

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

Mateo Sarmiento Bustamante,^{1*} Sheila K. Pierson,^{1*} Yue Ren,² Adam Bagg,³ Joshua D. Brandstadter,⁴ Gordan Srkalovic,⁵ Natalie Mango,¹ Daisy Alapat,⁶ Mary Jo Lechowicz,⁷ Hongzhe Li,² Frits van Rhee,⁸ Megan S. Lim⁹ and David C. Fajgenbaum¹

¹Center for Cytokine Storm Treatment & Laboratory, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; ²Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; ³Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; ⁴Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; ⁵Sparrow Herbert-Herman Cancer Center, Michigan State University College of Human Medicine, Lansing, MI; ⁶Department of Pathology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; ⁷Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA; ⁸Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR and ⁹Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York City, NY, USA.

**MSB and SKP contributed equally as first authors.*

Correspondence: D.C. Fajgenbaum
davidfa@pennmedicine.upenn.edu

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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 \pm 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 $< 45 \text{ mL/min/1.73}^2$ and/or a creatinine $>2.0\text{mg/dL}$. Liver dysfunction was defined as either aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $>2\text{x}$ upper limit of normal (ULN) and/or alkaline phosphatase $>2\text{x}$ ULN. Anemia was defined as a hemoglobin of $<12.5 \text{ g/dL}$ or $<11.5 \text{ g/dL}$ for males and females, respectively. Thrombocytopenia and thrombocytosis were defined as platelets $<150\text{k/uL}$ or $>400\text{k/uL}$, respectively. Leukopenia and leukocytosis were defined as a white blood cell count $<4.5\text{k/uL}$ or $>11\text{k/uL}$, 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

Clinical Minor Criteria	iMCD (n=102)			TAFRO (n=61)			NOS (n=41)			p-value
	Yes, n (%)	No, n (%)	NA	Yes, n (%)	No, n (%)	NA	Yes, n (%)	No, n (%)	NA	
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/ μ L	300.0 (246.0, 401.0)			271.0 (224.0, 331.0)			380.0 (293.0, 462.0)			1.3x10 ⁻⁴
Platelets min k/ μ L	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/min1.73m ²	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)	3.0x10 ⁻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	12 (11.8)	7 (11.5)	5 (12.2)
easily			
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/Ne rvousness/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 m ² , 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/ μ L, Median, IQR)	76 (74.5)	32.0 (17.5, 67.0)
Thrombocytosis (Platelets, k/ μ L, Median, IQR)	37 (36.3)	484.0 (427.0, 605.0)
Leukocytosis (WBC, k/ μ L, Median, IQR)	80 (78.4)	23.0 (15.6, 30.1)
Leukopenia (WBC, k/ μ L, 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

