A national, multicenter, retrospective study of Castleman disease in China implementing CDCN criteria

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Summary

Background Castleman disease (CD) is a group of rare and heterogenous lymphoproliferative disorders including unicentric CD (UCD), human herpesvirus-8(HHV-8)-associated multicentric CD (HHV8-MCD), and HHV-8-negative/idiopathic multicentric CD (iMCD). Knowledge of CD mainly comes from case series or retrospective studies, but the inclusion criteria of these studies vary because the Castleman Disease Collaborative Network (CDCN) diagnostic criteria for iMCD and UCD were not available until 2017 and 2020, respectively. Further, these criteria and guidelines have not been systematically evaluated.

Methods In this national, multicenter, retrospective study implementing CDCN criteria, we enrolled 1634 CD patients (UCD, n = 903; MCD, n = 731) from 2000 to 2021 at 40 Chinese institutions to depict clinical features, treatment options, and prognostic factors of CD.

Findings Among UCD, there were 162 (17.9%) patients with an MCD-like inflammatory state. Among MCD, there were 12 HHV8-MCD patients and 719 HHV-8-negative MCD patients, which included 139 asymptomatic MCD (aMCD) and 580 iMCD meeting clinical criteria. Of 580 iMCD patients, 41 (7.1%) met iMCD-TAFRO criteria, the others were iMCD-NOS. iMCD-NOS were further divided into iMCD-IPL (n = 97) and iMCD-NOS without IPL (n = 442). Among iMCD patients with first-line treatment data, a trend from pulse combination chemotherapy toward continuous treatment was observed. Survival analysis revealed significant differences between subtypes and severe iMCD (HR = 3.747; 95% CI: 2.112–6.649, $p < 0.001$) had worse outcome.

Interpretation This study depicts a broad picture of CD, treatment options and survival information in China and validates the association between the CDCN's definition of severe iMCD and worse outcomes, requiring more intensive treatment.

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Keywords: Castleman disease; Multicenter study; Treatment options; Survival analysis

Research in context

Evidence before this study

We searched PubMed for articles published before December 31st, 2021, for studies that analyzed the clinical features, treatment options, and prognostic factors of Castleman disease (CD), using the search terms ('Castleman disease', 'unicentric Castleman disease', 'multicentric Castleman disease', 'idiopathic Multicentric Castleman disease'). No restrictions on study type or language were implemented. We manually searched reference lists and retrieved articles as well. As a rare disease, knowledge about the clinical and prognostic features accumulates slowly and is mainly gathered from case series or retrospective studies. However, the inclusion criteria of these studies vary because the Castleman Disease Collaborative Network (CDCN) diagnostic criteria for iMCD and UCD were not available until 2017 and 2020, respectively. Further, these criteria and guidelines have not been systematically evaluated.

Added value of this study

This was the largest multicenter retrospective study carried out to date, which implemented the CDCN diagnostic criteria for CD and portrayed a broad picture of CD subtypes, treatment options and survival information in China. Moreover, this was the first attempt to validate the concept of 'severe iMCD' proposed by the CDCN in a large patient cohort. Likewise, this was the first large study to demonstrate worsened outcomes in iMCD-TAFRO compared to iMCD-NOS.

Implications of all the available evidence

The evidence-based CDCN diagnostic criteria and treatment guidelines for UCD and iMCD were important cornerstones for clinical researches in this rare disease. Our large retrospective study implementing CDCN criteria not only evaluated these criteria and guidelines, but also provided evidence for further iterations of these criteria. Moreover, a review of first-line treatment options of iMCD before the era of IL-6 directed therapy would further help physicians to treat this rare disease and facilitate clinical researches in this field.

Introduction

Castleman disease (CD) is a group of rare and heterogenous lymphoproliferative disorders with characteristic histopathological features that can be divided into unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD). Characteristic lymph node histopathological features include a spectrum from hyaline-vascular (HV), which involves atrophic germinal centers and hypervascularization to plasmacytic (PC), which involves hyperplastic germinal centers and polytypic plasmacytosis, with a mixed group with features of both. UCD involves a single region of enlarged lymph nodes, and MCD involves multiple regions of enlarged lymph nodes.[1,2] After exclusion of diseases that can have enlarged lymph nodes with 'Castleman-like' pathological features and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder, and skin changes) syndrome, MCD could be further divided into HHV-8 (human herpesvirus-8)-associated MCD and HHV-8-negative MCD.[2] According to the recently published China Castleman Disease Network (CCDN) consensus,[3] HHV-8-negative MCD patients can be classified into idiopathic MCD (iMCD) and probable iMCD, which we refer to as asymptomatic MCD (aMCD). iMCD is characterized by systemic inflammatory symptoms, cytopenias, and sometimes life-threatening organ dysfunction and can be recognized with the Castleman Disease Collaborative Network (CDCN) consensus criteria.[2] Asymptomatic MCD (aMCD) refers to a group of patients who do not have symptoms and a hyperinflammatory state and thus do not meet the CDCN diagnostic criteria for iMCD.

