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Review Article

Treatment of Immunoglobulin Light Chain Amyloidosis in China: A Scoping Review and Meta-Analyses for Single-Group Studies

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Abstract

Objective: Immunoglobulin light chain (AL) amyloidosis is an incurable plasma cell disorder that leads to multiple organ dysfunction. This scoping review aimed to map and assess current available evidence on treatment regimens and their efficacy and safety for patients with AL amyloidosis in China.

Methods: PubMed, Embase, and China National Knowledge Infrastructure were systematically searched using terms related to "AL amyloidosis" and "China". Studies were finally included on the treatment regimens for AL amyloidosis and the evidence were summarized on the efficacy and safety of the treatment regimens.

Results: Twenty-three studies were included (2 randomized controlled trials, 8 cohort studies, and 13 single-arm studies) which presented 1,552 Chinese patients. The most frequently involved organs were kidney (88.2%) and heart (66.5%). In patients with newly diagnosed AL amyloidosis, the efficacy of different treatment regimens was assessed in 17 studies the on hematological responses or organ responses. Substantial variations were observed in the efficacy. Hematologic Complete Responses (CRs) were 57%, 49%, 41%, 17%, 29% and 83% in newly diagnosed patients treated by Autologous Stem Cell Transplant (ASCT) with bortezomib induction, only ASCT, bortezomib-based, Melphalan-based, immunomodulatory drugs-based, and daratumumab-based regimens, respectively. ASCT with bortezomib induction had the highest cardiac, renal and liver response (81%, 64% and 73%, respectively) in a naïve comparison. However, organ responses were not reported for daratumumab-based regiments. Limited number of studies (n=3) enrolled relapse or refractory patients with AL amyloidosis showing that daratumumab yield a better outcome in comparison without adjustment.

Conclusions: It is worth to note that daratumumab-based regiments show promising response rate in patients with newly diagnosed AL amyloidosis. However, the substantial variation of efficacy/effectiveness of different regimens may result from the incomparable patients baseline characteristics. Further head-to-head clinical trials is needed to provide stronger evidence on the efficacy of various available regiments in Chinese patients.

Keywords: Immunoglobulin light chain amyloidosis; Chinese; Autologous stem cell transplant; Bortezomib; melphalan; Immunomodulatory drugs; Daratumumab

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Introduction

Amyloid Light chain (AL) amyloidosis is a rare plasma cell disorder caused by the deposition of misfolded immunoglobulin light chains in various organs and tissues, leading to organ dysfunction [1]. Usually, patients with AL amyloidosis have poor prognosis due to delayed diagnosis and advanced multiple organ damage [2]. Current treatment approaches in AL amyloidosis include proteasome inhibitors, immunomodulatory agents, anti-CD38 monoclonal antibodies, and Autologous Stem Cell Transplant (ASCT) in eligible patients [3]. The practical recommendations have comprehensively summarized the evolution and options of treatment for AL amyloidosis, involving ASCT with or without induction, or systemic chemotherapy [3]. Active agents include corticosteroids, melphalan, bortezomib, thalidomide, lenalidomide, daratumumab or the combinations of these drugs [4]. These regimens have been applied in Chinese population with AL Amyloidosis according to the local guidelines. To date, although the number of studies on the treatment of AL amyloidosis in Chinese population has increased, there is still no comprehensive review in respect to the efficacy of current treatment strategies, and the evidence of treatment for these patients remains unclear. Here in this review, we systematically reviewed the literature to elucidate the current progression of research on the treatment of AL amyloidosis in Chinese patients and summarize the efficacy and safety of the current available treatment regimens for these patients.

Methods

This scoping review was conducted and reported in accordance with the PRISMA Extension for Scoping Reviews [6]. It was registered on International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY 2021100096).

Eligibility criteria

The PICO framework was used to structure the eligibility criteria for the review. Population: Chinese population with AL amyloidosis. Intervention: all interventions identified by the searches, including ASCT-based regimen, bortezomib-based regimen, Immunomodulatory Drugs (IMiDs)-based regimen, melphalan-based regimen, or daratumumab-based regimen. The following studies were excluded: studies published before 2010, AL amyloidosis with Multiple Myeloma (MM), no available data, case reports, reviews, consensuses, theses, and questionnaires. Primary outcomes included hematologic response, organ response and response of hematologic and organ for patients with Mayo staging and renal involvement. Secondary outcomes included time to hematologic response, time to organ response, Progression-Free Survival (PFS), Overall Survival (OS), any grade Adverse Events (AE), and grade 3 or 4 AE.

