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Original Article

Clinical characteristics and outcomes of Castleman disease: a multicenter Consortium study of 428 patients with 15-year follow-up

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Abstract: Castleman disease (CD) has been reported as a group of poorly understood lymphoproliferative disorders, including unicentric CD (UCD) and idiopathic multicentric CD (iMCD) which are human immunodeficiency virus (HIV) negative and human herpes virus 8 (HHV-8) negative. The clinical and independent prognostic factors of CD remain poorly elucidated. We retrospectively collected the clinical information of 428 patients with HIV and HHV-8 negative CD from 12 large medical centers with 15-year follow-up. We analyzed the clinicopathologic features of 428 patients (248 with UCD and 180 with iMCD) with a median age of 41 years. The histology subtypes were hyaline-vascular (HV) histopathology for 215 patients (56.58%) and plasmacytic (PC) histopathology for 165 patients (43.42%). Most patients with UCD underwent surgical excision, whereas the treatment strategies of patients with iMCD were heterogeneous. The outcome for patients with UCD was better than that for patients with iMCD, 5-year overall survival (OS) rates were 95% and 74%, respectively. In further analysis, a multivariate analysis using a Cox regression model revealed that PC subtype, hepatomegaly and/or splenomegaly, hemoglobin ≤ 80 g/L, and albumin ≤ 30 g/L were independent prognostic factors of CD for OS. The model of iMCD revealed that age > 60 years, hepatomegaly and/or splenomegaly, and hemoglobin ≤ 80 g/L were independent risk factors. In UCD, single-factor analysis identified two significant risk factors: hemoglobin ≤ 100 g/L and albumin ≤ 30 g/L. Our study emphasizes the distinction of clinical characteristics between UCD and iMCD. The importance of poor risk factors of different clinical classifications may direct more precise and appropriate treatment strategies.

Keywords: Castleman disease, clinical characteristics, treatment, risk prognostic factors

Introduction

Castleman disease (CD) is a heterogeneous group of rare lymphoproliferative disorders that was first described by Dr. Benjamin Castleman in 1956 [1]. According to clinical features and the distribution of enlarged lymph nodes, CD can be subclassified into unicentric CD (UCD)

and multicentric CD (MCD). MCD is more aggressive and is frequently found in patients with human herpes virus 8 (HHV-8) and human immunodeficiency virus (HIV) infection, while MCD without HHV-8 and HIV infection is classified as idiopathic MCD (iMCD) [2]. Pathologically, CD can be classified into the hyaline-vascular (HV) variant and the plasmacytic (PC) variant [3]. The HV type is more common in patients with UCD, and the PC type is more common in patients with MCD.

As the etiology and pathogenesis of CD are unclear, the clinical characteristics and treatment options remain vague. The symptoms of UCD are often lighter, and most are related to enlarged lymph nodes and subsequent compression of adjacent tissues. Complete resection of the involved lesion is considered as the golden standard treatment [4]. The clinical presentation of HHV-8-associated MCD and iMCD varies from mild symptoms to life-threatening cytokine storms, which can both present with recurrent episodes of diffuse lymphadenopathy with systemic inflammatory symptoms, polyserositis, anemia, hypoalbuminemia, and multiple organ system dysfunctions. It can be fatal if improperly treated, and it easily develops into hematologic malignancies [5]. Because of the increasing attention on CD, especially iMCD, which has poor prognosis, an international expert group proposed an international consensus on the diagnosis and treatment of iMCD [6, 7].

Because of its rarity, current studies are mostly retrospective or case reports from single institutions. Here, we analyzed the clinical, laboratory, pathologic, and treatment data and the prognosis of 428 patients with CD from 12 major academic medical centers with 15-year follow-up in China and the US to better understand the disease. Through our retrospective study, we hope to improve our understanding of CD and optimize the diagnosis and prognosis. To the best of our knowledge, this study comprises the largest sample size currently analyzed.

Materials and methods

Patients

To establish the study cohort, we collected data of 428 patients with CD from 10 large medical centers in China (Sun Yat-Sen University Cancer Center, Sun Yat-sen Memorial Hospital, The First Affiliated Hospital of Sun Yat-Sen University, Guangdong Provincial People's Hospital, The First Affiliated Hospital of Zhejiang University, The Second Affiliated Hospital of Zhejiang University, Tianjin Medical University Cancer Hospital, Shandong Provincial Cancer Hospital, Jiangsu Nanjing University Hospital, and Shanxi Provincial Cancer Hospital) and two in the US (University of Texas M. D. Anderson Cancer Center and Indiana School of Medicine) between January 1994 and December 2017, which included 355 Asian and 73 American patients. All patients presented with an enlarged lymph node area, and CD diagnosis was confirmed based on international, evidence-based consensus diagnostic criteria for UCD and iMCD [7-9]. We excluded patients with lymph node hyperplastic disease, rheumatic disease, malignant tumor, and polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome and other diseases.

We collected the clinical information, including gender, age, race, clinical characteristics, laboratory results, radiological findings, pathologic types, and treatment strategies from the medical records. B symptoms were defined as fever above 38°C, night sweats, or weight loss ≥ 10% in the past 6 months. Treatment options included surgery, corticosteroids, cyclophosphamide, chemotherapy, rituximab, anti-interleukin-6 (IL-6) monoclonal antibody, thalidomide, radiation therapy, and watching and waiting. The dose, order, and regimen of drugs administered varied across patients.

Follow-up

All patients were followed up by outpatient services or over telephonic conversations (follow-up every 1 to 3 months). The last follow-up date was January 2018, and detailed follow-up records are available for 365 of total 428 patients. The median follow-up time was 41 months (range, 1 to 279 months). Overall survival (OS) was defined as the time from pathological diagnosis until death, loss to follow-up, or last follow-up. Treatment failure was defined as recurrence, disease progression, or death of any cause. Relapse or progression was determined by the Lugano classification. The

Table 1. The baseline demographic clinical features of patients with CD in our cohort (N = 428)

	Total	UCD		iMCD		*P* value
	N	N	No. of patients N (%)	N	No. of patients N (%)	
Gender	428	248		180		0.2237
Male			112 (45.16)		92 (51.11)	
Female			136 (54.84)		88 (48.89)	
Age (years)	394	235		159		< 0.0001
≤ 40			136 (57.87)		54 (33.96)	
40 < age ≤ 60			75 (31.91)		77 (48.43)	
> 60			24 (10.21)		28 (17.61)	
Ethnicity	428	248		180		0.9379
American			42 (16.94)		31 (17.22)	
Asian			206 (83.06)		149 (82.78)	
Histological subtype	380	221		159		< 0.0001
HV			170 (76.92)		45 (28.30)	
PC			51 (23.08)		114 (71.70)	
Clinical manifestation						
Fever	428	248	5 (2.02)	180	33 (18.33)	< 0.0001
Fatigue	428	248	11 (4.44)	180	34 (18.89)	< 0.0001
Pain	428	248	39 (15.73)	180	30 (16.67)	0.7938
B symptom	428	248	16 (6.45)	180	58 (32.22)	< 0.0001
ECOG	273	122		102		< 0.0001
0-2			122 (100)		78 (76.47)	
3-5			0		24 (23.53)	

CD, Castleman disease; UCD, unicentric Castleman disease; iMCD, idiopathic multicentric Castleman disease; HV, hyaline-vascular variant; PC, plasmacell variant; MIX, mixed cellular variant. B symptom include fever (above 38°C), night sweats, weight loss (more than 10% within 6 months). American include White, Black and Hispanic. The N(x) presents the number of patients and the percentage of each group. UCD and iMCD groups were compared by chi-square test. There is statistic difference when $P < 0.05$.

response was defined as complete response (CR) or partial response (PR), which was evaluated by the Castleman Disease Collaborative Network (CDCN). Some cases in this group were not included due to the lack of objective examination data (such as computerized tomography detection of changes in mass size), resulting in the number of efficacy evaluations being lower than the number of follow-up visits. Patients with survival times longer than 15 years were not included in the follow-up evaluation of risk factors affecting prognosis.

