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Longitudinal, natural history study reveals the disease burden of idiopathic multicentric Castleman disease

Short title: Disease burden of iMCD

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Data Availability

All source data reported in this study is available by contacting the ACCELERATE team at accelerate@uphs.upenn.edu.

Authorship Contributions

M.S.B.: Formal analysis, writing – original draft preparation, writing – review and editing, and visualization; S.K.P.: Conceptualization, formal analysis, writing – original draft preparation, writing – review and editing, and visualization; Y.R.: Formal analysis, writing- reviewing and editing; A.B.: Supervision, writing – review and editing; J.D.B.: Supervision, writing – review and editing; G.S.: Supervision, writing – review and editing; N.M.: Investigation, writing – review and editing; D.A.: Supervision, writing – review and editing; M.J.L.: Supervision, writing – review and editing; H.L.: Supervision, writing – review and editing; F.v.R.: Supervision, writing – review and editing; M.S.L.: Supervision, writing – review and editing; D.C.F.: Conceptualization, supervision, funding acquisition, writing – review and editing.

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Key Points:

- iMCD-TAFRO patients experience significant hospitalization burden as well as life-threatening multisystem organ involvement requiring medical interventions and therapies
- iMCD patients develop life-threatening morbidities during their disease course and experience reductions in quality-of-life

Abstract:

Idiopathic multicentric Castleman disease (iMCD) is a rare hematologic disorder with heterogeneous presentations ranging from moderate constitutional symptoms to life-threatening multiorgan system involvement. iMCD patients present with vastly different clinical subtypes, with some patients demonstrating thrombocytopenia, anasarca, fever/elevated C-reactive protein, reticulin fibrosis/renal failure, and organomegaly (TAFRO) and others demonstrating more mild/moderate symptoms with potential for severe disease (not otherwise specified, NOS). Due to its rarity and heterogeneity, the natural history and long-term burden of iMCD are poorly understood. We investigated real-world medical data from ACCELERATE, a large natural history registry of Castleman disease patients, to better characterize the long-term disease burden experienced by these patients. We found that iMCD-TAFRO patients face significant hospitalization burden, requiring more time in the hospital than iMCD-NOS patients during the year surrounding diagnosis (median [IQR] 36 [18, 61] days vs. 0 [0, 4] days; $p<0.001$). In addition, we found life-sustaining interventions such as mechanical ventilation (17%) and dialysis (27%) required among iMCD patients, predominantly iMCD-TAFRO patients. iMCD-NOS patients, however, spent a significantly greater proportion of time following disease onset in a state of disease flare (median 52.3% vs. 18.9%, $p=0.004$). Lastly, we observed severe iMCD-related morbidities, such as acute renal failure, sepsis and pneumonia, among others, arising after iMCD diagnosis, impairing patients' quality-of-life. These data demonstrate a substantial disease burden experienced by iMCD patients and emphasize the importance of ongoing research into iMCD to aid in disease control.

Introduction:

Idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder characterized by widespread lymphadenopathy and a systemic inflammatory syndrome. While the pathophysiology of the disease remains poorly understood, existing data has implicated interleukin 6 (IL6) and the mTOR and JAK-STAT pathways.[1–5] As with other inflammatory disorders, iMCD is characterized by constitutional symptoms and systemic inflammation that can lead to multiorgan failure or death.[6] Several different clinical subtypes of iMCD have been identified. Patients with the most severe subtype who demonstrate thrombocytopenia, anasarca, fever/elevated C-reactive protein, reticulin fibrosis/renal failure, and organomegaly are classified as TAFRO.[7] Other patients who do not meet TAFRO criteria are referred to as not otherwise specified (NOS) and typically present with a milder clinical phenotype.[7] A subset of NOS patients demonstrate thrombocytosis and hypergammaglobulinemia and have historically been described as idiopathic plasmacytic lymphadenopathy (IPL).[8]

A recent epidemiologic study based on United States (U.S.) insurance claims found approximately 1000 patients diagnosed with iMCD each year.[9] Diagnosis of iMCD is challenging as it is based on non-specific clinical features and characteristic lymph node histopathology. Underdiagnosis is likely as diagnostic criteria were not developed until 2017, and there is no known diagnostic serum biomarker.[10] Challenges with diagnosis and limited understanding of the disease burden may contribute to poor outcomes. Data from the U.S. before 2012 suggest a 35% five-year mortality and a 60% 10 year-mortality of iMCD patients whereas more recent data from electronic medical records suggest a 25% five-year mortality.[11,12] Three-year survival estimates based on a recent large cohort of patients in China were 65.7% for TAFRO patients, 87.2% for NOS patients without IPL characteristics, and

98.5% for NOS patients with IPL characteristics.[13] In the U.S. and Europe, siltuximab, a monoclonal antibody directed against IL6, is the only approved treatment and first-line recommended therapy.[14,15] Tocilizumab, a monoclonal antibody directed against the IL6 receptor, is recommended when siltuximab is not available and is approved for use in iMCD in Japan.[16] For patients with severe disease who do not respond to first-line treatment with IL6 blockade, multiagent cytotoxic chemotherapy is recommended.[15]

Due to its rarity and heterogeneous nature, the natural history and long-term burden of iMCD is not well understood. Given the limited understanding of the burden of disease and the significant consequences of underestimating the risks of iMCD[17], we sought to investigate the burden of iMCD on patients and the health care system. ACCELERATE (NCT02817997), a longitudinal natural history study of Castleman disease, is ideally positioned to characterize the natural history and burden associated with iMCD. Herein, we present data from ACCELERATE to demonstrate that iMCD patients face a high burden of disease involving severe multisystem organ involvement, the onset of life-threatening iMCD-related morbidities, long periods of hospitalizations during which interventions are frequently required, and extensive periods of time spent in active disease flare.

Methods

Study Population

Patients with a pathology report suggestive of Castleman disease (CD) were invited to enroll into ACCELERATE beginning in October 2016.[18] Enrollment is open to patients in the United States and globally. Given that the registry website is written in English and records from institutions in English-speaking countries are more feasibly obtained, there is a bias towards English-speaking patient enrollment. After enrollment, all available medical data from the time of symptom onset to the time of

analysis were collected from each patient's treating institution(s). Data were reviewed and abstracted into the study database, and each case underwent a rigorous, systematic review by three hematopathologists and four hematologist-oncologists to confirm the accuracy of an iMCD diagnosis. While it is impossible to know the exact number of patients in this study that have been reported in prior case reports/small series, it is possible that some patients have been included in previous case reports/small series.

Outcome definitions

Disease severity

Severe disease at diagnosis was classified according to the iMCD treatment guidelines and required at least two criteria: ECOG performance status ≥2 or hospitalization, fluid retention, hemoglobin ≤ 8.0 g/dL, pulmonary involvement/interstital pneumonitis with dyspnea, or stage IV renal dysfunction within 90 days of diagnosis by lymph node biopsy.[15]

Flare

To ensure standardization, we defined a new flare as the onset of at least two new iMCD disease symptoms or the clinical worsening of previously stable signs or symptoms. Flares also required at least one lab from the iMCD diagnostic minor criteria that was previously normal to become abnormal. A flare ended when a patient achieved at least 50% reduction of symptoms (minor criteria from the iMCD diagnostic criteria).[10]

iMCD-related morbidities and comorbid conditions

The SNOMED Clinical Terms (CT) ontology was used to categorize iMCD-related morbidities and comorbidities.

Patient Reported Outcome Surveys

Patients enrolled in ACCELERATE received outcome surveys every three months throughout the duration of their enrollment. Data were analyzed from patients who completed the survey at least once. Response data from the EQ5D-5L, a validated quality-of-life (QOL) questionnaire, and from the MCD Symptom Score, a validated MCD symptom survey developed for the phase II siltuximab clinical trial, were analyzed for the patient's most recent survey completion date.[14] The EQ5D-5L captures health on the day of the survey, as well as ease with each of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The MCD symptom survey captures 16 symptoms on a 1 to 6 scale with 1 being the least severe (did not experience) and 6 being the most severe (very severe). The sum of the responses comprises the total MCD Symptom Score. The 16 symptoms assessed include cough, shortness of breath, loss of appetite, fatigue, lack of energy, feeling weak, sores or rash on skin (skin lesions), itching, numbness or tingling, pain, fever, swollen lymph nodes, swelling or edema in other body areas, night sweats, and excessive daytime sweating.

Statistical Analyses

Chi-Square was used to compare proportions, and Wilcoxon rank sum was used to test for differences in continuous data. To compare hospitalization rates between iMCD patients and the general population, a matched case-control analysis was conducted using public data from the 2018 National Health Information Survey (NHIS), a cross-sectional household survey and the principal source of information on the health of the noninstitutionalized U.S. population.[19,20] Four controls were matched to each case on age (within one year), sex, and race.[19,20] Kruskal-Wallis followed by Wilcoxon rank sum with Bonferroni correction was used to compare controls with iMCD subtypes. Spearman rank correlation test was used to determine the correlation between QOL score and MCD symptom score. Analyses were performed using R v 4.04.

Ethical Approval

The ACCELERATE natural history registry has received ethical approval from the University of Pennsylvania IRB, with most recent approval on 3/09/2023 (Protocol: 824758)

Results

Patients with iMCD present with severe clinical and laboratory abnormalities

Of the 136 patients suspected to have iMCD that were reviewed, the ACCELERATE expert panel confirmed 102 (75%) met both clinical and pathological iMCD criteria.[10] The cohort with a confirmed diagnosis had a slight disposition towards males (n=58, 56.9%) with a median (interquartile range [IQR]) age of 35.3 (22.2, 47.5) years, and 65% identified as White (Table 1). The median (IQR) follow-up time after iMCD diagnosis was 3.4 (1.3, 6.1) years for the full cohort, 3.3 (1.2, 5.3) years for TAFRO patients, and 3.6 (1.6, 8.1) years for iMCD-NOS patients. Eight patients were deceased at the time of data collection (Supplemental Table 1). Sixty-one (60%) patients met TAFRO criteria[7] and 41 (40%) were classified as NOS. TAFRO patients tended to more commonly be male (TAFRO 62% compared to NOS 49%) and younger (mean [SD]: 33.0 [17.4] vs. 40.1 [13.9]) than NOS patients.