Data Sources and Search

A literature search was conducted in three databases including PubMed, Embase, and China National Knowledge Infrastructure (CNKI) from Jan 2010 and Feb 2021. Search terms included "amyloidosis", "amyloidos*" "amyloido*", "AL amyloidosis", "China", and their variants. Detailed search strategy for each database is shown in Supplementary Table S1. Additional studies were identified by searching the reference lists of retrieved studies and previously published reviews.

Study Selection

Duplicate records were removed using EndNote (Clarivate Analytics, Canada). Furthermore, the titles and abstracts were screened and labeled with inclusion, exclusion, or uncertainty. For the included and uncertain records, the full-text articles were reviewed to assess their eligibility. In case of disagreement, consensus was reached through discussion. The quality of all included studies were checked. The results of the quality assessment of the included studies are shown in Supplementary Table S3-S5.

Table 1: Therapeutic regimens of 23 included studies in the review.

Patients	Regimens	No. of patients (%)	No. of studies (n)
Newly diagnosed	**ASCT**	380	8
	No induction	180(47.4%)	7
	Bortezomib-based induction	152(40.0%)	2
	Other chemotherapeutic induction*	48(12.6%)	2
	Non-ASCT	731	15
	Bortezomib-based regimen	397(54.3%)	10
	Other traditional agents	327	7
	Melphalan-based regimen	123(16.8%)	3
	IMiDs-based regimen	101(13.8%)	2
	Mixed regimens#	103(14.1%)	2
	Daratumumab based regimen	7(1.0%)	1
Relapsed or refractory	**Non-ASCT**	43	3
	IMiDs-based regimen	10	1
	Daratumumab-based regimen	33	2
Newly diagnosed and relapsed or refractory	**Non-ASCT**	56	3
	Bortezomib-based regimen	56	3

Note: *other chemotherapeutic induction include: (1) bortezomib or melphalan or IMiDs induction (2) melphalan or IMiDs or vincristine induction. #Mixed regimens include: (1) melphalan or IMiDs regimen (2) bortezomib and doxycycline

Data Extraction

A data extraction form was developed to obtain study information including cities or region of the study locations, study population, study design, sample size, treatment of AL amyloidosis (regimens, duration, dose, timing), and clinical outcomes, including but not limited to hematological responses and organ responses, OS, PFS and AE. Any disagreements being resolved through discussion.

Statistical Analyses

This scoping review quantitatively and qualitatively demonstrated the information on publication and main outcomes of the various therapeutic regimens. The Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) were the primary effect measure to indicate the association between treatments and clinical outcomes. Statistical heterogeneity was assessed by the Cochrane Q test ($P<0.1$ indicating significance) and quantified by the I^2 statistic ($I^2>50\%$ for a significant heterogeneity) [7,8]. Fixed-effect model were conducted and switched to random-effects model analysis when $I^2>50\%$. Two-sided $P<0.05$ was considered statistically significant. In terms of studies with no events, a fixed value (0.5) was added to the cells of the table. All analyses were performed using R software (meta-package, the R Core Team 2020).

Table 2: Characteristics of 23 included studies in the review.