Statistical analysis

Statistical analyses were carried out using SPSS 22.0 (IBM, Armonk, NY, USA). Descriptive statistics were used to analyze the characteristics and treatment outcomes. Different groups were compared using chi-square and Fisher's exact. We used the Kaplan-Meier method to perform univariate analyses of possible prognostic factors for OS, and the log-rank test was used to analyze the survival rate between the two groups. GraphPad Prism software (GraphPad Software, San Diego, California, USA) was used to draw survival curves and to analyze the influence of single factors on OS. Finally, the Cox regression model was used to analyze independent prognostic factors in CD or iMCD. A logarithmic rank test was used to calculate the *P* value, and $P < 0.05$ was considered to indicate statistical significance.

Results

UCD vs. iMCD

We compared the clinical characteristics between patients with UCD and iMCD. The results are shown in **Table 1**. Histopathological and radiological findings were used to classify the

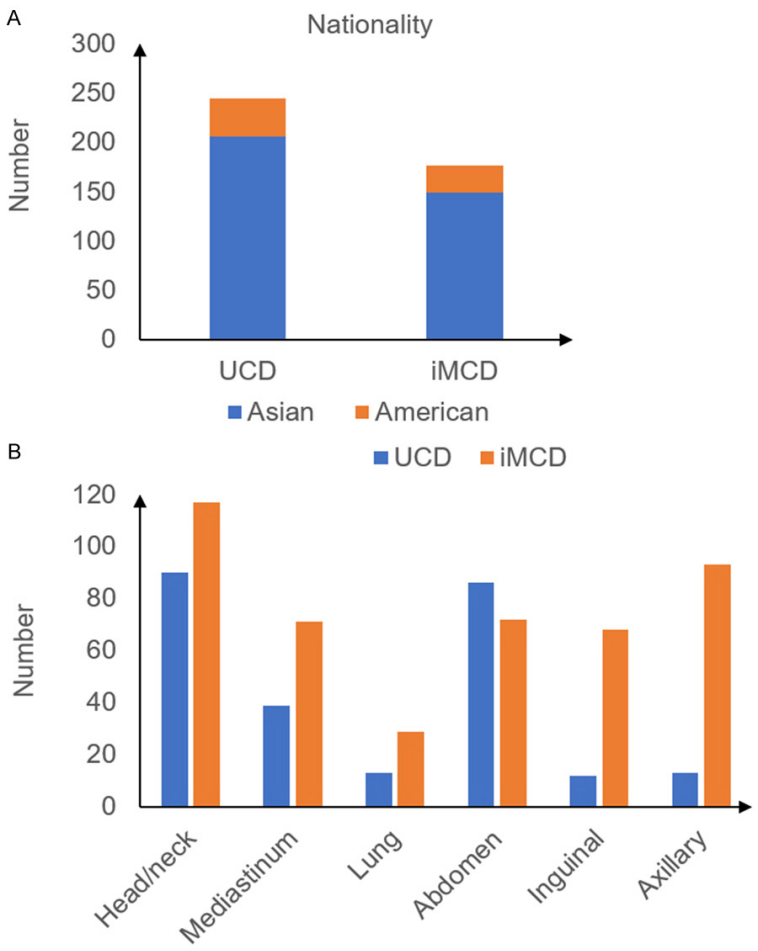

Figure 1. Correlation between the location and nationality of the affected lymph node and UCD/iMCD. Two patients who survived for more than 15 years were excluded. UCD, unicentric castleman disease. iMCD, idiopatic multicentric castleman disease.

patients as UCD (n = 248) and iMCD (n = 180). The group consisted of Asians (n = 355), Americans (n = 73), and patients of unknown nationality (**Figure 1**). Of the available data (n = 394), the median age was 41 years. Patients with UCD (median age, 38 years; range, 7 to 84 years) were significantly younger than patients with iMCD (median age, 47 years; range, 11 to 75 years). There was also a significant difference in age (age ≤ 40 vs. 40 < age ≤ 60 vs. age > 60) between patients with UCD and iMCD.

The lymph nodes of most patients with UCD were histologically classified as HV subtype (76.92%). Most lymph nodes of patients with iMCD were of the PC subtype (71.7%), with only 28.3% being of the HV subtype (**Table 1**). Patients with iMCD commonly had symptoms of systemic inflammation. Fever (33/180, 18.33%), fatigue (34/180, 18.89%), and B symptoms (58/180, 32.22%) occurred more frequently in patients with iMCD. In patients with UCD, the most common invasions were head/neck (36.3%) and abdomen (34.7%), and in some patients the mediastinum was also involved (15.4%). iMCD was mainly found in the head/neck (26%) and armpit (20.7%) (**Figure 1**). However, UCD had larger masses than iMCD, with a mean size of 46 mm (maximum diameter range, 20-110 mm) compared with the 23 mm masses of iMCD (maximum diameter range, 10-100 mm) ($P < 0.01$). There was also a rare case of family history of iMCD in the US, one brother with UCD and one daughter with iMCD.

Laboratory findings

At presentation, patients with iMCD commonly had symptoms of systemic inflammation (**Table 2**). iMCD were much more likely to experience anemia than UCD ($P < 0.01$). Of the 409 patients whose platelet counts were measured, platelet count less than 100 × 10^9/L occurred in 19 of the iMCD, which compared with 5 of UCD ($P < 0.01$). Elevation of β2-microglobulin, alkaline phosphatase, C-reactive protein, and erythrocyte sedimentation rate were significantly more common in iMCD than in UCD ($P < 0.01$). Among patients with iMCD, 58.24% had decreased albumin, whereas in patients with UCD, the percentage was 22.73% ($P < 0.01$). Of the 428 patients who had the record data of computed tomography or color ultrasonic, patients with iMCD frequently presented with serous effusion (46/180, 25.55%) and hepatomegaly and/or splenomegaly (71/180, 39.44%; $P < 0.01$).

Histopathological findings

Considering that this study was conducted over a considerable period of time, some pathologi-

Table 2. The baseline laboratory results of patients with CD in our cohort (*N* = 428)

	Total	UCD		iMCD		*P* value
	N	N	No. of patients N (%)	N	No.of patients N (%)	
WBC	410	233		177		0.0141
≤ 4 × 10^9/L			18 (7.73)		23 (12.99)	
4-10 × 10^9/L			195 (83.69)		127 (71.75)	
> 10 × 10^9/L			20 (8.58)		27 (15.25)	
Hemoglobin	410	233		177		
≤ 100 g/L			12 (5.15)		56 (31.64)	< 0.0001
≤ 80 g/L			3 (1.29)		27 (15.25)	< 0.0001
Platelets	409	232		177		< 0.0001
≤ 100 × 10^9/L			5 (2.16)		19 (10.73)	
100-300 × 10^9/L			186 (80.17)		96 (54.24)	
> 300 × 10^9/L			41 (17.67)		62 (35.03)	
Serous effusion	428	248	5 (2.02)	180	46 (25.55)	< 0.0001
Hepatomegaly and/or splenomegaly	428	248	6 (2.42)	180	71 (39.44)	< 0.0001
Mass > 5 cm	331	194	88 (45.36)	137	24 (17.52)	< 0.0001
Elevated LDH	355	201	13 (6.47)	154	23 (14.94)	0.0088
Elevated β2-MG	226	113	13 (11.50)	113	81 (71.68)	< 0.0001
Elevated ESR	169	62	14 (22.58)	107	56 (52.34)	0.0001
Decreased Alb	245	154	35 (22.73)	91	53 (58.24)	< 0.0001
Elevated CRP	176	78	17 (21.79)	98	56 (57.14)	< 0.0001
Elevated AKP	218	119	10 (8.40)	99	26 (26.26)	0.0004