First, we investigated disease severity at diagnosis and across age ranges. Of the 100 patients with sufficient information to determine disease severity at diagnosis, 77 (77%) initially presented with severe disease. Notably, we found iMCD affected individuals of all ages, with the youngest patient in the cohort diagnosed at 1.8 years and the oldest at 74.4 years. We examined severity by age range visually and observed that the majority of patients <30 or >60 years of age presented with severe disease (Figure 1A). When we examined this trend statistically, we found a

significant difference among the groups ($p=5.3x10^{-4}$). Patients <30 and patients >60 were more likely to have severe disease (94.6% and 90.0%, respectively) as compared to patients between 30 and 60 (62.2%, Supplemental Table 2). All but one patient >60 years presented with severe disease and all but two patients <30 years presented with severe disease, while a large proportion of patients in the 30-60 year age group presented with mild-moderate disease, which likely affected this result (Figure 1A).

We next investigated the clinical and laboratory abnormalities present at diagnosis (Supplemental Table 3). Specifically, we focused on the degree of anemia and hypoalbuminemia as markers of disease activity at diagnosis in this cohort. Across all patients, median (IQR) hemoglobin was 7.8 (6.6, 10.5) g/dL and median (IQR) albumin was 2.2 (1.8, 2.9) g/dL; patients in both TAFRO and NOS subtypes demonstrated median levels less than the lower limit of normal. Eighty-seven (85.3%) patients demonstrated anemia and 81 (79.4%) demonstrated hypoalbuminemia at diagnosis (Figure 1B). We also identified the proportion of patients overall and by subtypes demonstrating clinical abnormalities (Figure 1C, Supplemental Table 3). A large majority of patients presented with fluid retention (84%), splenomegaly (72%), and/or hepatomegaly (60%). While TAFRO patients accounted for most patients with these clinical signs, we found a substantial subset of NOS patients with the same severe clinical features. Among the 102 patients, 77 (76%) presented with severe disease at diagnosis, including 57 (93%) TAFRO patients and 20 (51%) NOS patients (Table 1). These data demonstrate that iMCD can affect patients of any age and subtype with severe and burdensome disease.

iMCD-TAFRO patients face significant hospitalization burden

We examined the number of hospitalized days due to iMCD symptoms as another measure of the disease burden. In the year surrounding diagnosis (six months before or after diagnostic biopsy), iMCD patients were hospitalized for a median (IQR) of 18

(0.5, 38.0) days. When we stratified by days hospitalized prior to and following diagnosis, we found that patients were hospitalized a median (IQR) of 5 (0, 13.8) days in the six months preceding diagnosis (Figure 2A). In the six months following diagnosis, patients were hospitalized a median (IQR) of 7.5 (0, 25.0) days. Eleven patients (10.8%) spent over 60 days in the hospital in the year surrounding diagnosis, highlighting the morbidity of the disease.

Next, we examined hospitalizations by subtype to evaluate any differences in burden of hospitalizations. We found that TAFRO patients experienced significantly more hospitalized days than NOS patients. The median (IQR) days hospitalized in the year surrounding diagnosis was 36 (18, 61) for TAFRO patients and 0 (0, 4) for NOS patients ($W=153.5$, $p=1.3\times10^{-13}$, Figure 2B). In order to understand both subtypes in the context of a general population and given that the majority of our cohort was U.S.-based, we accessed the NHIS 2018 survey data[20] and identified a control population of 408 individuals matched on age (±1 year), sex, and race. In a 12-month period, control patients were hospitalized for a median (IQR) of 0 (0, 0) days. The number of days hospitalized differed between the general population and both TAFRO ($W=47.5$, $p<2.2\times10^{-16}$) and NOS ($W=5638$, $p=8.3\times10^{-13}$) patients. This demonstrates that compared to the general population, patients with iMCD require substantially greater use of the health care system and frequently need hospitalization.

We hypothesized that initiating a treatment course for iMCD would result in reduced hospitalization time. First, we compared the proportion of patients hospitalized at the initiation of the first iMCD treatment regimen, excluding corticosteroid monotherapy, to the proportion hospitalized four weeks after initiating a treatment regimen. Four weeks after initiation was selected to allow sufficient time for the respective treatment regimen to have an effect. Among the 99 patients who received at least one treatment regimen, 49 (49.5%) were hospitalized at the time of

regimen start. After four weeks of treatment, the proportion hospitalized had been reduced to 20 (20.2%) patients ($X=17.4$, $p=3.0x10^{-5}$). We stratified by regimen type for the regimens most frequently administered as a first-line therapy, including siltuximab ± corticosteroids, tocilizumab ± corticosteroids, rituximab ± corticosteroids, chemotherapy-based regimens, and immunomodulator(s) ± corticosteroids. Corticosteroid monotherapy was not included in this analysis given that this approach is not recommended and patients often receive a short course while awaiting a correct diagnosis. We found that among the 32 patients treated with siltuximab ± corticosteroids as first-line therapy, 11 (34.3%) were hospitalized at the time of regimen initiation, and two (6.3%) were hospitalized four weeks after regimen initiation ($p=0.01$). While fewer patients were hospitalized four weeks after starting treatment with each of the other regimens, we did not find any other statistically significant differences, though low sample sizes limit interpretation (Supplemental Table 4). Overall, these data demonstrate the clear burden of hospitalizations early in the iMCD disease course and the importance of administering targeted therapy at the time of diagnosis.

iMCD patients require urgent interventions and demonstrate multisystem organ involvement

Considering the degree of hospitalization burden, we next investigated the distribution of organ system involvement among iMCD patients ± 365 days from diagnosis (Supplemental Methods). Cytopenias were the most common lab abnormalities, experienced by 97.1% (n=99) of the cohort. This was most often anemia, which was present in 87 (85.3%) patients. We also found large proportions of patients experiencing symptoms or lab abnormalities related to other organ systems, such as pulmonary (n=90, 88.2%), gastrointestinal (n=86, 84.3%), hepatic (n=76, 74.5%), neurological (n=68, 66.7%), renal (n=63, 61.8%), cardiovascular

(n=63, 61.8%), and ocular (n=27, 26.5%) systems (Figure 3A, Supplemental Tables 5 and 6).

Next, we looked at life-sustaining interventions related to organ system involvement. We found that 27 (26.5%) patients required dialysis and 17 (16.7%) patients required a ventilator during at least one iMCD-related hospitalization. Additionally, 47 (46.0%) patients required paracentesis, 42 (41.1%) patients received a red blood cell transfusion, and 22 (21.6%) patients received a platelet transfusion (Figure 3B). These interventions, including all platelet transfusions, were mostly required for TAFRO patients.

We also quantified the proportion of time patients spent in a state of flare. We found that NOS patients spent a significantly greater proportion of time in flare from presentation until last known follow-up (median [IQR]: 52.3% [21.0, 99.6]) compared to TAFRO patients (18.9% [10.8, 52.5], W=1673, p=0.004, Figure 3C-3D). Of the eight deceased patients in this cohort, six were TAFRO and five of these TAFRO patients died within two years of diagnosis. These data suggest that while TAFRO patients experience a greater degree of organ failure and more hospital interventions, NOS patients experience a longer continuation of milder, chronic symptoms.

iMCD patients develop severe iMCD-related morbidities and comorbidities following diagnosis

We next sought to identify and quantify the morbidities and comorbidities diagnosed both before and after iMCD diagnosis. Prior to iMCD diagnosis, we found that the most common conditions diagnosed amongst the full cohort were hypertension (n=26, 25.5%), obesity (n=23, 22.5%), asthma (n=21, 20.6%), gastroesophageal reflux disease (n=14, 13.7%), and depression (n=11, 10.8%) (Figure 4A).

Stratification by iMCD subtype did not reveal apparent differences in conditions identified before iMCD diagnosis (Supplemental Figure 1).

Following iMCD diagnosis, 48% (n=49) of the iMCD cohort developed acute renal failure, 15.7% (n=16) developed chronic kidney disease, 13.7% (n=14) developed iron deficiency anemia, 10.7% (n=11) developed pneumonia, 6.9% (n=7) developed sepsis, and 6.9% (n=7) developed thrombotic microangiopathy (Figure 4B). Acute renal failure was the most common iMCD-related morbidity diagnosed following disease onset in both subtypes (Supplemental Figure 2). Sepsis and thrombotic microangiopathy, however, were primarily diagnosed in TAFRO patients. We also stratified the top three morbidities arising for the full cohort following iMCD onset by organ systems, revealing other serious conditions such as atypical hemolytic uremic syndrome (n=5, 4.9%), acute cholecystitis (n=5, 4.9%), and congestive heart failure (n=4, 3.9%) (Supplemental Table 7). Few malignancies were identified following diagnosis; the most common malignancy was papillary thyroid carcinoma, which occurred in two patients 1.3 and 3.6 years after iMCD diagnosis (Supplemental Table 8).

Quality-of-life is negatively correlated with iMCD symptoms

We queried patients about their experiences living with iMCD by asking about QOL and the presence of ongoing iMCD-related symptoms. Fifty-nine (57.8%) patients responded. At a median (IQR) 3.9 (2.3, 8.0) years after diagnosis, iMCD patients reported a median (IQR) QOL score of 80 (71.5, 90.0) from the EQ5D-5L, on a scale of 0 to 100 with 0 being the worst health imaginable and 100 being the best health imaginable. This compares to the general U.S. population, which has a mean score of 80.4.[21] That same day, they reported a median (IQR) MCD symptom score of 29.5 (20, 37), ranging from 16 to 96 with 16 being the best possible score (no iMCD symptoms) and 96 being the worst possible score. We examined if there was any relationship between a patient's QOL score and number of days hospitalized prior to

completing the survey, but saw no correlation (R=0.038, p=0.8, Supplementary Figure 3). We also looked for differences in subsequent QOL scores between patients who presented with severe disease and mild/moderate disease at baseline as well as between TAFRO and non-TAFRO patients and found no significant differences between groups (TAFRO vs NOS: W=481, p=0.31; Severe vs mild/moderate at baseline: W=298.5, p=0.61). We determined the correlation between QOL score and MCD symptom score based on data collected a median (IQR) of 3.9 (2.3, 8.0) years after diagnosis. QOL scores were negatively correlated with MCD symptom score (R=-0.69, p<0.001, Figure 5). This negative correlation appeared to hold for both patients of NOS and TAFRO subtypes. This suggests that several years after diagnosis, patients reporting active iMCD symptoms may be having a decrease in their QOL from those symptoms.