Characteristics	ASCT		Non-ASCT	
	Total number of patients, n (%) ASCT	No. of studies (n)	Total number of patients, n (%) Non ASCT	No. of studies (n)
Age (n_{total} = 1135)	400	6	735	16
Range of median	50-55		53-66	
Gender (n_{total} = 1097)	362	6	735	16
Male	199(55.0%)		445(60.5%)	
Female	163(45.0%)		290(39.5%)	
Disease course (n_{total} = 1066)	331	5	735	16
Newly diagnosed	331(100.0%)		571(77.7%)	
Relapsed /Refractory	—		29(3.9%)	
Both*	—		135(18.4%)	
Type of light chains (n_{total} = 649)	79	4	570	12
Lambda	62(78.5%)		445(78.1%)	
Kappa	17(21.5%)		125(21.9%)	
Mayo 2004 cardiac staging system (n_{total} = 507)	258	2	249	4
I	139(53.9%)		47(18.9%)	
II	76(29.5%)		115(46.2%)	
III	43(16.7%)		87(34.9%)	
Mayo 2012 cardiac staging system (n_{total} = 502)	227	1	275	7
I	136(59.9%)		119(43.3%)	
II	55(24.2%)		63(22.9%)	
III	36(15.9%)		77(28.0%)	
IV	0		16(5.8%)	
Clonal plasma cell in bone marrow	247	2	95	3
≥10% (n_{total} = 342)	0		0	
ECOG (n_{total} = 306)	283	2	23	2
0	35(12.4%)		—	
1	148(52.3%)		6(26.1%)	
2	100(35.3%)		7(30.4%)	
3	—		8(34.8%)	
4	—		2(8.7%)	
Organ involvement				
Renal	357/362(98.6%)	6	604/714(84.6%)	15
Cardiac	193/362(53.3%)	6	528/684(77.2%)	14
Soft tissue	2/31(6.5%)	1	26/220(11.8%)	5
Gastrointestinal tract	—	—	5/12(42.0%)	1
Liver	25/327(7.6%)	4	106/629(16.9%)	11
Nerves	12/347(3.5%)	5	48/462(10.4%)	7

Note: *means the articles included patients who were newly diagnosed and relapsed/refractory.

Results

Study Selection

Figure 1 shows the study selection process. The initial search yielded 891 records. We excluded 134 duplicates leaving 757 records, of which 195 were removed after title and abstract screening determined they were irrelevant to our analysis. After full-text review, 26 of 562 reports remained [15-40]. Three records were further excluded because of noted duplications of hospital, patient sample size, recruitment time, and intervention details. Finally, 23 studies were included for this analysis [15,16,18-22,24-28,30-40].

Study Characteristics

The included studies were published between 2010 and 2021 and were with the number of patients ranging from 10 to 332, with a total of 1,552. For study designs, thirteen studies were single-arm, eight were cohort, and two were randomized clinical trials. These studies were conducted in six cities in China (12 in Nanjing, 9 in Beijing, 2 in Xi'an, and 1 in Guangzhou, Shanghai, and Zhengzhou). The Medical School of Nanjing University Affiliated Jinling Hospital conducted half of the studies (50%), followed by Peking Union Medical College Hospital (20.8%), and Xijing Hospital (8.3%).

Pooled Patient Characteristics

A total of 1,552 patients were available for final analysis. For patients undergoing ASCT, the range of median age was 50 to55 years, and 55.0% were males. While for patients treated with non-ASCT, the range of median age was 53 to 66 years, and 60.5% were male, those were older than patients undergoing ASCT. Most included patients were newly diagnosed. Patients who did not receive ASCT had more advanced disease than those who received ASCT according to 2004 and 2012 Mayo staging system. No patients had clonal plasma cells ≥10%. 35.3% of 283 patients undergone ASCT had ECOG performance status ≥2. The most involved organs at the time of diagnosis were renal, cardiac, gastrointestinal tract, soft tissue, and ner-

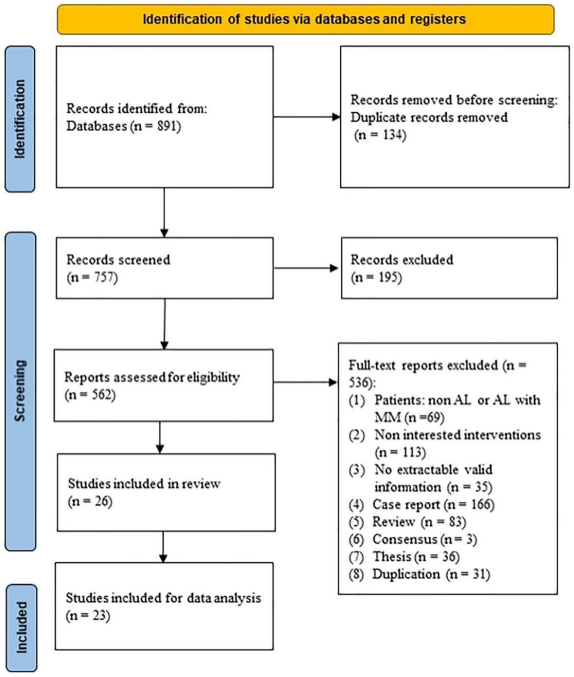

Figure 1:

vous system. Patients received non ASCT treatment had a lower proportion of cardiac, soft tissue, liver and nerve involvement. Patient characteristics are summarized in Table 2 and Supplementary Table S2.