WBC, white blood cells. Serous effusion includes pleural effusion, abdominal effusion, pericardial effusion, and pelvic effusion. Elevated LDH, lactate dehydrogenase over test baseline. Elevated β2-MG, β2 microglobulin > 2.4 mg/L. Elevated ESR, erythrocyte sedimentation rate > 20 mm/h. Decreased ALB, albumin < 40 g/L. Elevated CRP, C-reactive protein > 10 mg/L. Elevated AKP, alkaline phosphatase > 126 U/L. The N(x) presents the number of patients and the percentage of each group. UCD and iMCD groups were compared by chi-square test. P < 0.05 was considered to indicate significant differences.

cal diagnoses were not covered in a standardized or comprehensive manner in the early years of the study. Therefore, in the histopathological analysis, we only included 380 cases with detailed pathological diagnosis records (**Table 3**). Of 380 CD cases, 215 (56.58%) could be classified as HV subtype, and 165 (43.42%) could be classified as PC subtype. Patients with HV subtype (median age, 37 years; range, 7 to 81 years) were younger than patients with PC subtype (median age, 48 years; range, 10 to 84 years). Most patients with PC subtype had obvious systemic symptoms and showed significant changes in laboratory indicators. Elevation of lactate dehydrogenase, β2-microglobulin, alkaline phosphatase, and C-reactive protein were significantly more common in patients with PC subtype (P < 0.01). Of 68 (85%) cases with PC subtype also accompanied with decreased albumin and this patient group often presented with anemia and thrombocytopenia (P < 0.01). In contrast, patients with HV subtype had fewer symptoms and inflammatory changes.

Treatment outcome

Among the 417 patients with relatively complete treatment data, there were 243 UCD cases and 174 iMCD cases. The curative effect was calculated according to the treatment options (**Table 4**). Information with respect to treatment outcome was analyzed to effectively assess treatment effects. Only some patients had a detailed treatment evaluation.

Complete surgical resection was performed in 230 (94.65%) patients diagnosed with UCD as first-line treatment. Ten patients received drugs or radiation with surgical biopsy, and two patients chose to watch and wait. Of these patients, 126 (92.65%) who underwent complete surgical resection achieved a response,

Table 3. The baseline demographic clinical features of patients with CD in our cohort (*n* = 380)

	Total	HV		PC		*P* value
	N	N	No. of patients N (%)	N	No. of patients N (%)	
Clinical subtype	380	215		165		< 0.0001
UCD			170 (79.07)		51 (30.91)	
iMCD			45 (20.93)		114 (69.09)	
Gender	380	215		165		0.3155
Male			97 (45.12)		83 (50.30)	
Female			118 (54.88)		82 (49.70)	
Age (years)	360	212		148		< 0.0001
≤ 40			127 (59.91)		47 (31.76)	
40 < age ≤ 60			65 (30.66)		72 (48.65)	
> 60			20 (9.43)		29 (19.59)	
Ethnicity	380	215		165		0.1344
American			47 (21.86)		26 (15.76)	
Asian			168 (78.14)		139 (84.24)	
Clinical manifestation						
Fatigue	380	215	12 (5.58)	165	29 (17.58)	0.0001
Pain	380	215	31 (14.42)	165	27 (16.36)	0.6012
B symptom	380	215	20 (9.30)	165	54 (32.73)	< 0.0001
ECOG	212	132		80		< 0.0001
0-2			131 (99.24)		58 (72.50)	
3-5			1 (0.76)		22 (27.50)	
WBC	364	207		157		0.0373
≤ 4 × 10^9/L			18 (8.70)		16 (10.19)	
4-10 × 10^9/L			172 (83.09)		115 (73.25)	
> 10 × 10^9/L			17 (8.21)		26 (16.56)	
Hemoglobin						
≤ 100 g/L	364	207	11 (5.31)	157	51 (32.48)	< 0.0001
≤ 80 g/L	364	207	5 (2.42)	157	28 (17.83)	< 0.0001
Platelets	363	207		156		< 0.0001
≤ 100 × 10^9/L			1 (0.48)		17 (10.90)	
100-300 × 10^9/L			165 (79.71)		86 (55.13)	
> 300 × 10^9/L			41 (19.81)		53 (33.97)	
Serous effusion	380	215	9 (4.19)	165	38 (23.03)	< 0.0001
Hepatomegaly and/or Splenomegaly	380	215	12 (5.58)	165	54 (32.73)	< 0.0001
Mass > 5 cm	311	194	82 (42.27)	117	27 (23.08)	0.0006
Elevated LDH	308	173	8 (4.62)	135	23 (17.04)	0.0003
Elevated β2-MG	185	78	15 (19.23)	107	66 (61.68)	< 0.0001
Elevated ESR	149	58	14 (24.14)	91	47 (51.65)	0.0008
Elevated CRP	158	89	15 (16.85)	69	46 (66.67)	< 0.0001
Decreased Alb	245	165	71 (43.03)	80	68 (85.00)	< 0.0001
Elevated AKP	176	78	11 (14.10)	98	19 (19.39)	0.4220

The N(x) presents the number of patients and the percentage of each group. HV and PC groups were compared by chi-square test. P < 0.05 was considered to indicate significant differences.

and 10 (7.35%) patients suffered from disease recurrence or progression. Of these 10 patients, two patients who underwent re-operation achieved CR, and two patients achieved

Table 4. Treatment outcomes of patients with CD

First-line	Patients (N)	Patients with follow-up data (N)	Patients with treatment evaluation data (N)	Response* (N)	No response* (N)	Treatment failure* (N)
UCD	243	201	145	129	3	13
Surgery (total excision)	230	189	136	126	1	9
Drugs or radiation with surgical biopsy	10	9	9	4	1	4
Watch and wait	3	3	3	3	/	/
iMCD*	170	153	120	55	27	38
Corticosteroid monotherapy	13	13	7	2	4	1
CTX/Thalidomide/Rituximab + Corticosteroid	13	9	7	4	3	/
Cytotoxic chemotherapy	75	71	59	32	13	14
CHOP or CHOP-like	56	54	46	22	14	10
Rituximab based (R-CHOP or R-COP)	17	15	14	9	1	4
Others*	2	2	1	1	/	/
Anti-interleukin 6 monoclonal antibody*	8	8	8	4	1	3
Tocilizumab with other agents	1	1	1	/	/	/
Siltuximab with or without any agent	7	7	6	3	1	2
Watch and wait (include biopsy)	61	52	26	13	7	6

The treatment of patients with iMCD excluded one patient who received biopsy and radiotherapy, one patient who received cyclophosphamide monotherapy, and two patients who received rituximab monotherapy, because of the low numbers of cases. CHOP includes cyclophosphamide, doxorubicin, vincristine, and prednisone. CHOP-like is based on COP. *Others include fludarabine/cyclophosphamide and cyclophosphamide/Vindesine cytotoxic chemotherapy, excluding CHOP-like or R-CHOP-like. Anti-interleukin-6 monoclonal antibody was always used in combination with drugs such as thalidomide and corticosteroid. The proportion alive at follow-up only includes patients with available treatment information. *Response = complete remission and partial remission; *No response = stable disease; *Failure = disease progression, invalidity, or death.