Discussion

iMCD is a rare and heterogeneous disorder, and its full impact on iMCD patients' lives is still not well understood. Since the consensus diagnostic criteria for iMCD are relatively new, long-term epidemiological and medical data from patients with confirmed iMCD are sparse. The ACCELERATE natural history registry is ideally suited to better understand the burden of disease as the most extensive source of longitudinal clinical data (median 3.4 years of follow-up post diagnosis) for these patients. ACCELERATE also provides independent adjudication about the accuracy of diagnosis for each patient through a panel of clinicians and hematopathologists who are experienced in diagnosing and treating iMCD.[18] We found that patients with iMCD require extensive use of the health care system and experience long-term

effects with regards to iMCD-related morbidities and comorbidities, time in disease flare, and QOL.

iMCD is composed of distinct clinical subtypes and, importantly, we found differences in the burden of disease between these subtypes. Patients with TAFRO required significantly longer hospital stays and disproportionately required interventions such as dialysis, mechanical ventilation, and transfusions, illustrating the severe, life-threatening nature of this disease. NOS patients, however, spent a significantly greater proportion of time following diagnosis in a state of flare compared to TAFRO patients. These data reveal the challenges iMCD patients experience across the spectrum of clinical subtypes and severity. The patient reported outcome data from our study indicate that patients of both subtypes continue to experience an impact on their QOL even years after diagnosis and that persistent iMCD-related symptoms significantly hamper QOL. Notably, QOL scores reflect patients who have thus far survived their disease and therefore maybe biased towards a healthier subset of the disease population.

Though NOS patients required significantly less time in the hospital, we found that 51.3% met criteria for severe disease at presentation. This remains lower than the 93.4% of TAFRO patients who presented with severe disease. A recent study from China characterizing 418 iMCD-NOS patients applied the same definition of severity and found that only 87 (21%) patients met criteria for severe disease at presentation.[13] They also noted a lower 3-year overall survival (OS) among NOS patients with severe (76%) compared to mild/moderate (94%) disease and found that severity at diagnosis was associated with death. Notably, our study showed a high proportion of patients in both younger (<30) and advanced (>60) age groups who presented with severe disease. In our study, patients under 30 years were significantly more likely to present with severe disease, and nearly all patients <18 years presented with severe disease. This may be associated with the median age of

the TAFRO subtype of patients being 31 years, compared to 39 years for NOS, and with the fact that 93% of TAFRO patients presented with severe disease. The relatively young age of diagnosis, burden of disease, and availability of disease controlling therapies highlight the importance of rapid diagnosis and treatment.

This study found that iMCD patients experienced a higher degree of hospitalization than the general population experiences in a given year, though this was primarily due to the increased rates of hospitalization among iMCD-TAFRO patients.[20] Our finding that patients required extensive hospital care in the year surrounding diagnosis is consistent with a recent claims-based study.[17] We found that after four weeks of the first-administered treatment regimen, the proportion of hospitalized patients significantly decreased, including among patients treated with siltuximab ± corticosteroids (34% vs 6%), which is the current consensus first-line recommendation[15].

Prior to diagnosis with iMCD, we found that the most frequent conditions diagnosed in our cohort were similar to those among the general U.S. population. A report from the Agency for Healthcare Research and Quality found hypertension, diabetes, and chronic respiratory disease to be among the most common conditions associated with inpatient stays and that depression was found in 10% of patients requiring inpatient hospitalization, which is similar to our findings prior to iMCD diagnosis.[22] We did not identify a condition present in a large proportion of iMCD patients prior to iMCD diagnosis that might suggest a predisposition or trigger to iMCD, which has an as-yet-unknown etiology. Following iMCD diagnosis, patients in both the TAFRO and NOS subtypes developed life-threatening morbidities, most commonly acute renal failure. Consistent with previous reports, we found a high degree of both renal and hepatic dysfunction.[17]

In this cohort, few patients developed a malignancy following iMCD diagnosis. In fact, only one patient developed a myeloid malignancy (myelodysplastic

syndrome), which contrasts with a key finding from a systematic literature review and a claims-based study that found an increase in myeloid and solid malignancies.[17,23] No patients developed diffuse large B-cell lymphoma despite previous reports of its association with MCD, though predominantly in HHV8+ MCD.[24-26] We found that our rate of malignancies was comparable to the control population from the claims-based study.[17] This discrepancy may be due to insufficient follow-up time to detect subsequent malignancies or to more rigorous validation of the iMCD diagnosis in our cohort and recent formalization of exclusion criteria for iMCD. Specifically, iMCD diagnostic criteria preclude patients from being concurrently diagnosed with iMCD and a number of malignancies given the overlapping histopathology and the fact that malignancies can cause reactive lymph node changes that resemble iMCD. Therefore, it is possible that some patients in the claims-based study who should have only been classified as having a malignancy were incorrectly classified as having both. Conversely, our strict inclusion criteria might have inadvertently excluded true iMCD patients who also developed malignancies.

Several limitations are present in this study. First, 13 patients within the NOS subtype met IPL criteria (thrombocytosis and hypergammaglobulinemia) and may represent a distinct subtype from other iMCD-NOS patients.[27] Due to the low number of patients and the similar, more moderate presentation, these patients were combined with other non-TAFRO patients in the NOS category.[13] Second, our study includes a higher proportion of TAFRO patients compared to NOS, which may not be representative of the whole iMCD population. To address this, we stratified our analyses between TAFRO and NOS subtypes. It is possible that the higher number of TAFRO patients in this study is a result of patients with more severe disease being more likely to seek resources online and thus enroll into the ACCELERATE registry. However, the study design for our registry is biased towards patients that survive and

who are able to enroll themselves into a registry compared to patients who die shortly after diagnosis and would need a family member to enroll them.

Ultimately, these data demonstrate that an iMCD diagnosis imparts a long-term burden of disease on patients which results in high rates of hospitalization, the development of life-threatening iMCD-related morbidities and comorbidities requiring intensive interventions, and reduced QOL from active symptoms. These data demonstrate the importance of ongoing research into iMCD, the need to recognize and diagnose iMCD sooner, and focused efforts to identify diagnostic and/or disease biomarkers to aid in disease management.

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Table 1. Cohort characteristics

	iMCD (n=102)	TAFRO (n=61)	NOS (n=41)
Self-reported Sex, n (%)			
Female	44 (43.1)	23 (37.7)	21 (51.2)
Age at diagnosis			
Median (IQR)	35.3 (22.2, 47.5)	31.4 (17.9, 47.1)	39.3 (31.3, 50.0)
Range	1.8, 74.4	1.8, 65.7	14.1, 74.4
Severity at diagnosis, n (%)			
Severe	77 (77.0)	57 (93.4)	20 (51.3)
Mild/moderate	23 (23.0)	4 (6.6)	19 (48.7)
Data not available	2	0	2
Race, n (%)			
White	66 (64.7)	44 (72.1)	22 (53.7)
Black/African American	12 (11.8)	6 (9.8)	6 (14.6)
Asian	14 (13.7)	6 (9.8)	8 (19.5)
Native Hawaiian/Pacific Islander	1 (1.0)	1 (1.6)	0
American Indian/Alaska Native	1 (1.0)	0	1 (2.4)
Other/refused to answer	8 (7.8)	4 (6.6)	4 (9.8)
Country of Enrollment, n (%)			
United States	91 (89.2)	53 (86.9)	38 (92.7)
Canada	5 (4.9)	4 (6.6)	1 (2.4)
Australia	3 (2.9)	2 (3.3)	1 (2.4)
Bermuda	1 (1.0)	1 (1.6)	0
New Zealand	1 (1.0)	0	1 (2.4)
Cayman Islands	1 (1.0)	1 (1.6)	0
Histopathological Subtype, n (%)			
Hypervascular/Hyaline Vascular	63 (60.0)	45 (73.8)	18 (43.9)
Mixed	27 (28.2)	15 (24.6)	12 (29.3)
Plasmacytic	7 (5.9)	0 (0.0)	7 (17.1)
Not Specified	5 (4.7)	1 (1.6)	4 (9.8)

Figure Legends

Figure 1

Idiopathic multicentric Castleman disease (iMCD) patients demonstrate severe disease at diagnosis. (A) A large proportion of patients across all ages demonstrated severe disease. Notably, 95% of patients under the age of 30 presented with severe disease at diagnosis. (B) Within the cohort of 102 iMCD patients, 87 (85.3%) demonstrated anemia and 81 (79.4%) demonstrated hypoalbuminemia at diagnosis. *: hemoglobin normal lower limit males, 12.5 g/dL; †: hemoglobin normal lower limit females: 11.5 g/dL; ‡ albumin normal lower limit: 3.5 g/dL (C) A large majority of patients presented with clinical symptoms ranging from mild to severe. Patients of both clinical subtypes, TAFRO and NOS, demonstrated clinical abnormalities.

Figure 2

Idiopathic multicentric Castleman disease (iMCD) patients face a high burden of hospitalizations. (A) Patients are hospitalized a large proportion of time in the six months leading up to diagnosis and the six months following diagnosis (year around diagnosis). Graph depicts each patient on the Y axis with the time hospitalized prior to diagnosis and the number of days hospitalized after diagnosis. Red indicates time TAFRO patients spent hospitalized, and blue indicates time NOS patients spent hospitalized. In the 6 months prior to diagnosis, patients were hospitalized a mean (SD) of 10.6 (17.5) days and a median (IQR) of 5 (0, 13.8) days, while in the year following diagnosis, patients are hospitalized a mean (SD) of 18.9 (28.2) days and a median (IQR) of 7.5 (0, 25.0) days. (B) A US sample from the 2018 National Health Information Survey (NHIS), a proxy for the general population, spend a significantly shorter amount of time hospitalized in a 12 month period (median [IQR]: 0 [0,0], mean [SD]: 0.24 [1.3] than each TAFRO (median [IQR]: 35 [18,61], mean [SD]: 46.0 [42.0], $p<2.2x10^{-16}$) and NOS (median [IQR]: 0 [0,4], mean [SD]:4.9 [9.0], $p=8.3x10^{-}$

^{13}) patients spend hospitalized in the year around diagnosis, and TAFRO patients are hospitalized significantly more days than NOS patients within the year of diagnosis ($p=1.3x10^{-13}$). Statistical significance: *** indicates $p<0.001$

Figure 3

Idiopathic multicentric Castleman disease (iMCD) patients experience a range of organ system involvement, require various hospital interventions, and demonstrate ongoing flares. (A) Organ system involvement in iMCD ranked from most frequently observed to least frequently observed. Over 97% of the iMCD cohort experienced some hematopoietic dysfunction. Notably, both TAFRO and NOS experienced significant organ system involvement and dysfunction. (B) Severity of organ dysfunction is reflected by the degree of health care intervention(s) required. Over one-quarter of patients (n=27 [26.5%]) required the use of a ventilator, and 17 (16.7%) patients required dialysis. Additionally, 47 (46.0%) patients required fluid removal (paracentesis), 42 (41.1%) patients received a red blood cell transfusion (RBC), and 22 (21.6%) patients received a platelet transfusion. (C) NOS patients spent a significantly greater proportion of time in flare from presentation until last known information (median [IQR]: 52.3% [21.0, 99.6]) compared to TAFRO patients (18.9% [10.8, 52.5], W=1673, p=0.004). (D) Each patient is represented by a vertical bar. The bar extends the length of follow-up from the start of the first flare. NOS patients are represented on the left, and TAFRO patients are represented on the right. The blue bar represents the proportion of time NOS patients spent in flare. The red bar represents the proportion of time TAFRO patients spent in flare. The designation ‘d’ indicates a deceased patient.