Major Regimens in Studies

The detailed therapeutic regimens are presented in Table 2. For Newly Diagnosed AL Amyloidosis (NDAL), eight studies were focused on ASCT, of which seven studies reported ASCT without induction therapies. In all newly diagnosed patients that received ASCT, 47.4% of patients treated with ASCT did not receive induction, 40.0% of patients received bortezomib-based induction, and 12.6% of patients received other chemotherapeutic induction prior to ASCT.

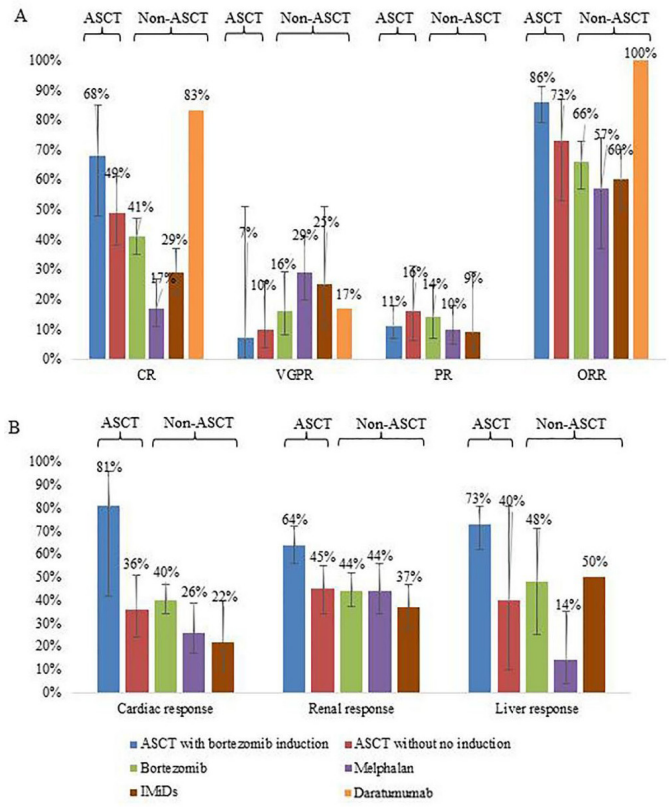

Figure 2:

For patients who did not receive ASCT as part of the initial treatment, bortezomib-based regimen (54.3%) was the most common treatment (bortezomib-cyclophosphamide-dexamethasone, bortezomib-dexamethasone), followed by melphalan-based regimen (16.8%) and iMiDs-based regimen (13.8%).

Of the 3 studies evaluating treatments for patients with Relapsed/Refractory AL Amyloidosis (RRAL), two were daratumumab studies. The number of investigations in specific relapsed or refractory patients are limited with one for IMiD-based regimens and one for daratumumab-based regimens. In addition, three studies reported bortezomib-based regimens in both NDAL and RRAL.

Outcomes of Treatments for NDAL

Haematological Responses

In five studies reported [22,25,30,40], the median time to original haematologic response was 1 month for ASCT, 4 months for IMiDs-based regimen, and 1 to 2 months for bortezomib-based regimen. In three studies [30,34,40], the median time to the best haematologic response, was 4, 2 and 5 months for ASCT, bortezomib-based regimen, and melphalan-based regimen, respectively. The pooled Complete Response (CR) rate was higher in patients who underwent ASCT with (68%, n=28) or without induction (49%, n=77) than in patients treated with non-ASCT regimens. Furthermore, patients who underwent ASCT with induction had the highest overall response rate (86%), followed by those treated with ASCT without induction (73%), bortezomib (66%), IMiDs (60%) and melphalan (57%). Patients treated with daratumumab (n=6) achieved deep remission with a CR, VGPR and ORR rate of 83.3%, 16.7% and 100% respectively [16]. The haematological responses of different treatment regimens are summarised in Figure 2A and Table S6. One study [26] (n=38) showed patients with AL amyloidosis and cardiac stage III (38.9%) achieved a lower ORR than patients with cardiac stage I and II (72.7% and 55.6%, respectively).