As a rare disease, knowledge about the clinical and prognostic features accumulates slowly and is mainly gathered from case series or retrospective studies.[4–10] However, the inclusion criteria of patients in these studies vary because no diagnostic criteria existed before the CDCN developed criteria for iMCD in 2017.[2] For example, several studies included POEMS syndrome patients in the analysis,[4,5,7,8] and some studies[7,10] included both UCD and MCD patients in the same model to identify prognostic factors for CD or both HHV8-MCD and iMCD as risk factors for MCD, which might not be appropriate from the present understanding of heterogeneity between these entities. Moreover, although consensus on the treatment of UCD and iMCD has been reached[1,11] by the CDCN, there is wide heterogeneity in the approaches and regimens used to treat patients, especially in countries such as China, where siltuximab,[12] the recommended first-line treatment option for iMCD,[2] is still not widely available. To welcome the era of IL-6-directed therapy, it is necessary to review the treatment patterns and changes in the trend of treatment approaches at this time. Finally, although CDCN consensus treatment guidelines proposed the concept of severe-iMCD as a subgroup of patients that require more intensive treatment due to increased risk of death,[11] this concept was based mainly on expert opinion and has not been tested in large-scale analyses.

To address these knowledge gaps, we conducted this large, multicenter, retrospective study, enrolling patients from 40 hospitals in 24 provincial-level administrative regions in China. To the best of our knowledge, this is the first study of its kind to implement and evaluate the CDCN diagnostic criteria for CD. Moreover, this was the world's largest retrospective study to date in the field of CD and the largest study in China to depict the treatment patterns and prognosis of Chinese CD patients before the era of IL-6-directed therapy.

Methods

Study design and participants

We conducted this large, observational, retrospective study, enrolling patients with CD from 2000 to 2021 at 40 Chinese institutions. These hospitals were the referral centers of their located provincial-level administrative regions that had experience in the diagnosis and treatment of this disease (Fig. 1). Patients were eligible for inclusion if they had a confirmed diagnosis of CD according to the criteria proposed by the CDCN.[1,2] UCD was defined as involvement of a single lymph node or multiple lymph nodes within a single lymph node region with a pathology consistent with CD. MCD was defined as the involvement of multiple lymph node regions (enlarged lymph nodes ≥1 cm in short-axis diameter in ≥2 lymph node stations) with pathological features consistent with CD features. Patients with diseases that might present with 'Castleman-like' lymph node pathological features, such as HIV infection, EBV-lymphoproliferative disorders, POEMS syndrome, connective tissue diseases, lymphomas, plasmacytomas and FDC sarcoma, were excluded from this study. The MCD patients enrolled in this study were further classified into HHV-8-associated MCD and HHV-8-negative MCD groups. HHV-8 status was confirmed by blood PCR or LANA-1 (latency-associated nuclear antigen) staining by immunohistochemistry. For HHV-8-negative MCD, patients who fulfilled both major criteria and at least 2 of 11 minor criteria proposed by the CDCN and did not meet any of the exclusion criteria were diagnosed with iMCD; patients who did not have symptoms or a hyperinflammatory state and thus did not meet the minor diagnostic criteria of iMCD were considered to have asymptomatic MCD (aMCD) according to the China Castleman Disease Network (CCDN) consensus.[3] UCD patients with an MCD-like inflammatory state were defined as UCD-MIS,[13] and iMCD patients were further classified into iMCD-not otherwise specified (iMCD-NOS) and iMCD-TAFRO groups. TAFRO was an acronym for thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis of bone marrow (R) and organomegaly (O).[11] Moreover, based on the severity of the