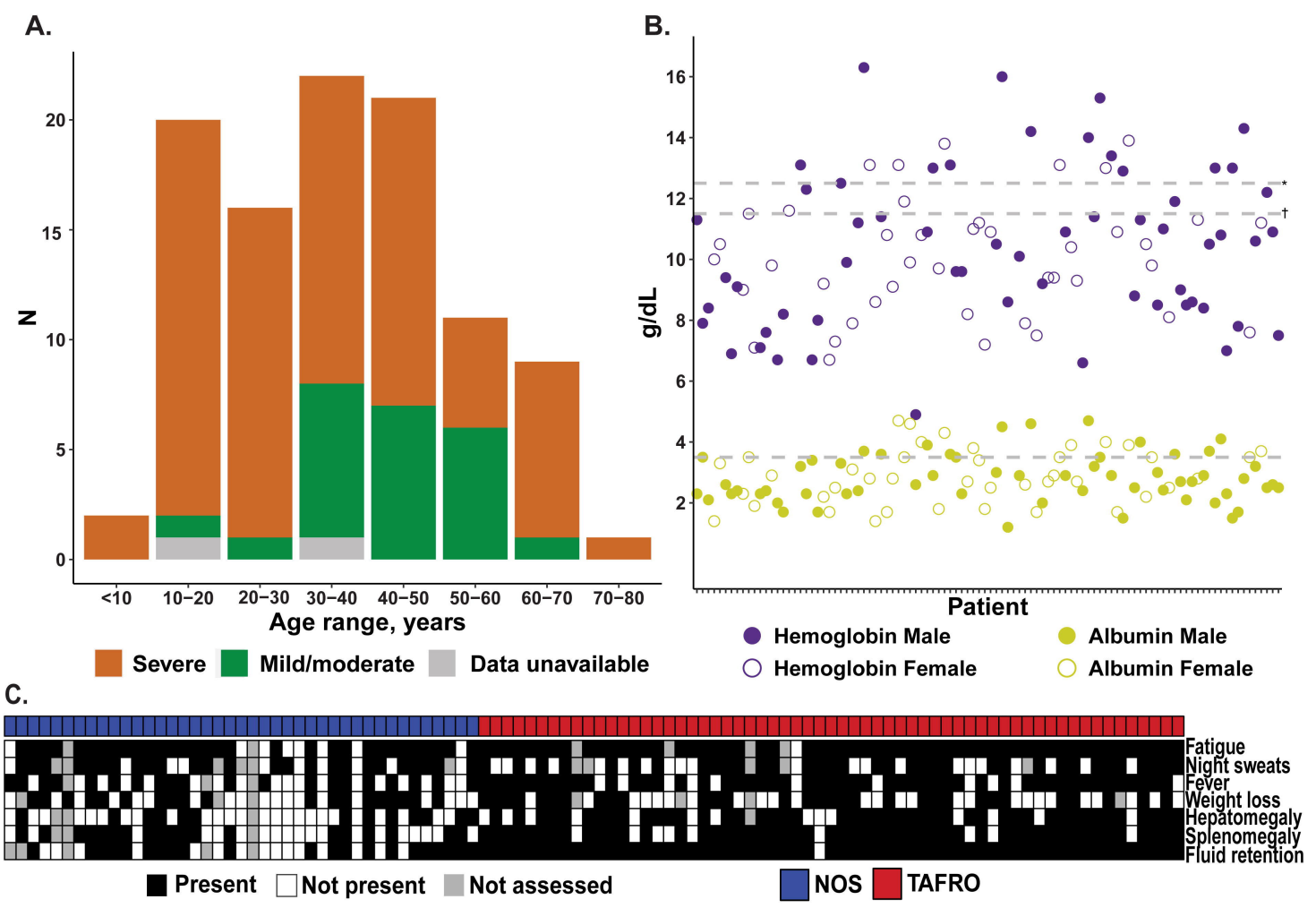
Figure 4

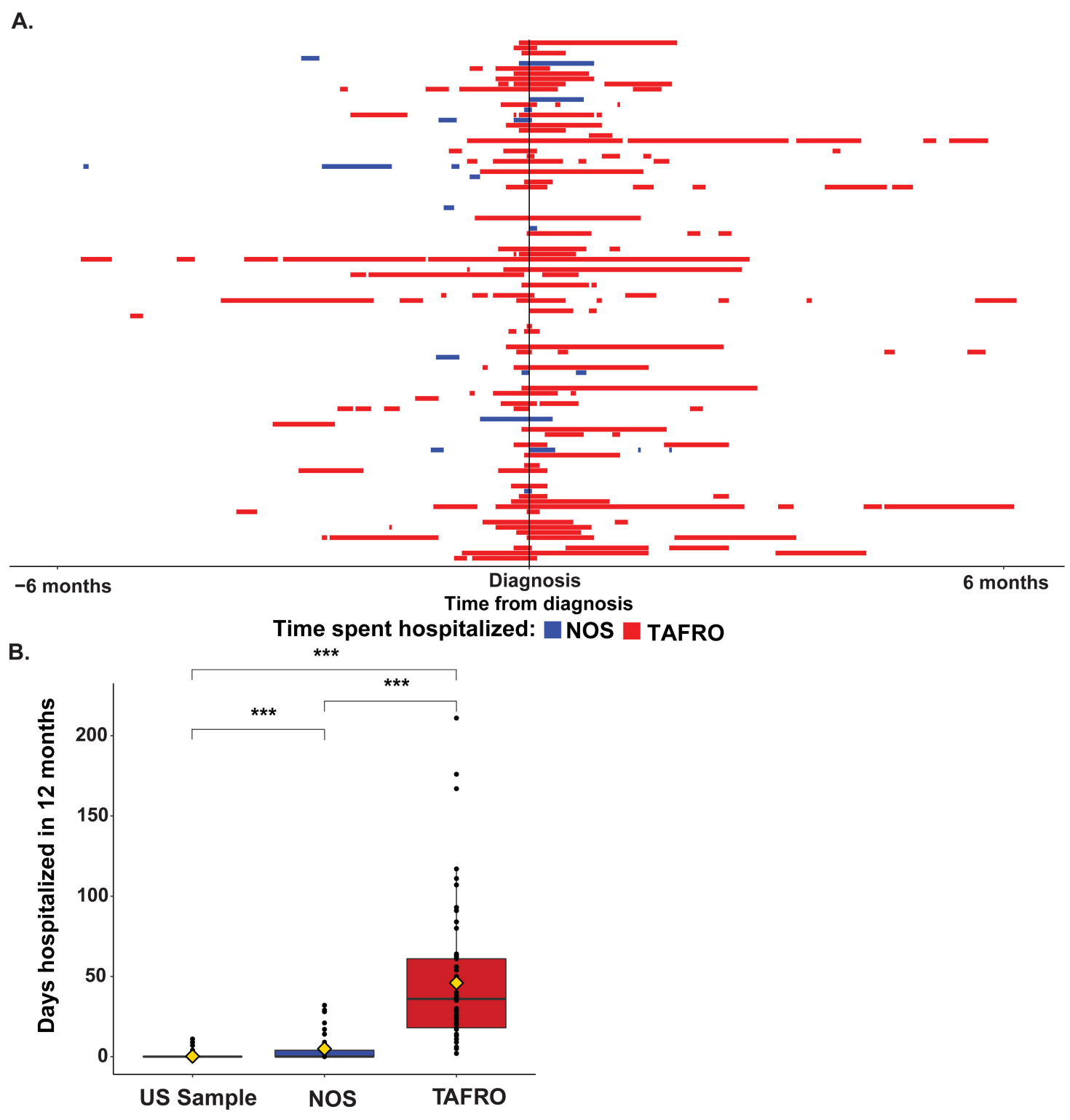
Idiopathic multicentric Castleman disease (iMCD) patients have a high degree of comorbid and morbid conditions contributing to the burden of disease. (A) Prior to