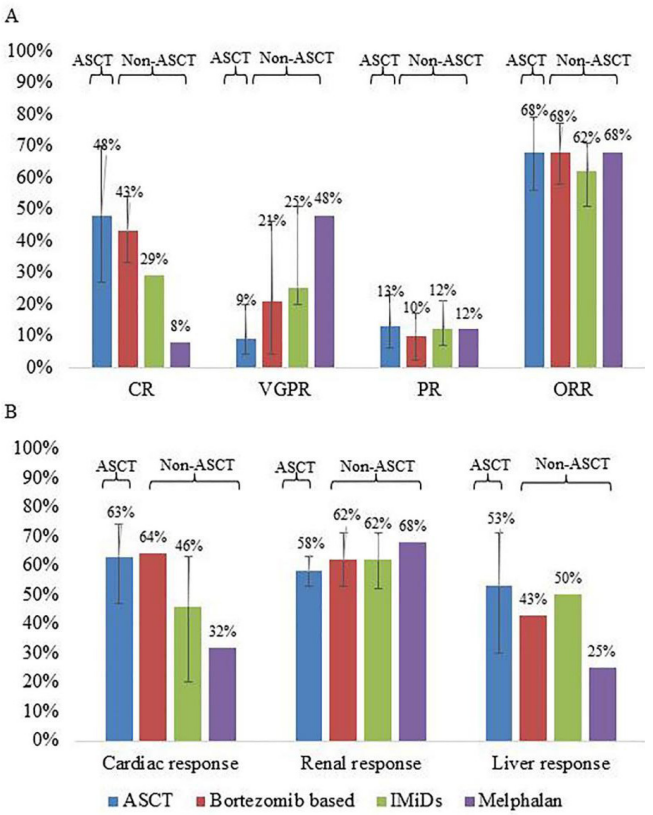

Figure 3:

Organ responses: Four studies [18,36,40] reported the median time to organ response ranged from 6 to 8 months for ASCT [30,34] and 3 months for bortezomib-based regimen [12]. Patients who underwent ASCT with induction therapy had the highest cardiac (81%, n=7), renal (64%, n=146) and liver (73%, n=88) response rates. Organ response rates to different treatment regimens are summarised in Figure 2B and Table S7. One study [22] (n=52) reported the cardiac response rate was lower in patients with cardiac stage III (15.0%) than in those with stage I (80.0%) and II (31.8%) when treated with bortezomib.

Patients with renal involvement: Only a few studies with small sample sizes described the treatment efficacy of different regimens in patients with renal involvement. Although ASCT and bortezomib-based treatment had a deep haematologic response compared with other regimens, there was not much difference in ORR rate between the different treatments. Cardiac (32% to 64%), renal (58%-68%), and liver (25%-53%) response rates are presented in Figure 3 and Table S8.

Progression-free survival (PFS) and overall survival (OS): In two studies, the 3-year PFS rate was 92.6% and 66.7% for with patients AL amyloidosis treated with ASCT (n=27) and bortezomib therapy (n=42), respectively [30,40]. Two studies reported a 6-month OS rate of 67.7% for bortezomib (n=62) and 83.2% for melphalan (n=30) [19,30]. The pooled 3-year OS rate was 82% (95% CI, 59%-93%) for ASCT (3 studies, n=57), 65% (95% CI, 54%-74%) for bortezomib (3 studies, n=88), 63% (95% CI, 55%-71%) for melphalan (3 studies, n=126), and 71% (95% CI, 61%-79%) for IMiDs (2 studies, n=101). See table S9 for additional information.

Safety: Adverse Events (AEs) varied in different studies and were heterogeneous for different treatment regimens. One study (n=28) reported the most common (≥15%) grade 3 or 4 AEs were infection (28.6%), thrombocytopenia (28.6%), gastrointestinal toxicity (25.0%), neurological lesion (17.9%), and oedema (17.9%) in patients who received bortezomib induction followed by ASCT [37]. In one study (n=15), bone marrow suppression occurred in all patients (100%) who underwent ASCT [36]. Neuralgia (20.9%) and gastrointestinal reactions (19.4%) were the most common (≥15%) grade 3 or 4 AEs in patients treated with bortezomib (n=72) [22].

