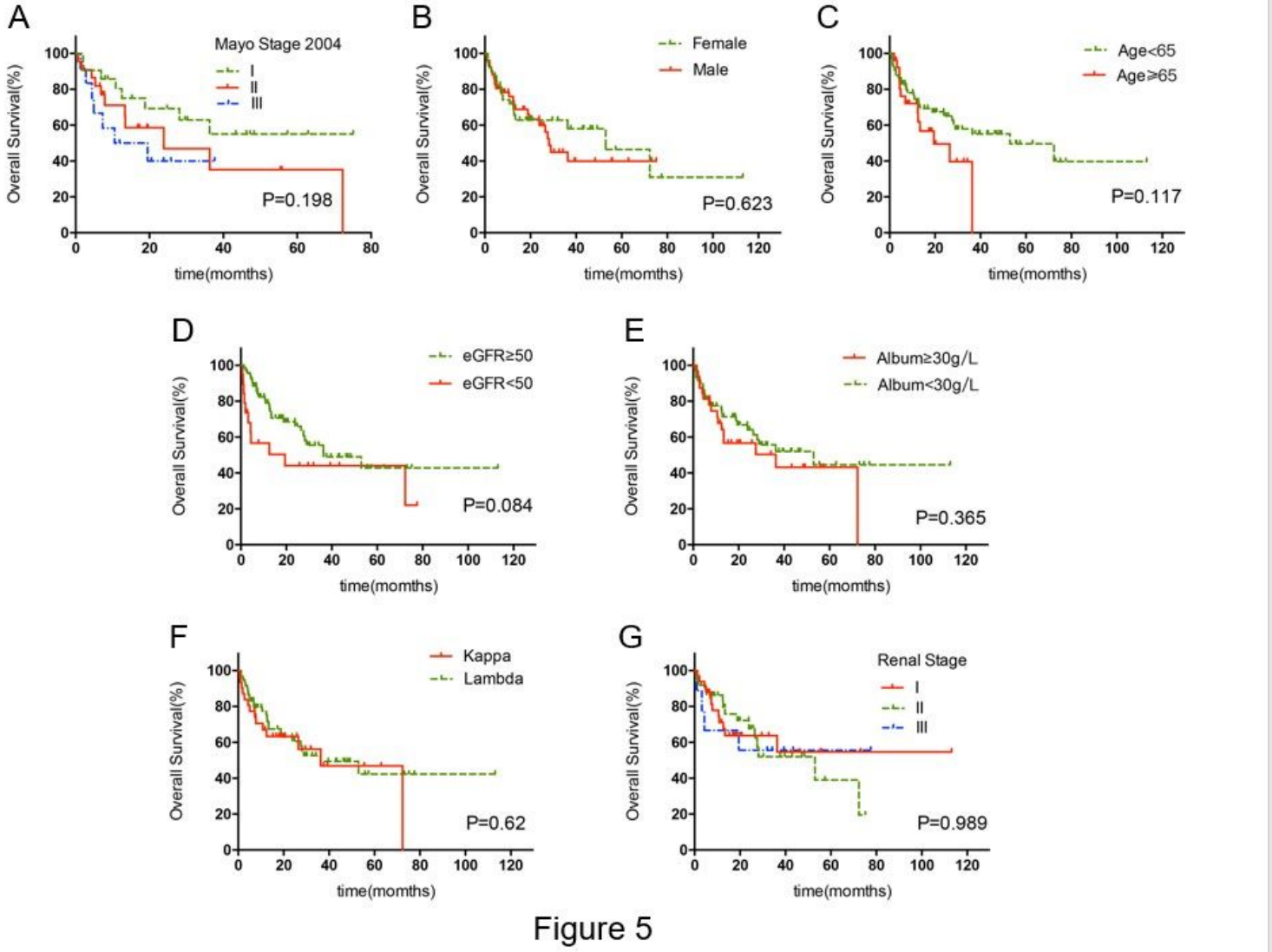

Figure 5

Figure 5

Overall survival of patients according to (A) the Mayo stage 2004 (stage I vs stage II P=0.193; stage I vs stage III P=0.116; stage II vs stage III P=0.490), (B) sex (P=0.623), (C) age (P=0.117), (D) eGFR (P=0.084), (E) albumin (P=0.365), (F) light-chain isotype (P=0.62) and (G) renal stage (P=0.989).