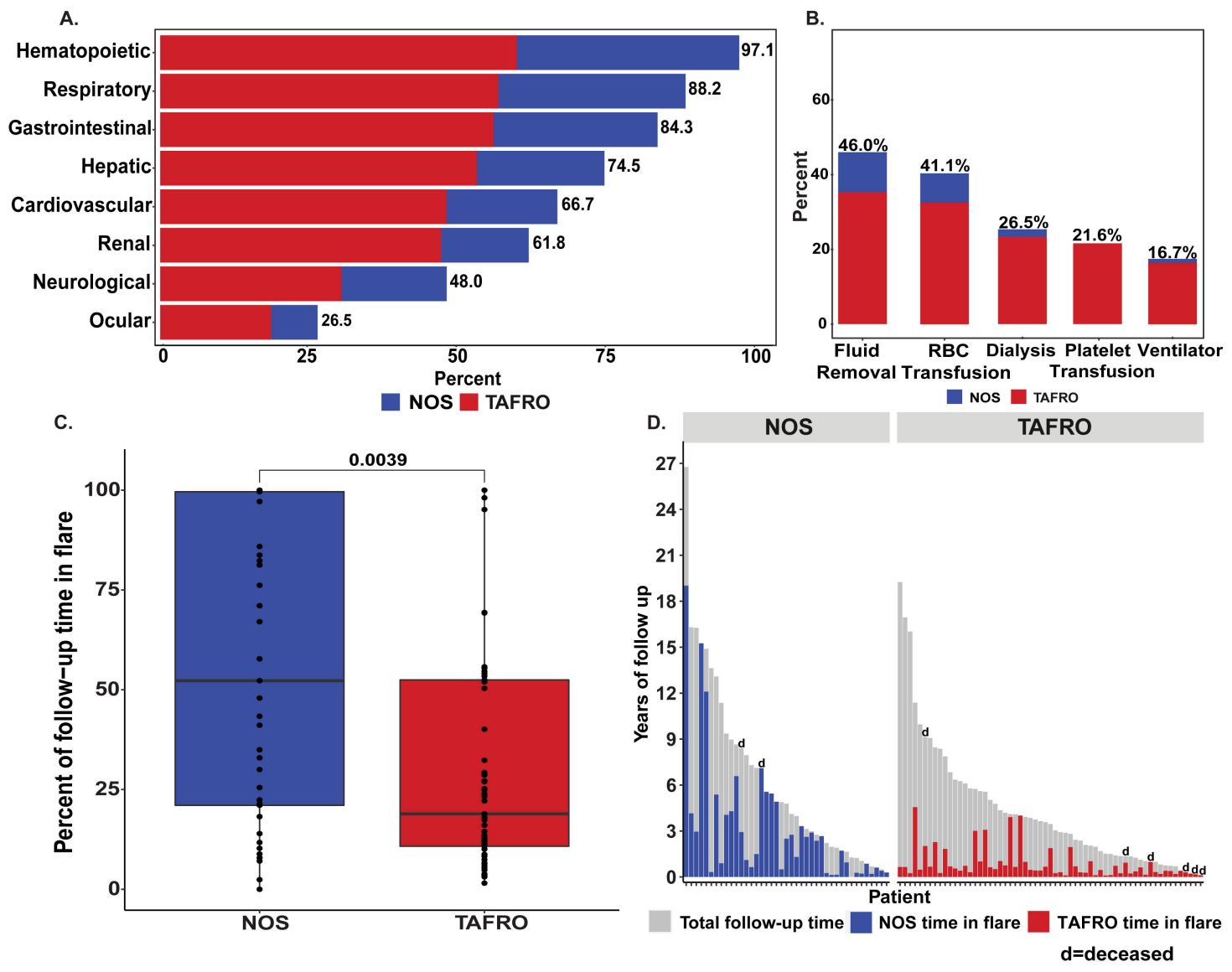
diagnosis, the most commonly diagnosed comorbidities amongst the full cohort mirrored common comorbidities among the US population and included hypertension (n=26, 25.5%), obesity (n=23, 22.5%), asthma (n=21, 20.6%), gastroesophageal reflux disease (GERD, n=14, 13.7%), and depression (n=11, 10.8%). (B) Following iMCD diagnosis, patients experienced an array of burdensome comorbidities and morbidities including acute renal failure (n=49, 48.0%), chronic kidney disease/chronic renal insufficiency (CKD/CRI, n=16, 15.7%) and iron deficiency anemia (n=11, 10.8%) among others. ADHD: Attention-Deficit Hyperactivity Disorder, TMA: Thrombotic Microangiopathy, OSA: Obstructive Sleep Apnea.

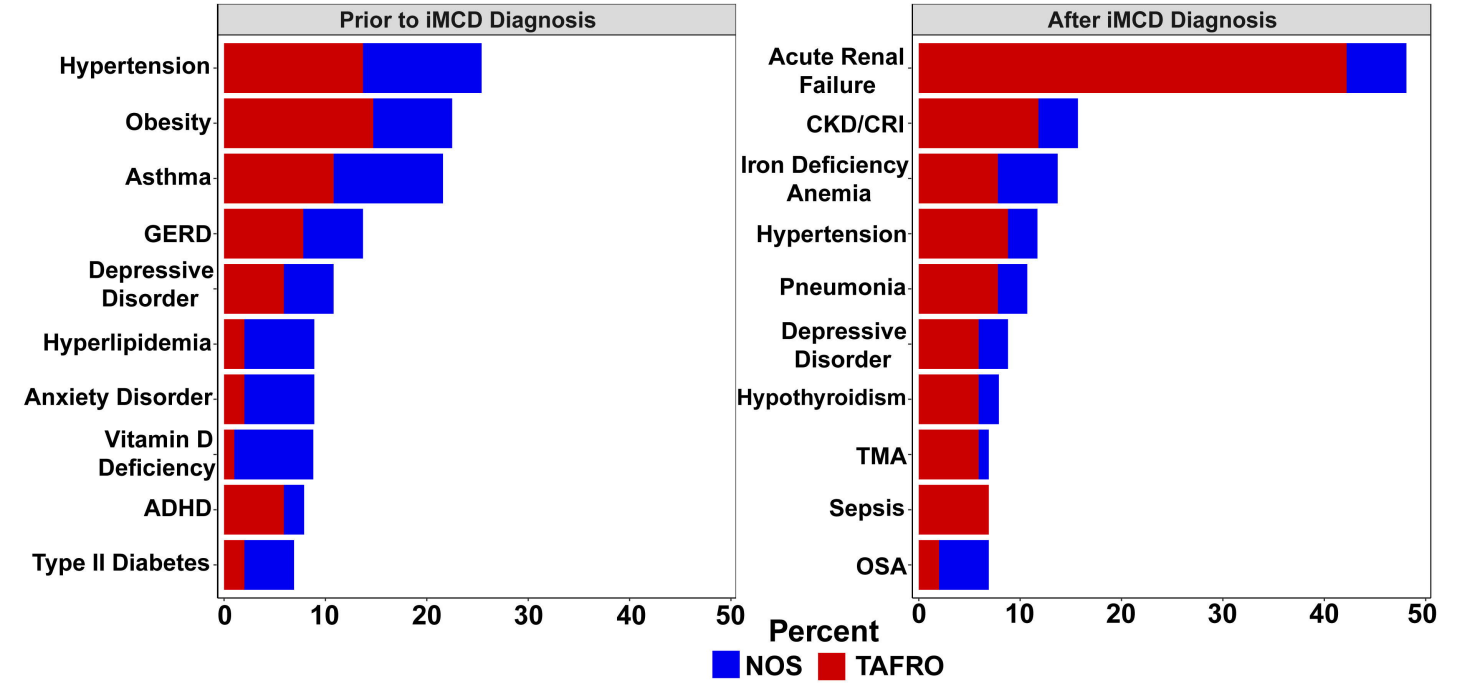
Figure 5

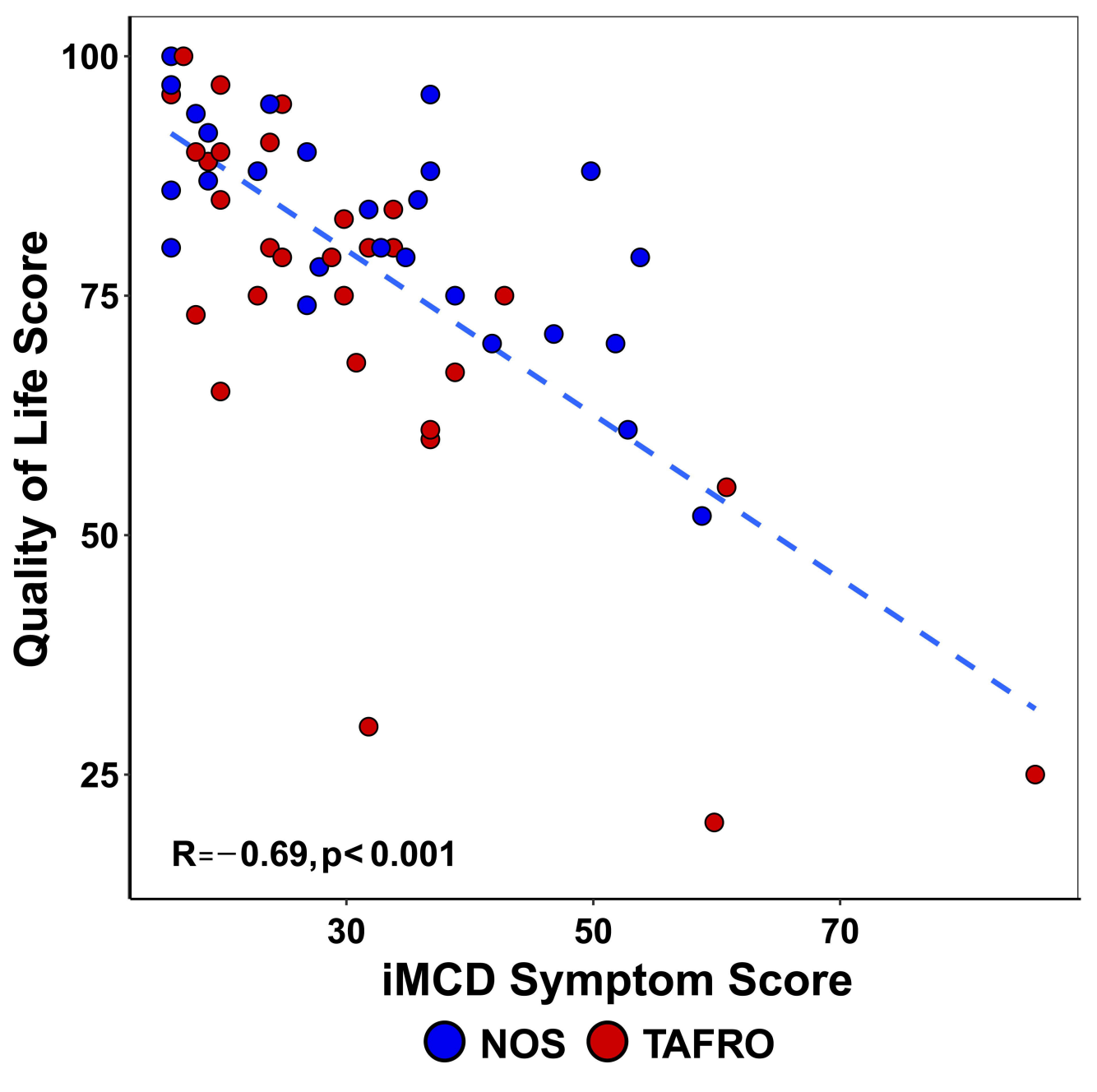
Quality of life is inversely correlated with degree of idiopathic multicentric Castleman disease (iMCD) symptoms. Correlation between quality-of-life score and iMCD symptom score based on data. Lower quality-of-life correlates with higher iMCD symptom score and higher quality-of-life correlates with lower iMCD symptom score ($R=-0.69$, $p<0.001$).