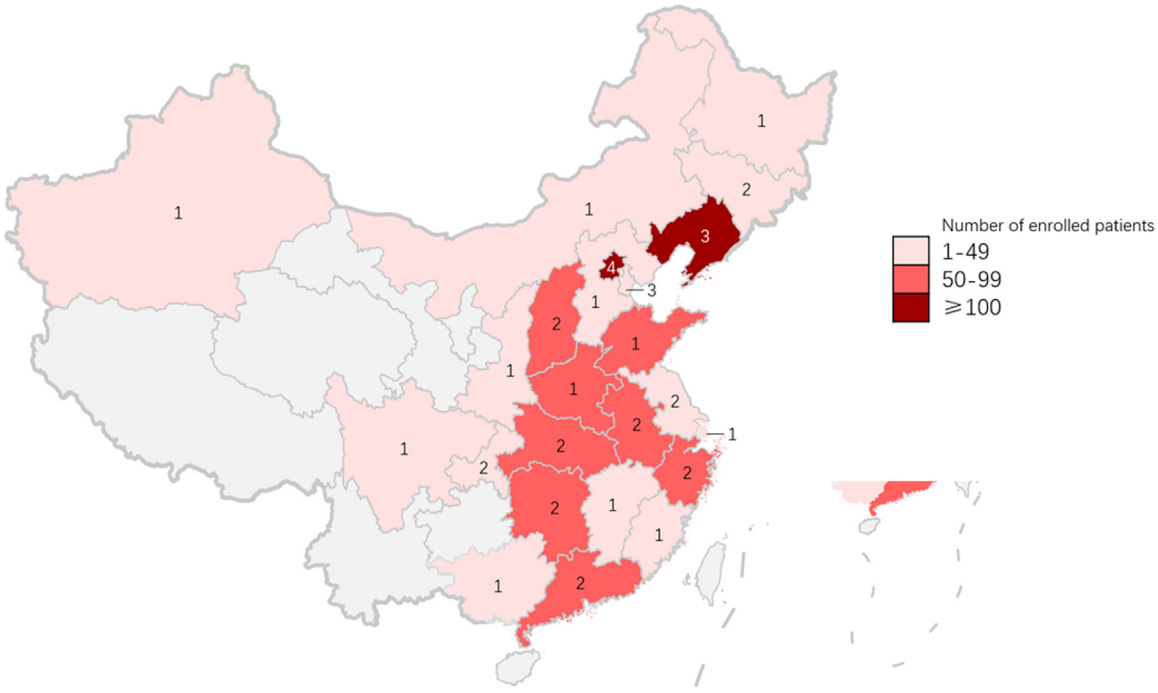

Fig. 1: Distributions of institutions of the study. The numbers on the map indicate numbers of hospitals participating this study in each province and autonomous region and municipality. The different colors for each provincial-level administrative region represents numbers of patients enrolled in that region.

disease, iMCD patients were classified as having severe or mild/moderate/nonsevere disease according to the CDCN definition[11]: severe iMCD should have at least 2 of the 5 following criteria: ECOG ≥2, stage IV renal dysfunction, anasarca, hemoglobin ≤80 g/L, or pulmonary involvement/interstitial pneumonitis with dyspnea. Among iMCD-NOS patients, patients would be further classified as iMCD-idiopathic plasmacytic lymphadenopathy (iMCD-IPL), a recently recognized independent subtype,[14] if they had high platelets, elevated IgG level and PC or mixed pathological subtypes; patients who did not fulfill the above criteria would be defined as iMCD-NOS without IPL. The enrollment of patients was conducted by physicians who were experienced at the diagnosis and treatment of CD at local centers with the help of an on-line database designed according to CDCN criteria. Physicians at the leading center of the study further verified the diagnosis and classification of enrolled patients based on data collected in the on-line database.

Demographic, clinical, laboratory, and treatment-related data, including age, sex, past medical history, CD subtypes, symptoms and signs, radiological findings, and treatment options, were extracted from patient medical records. Patient follow-up information was collected from medical record systems and via telephone contact. The patients were followed until December 31, 2021, and the survival status was documented.

The study was performed in accordance with the Declaration of Helsinki, with prior approval of the institutional review board and the ethics committee of the local hospital.

Outcomes

The primary outcomes were the distribution of different CD subtypes, descriptions of demographic and clinical characteristics, treatment options and overall survival. Overall survival was defined as the time interval between diagnosis and either death or the last follow-up.

Statistical analysis

Statistical analyses were performed with SPSS 22(SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for demographics, CD subtypes, clinical features, and treatment options. For continuous data, medians and ranges were presented. For categorical data, frequencies and percentages were presented. The Kaplan–Meier method was used to depict survival curves and to estimate survival rates at 3 years after diagnosis. The log-rank test was used to compare survival curves for different clinical subtypes of CD patients, and $p < 0.05$ was used as a threshold for significant differences. The univariate Cox proportional hazards model was used to estimate hazard ratios (HRs) and to test survival differences between groups. Patients with missing data in a

certain variable were excluded from regression analyses in case that variable was included into such analyses.

Role of funding source

The funders of the study had no role in the design or conduct of the study, including data collection, management, analysis, or interpretation of the results; preparation and writing of the manuscript.

Results

Patient characteristics and treatment options

A total of 1634 CD patients from 40 Chinese hospitals (Fig. 1) were enrolled in this study, including 903 (55.7%) UCD patients and 731 (44.7%) MCD patients.

Among the UCD patients (n = 903), there were 385 (42.6%) males and 518 (57.4%) females. The median age at diagnosis was 40 years (range: 2–78 years). Adult patients (≥18 y/o) accounted for 92.6% of all UCD patients. Among the 668 patients who had information of time intervals between symptom onset and diagnosis of UCD, there were 177 (26.5%) patients whose time intervals to diagnosis were ≥12 months and the maximum time interval to diagnosis was 362 months. Involved lymph node regions included abdominal/retroperitoneal (35.7%), cervical (25.7%), mediastinal/hilar (23.1%), axillary (6.4%), pelvic (6.1%), inguinal (2.7%), and infraclavicular (0.3%) lymph nodes (Fig. 2). For 672 patients with pathological subtype information, 531 patients (79.0%) were classified as having the HV histopathologic variant, 88 patients (13.1%) were classified as having PC histopathologic variant, and 53 patients (7.9%) were classified as having a mixed subtype. Of the 903 UCD patients, 53 patients (5.9%) had documented paraneoplastic pemphigus (PNP); 35 patients (3.9%) had bronchiolitis obliterans (BO); and 5 patients (0.6%) had osteosclerotic bone lesions. 162 patients (17.9%) who had constitutional symptoms accompanied by an inflammatory state resembling iMCD were classified as having UCD with an MCD-like inflammatory state (UCD-MIS). A total of 682 patients had documented information of whether they received chemotherapy. Of them, 62 patients (9.1%) underwent chemotherapy as part of their first-line treatment. More than half of them (32/62) had UCD-MIS.