CR and PR after cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) treatment or radiotherapy. Among the patients who received drug or radiation treatment with surgical biopsy (R-CHOP/CHOP, rituximab monotherapy, and radiotherapy), four patients achieved CR/PR, two patients achieved a stable condition, and two patients progressed (one patient who received cyclophosphamide combined with hormone and one patient who received rituximab). Two other patients chose to watch and wait; the mass shrank spontaneously, and the patients achieved CR.

Treatments differed considerably among patients with iMCD. Among the 13 patients treated with glucocorticoid monotherapy, two patients achieved CR/PR. The curative effects of glucocorticoid monotherapy and of glucocorticoid combined with other drugs were not significantly different ($P > 0.05$). Most patients (75/174, 43.1%) chose chemotherapy. Among the 17 patients treated with rituximab-based chemotherapy (R-CHOP or R-COP), 9 patients (64.28%) showed a response, and treatment failed in four (28.57%) patients ($P > 0.05$). Among the 56 patients who received CHOP or a CHOP-like regimen, 22 patients (47.8%) showed a response, and treatment failed in 10 (21.73%) patients ($P > 0.05$). In the present study, seven patients were treated with siltuximab monotherapy or siltuximab combined with other drugs; of these patients, three achieved CR/PR, and treatment failed in one patient, despite autologous stem cell transplantation after combination therapy. Only one patient chose tocilizumab with other drugs who achieved CR. Among the 61 patients who chose to watch and wait, 13 cases improved spontaneously and 6 did not. Due to the lack of detailed clinical and laboratory data, it was difficult to further analyze these patients.

Univariate survival analysis

In the present study, follow-up data were available for 365 patients with CD (203 with UCD and 160 with iMCD), excluding two patients with CD who survived for more than 15 years. The median follow-up time for CD was 41 months (range, 0.53 to 173.6 months). By the last follow-up, 50 patients were dead (7 UCD cases and 43 iMCD cases). In the group of UCD, one patient died of unknown cause who was a 33-year-old female with severe anemia,

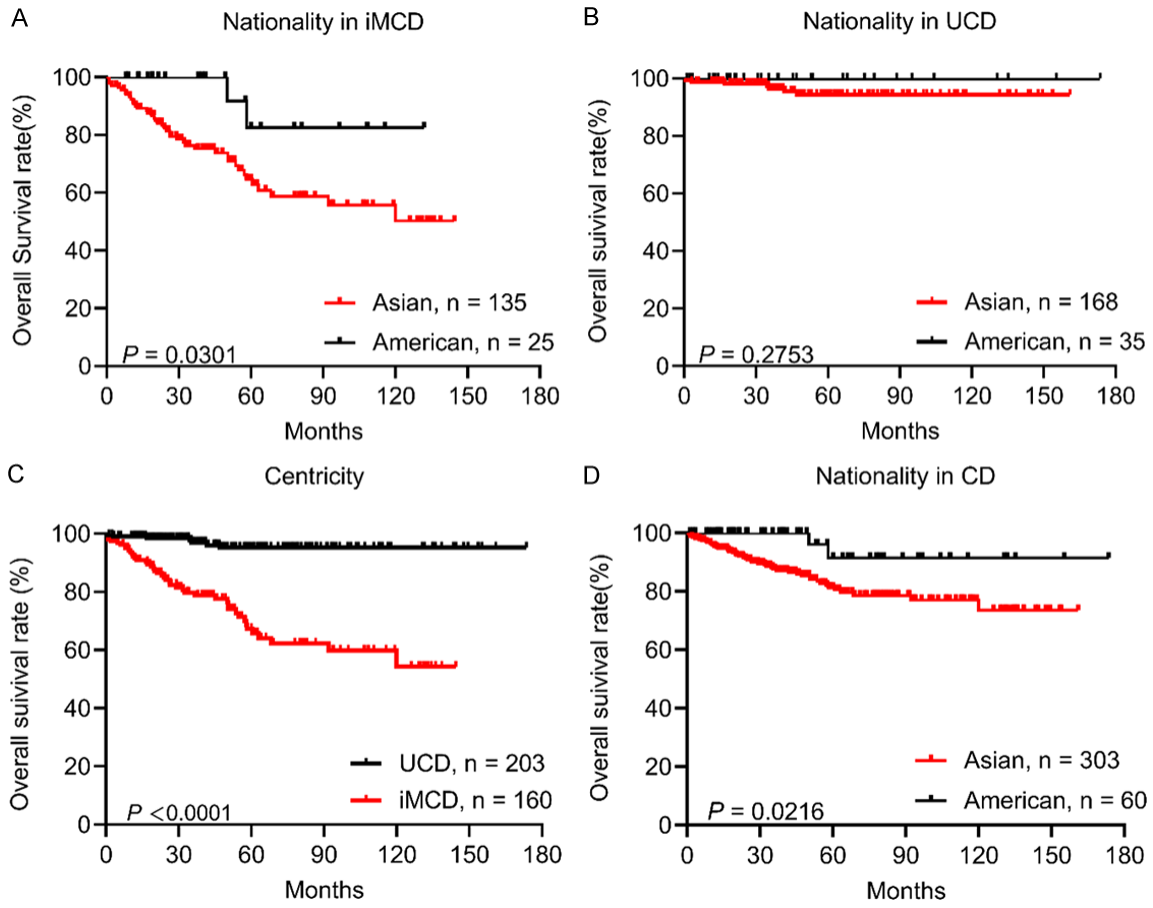

Figure 2. Overall survival of multicentricity and nationality in patients with CD. Patients with iMCD (A) was correlated with significantly poorer overall survival. Asian patients with CD (B) or iMCD (C) were correlated with inferior overall survival. (D) There was no difference between patients with UCD for Asian and Amierican. Two patients who survived for more than 15 years were excluded. CD, castleman disease. iMCD, idiopatic multicentric castleman disease.

high ESR, and low protein at onset; a 27-year-old female with paraneoplastic pemphigus who died of disease recurrence and progression; a 50-year-old male with renal insufficiency died of disease recurrence and progression; a 28-year-old male who died of recurrent disease progression; a 54-year-old male, died of cerebrovascular accident and the remaining two patients died of unknown cause who were of no obvious special. In the group of iMCD, 22 patients died of disease progression and recurrence, 2 patients died of infection. The cause of death in 5 cases was unknown, but they all complicated other diseases or diagnosed severe iMCD. There were 2 patients died of cardiovascular accidents and the remaining 12 cases had unknown causes of death. The 5-year OS of patients with CD was 87%. For patients with UCD, the 5-year OS was 95%. For patients with iMCD, the 5-year OS was 74%. The log-rank test for OS showed a significant difference between UCD and iMCD ($P < 0.001$).

Using the Kaplan-Meier method and the log-rank test, we conducted a univariate analysis and identified 10 significant risk factors of CD: multicentricity (**Figure 2**), age > 60 years, PC subtype, fever, B symptoms, serous effusion, hepatomegaly and/or splenomegaly, hemoglobin ≤ 80 g/L, albumin ≤ 30 g/L, and elevation of erythrocyte sedimentation rate and β2-microglobulin ($P < 0.05$; some results showed in Figure S1). The survival rate was lower among the Asian population than among the American population ($P < 0.05$; **Figure 2**).