A.
N
Age range, years
<10
10–20
20–30
30–40
40–50
50–60
60–70
70–80
Severe
Mild/moderate
Data unavailable
B.
g/dL
Patient
Hemoglobin Male
Hemoglobin Female
Albumin Male
Albumin Female
C.
Fatigue
Night sweats
Fever
Weight loss
Hepatomegaly
Splenomegaly
Fluid retention
Present
Not present
Not assessed
NOS
TAFRO


A.
−6 months
Diagnosis
6 months
Time from diagnosis
Time spent hospitalized: NOS TAFRO
B.
***
***
***
Days hospitalized in 12 months
200
150
100
50
0
US Sample
NOS
TAFRO


A.
Hematopoietic
Respiratory
Gastrointestinal
Hepatic
Cardiovascular
Renal
Neurological
Ocular
97.1
88.2
84.3
74.5
66.7
61.8
48.0
26.5
0
25
50
75
100
Percent
NOS
TAFRO
B.
Percent
60
40
20
0
46.0%
41.1%
26.5%
21.6%
16.7%
Fluid Removal
RBC Transfusion
Dialysis
Platelet Transfusion
Ventilator
NOS
TAFRO
C.
0.0039
Percent of follow−up time in flare
100
75
50
25
0
NOS
TAFRO
D.
NOS
TAFRO
Years of follow up
27
24
21
18
15
12
9
6
3
0
Patient
Total follow-up time
NOS time in flare
TAFRO time in flare
d=deceased


Prior to iMCD Diagnosis
Hypertension
Obesity
Asthma
GERD
Depressive Disorder
Hyperlipidemia
Anxiety Disorder
Vitamin D Deficiency
ADHD
Type II Diabetes
0
10
20
30
40
50
After iMCD Diagnosis
Acute Renal Failure
CKD/CRI
Iron Deficiency Anemia
Hypertension
Pneumonia
Depressive Disorder
Hypothyroidism
TMA
Sepsis
OSA
0
10
20
30
40
50
Percent
NOS
TAFRO


100
75
50
25
Quality of Life Score
R=−0.69, p< 0.001
30
50
70
iMCD Symptom Score
NOS
TAFRO

Supplemental Methods:

Organ system involvement

Organ system involvement was determined according to the presence of a sign, symptom, or laboratory abnormality that was recorded in the patient's medical record +/- 365 days from the date of a patient's diagnostic lymph node excision. Organ systems assessed include the renal, hepatic, ocular, cardiovascular, respiratory, gastrointestinal (GI), hematopoietic, and nervous systems. Clinical data was used to determine ocular, cardiovascular, respiratory, GI, and nervous system involvement, and laboratory data was used to determine additional kidney, liver and hematopoietic dysfunction ± 365 days from diagnostic excision. Renal involvement included any later described lab abnormality, dysuria, renal failure, and various other organ signs/symptoms. Hepatic involvement included any later described lab abnormality, jaundice, liver failure, and others. Ocular involvement included any visual disturbances, ocular bleeds, and others. GI involvement included abdominal pain, abdominal bloating/distention, nausea, vomiting, diarrhea, and others. Hematopoietic involvement included any later described lab abnormality, easy bruising, and others. Nervous system involvement included any form of neuropathy, delirium, confusion, mood changes, and others. For lab identified dysfunction, stage IIIb renal dysfunction was defined as an eGFR of < 45 mL/min/1.73^2 and/or a creatinine >2.0mg/dL. Liver dysfunction was defined as either aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2x upper limit of normal (ULN) and/or alkaline phosphatase >2x ULN. Anemia was defined as a hemoglobin of <12.5 g/dL or <11.5 g/dL for males and females, respectively. Thrombocytopenia and thrombocytosis were defined as platelets <150k/uL or >400k/uL, respectively. Leukopenia and leukocytosis were defined as a white blood cell count <4.5k/uL or >11k/uL, respectively.

Supplemental Table 1. Deceased patient information

	iMCD (n=8)	TAFRO (n=6)	NOS (n=2)
Age at death, years			
Median (IQR)	55.8 (28.3, 65.9)	63.2 (27.7, 66.6)	41.5 (36.8, 46.1)
Range	14.7, 69.5	14.7, 69.5	32.2, 50.7
Time from diagnosis to death, years			
Median (IQR)	0.7 (0.1, 5.9)	0.2 (0.1, 1.0)	6.6 (5.9, 7.4)
Range	0.05, 8.7	0.05, 8.7	5.2, 8.1

Supplemental Table 2. Disease severity by age group

Disease Severity:	<30 years (n=37)	30-60 years (n=53)	>60 years (n=10)
Mild/moderate, n (%)	2 (5.4%)	20 (37.7%)	1 (10.0%)
Severe, n (%)	35 (94.6%)	33 (62.3%)	9 (90.0%)

Supplemental Table 3. Clinical characteristics

	iMCD (n=102)			TAFRO (n=61)			NOS (n=41)			
Clinical Minor Criteria	**Yes, n (%)**	**No, n (%)**	**NA**	**Yes, n (%)**	**No, n (%)**	**NA**	**Yes, n (%)**	**No, n (%)**	**NA**	**p-value**
Constitutional Sx	94 (93.1)	7 (6.9)	1	59 (96.7)	2 (3.3)	0	35 (87.5)	5 (12.5)	1	0.1101
Fatigue	87 (90.6)	9 (9.4)	6	56 (92.2)	1 (1.8)	4	31 (79.5)	8 (20.5)	2	0.0029
Night sweats	60 (65.9)	31 (34.1)	11	35 (62.5)	21 (37.5)	5	25 (71.4)	10 (28.6)	3	0.3819
Fever	70 (70.7)	29 (29.3)	3	50 (82.0)	11 (18.0)	0	20 (52.6)	18 (47.4)	3	0.0018
Weight loss	50 (52.6)	45 (47.4)	7	31 (54.4)	26 (45.6)	4	19 (50.0)	19 (50.0)	3	0.6749
Organomegaly	77 (77.8)	22 (22.2)	3	55 (90.2)	6 (9.8)	0	22 (57.9)	16 (42.1)	3	$2.0x10^{-4}$
Hepatomegaly	59 (60.2)	39 (39.8)	4	46 (76.7)	14 (23.3)	1	13 (34.2)	25 (65.8)	3	$3.0x10^{-5}$
Splenomegaly	71 (71.7)	28 (28.3)	3	52 (85.2)	9 (14.8)	0	19 (50.0)	19 (50.0)	3	$1.5x10^{-4}$
CD Skin Disorder	3 (3.5)	82 (96.5)	17	3 (5.8)	49 (94.2)	9	0	33 (100.0)	8	0.279
LIP	0 (0.0)	67 (100.0)	35	0 (0.0)	46 (100.0)	15	0 (0.0)	21 (100.0)	20	1.0
Fluid Retention	81 (83.5)	16 (16.5)	5	60 (98.4)	1 (1.6)	0	21 (58.3)	15 (41.7)	5	<0.00001
Proteinuria	55 (70.5)	23 (29.5)	24	40 (72.7)	15 (27.3)	6	15 (65.2)	8 (34.8)	18	0.5072
Lab Minor Criteria, Median (IQR)										
CRP mg/L	132.4 (32.5, 216.7)			167.0 (42.8, 266.0)			61.0 (10.6, 160.7)			0.004
ESR mm/hr	82.0 (49.5, 114.3)			91.0 (67.0, 118.0)			69.0 (31.0, 105.0)			0.024
Hemoglobin g/dL	7.8 (6.6, 10.5)			6.8 (6.5, 8.0)			10.5 (8.3, 11.9)			$2.0x10^{-7}$
Platelets max k/µL	300.0 (246.0, 401.0)			271.0 (224.0, 331.0)			380.0 (293.0, 462.0)			$1.3x10^{-4}$
Platelets min k/µL	64.0 (23.0, 169.0)			28.0 (15.0, 58.0)			212.0 (139.0, 325.0)			$2.8x10^{-15}$
Albumin g/dL	2.2 (1.8, 2.9)			1.9 (1.6, 2.3)			2.9 (2.4, 3.7)			$7.4x10^{-8}$
Creatinine mg/dL	1.6 (1.1, 2.6)			2.1 (1.5, 3.5)			1.1 (0.8, 1.3)			$8.1x10^{-8}$
eGFR mL/min1.73m2	51.0 (24.5, 60.0)			33.6 (17.0, 60.0)			60.0 (56.0, 60.0)			$4.0x10^{-4}$
IgG mg/dL	1324.0 (897.5, 2079.8)			1060.0 (784.8, 1527.5)			2084.5 (1204.8, 3604.0)			$3.3x10^{-5}$
Gammaglobulin g/dL	1.4 (0.9, 2.47)			1.19 (0.9, 1.7)			2.6 (1.2, 4.4)			0.01

Supplemental Table 4. Regimen effect on hospitalizations

	Hospitalized at regimen initiation	**Hospitalized four-weeks post regimen initiation**	**p-value**
All regimens	49/99 (49.5)	20/99 (20.2)	3.0×10^{-5}
Siltuximab ± corticosteroids	11/32 (34.4)	2/32 (6.3)	0.01
Tocilizumab ± corticosteroids	7/10 (70.0)	3/10 (30.0)	0.18
Rituximab ± corticosteroids	4/16 (25.0)	0/16 (0.0)	0.10
Chemotherapy-based	9/13 (69.2)	6/13 (46.2)	0.43
Immunomodulator(s) ± corticosteroids	6/10 (60.0)	2/10 (20.0)	0.17
Other	12/19 (63.1)	7/19 (36.8)	0.18

Supplemental Table 5. Forms of organ system involvement experienced by iMCD patients