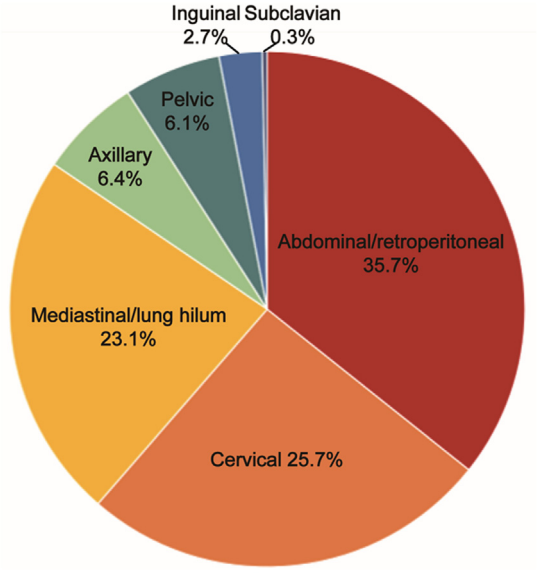

Fig. 2: Distribution of lymph node involvement in UCD patients.

Among the MCD patients (n = 731), there were 572 patients who had information of time intervals between symptom onset and diagnosis of MCD. 215 patients (37.6%) were diagnosed ≥12 months after the initial onset of symptoms and the maximum time interval to diagnosis was 353 months. Of the 731 MCD patients, there were 12 HHV-8-positive patients (1.64%). All these 12 patients were HIV negative. Of the remaining 719 HHV-8-negative patients, there were 421 (58.6%) males and 298 (41.4%) females. The median age at diagnosis was 47 years (range: 5–77 years) and adult patients (≥18 y/o) accounted for 96.7%. There were 593 patients who had pathological subtype information: 184 patients (31.0%) had the HV histopathologic subtype, 310 patients (52.3%) had the PC histopathologic subtype, and 99 patients (16.7%) had the mixed histopathologic subtype. A total of 580 patients were classified as having iMCD (80.7%), and 139 patients (19.3%) were classified as having aMCD. Among the 580 iMCD patients, 150 patients (25.9%) were classified as severe iMCD patients at time of diagnosis. According to the CDCN criteria, there were 41 iMCD patients (7.1% of 580 iMCD patients) who could be classified as iMCD-TAFRO; and 539 iMCD patients were defined as iMCD-NOS patients. Among the 539 iMCD-NOS patients, 97 (18.0%) patients were classified as iMCD-IPL. Information on first-line treatment options was available in 376 iMCD patients. A trend from pulse combination chemotherapy (e.g., CHOP or CHOP-like therapy) toward a continuous treatment approach (e.g., the TCP or BCD regimen and IL-6 targeted therapy) was observed in recent years (Fig. 3). Before 2010, CHOP or CHOP-like therapy was the first choice for iMCD, accounting for 66.7% of all first-line treatments. This proportion decreased with time, and since 2020, only 5.2% of patients received this combination chemotherapy as first-line treatment. In contrast, the thalidomide-based continuous therapy approach became the first choice for iMCD (34.4% after 2020).

Survival analysis

A total of 591 UCD patients had follow-up information. With a median follow-up time of 31.8 months (range: 0.13–257 months), 13 patients (2.2%) died. The most common cause of death was deterioration from BO (6/13). The median survival for UCD was not