UCD had a good prognosis after primary lesion resection, while iMCD had a poor prognosis. In UCD, we identified two significant risk factors: hemoglobin ≤ 100 g/L and albumin ≤ 30 g/L (**Figure 3**). In this study, serous effusion, he-

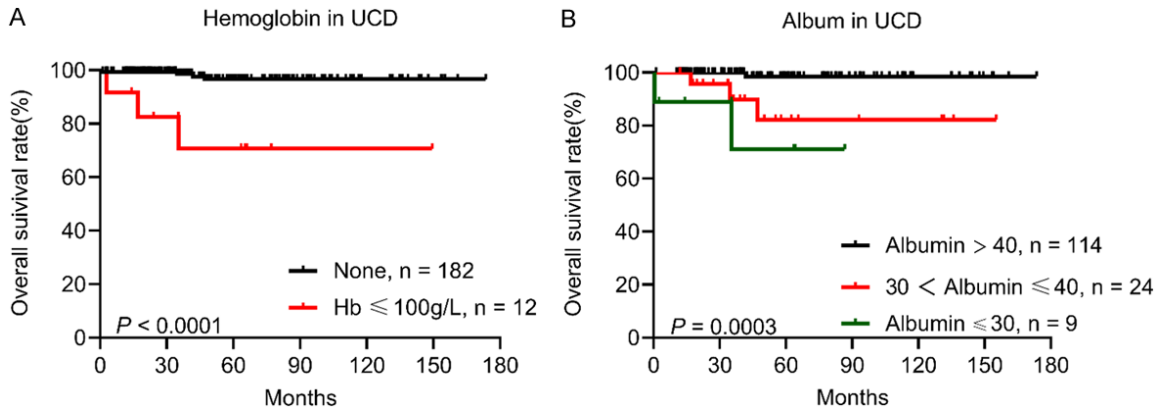

Figure 3. Overall survival of hemoglobin and albumin in patients with UCD. (A) Hemoglobin ≤ 100 g/L and (B) Albumin ≤ 30 g/L were associated with poor prognosis in patients with UCD. One patient who survived for more than 15 years were excluded. CD, castleman disease. UCD, unicentric castleman disease.

patomegaly and/or splenomegaly, leukopenia, and albumin ≤ 30 g/L were significantly associated with OS of patients with iMCD (P < 0.001; **Figure 4**). Age > 60 years, B symptoms, and hemoglobin ≤ 80 g/L were also associated with OS of patients with iMCD (P < 0.05), but PC subtype did not correlate with better OS, although a trend toward better survival is suggested among HV subtype (**Figure 4**). The patients with iMCD who chose to watch and wait had a poorer prognosis than patients with iMCD who were treated (P < 0.05).

Multivariate analysis of risk factors

The Cox proportional hazards model was used to perform a multivariate analysis of factors affecting CD, including multicentricity, pathological subtype, age, B symptoms, hepatomegaly and/or splenomegaly, hemoglobin ≤ 80 g/L, and albumin ≤ 30 g/L. The results showed that PC subtype, hepatomegaly and/or splenomegaly, hemoglobin ≤ 80 g/L, and albumin ≤ 30 g/L were independently associated with OS (**Table 5**). Further, we generated a model of iMCD, including pathological subtype, age, B symptoms, serous effusion, hepatomegaly and/or splenomegaly, leukopenia, hemoglobin ≤ 80 g/L, and albumin ≤ 30 g/L. The results showed that age > 60 years, hepatomegaly and/or splenomegaly, and hemoglobin ≤ 80 g/L were independent risk factors for the prognosis of iMCD (**Table 5**).

Discussion

Most studies on clinical, laboratory, treatment, and prognosis data of patients with CD are single randomized and controlled trials, small series research, and case reports [10, 11]. In order to obtain more information, we performed a large study of patients with CD from Chinese and American medical centers, which comprises the largest sample size reported thus far and different ethnic groups with 15-year follow-up. In particular, our study provides valuable and comprehensive information on clinical characteristics and prognostic factors that advance our understanding of CD, especially iMCD.

We show the heterogeneity between patients with UCD and iMCD as well as within each pathological subtype. CD affects patients of all ages, with a peak frequency during adulthood. The median age of patients with UCD (38 years) was significantly lower than that of patients with iMCD (47 years), which is consistent with the median age of Japanese (43 years, *n* = 342) and American (55 years, *n* = 59) patients with MCD [12, 13]. Consistent with previous studies, the changes in symptoms and laboratory indicators were more pronounced in iMCD, and the masses of UCD were larger than those of iMCD [13-15]. A few cases of UCD also had systemic inflammation, aggressive symptoms, and abnormal laboratory results, although these indicators lacked diagnostic specificity. There is a certain proportion of crossover between UCD and iMCD in all aspects. Pathological changes are the basis of clinical manifestation. The HV subtype was more prevalent in patients with UCD (76.92%), and the PC subtype was more prevalent in patients with iMCD (71.7%), as we reported before [15, 16]. The differences in clinical manifestations between