Organ Sign/Symptom (N, %)	iMCD (N=102)	TAFRO (N=61)	NOS (N=41)
Cardiovascular	**68 (66.7)**	**49 (80.3)**	**19 (46.3)**
Tachycardia	**51 (50.0)**	40 (65.6)	11 (26.8)
Abnormal EKG/ECG	**20 (19.6)**	15 (24.6)	5 (12.2)
Hypertension	**13 (12.7)**	9 (14.8)	4 (9.8)
Cardiomegaly	**11 (10.8)**	7 (11.5)	4 (9.8)
Hypotension	**9 (8.8)**	7 (11.5)	2 (4.9)
Palpitations	**9 (8.8)**	3 (4.9)	6 (14.6)
Heart failure	**4 (3.9)**	3 (4.9)	1 (2.4)
Bradycardia	**3 (2.9)**	2 (3.3)	1 (2.4)
Injury to heart from strain	**3 (2.9)**	3 (3.9)	0
Pericardial effusion	**3 (2.9)**	2 (3.3)	1 (2.4)
Endotheliopathy	**1 (1.0)**	0	0
Coronary artery disease	**1 (1.0)**	0	1 (2.4)
JVD	**1 (1.0)**	0	1 (2.4)
Pericarditis	**1 (1.0)**	1 (1.6)	0
Right hemisphere infarct	**1 (1.0)**	1 (1.6)	0
Gastrointestinal	**86 (84.3)**	**57 (93.4)**	**28 (68.3)**
Abdominal Pain/Bloating/N/V/D	**83 (81.4)**	56 (91.8)	27 (65.9)
Cholelithiasis	**4 (3.9)**	3 (4.9)	1 (2.4)
Retroperitoneal hematoma	**2 (2.0)**	2 (3.3)	0
Ileus	**1 (1.0)**	1 (1.6)	0
Colonic ischemia	**1 (1.0)**	1 (1.6)	0
Hematopoietic	**99 (97.1)**	**61 (100.0)**	**38 (62.3)**
Lab dysfunction	**99 (97.1)**	61 (100.0)	38 (62.3)

Bruise easily/anemia/bleed easily	**12 (11.8)**	7 (11.5)	5 (12.2)
Epistaxis	**8 (7.8)**	5 (8.2)	3 (7.3)
Body aches/myalgias	**5 (4.9)**	4 (6.6)	1 (2.4)
Cold/heat intolerance	**3 (2.9)**	2 (3.3)	1 (2.4)
Bone marrow failure	**1 (1.0)**	1 (1.6)	0
Reynaud's	**1 (1.0)**	1 (1.6)	0
Hepatic	**76 (74.5)**	**55 (90.2)**	**23 (37.7)**
Hepatomegaly	**69 (67.6)**	49 (80.3)	20 (48.8)
Lab dysfunction	**28 (27.5)**	24 (39.3)	4 (9.8)
Jaundice	**2 (2.0)**	2 (3.3)	0
Cirrhotic liver/liver pain	**2 (2.0)**	0	2 (4.9)
Acute liver failure	**1 (1.0)**	1 (1.6)	0
Neurological	**68 (66.7)**	**38 (62.3)**	**30 (73.2)**
Neuropathy	**38 (37.3)**	22 (36.1)	16 (39.0)
Headache/migraine	**38 (37.3)**	24 (39.3)	14 (34.1)
Altered mental status, confusion, dizziness, lightheadedness, brain fog, hallucinations	**25 (24.5)**	15 (24.6)	10 (24.4)
Insomnia	**9 (8.8)**	7 (11.5)	2 (4.9)
Anxiety/Depression/Nervousness/Mood change	**9 (8.8)**	7 (1.5)	2 (4.9)
Generalized weakness	**7 (6.9)**	5 (8.2)	2 (4.9)
Seizures	**5 (4.9)**	5 (8.2)	0
Gross motor delay	**2 (2.0)**	2 (3.3)	0
Tremors	**2 (2.0)**	2 (3.3)	0
Brain coma	**1 (1.0)**	1 (1.6)	0
Ocular	**27 (26.5)**	**19 (31.1)**	**8 (19.5)**

Blurred vision/vision changes/visual disturbance	**22 (21.6)**	15 (24.6)	7 (17.1)
Conjunctival pallor, conjunctival injection	**5 (4.9)**	4 (6.6)	1 (2.4)
scleral icterus	**1 (1.0)**	1 (1.6)	0
conjunctival hemorrhage	**1 (1.0)**	1 (1.6)	0
Left eye pain	**1 (1.0)**	0	1 (2.4)
Renal	**63 (61.8)**	**48 (78.7)**	**15 (36.6)**
Lab dysfunction	**49 (48.0)**	39 (63.9)	5 (12.2)
Dysuria, change in appearance of urine, increased or decreased urinary frequency	**24 (23.5)**	17 (27.9)	7 (17.1)
Acute renal failure/insufficiency/dysfunction	**21 (20.6)**	18 (29.5)	3 (7.3)
Adrenal gland hemorrhage/renal vein thrombosis	**2 (2.0)**	2 (3.3)	0
Kidney stones/kidney obstruction /kidney pain/	**4 (3.9)**	2 (3.3)	0
Renal cyst	**2 (2.0)**	0	2 (4.9)
Cushingoid Appearance	**2 (2.0)**	2 (3.3)	2 (4.9)
Histiocytic glomerulopathy	**1 (1.0)**	1 (1.6)	0
Membrane-proliferative glomerulonephritis	**1 (1.0)**	0	0
Thrombotic microangiopathy	**1 (1.0)**	1 (1.6)	1 (2.4)

Respiratory	**90 (88.2)**	**58 (95.1)**	**32 (78.0)**
Dyspnea	**85 (83.3)**	56 (91.8)	29 (70.7)
Atelectasis	**46 (45.1)**	38 (62.3)	8 (19.5)
Cough	**41 (40.2)**	24 (39.3)	17 (41.5)
Chest Pain	**31 (30.4)**	21 (34.4)	10 (24.4)
URI symptoms (congestion, runny nose, sore throat)	**24 (23.5)**	15 (24.6)	9 (22.0)
Diminished/decreased breath sounds	**10 (9.8)**	8 (13.1)	2 (4.9)
Rales, rhonchi, wheezing, crackles, rub, stridor	**10 (9.8)**	6 (9.8)	4 (9.8)
Hypoxia/O2 requirement	**6 (5.9)**	5 (8.2)	1 (2.4)
Pulmonary Edema	**6 (5.9)**	5 (8.2)	1 (2.4)
Pulmonary nodules	**4 (3.9)**	2 (3.3)	2 (4.9)
Respiratory failure	**4 (3.9)**	4 (6.6)	0
Pleurisy	**4 (3.9)**	1 (1.6)	3 (7.3)
Bilateral ground glass opacities	**3 (2.9)**	3 (4.9)	0
Pneumothorax	**1 (1.0)**	0	1 (2.4)
Other Dysfunctions	**11 (10.8)**	**7 (11.5)**	**4 (9.8)**
Penile/scrotal pain	**6 (5.9)**	5 (8.2)	1 (2.4)
Back pain	**5 (4.9)**	3 (4.9)	2 (4.9)
Mouth sores/ulcers	**3 (2.9)**	2 (3.3)	1 (2.4)
Ear bleeding	**1 (1.0)**	1 (1.6)	0
Sclerotic lesions	**1 (1.0)**	0	1 (2.4)

Supplemental Table 6. Laboratory values for identified organ dysfunction

Lab Identified Dysfunction	**Unique patients meeting lab dysfunction criteria, n (%)**	**Lab Values**
Liver Dysfunction	**28 (27.5)**	
Alk Phos (U/L, Median, IQR)	24 (37.3)	566 (473.3, 841.5)
ALT and AST (U/L, Median, IQR)	16 (29.4)	ALT: 199.0 (138.0, 273.3) AST: 164.0 (134.0, 262.8)
Kidney Dysfunction	**49 (48.0)**	
Creatinine (mg/dL, Median, IQR)	42 (41.2)	3.3 (2.4, 5.0)
eGFR (mL/min/1.73 m2, Median, IQR)	38 (37.3)	19.5 (15.3, 31.9)
Hematopoietic Dysfunction	**99 (97.1)**	
Anemia (Hemoglobin, g/dL, Median, IQR)	87 (85.3)	7.1 (6.5, 8.7)
Thrombocytopenia (Platelets, k/µL, Median, IQR)	76 (74.5)	32.0 (17.5, 67.0)
Thrombocytosis (Platelets, k/µL, Median, IQR)	37 (36.3)	484.0 (427.0, 605.0)
Leukocytosis (WBC, k/µL, Median, IQR)	80 (78.4)	23.0 (15.6, 30.1)
Leukopenia (WBC, k/uL, Median, IQR)	56 (54.9)	2.8, (1.2, 3.6)

Supplemental Table 7. Top 3 iMCD-related morbidities and comorbidities arising following disease onset by organ system

iMCD-related morbidities and comorbidities following diagnosis (N, %)	**iMCD (n=102)**
Cardiac	
Hypertension	12 (11.7)
Congestive Heart Failure	4 (3.9)
Cardiac Arrhythmia	3 (2.9)
Respiratory	
Pneumonia	10 (9.8)
Obstructive Sleep Apnea	7 (6.9)
Respiratory Failure	3 (2.9)
Renal	
Acute Renal Failure	49 (48.0)
Chronic Kidney Disease	12 (11.8)
Kidney Stone	3 (3.8)
Gastrointestinal	
Gastritis	5 (4.9)
Acute Cholecystitis	5 (4.9)
Gastroesophageal Reflux Disease	5 (4.9)
Hematopoietic	
Iron Deficiency Anemia	14 (13.7)
Thrombotic Microangiopathy	7 (6.9)
Atypical Hemolytic Uremic Syndrome	5 (4.9)
Endocrine/Metabolic	8 (7.8)
Hypothyroidism	8 (7.8)
Vitamin D Deficiency	7 (6.9)
Type II Diabetes	5 (4.9)
Infectious	
Sepsis	7 (6.9)
COVID-19	5 (4.9)
Clostridium difficile colitis	4 (4.9)
Mood Disorder	
Depressive Disorder (Depression)	9 (8.8)
Post-Traumatic Stress Disorder	4 (3.9)
Anxiety Disorder	4 (3.9)