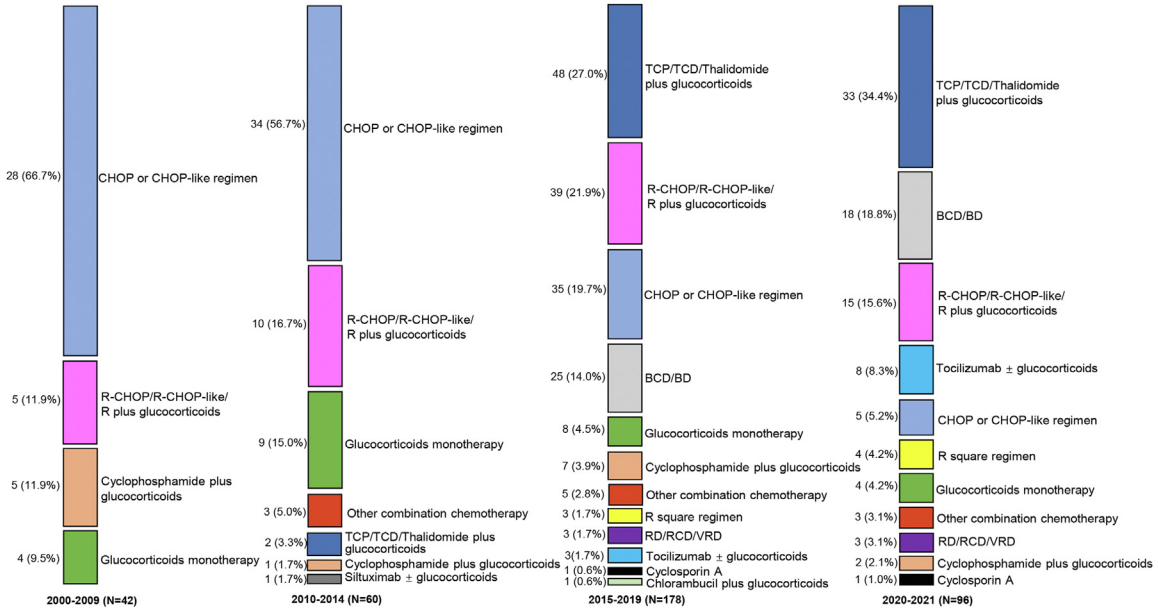

Fig. 3: Changes in the trends of first-line treatment for iMCD patients. Abbreviations: BCD (bortezomib, cyclophosphamide, and dexamethasone), BD (bortezomib, and dexamethasone), CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), R-CHOP/R plus glucocorticoids (R = rituximab), RCD (lenalidomide, cyclophosphamide, and dexamethasone), RD (lenalidomide plus dexamethasone), R-square (rituximab plus lenalidomide), TCD (thalidomide, cyclophosphamide, and dexamethasone), TCP (thalidomide, cyclophosphamide, and prednisone), VRD (bortezomib, lenalidomide, and dexamethasone).

reached, and the estimated 3-year overall survival was 98.0% (Fig. 4a).

Among the 580 iMCD patients (iMCD-NOS without IPL, iMCD-IPL and iMCD-TAFRO patients), there were 455 patients who had follow-up data. With a median follow-up time of 29 months (range: 1–232), 60 patients (13.2%) died. Fourteen patients (3.1%) died within 3 months, and most of them (9/14) died from disease progression. The median survival for iMCD patients (iMCD-NOS without IPL and iMCD-IPL) was not reached, and the median survival for iMCD-TAFRO patients was 64 months. The estimated 3-year overall survival rates for iMCD-NOS without IPL, iMCD-IPL and iMCD-TAFRO patients were 87.2%, 98.5% and 65.7%, respectively (Fig. 4b). Significant differences in survival were observed among different subtypes of iMCD patients (Fig. 4b) (iMCD-IPL versus iMCD-NOS without IPL, HR = 0.32, 95% CI 0.16–0.64, $p = 0.001$; iMCD-IPL versus iMCD-TAFRO, HR = 0.03, 95% CI 0.01–0.09, $p < 0.001$; iMCD-NOS without IPL versus iMCD-TAFRO, HR = 0.13, 95% CI 0.05–0.33, $p < 0.001$).

Among the 539 iMCD-NOS patients, 418 patients had sufficient follow-up information. With a median follow-up time of 30 months (range: 1–232 months), 47 patients (11.2%) died. Univariate Cox regression identified that older age (HR = 1.037; 95% CI 1.016–1.059, $p = 0.001$), male sex (HR = 2.150; 95% CI 1.094–4.224, $p = 0.026$), history of chronic diseases (HR = 2.255; 95% CI 1.267–4.011, $p = 0.006$), severe iMCD (at time of diagnosis) (HR = 3.747; 95% CI 2.112–6.649, $p < 0.001$), presence of serous cavity effusion (HR = 2.628; 95% CI 1.473–4.689, $p = 0.001$), and not having an elevated serum IgG level (HR = 0.417; 95% CI 0.222–0.783, $p = 0.006$) were associated with death (Table 1). The Kaplan–Meier method was used to delineate the survival curves of patients with severe iMCD-NOS and non-severe iMCD-NOS (log rank analysis, HR 3.75, 95% CI 2.11–6.65, $p < 0.001$) (Fig. 4c). The estimated 3-year overall survival rates for severe and nonsevere iMCD-NOS patients were 75.6% and 93.8%, respectively. Given the small sample size of iMCD-TAFRO, a sub-analysis of outcomes associated with death was not performed.

Discussion

According to our knowledge, this is the largest retrospective study that implemented the CDCN diagnostic criteria to date and has been able to evaluate it. As a study that enrolled patients from all over China, the country with the largest population, this study reflects the current status of Castleman disease in China and provides important descriptive statistics of CD from multicenter data. We also noticed delays to diagnosis in Chinese CD patients (especially in MCD patients), possibly due to the rarity of the disease.