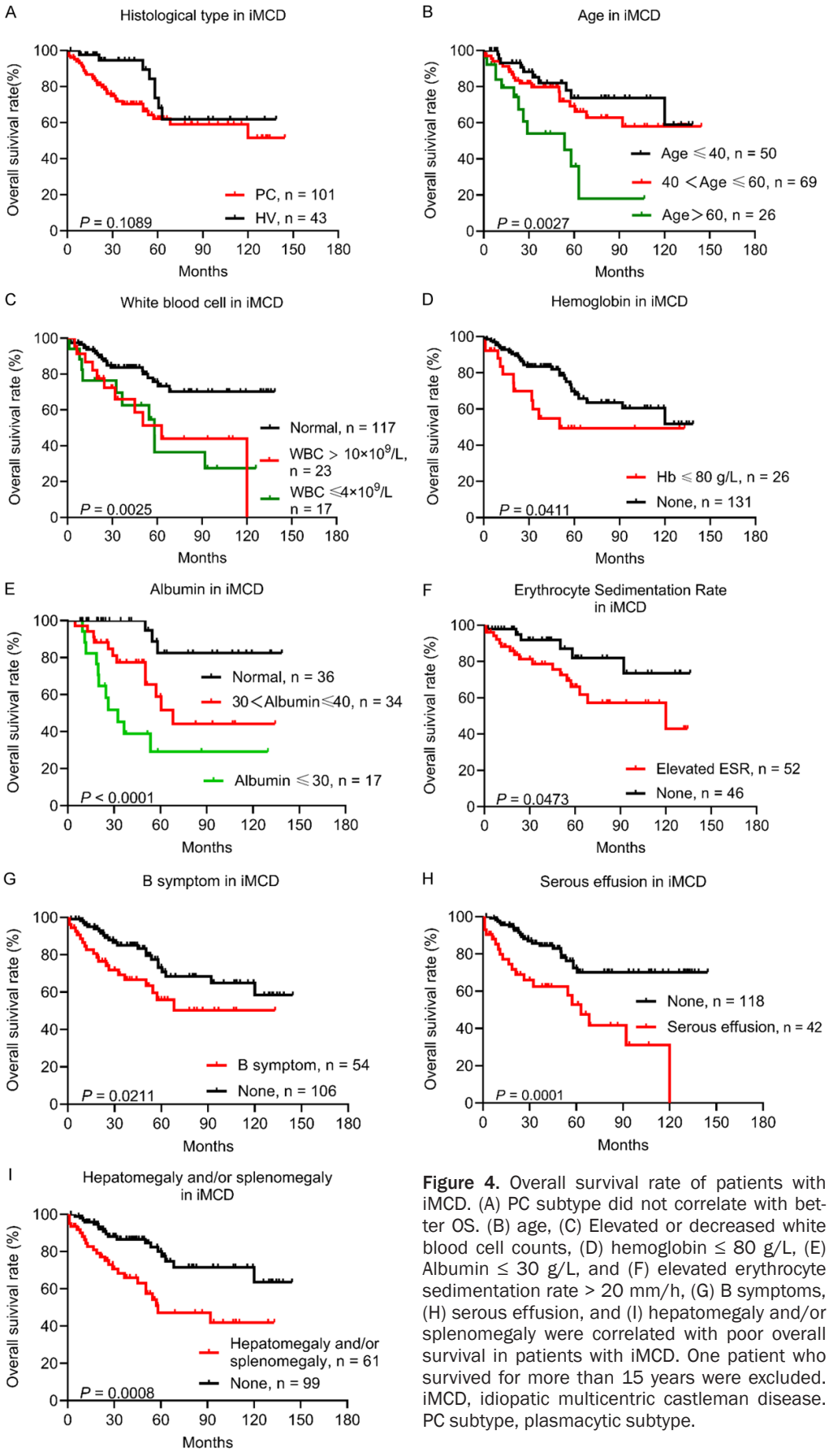

Figure 4. Overall survival rate of patients with iMCD. (A) PC subtype did not correlate with better OS. (B) age, (C) Elevated or decreased white blood cell counts, (D) hemoglobin ≤ 80 g/L, (E) Albumin ≤ 30 g/L, and (F) elevated erythrocyte sedimentation rate > 20 mm/h, (G) B symptoms, (H) serous effusion, and (I) hepatomegaly and/or splenomegaly were correlated with poor overall survival in patients with iMCD. One patient who survived for more than 15 years were excluded. iMCD, idiopatic multicentric castleman disease. PC subtype, plasmacytic subtype.

Table 5. Multivariate analysis of CD and iMCD

Factor	OS in patients with CD		
	HR	95% CI	*P* value*
PC subtype	3.853	1.587-9.357	**0.0029**
Hepatomegaly and/or splenomegaly	3.495	1.626-7.511	**0.0013**
Hemoglobin (≤ 80 g/L)	2.290	1.028-5.101	**0.0042**
Albumin (≤ 30 g/L)	1.671	1.068-2.614	**0.0247**
iMCD	1.655	0.490-5.589	0.3617
Factor	OS in patients with iMCD		
	HR	95% CI	*P* value*
Age (>60 years)	2.288	1.307-4.003	**0.0037**
Hepatomegaly and/or splenomegaly	3.248	1.532-7.314	**0.0024**
Hemoglobin (≤ 80 g/L)	2.699	1.133-6.431	**0.0250**
PC subtype	1.360	0.388-4.763	0.1948

**P* values ≤ 0.05 shown as bold indicated a statistically significant difference.

patients with PC and patients with HV were similar to those between patients with iMCD and patients with UCD. The pathological changes are the basis of the clinical manifestations. It may related to the differences between the pathogeneses of CD and elderly people often accompanied by immunodeficiency. It has been hypothesized that it involves autoimmunity/auto-inflammation, paraneoplastic syndrome, and viral infection [16, 17]. In our analysis, there was a patient with one brother who had UCD and one daughter who had iMCD. A family history of iMCD has also been found in a previous study, with two patients who had a *FAS* mutation [18]. Another study found that mutation of the *MEFV* gene may contribute to systemic reactions of MCD [19]. Due to the lack of second-generation sequencing, we were unable to identify the pathogenesis in this study.

Great differences with respect to treatment were observed between patients with UCD and iMCD. For patients with UCD, complete resection of the involved lesion is considered as the golden standard treatment, and the 5-year OS rate approaches 100% [8]. Unlike UCD, no standard treatment has been established for iMCD, and the outcome is less favorable. A variety of agents have been used to treat MCD, including corticosteroids, cytotoxic chemotherapy, thalidomide, immunoglobulin, rituximab, anti-IL-6 antibody (siltuximab and tocilizumab), and mTOR pathway inhibitors [20-22]. Corticosteroids can quickly and effectively relieve clinical symptoms, which is a major advantage over other drugs. However, the CR rate has been reported to be low. In the present analysis, the effective rate of 13 patients who underwent glucocorticoid monotherapy was about 30% and 50% of patients with iMCD are resistant to glucocorticoids. The CR and PR rates with rituximab or rituximab-based chemotherapy regimens as first-line therapy were 20% and 48%, respectively. Cytotoxic chemotherapy may induce responses, and the overall remission rate of chemotherapy can be as high as 78%, but many patients will progress or experience infectious toxicities [6, 15, 20]. In our study, only two patients chose rituximab monotherapy, compared with 75 patients who chose chemotherapy. Of these 75 patients, 17 (22.67%) patients chose R-CHOP/R-CHOP-like treatment, and others chose CHOP/CHOP-like treatment. The remission rate of cytotoxic chemotherapy was over 50%, which was not significantly different from that of other treatment regimens, but considerable toxicity and frequent relapses deter its use [23, 24]. Considering the increased expression of IL-6, anti-IL-6 therapy may be more beneficial [9]. Due to drug inaccessibility, few patients received the new drugs. Only 11 patients were treated with anti-IL-6 therapy; of these, eight cases were treated with siltuximab, with an effective rate of 42.85% (3/7), similar to the 34% remission rate of siltuximab observed in the only randomized controlled trial of iMCD [22], but there was no obvious advantage compared with other treatment groups. For iMCD with no obvious symptoms, watching and waiting can be chosen. However, the failure rate of watching and waiting was 50% (13/26), suggesting that long-term observation and timely treatment are necessary. In conclusion, the treatment regimen must be selected based on drug accessibility and experiences. The severity, prognostic factors, and biomarkers that are available to select patients who will respond to these treatments are limited, which need more studies.

In the present study, the different prognostic factors between CD and iMCD may be related to the overall effect of UCD inclusion in the analysis or statistical bias. By single-factor

analysis, anemia and hypoproteinemia also affect UCD, as reported by Lan X et al [16, 25]. Patients with iMCD had significantly worse survival rates, with a 5-year OS of 74% ($P < 0.001$), which is consistent with previous reports [26, 27]. Due to the lack of an optimal treatment for iMCD, it is important to identify prognostic factors to help determine treatment strategies. Meta-analysis of 416 cases has suggested five prognostic factors by univariate analysis, including multicentricity, pathology type, the presence of symptoms, gender, and age [27]. A study reported by the MD Anderson Cancer Center suggested that multicentricity, PC subtype, and anemia were associated with poor prognosis in patients from North America [15]. In our study, PC subtype and anemia were associated with poor prognosis. A retrospective study executed by Peking University obtained similar results [28]. Hepatomegaly and/or splenomegaly is a common symptom in iMCD [13, 15, 29, 30]. Furthermore, previous studies found that hypoproteinemia is an independent prognostic risk factor in HIV-negative patients with CD (n = 71) and patients with MCD (n = 185) [25, 31]. We also found that hypoproteinemia (≤ 30 g/L) is an independent risk factor for patients with CD and for patients with iMCD. Other unfavorable prognostic factors have been reported, including increased IL-6 levels, the presence of extravascular fluid accumulation, clinical complications, and splenomegaly [28, 31-33]. The prognosis of CD in Asian patients was worse than that in American patients, of which may be due to statistical bias or factors associated with geography and race, but future studies are needed to confirm this. Combined with literature reports and the above analysis, the pathological types and clinical classification have not changed, and to obtain the best treatment effect under existing conditions, the control of systemic inflammation should be enhanced, anemia and hypoalbuminemia should be prevented, and liver function should be protected.