Treatments for RRAL

One study [15] of daratumumab for the treatment of RRAL amyloidosis reported an ORR rate of 84.2% (n=19), cardiac response rate of 50% (n=10), and renal response rate of 58.3% (n=12). Rates of CR (14.3%), PR (28.6%), ORR (42.9%), cardiac response (28.6%) and renal response (0.0%) in IMiDs-based regimen were also reported for the treatment of RRAL amyloidosis (n=7) [24].

Discussion

To our knowledge, this scoping review is the first synthesis of the literature on current treatment regimens in Chinese patients with AL amyloidosis. It provides a comprehensive landscape of evidence on demographic characteristics, treatment modalities and clinical outcomes from 23 heterogeneous studies in 1552 patients. The findings suggest that a significant proportion of the studies were focused on ASCT and bortezomib-based therapies. Evidence on the emerging therapies, such as daratumumab-based regimens, is sparse. Moreover, there were limited numbers of studies investigating the efficacy/effectiveness and AEs in subgroup patients.

In our aggregated analysis, ASCT was a highly effective therapy with higher rates of deep haematologic and organ responses in patients with AL amyloidosis compared with traditional regimens. Two of 8 studies conducted induction therapy prior to ASCT and suggested induction yielded better outcomes. A retrospective study [41] of 629 patients demonstrated a benefit of ASCT in AL amyloidosis. In that study, the median overall survival was 7.63 years with a median follow-up of 8 years, and patients achieving a haematologic CR were more likely to have longer OS (not reached vs. 6.3 years). Because of the association between deep remission, superior survival benefit, and reduced Transplant-Related Mortality (TRM) [42] in selected patients, ASCT remains an important first-line treatment option [43,44].

As for patients who were ineligible for ASCT, current treatments for AL amyloidosis were mainly based on anti-plasma cell therapies including alkylating agents, proteasome inhibitors, and immunomodulatory agents. A Mayo clinic study showed that due to a growing availability of effective treatments and potentially better patient baselines resulting from earlier diagnosis, the death rate within 6 months of diagnosis has decreased in recent periods for non-ASCT patients, although one third of patients still died within 6 months of diagnosis [45]. Achieving rapid and deep haematologic responses and relieving or potentially reversing organ dysfunction could improve survival outcomes [46,47].

In our review, bortezomib-based regimens were the most used therapies for newly diagnosed patients with AL amyloidosis. The deep remission rate (CR: 41; VGPR: 16%) and organ response rates (cardiac: 40%; renal: 44%) were higher in bortezomib than with other chemotherapies, and daratumumab-based regimen showed encouraging results with CR of 83.3% and VGPR of 16.7%. In the phase 3 ANDROMEDA study, the addition of daratumumab to VCd (DVCd) resulted in a significant improvement in the rates of complete haematologic response (53% vs 18%), as well as cardiac (42% vs 22%) and renal (54% vs 27%) responses [48].

This study followed the reporting guidelines of PRISMA Extension [49] for Scoping Reviews and presented and summarised evidence from as many studies as possible. Nonetheless, there are several potential limitations. First, although we conducted a comprehensive literature search, it is still possible some studies were overlooked. Second, this study was limited by the bias of included studies, which may not fully reflect the current situation surrounding treatment options available to patients with AL amyloidosis in China. Third, due to the limited amount of data available, statistical analysis of the efficacy and safety of some treatment regimens could not be completely assessed.

Conclusions

According to the present study, current evidence of treatment for Chinese patients with AL amyloidosis was mostly derived from real-world retrospective analyses. ASCT was an effective therapy, and bortezomib-based regimens were the most used therapies for patients with AL amyloidosis in China. Several studies also observed that daratumumab-based regiments had promising response rate in patients with newly diagnosed AL amyloidosis. Our results showed there is limited data about the treatment patterns and outcomes of patients with AL amyloidosis in China. Treatments for Chinese patients with AL amyloidosis need to be further investigated.

Author Statements

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Author Contributions

(I) Conception and design: Jin Lu, Xianghua Huang and Xiaohong Wang; (II) Administrative support: Xin Gao and Bin Wang; (III) Provision of study materials or patients: Xīn Gào, Lingjie Xu, and Wang Liu; (IV) Data analysis and interpretation: Jin Lu, Xianghua Huang and Xiaohong Wang; (V) Manuscript writing: All authors; (VI) Final approval of manuscript: All authors

Conflict of Interest Statement

The authors report there are no competing interests to declare.

Data Statement

It is available from the corresponding author upon reasonable request.

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