For UCD patients, the median age at diagnosis, female-to-male ratio and distribution of involved lymph

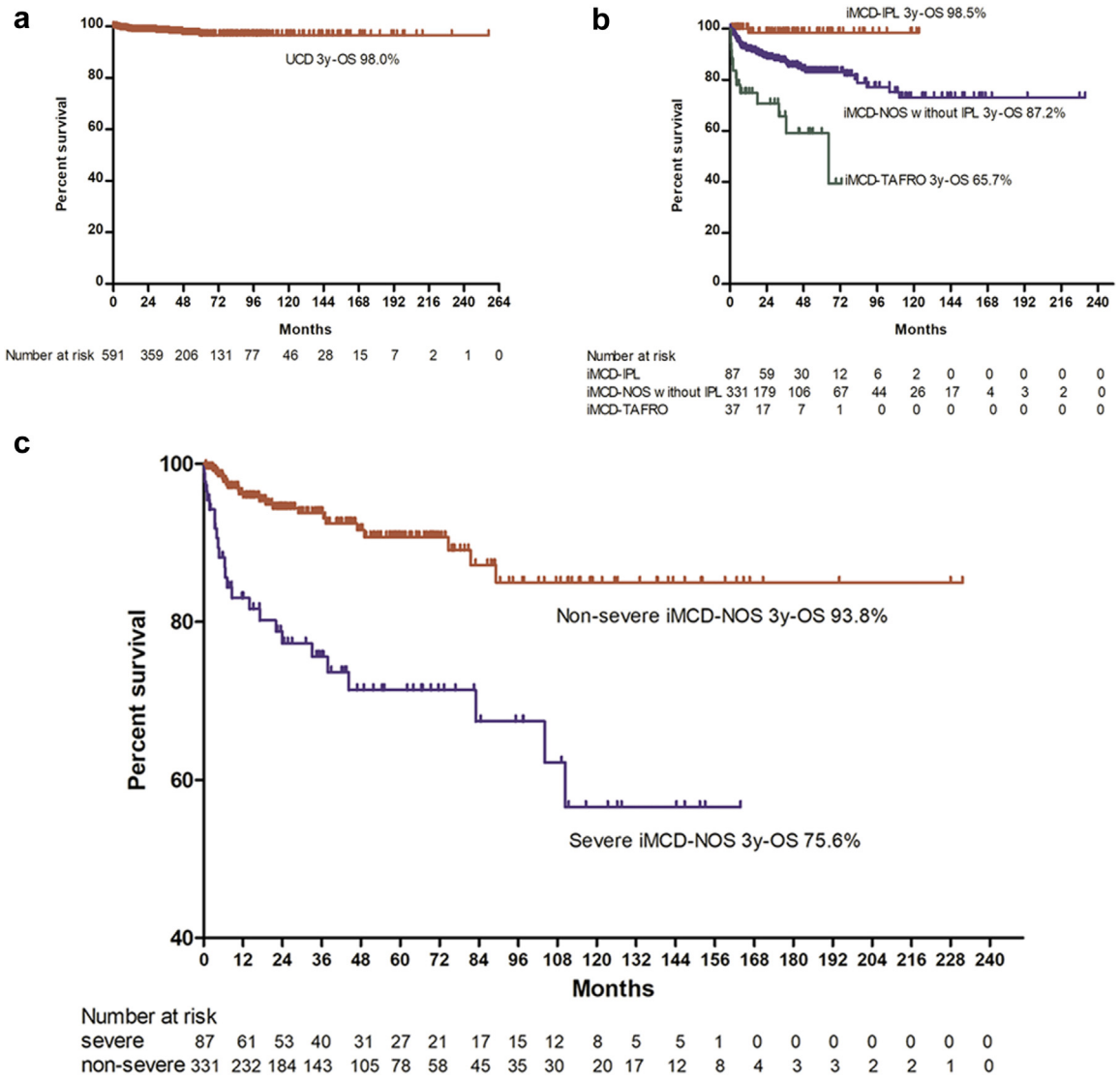

Fig. 4: Survival curves of different subtypes of CD patients. (a) Survival curve of UCD patients; (b) Survival curves of different subtypes of iMCD; (c) Survival curves of iMCD-NOS patients suggest that severe iMCD is a significant risk factor for survival.

node regions were similar to the previously reported data: UCD mainly occurs in younger adults, with a slightly increased incidence in women than in men[15–17] which is also consistent with a previous Chinese study (patients younger than 40 years accounted for 66.1% of UCD and 52.1% UCD patients were female)[5]; moreover, the most commonly involved lymph node regions in this study (abdominal/retroperitoneal 35.7%, cervical 25.7%, and mediastinal/hilar 23.1%) were comparable to those of previously reported case series (abdominal/retroperitoneal 32%, cervical 20%, chest 24%).[15] As many previous reports come from Europe, Japan, and the US, these findings suggest that the clinical picture of UCD may not be associated with particular ethnicities. This study also highlighted a group of UCD patients with an MCD-like inflammatory state, which accounted for 17.9% of all UCD patients, a proportion very similar to that of a Chinese single-center experience of 16.4%.[13] Moreover, the distribution of pathological subtypes in our study, which revealed a predominance of HV subtype in UCD, was also consistent with prior Chinese and western studies.[5,6,15,18]

For MCD patients, the proportion of patients with HHV-8 infection was low, similar to previously reported data from Japan,[9] but lower than what has been reported historically in western countries.[19] For iMCD patients, the demographic features of Chinese patients were not only consistent with prior Chinese CD studies, but also