This study has several limitations. First, as a retrospective study, there may be a bias for patient selection and data collection. We excluded some laboratory tests because data were not available, including C-reactive protein levels and the erythrocyte sedimentation rate. Second, because of the heterogeneous treatments of patients with iMCD, we could not further compare the effects of different treatment strategies. In addition, only a small number of patients with iMCD in our study received anti-IL-6 or rituximab as first-line therapy, mostly for drug inaccessibility. The role of these new agents in iMCD treatment requires further investigation. The present study has several strengths. First of all, with the sample size being the largest reported to date, this multicenter study identified the clinical characteristics and prognostic factors of CD, especially iMCD. Second, the study indicated that the unfavorable prognostic factors of UCD and MCD were not identical, which suggests that different therapeutic strategies need to be followed for different clinical classifications. Finally, the results indicated that PC subtype, hepatomegaly and/or splenomegaly, hemoglobin ≤ 80 g/L, and albumin ≤ 30 g/L are independent prognosis factors of CD. Age > 60 years, hepatomegaly and/or splenomegaly, and anemia were independent risk factors for the prognosis of iMCD. Therefore, except chemotherapy and resection, appropriate medical supportive treatment should be considered, such as splenectomy, correction of anemia, and supplementation of albumin. Further studies are needed to confirm these prognostic factors and investigate the optimal treatment for iMCD.

In general, CD is a highly heterogeneous disorder, and little is known about its pathogenesis, clinical manifestation, treatment, and prognosis. No standard treatment for CD has been established. In the present study, we identified differences in clinical features and prognostic factors between UCD and iMCD. We found significant risk factors of CD and iMCD, which were not identical. Comparison of the results of our study with other case reports or small-scale studies can provide a better understanding of the pathophysiology of CD, enabling faster and more efficient diagnosis and effective treatment. We hope our study provides a clear understanding of the differences between UCD and iMCD, and the risk factors identified in the present study can provide a reference for therapeutic decision-making and prognosis assessment. It is essential to continue to explore the etiology, classification, treatment, and prognosis of CD in future investigations.

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Disclosure of conflict of interest

None.

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References

[1] Castleman B, Iverson L and Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 1956; 9: 822-830.

[2] Fajgenbaum DC, van Rhee F and Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. Blood 2014; 123: 2924-2933.

[3] Dispenzieri A and Fajgenbaum DC. Overview of Castleman disease. Blood 2020; 135: 1353-1364.

[4] Talat N, Belgaumkar AP and Schulte KM. Surgery in Castleman's disease: a systematic review of 404 published cases. Ann Surg 2012; 255: 677-684.

[5] Liu AY, Nabel CS, Finkelman BS, Ruth JR, Kurzrock R, van Rhee F, Krymskaya VP, Kelleher D, Rubenstein AH and Fajgenbaum DC. Idiopathic multicentric Castleman's disease: a systematic literature review. Lancet Haematol 2016; 3: e163-175.

[6] van Rhee F, Voorhees P, Dispenzieri A, Foss A, Srkalovic G, Ide M, Munshi N, Schey S, Streetly M, Pierson SK, Partridge HL, Mukherjee S, Shilling D, Stone K, Greenway A, Ruth J, Lechowicz MJ, Chandrakasan S, Jayanthan R, Jaffe ES, Leitch H, Pemmaraju N, Chadburn A, Lim MS, Elenitoba-Johnson KS, Krymskaya V, Goodman A, Hoffmann C, Zinzani PL, Ferrero S, Terriou L, Sato Y, Simpson D, Wong R, Rossi JF, Nasta S, Yoshizaki K, Kurzrock R, Uldrick TS, Casper C, Oksenhendler E and Fajgenbaum DC. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman di sease. Blood 2018; 132: 2115-2124.

[7] Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, Simpson D, Liu AY, Menke D, Chandrakasan S, Lechowicz MJ, Wong RS, Pierson S, Paessler M, Rossi JF, Ide M, Ruth J, Croglio M, Suarez A, Krymskaya V, Chadburn A, Colleoni G, Nasta S, Jayanthan R, Nabel CS, Casper C, Dispenzieri A, Fossa A, Kelleher D, Kurzrock R, Voorhees P, Dogan A, Yoshizaki K, van Rhee F, Oksenhendler E, Jaffe ES, Elenitoba-Johnson KS and Lim MS. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017; 129: 1646-1657.

[8] van Rhee F, Oksenhendler E, Srkalovic G, Voorhees P, Lim M, Dispenzieri A, Ide M, Parente S, Schey S, Streetly M, Wong R, Wu D, Maillard I, Brandstadter J, Munshi N, Bowne W, Elenitoba-Johnson KS, Fössa A, Lechowicz MJ, Chandrakasan S, Pierson SK, Greenway A, Nasta S, Yoshizaki K, Kurzrock R, Uldrick TS, Casper C, Chadburn A and Fajgenbaum DC. International evidence-based consensus diagnostic and treatment guidelines for unicentric Castleman disease. Blood Advances 2020; 4: 6039-6050.

[9] Carbone A, Borok M, Damania B, Gloghini A, Polizzotto MN, Jayanthan RK, Fajgenbaum DC and Bower M. Castleman disease. Nat Rev Dis Primers 2021; 7: 84.

[10] Soumerai JD, Sohani AR and Abramson JS. Diagnosis and management of Castleman disease. Cancer Control 2014; 21: 266-278.

[11] Munshi N, Mehra M, van de Velde H, Desai A, Potluri R and Vermeulen J. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. Leuk Lymphoma 2015; 56: 1252-1260.

[12] Robinson D, Reynolds M, Casper C, Dispenzieri A, Vermeulen J, Payne K, Schramm J, Ristow K, Desrosiers MP, Yeomans K, Teltsch D, Swain R, Habermann TM, Rotella P and Van de Velde H. Clinical epidemiology and treatment patterns of patients with multicentric Castleman disease: results from two US treatment centres. Br J Haematol 2014; 165: 39-48.

[13] Murakami M, Johkoh T, Hayashi S, Ohshima S, Mizuki M, Nakatsuka SI, Tomobe M, Kuroyanagi K, Nakasone A and Nishimoto N. Clinicopathologic characteristics of 342 patients with multicentric Castleman disease in Japan. Mod Rheumatol 2020; 30: 843-851.