Supplemental Table 8. Malignancies following iMCD diagnosis

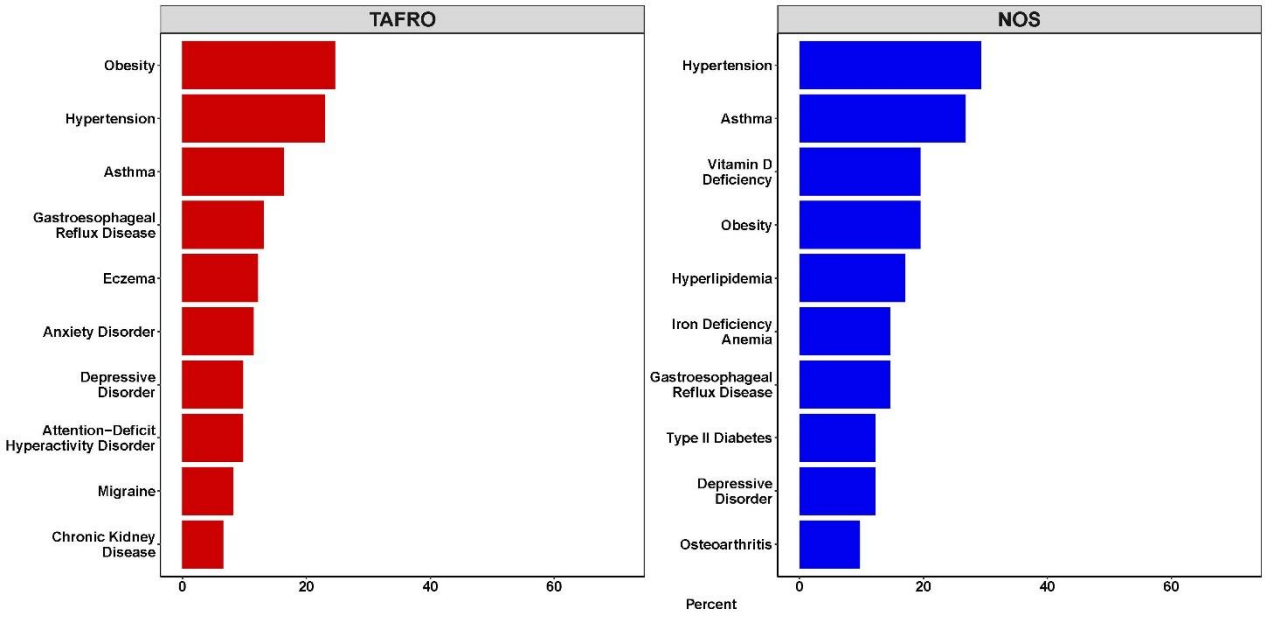
Patient	Malignancy	Time from iMCD diagnosis to Malignancy (in days)
Patient 1 (TAFRO)	Myelodysplastic Syndrome	1140
Patient 2 (NOS)	Papillary Thyroid Carcinoma	1314
Patient 3 (TAFRO)	Papillary Thyroid Carcinoma	480
Patient 4 (NOS)	Primary malignant neoplasm of rectum	513
Patient 5 (TAFRO)	Inflammatory Myofibroblastic Tumor	865
Patient 6 (NOS)	Malignant Lymphoma	2950
Patient 7 (NOS)	Basal Cell Carcinoma*	530
Patient 8 (TAFRO)	Thymoma*	71
Patient 9 (NOS)	Tubular Adenoma*	927
Patient 9 (NOS)	Polyp of Colon*	927
Patient 10 (NOS)	Thyroid Nodule*	423

*Premalignant or precancerous findings are included to better represent patients at-risk for cancer

Supplemental Figure 1. Comorbidities diagnosed prior to iMCD diagnosis

A. TAFRO

B. NOS

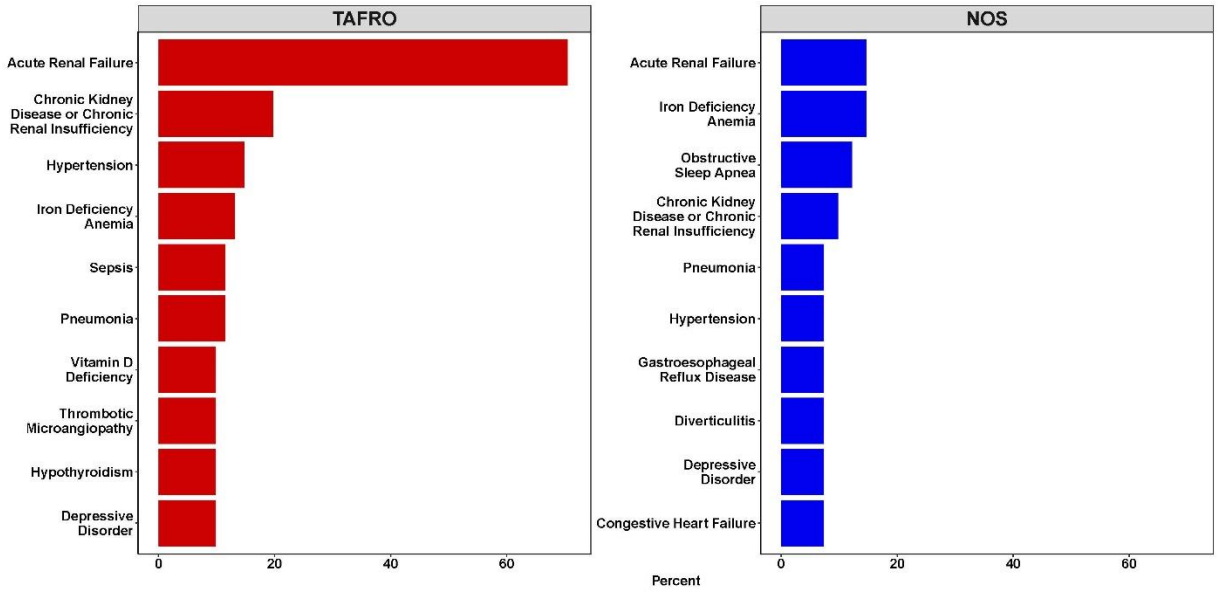


Top 10 most frequently observed comorbidities among iMCD patients prior to diagnosis with iMCD. Data presented in rank order for (A) TAFRO and (B) NOS patients.

Supplemental Figure 2. Comorbidities and Morbidities diagnosed after iMCD diagnosis

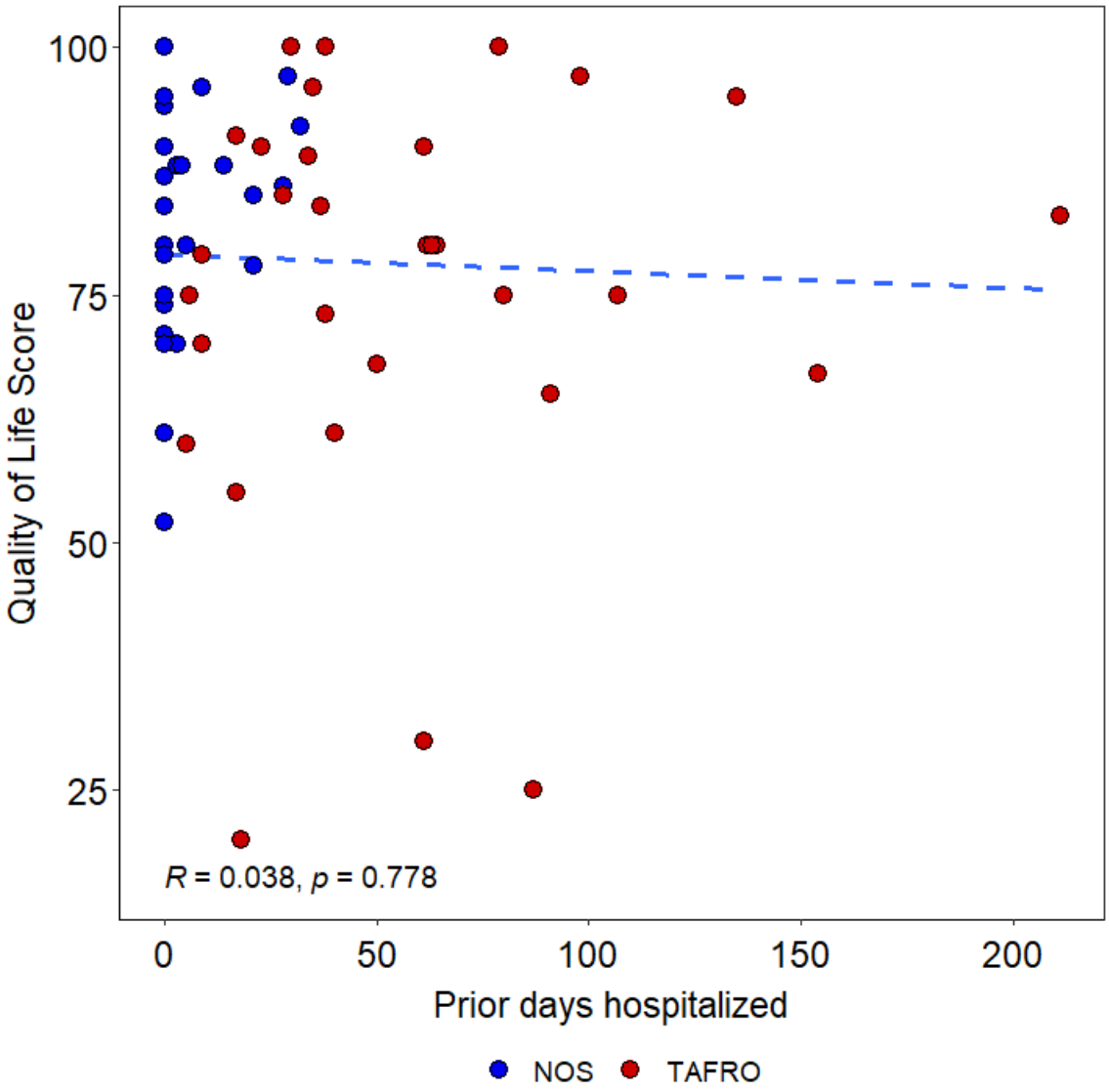
A. TAFRO

B. NOS



Top 10 most frequently observed comorbidities and morbidities among iMCD patients after diagnosis with iMCD. Data presented in rank order for (A) TAFRO and (B) NOS patients.

Supplemental Figure 3. Correlation between days hospitalized prior to survey completion and self-reported quality of life score



Days hospitalized prior to completion of quality of life score has no correlation with self-reported quality of life score (R=0.038, p=0.778)