	Risk factors	Univariate analysis	
		HR (95% CI)	p
Demographic characteristics	Age at CD diagnosis (years)	1.037 (1.016–1.059)	0.001
	Sex, male (n)	2.150 (1.094–4.224)	0.026
	Chronic diseases (n)[a]	2.255 (1.267–4.011)	0.006
	Prior history of TB (n)	0.048 (0.000–246.369)	0.486
	Prior history of malignancies (n)	2.095 (0.751–5.843)	0.158
CD subtypes	PC variate (n)[d]		0.228
	Severe iMCD (n)	3.747 (2.112–6.649)	<0.001
Symptoms and signs	Constitutional symptoms (n)[b]	1.697 (0.758–3.798)	0.198
	Hepatosplenomegaly (n)[d]		0.833
	Rash (n)	1.310 (0.666–2.575)	0.434
	Serous cavity effusion (n)	2.628 (1.473–4.689)	0.001
	ECOG ≥ 1 (n)	1.975 (0.834–4.680)	0.122
Laboratory and imaging results	Hemoglobin (g/L)	1.007 (0.995–1.019)	0.235
	Albumin (g/L)	1.010 (0.969–1.053)	0.641
	hsCRP (mg/L)	0.994 (0.987–1.001)	0.097
	eGFR < 60 (ml/min) (n)[d]		0.485
	Elevated IgG (n)	0.417 (0.222–0.783)	0.006
	Elevated IL-6 (n)[d]		0.764
	Interstitial lung disease (n)[d]		0.584
Treatment	Continuous treatment strategy (n)[c,d]		0.764

CD, Castleman disease; ECOG, Eastern, Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; hsCRP, hypersensitive C-reactive protein; IgG, immunoglobin G; IL-6, interleukin-6; iMCD, idiopathic multicentric Castleman disease; PC, plasma cell. [a]Chronic diseases: hypertension, diabetes, coronary heart disease, cerebral infarction, chronic liver disease, chronic kidney disease. [b]Constitutional symptoms: presence of any of the following symptoms: night sweat, fatigue, anorexia, fever, or weight loss. [c]Continuous treatment strategy: glucocorticoid monotherapy, cyclophosphamide plus glucocorticoids, thalidomide-based therapy, bortezomib-based therapy, lenalidomide-based therapy, IL-6-targeted therapy, sirolimus, or cyclosporin A. [d]These variables did not meet proportional hazards (PH) assumption. Thus, HRs were not presented in the table. Moreover, p values for these variables listed in the table were log-rank p-values (please refer to Supplement Fig. S2 for Kaplan–Meier curves for these variables).

Table 1: **Survival analysis of 418 iMCD-NOS patients using the Cox regression model.**

similar to the previously reported western data, which suggested that iMCD can occur at any age with a male predominance.[5,16,19] The most common pathological subtype of MCD in our cohort was PC subtype, which was also consistent with prior literature,[18] including previous CD studies in western pacific region.[5,9] Moreover, the study emphasized a subgroup of HHV-8-negative MCD patients who had multiple regions of enlarged lymph nodes but did not have symptoms (other than lymphadenopathy) or a hyperinflammatory state. According to the 2017 CDCN consensus diagnostic criteria for iMCD,[2] these patients met both the major criteria but did not meet the minor criteria (laboratory or clinical) and thus could not be classified as iMCD; these cases were considered to be probable iMCD. In 2021, the CCDN (China Castleman Disease Network) classified this subgroup of HHV-8 negative MCD patients into aMCD[3]; this classification was used in this study.

Our study also showed the survival data of CD patients: UCD patients had a very good overall survival, while iMCD-TAFRO patients had the worst prognosis (Fig. 4). These findings were consistent with those of other researchers[4–6], which again emphasized the rationality of the CDCN criteria to classify CD patients into UCD, iMCD-NOS and iMCD-TAFRO.[1,2] This is the largest study to evaluate and show differences in outcomes between iMCD-NOS and iMCD-TAFRO. Moreover, this is also the largest study to describe the prognosis of iMCD-IPL, a unique subtype of iMCD-NOS. The result of our study, which revealed a better outcome of iMCD-IPL patients compared with other iMCD-NOS patients, was consistent with prior literature[20] and further suggested a re-classification of iMCD-NOS patients proposed by CDCN.[2]

For iMCD-NOS patients, with a Cox regression model, we identified severe iMCD as a significant risk factor for survival. Severe iMCD was a concept first raised by the CDCN in 2018[11] that requires at least 2 of the 5 following criteria: ECOG ≥2, stage IV renal dysfunction, anasarca, hemoglobin ≤80 g/L, or pulmonary involvement/interstitial pneumonitis with dyspnea. This concept was put forward mainly based on expert opinion to identify patients at increased risk of death who need more intensive therapies but it required more evidence. In fact, prior studies that focused on the survival analysis of MCD patients found different risk factors for overall survival, which might be due to the

differences in the inclusion criteria of patients as well as the sample size. For example, Zhang et al.[5] retrospectively analyzed 64 MCD patients and also included patients with POEMS syndrome and found that older age, splenomegaly and hypoalbuminemia were risk factors for poorer MCD prognosis. Seo et al.[8] enrolled 32 MCD patients, 11% of whom were patients with POEMS syndrome who did not meet the iMCD criteria of the CDCN, and identified extravascular fluid accumulation and disseminated disease as risk factors for survival using univariate analysis. Zhang et al. enrolled 76 MCD patients and also included patients who did not meet the iMCD criteria of the CDCN; they found that impaired renal function was a risk factor for survival. Our study is the largest study to date that enrolled 418 iMCD-NOS patients for survival analysis. Aside from previously reported risk factors such as older age and the presence of serous cavity effusion, this study for the first time validated the concept of severe iMCD in a large-scale retrospective survival analysis (Fig. 4c).