[14] Casper C, Teltsch DY, Robinson D Jr, Desrosiers MP, Rotella P, Dispenzieri A, Qi M, Habermann T and Reynolds MW. Clinical characteristics and healthcare utilization of patients with multicentric Castleman disease. Br J Haematol 2015; 168: 82-93.
[15] Yu L, Tu M, Cortes J, Xu-Monette ZY, Miranda RN, Zhang J, Orlowski RZ, Neelapu S, Boddu PC, Akosile MA, Uldrick TS, Yarchoan R, Medeiros LJ, Li Y, Fajgenbaum DC and Young KH. Clinical and pathological characteristics of HIV- and HHV-8-negative Castleman disease. Blood 2017; 129: 1658-1668.
[16] Yu L, Shi M, Cai Q, Strati P, Hagemeister F, Zhai Q, Li L, Fang X, Li J, Sun R, Zhang S, Yang H, Wang Z, Qian W, Iwaki N, Sato Y, Zhang L, Li J, Oksenhendler E, Xu-Monette ZY and Young KH. A novel predictive model for idiopathic multicentric Castleman disease: the international Castleman D isease consortium study. Oncologist 2020; 25: 963-973.
[17] Fajgenbaum DC and Shilling D. Castleman disease pathogenesis. Hematol Oncol Clin North Am 2018; 32: 11-21.
[18] Baker TS, Gambino KJ, Schriefer L, Lim JY, Steinberg KM, Fajgenbaum DC, Martín García-Sancho A and Byun M. A novel FAS mutation with variable expressivity in a family with unicentric and idiopathic multicentric Castleman disease. Blood Adv 2018; 2: 2959-2963.
[19] Endo Y, Koga T, Otaki H, Sasaki D, Sumiyoshi R, Furukawa K, Tanaka Y, Katsunori Y and Kawakami A. Idiopathic multicentric Castleman disease with novel heterozygous Ile729Met mutation in exon 10 of familial Mediterranean fever gene. Rheumatology (Oxford) 2021; 60: 445-450.
[20] Kapriniotis K, Lampridis S, Mitsos S, Patrini D, Lawrence DR and Panagiotopoulos N. Biologic agents in the treatment of multicentric Castleman disease. Turk Thorac J 2018; 19: 220-225.
[21] Stern RM and Berliner N. Targeting the mTOR pathway in idiopathic multicentric Castleman disease. J Clin Invest 2019; 129: 4086-4088.
[22] van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar R, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J and Casper C. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014; 15: 966-974.
[23] Seo S, Yoo C, Yoon DH, Kim S, Park JS, Park CS, Huh J and Suh C. Clinical features and outcomes in patients with human immunodeficiency virus-negative, multicentric Castleman's disease: a single medical center experience. Blood Res 2014; 49: 253-258.
[24] Zhu SH, Yu YH, Zhang Y, Sun JJ, Han DL and Li J. Clinical features and outcome of patients with HIV-negative multicentric Castleman's disease treated with combination chemotherapy: a report on 10 patients. Med Oncol 2013; 30: 492.
[25] Lan X, Li Z and Zhang M. Analysis of clinical characteristics and prognosis factors of 71 cases with HIV-negative Castleman's disease: hypoproteinemia is an unfavorable prognostic factor which should be treated appropriately. J Cancer Res Clin Oncol 2018; 144: 1265-1277.
[26] Zhang L, Li Z, Cao X, Feng J, Zhong D, Wang S, Zhou D and Li J. Clinical spectrum and survival analysis of 145 cases of HIV-negative Castleman's disease: renal function is an important prognostic factor. Sci Rep 2016; 6: 23831.
[27] Talat N and Schulte KM. Castleman's disease: systematic analysis of 416 patients from the literature. Oncologist 2011; 16: 1316-1324.
[28] Dong Y, Wang M, Nong L, Wang L, Cen X, Liu W, Zhu S, Sun Y, Liang Z, Li Y, Ou J, Qiu Z and Ren H. Clinical and laboratory characterization of 114 cases of Castleman disease patients from a single centre: paraneoplastic pemphigus is an unfavourable prognostic factor. Br J Haematol 2015; 169: 834-842.
[29] Liu AY, Nabel CS, Finkelman BS, Ruth JR, Kurzrock R, van Rhee F, Krymskaya VP, Kelleher D, Rubenstein AH and Fajgenbaum DC. Idiopathic multicentric Castleman's disease: a systematic literature review. Lancet Haematol 2016; 3: e163-e175.
[30] Luo JM, Li S, Huang H, Cao J, Xu K, Bi YL, Feng RE, Huang C, Qin YZ, Xu ZJ and Xiao Y. Clinical spectrum of intrathoracic Castleman disease: a retrospective analysis of 48 cases in a single Chinese hospital. BMC Pulm Med 2015; 15: 34.
[31] Zhang X, Rao H, Xu X, Li Z, Liao B, Wu H, Li M, Tong X, Li J and Cai Q. Clinical characteristics and outcomes of Castleman disease: a multicenter study of 185 Chinese patients. Cancer Sci 2018; 109: 199-206.
[32] Shin DY, Jeon YK, Hong YS, Kim TM, Lee SH, Kim DW, Kim I, Yoon SS, Heo DS, Park S and Kim BK. Clinical dissection of multicentric Castleman disease. Leuk Lymphoma 2011; 52: 1517-1522.
[33] Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR and Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol 2020; 16: 335-345.

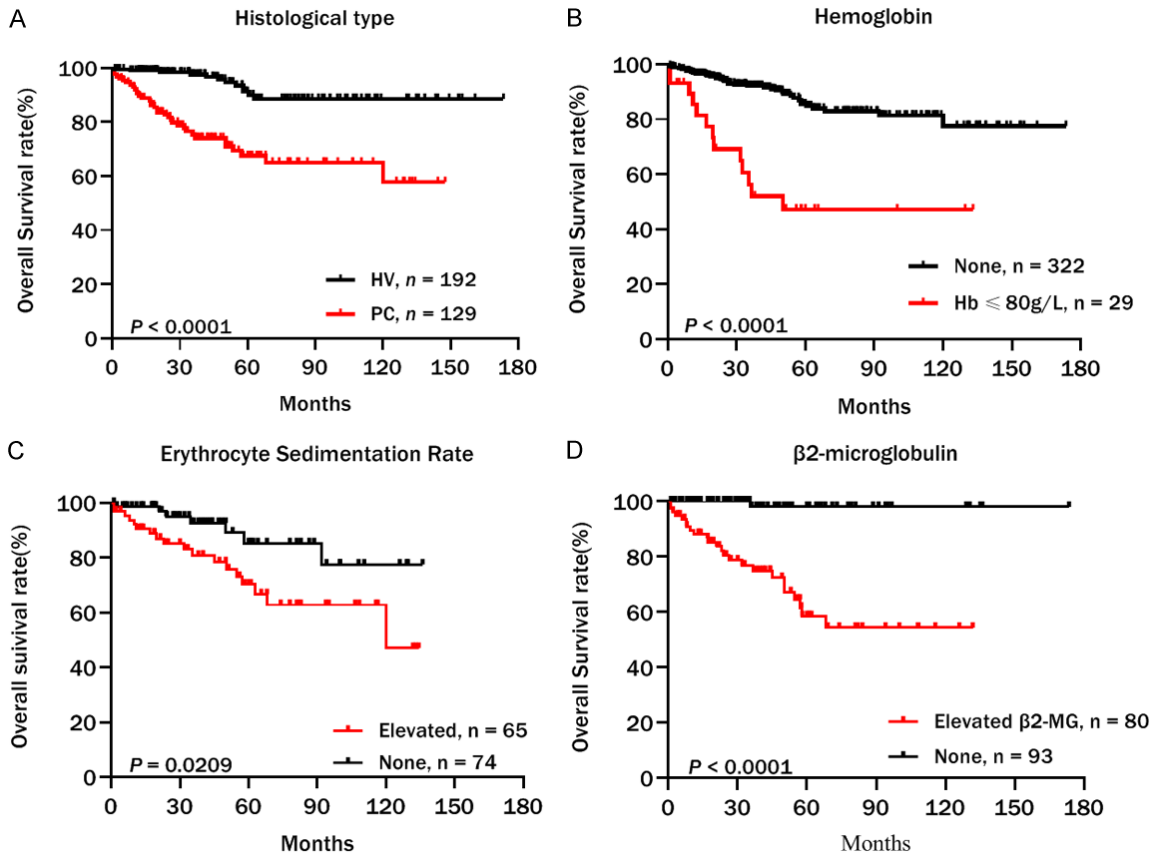

Figure S1. Overall survival rate of the clinical features in all patients diagnosed with CD Patients with (A) PC subtype, (B) hemoglobin ≤ 80 g/L, (C) elevated erythrocyte sedimentation rate > 20 mm/h, and (D) elevated β2-macroglobulin > 2.4 mg/L were correlated with poor overall survival. Two patients who survived for more than 15 years were excluded. CD, castleman disease. PC subtype, plasmacytic subtype.