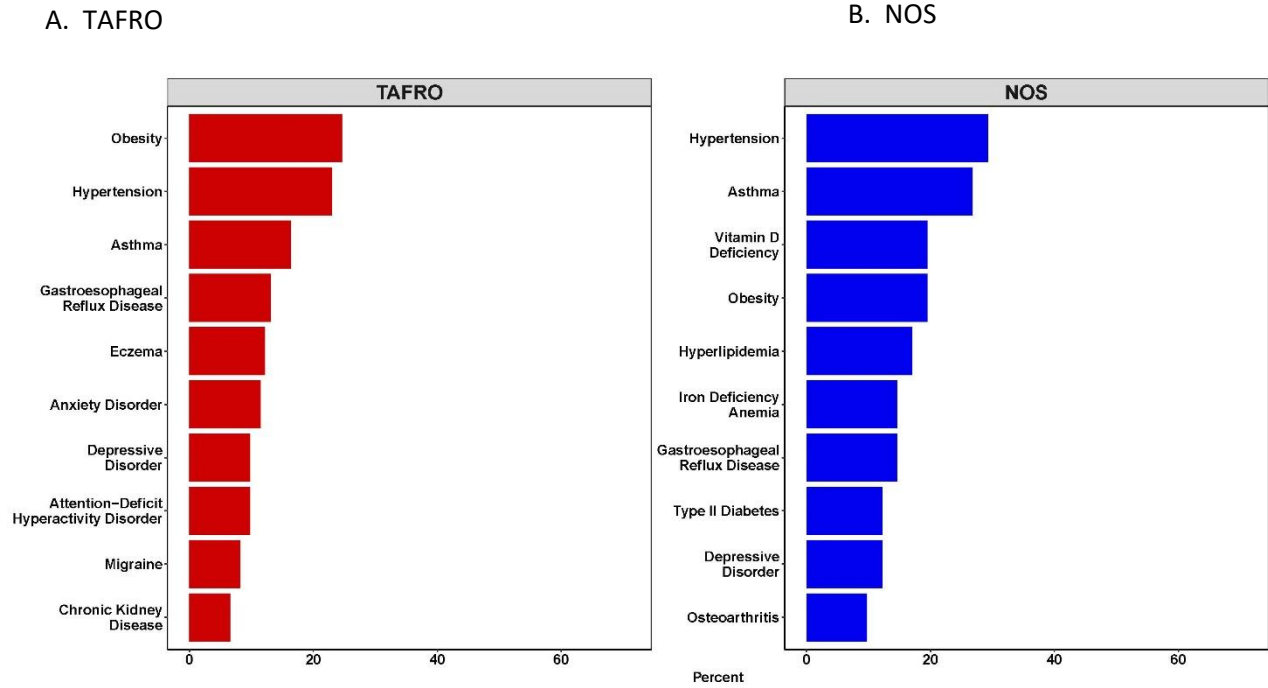
iMCD-related morbidities and comorbidities following diagnosis (N, %)	iMCD (n=102)
Cardiac	
Hypertension	12 (11.7)
Congestive Heart Failure	4 (3.9)
Cardiac Arrhythmia	3 (2.9)
Respiratory	
Pneumonia	10 (9.8)
Obstructive Sleep Apnea	7 (6.9)
Respiratory Failure	3 (2.9)
Renal	
Acute Renal Failure	49 (48.0)
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	
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

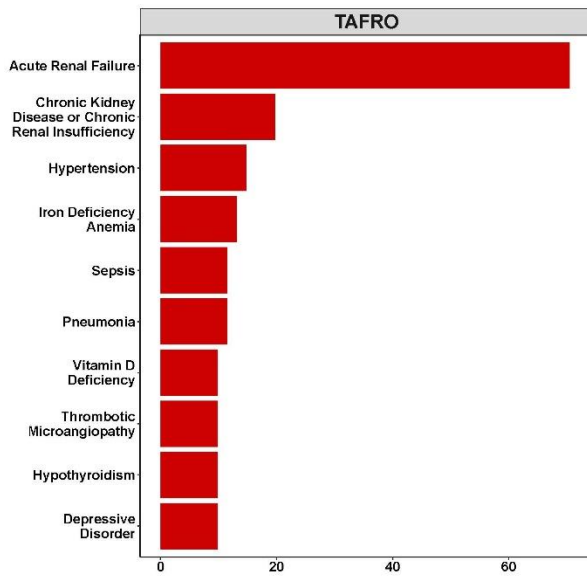
Supplemental Figure 1. Comorbidities diagnosed prior to iMCD diagnosis



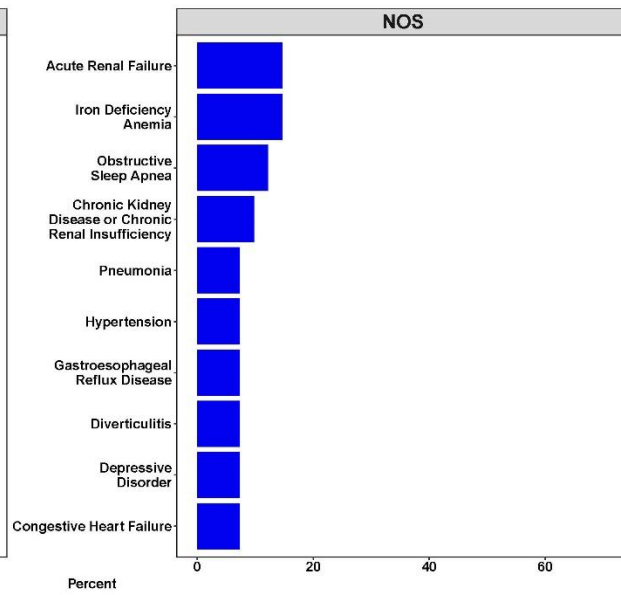
Top 10 most frequently observed comorbidities among iMCD patients prior to diagnosis with iMCD. Data presented in rank order for (A) TAFRO and (B) NOS patients.

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