Siltuximab, an anti-IL-6-targeted therapy that has been approved for iMCD in over 50 countries worldwide, has just been approved by the NMPA (National Medical Products Administration of China) and will soon be available in China. As IL-6-targeted treatment was the recommended first-line therapy for iMCD according to the CDCN evidence-based consensus treatment guidelines,[11] one could expect that the availability of siltuximab in China will have a great impact on the treatment strategy of iMCD. Thus, it is important to review the current treatment options before the era of IL-6-directed therapy in China. Our study depicted the first-line treatment patterns of iMCD patients in China in the current era. Inspired by the treatment strategy of siltuximab, a drug that is continuously given to patients with iMCD who respond to the treatment, a continuous treatment approach has been increasingly employed by Chinese physicians. For example, before 2015, the CHOP or CHOP-like regimen (a pulse combination chemotherapy) was used in 60.8% of all iMCD patients and was the most commonly used treatment option. This strategy of pulse combination chemotherapy was also used for the majority of MCD patients in prior Chinese CD studies[4,5] as well as in a Korean study published in 2014[8] which also focused on CD patients in western pacific region. Since 2015, the percentage of CHOP or CHOP-like regimens as first-line treatment in China has declined to 14.6%. Instead, the use of thalidomide-based treatment, an oral treatment regimen with a continuous treatment approach, increased to 34.4% after 2020, and it became the most commonly used treatment in China. Moreover, glucocorticoid monotherapy, a common treatment strategy in the past,[21] as well as glucocorticoids plus cyclophosphamide are no longer mainstream treatment options and have accounted for only 6.3% since 2020. Another important finding was that the proportion of patients who received tocilizumab, which heralded the era of IL-6 targeted therapy, increased rapidly (8.3%). Although the approval of siltuximab might bring significant changes in the treatment pattern of iMCD in China, we should also note that even in the U.S., the first country in which siltuximab was approved, there was a significant portion of patients who did not receive siltuximab treatment, with between 9 and 40% of iMCD patients receiving the FDA-approved and established first-line treatment recommendations.[22,23] As a result, treatment options such as thalidomide-based regimens,[24] which reflect a similar continuous treatment approach as siltuximab, might still be an important treatment option in the era of IL-6-directed therapy, and depicting a whole picture of the treatment options at this time is crucial to guide Chinese physicians in the future.

This study had several limitations. First, the pathology reviews were carried out at individual centers and we did not have a central pathology lab to review each patient's specimen. This limitation might be overcome because the centers included in this study were all referral centers of their located provincial-level administrative regions that were experienced in the diagnosis and treatment of CD, and the pathologists from these hospitals were all trained by the CCDN. Second, the retrospective nature of the study might bring limitation with regard to the proper diagnosis of Castleman disease. Third, follow-up data were not available for all patients, and survival analysis was only performed for patients with follow-up information, which might overestimate the survival rate of this cohort, as some of the nonsurviving patients who were lost to follow-up were not included for analysis. Fourth, although the sample size of the study was large, the median follow-up time was relatively short, and a longer follow-up time in the future would better delineate the survival status of Chinese CD patients. Awareness of these limitations would aid in the design of future CCDN studies and ultimately benefit Chinese CD patients.

In conclusion, this was the largest multicenter retrospective study carried out to date, which implemented the CDCN diagnostic criteria for CD and delineated a broad picture of CD subtypes, treatment options and survival data in China. For the first time, the rationality of the concept of severe iMCD proposed by the CDCN was validated in a large patient cohort. Likewise, this was the first large study to demonstrate worsened outcomes in iMCD-TAFRO compared to iMCD-NOS.

Contributors

Contribution: J.L. and L.Z. designed the study. L.Z., Y.-j.D., H.-l.P., H.L., M.-z.Z., H.-h.W., Q.-h.L., L.-p.S., L.-y.Z., W.-j.W., L.H., X.-j.Y., L.F., W.-j.T., Z.-l.L, L.-t.B., Y.L., G.-x.G., L.G., T.-b.L., Y.-q.W., Y.L., L.Y., H.Z., C.-y.S., W.-b.Q., D.-h.Z., H.-l.Z., K.-y.D., X.-b.W., O.B., W.-r.H., B.C., L.Y., J.S., D.G., T.C., J.L., S.-y.W., L.-m.M., J.L. enrolled patients and collected data. L.Z., Y.-j.D., H.-l.P., D.C.F. and J.L. interpreted the data and wrote the manuscript. All authors had access to primary data and gave final approval to submit for publication.

Data sharing statement

The data that support the findings of this study are available from the corresponding author (J.L.) upon reasonable request.

Editor note

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Declaration of interests

D.C.F. has received research funding and consulting fees from EUSA Pharma. The remaining authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100720.

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