Organ dysfunction, thrombotic events and malignancies in patients with idiopathic multicentric castleman disease: a population-level US health claims analysis

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TO THE EDITOR:

Idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder characterized by a hyperinflammatory state driven primarily by hypercytokinemia, particularly interleukin-6 (IL-6) [1–3]. iMCD patients have historically poor outcomes [4], particularly among patients who were not properly treated [5]. Among several factors, one potential reason for delayed treatment initiation could be a lack of understanding of the clinical trajectory of iMCD patients regarding the development of disease-associated morbidities over time. A better understanding of the natural history of iMCD, particularly the evolution and prevalence of morbidities, will be helpful for making timely decisions about appropriate treatment and potentially mitigate morbidity burden in these patients. The primary objective of this study was to evaluate the pattern of morbidities and their prevalence in iMCD patients using a nationally representative health claims dataset. We additionally analyzed healthcare utilization of iMCD patients by evaluating length of hospital stays and visits to emergency departments by these patients.

Anonymized longitudinal patient data were sourced from Truven MarketScan® Research Databases (IBM), covering 235 million US citizens (commercially-insured, on Medicare, or Medicaid) from January 2006 to December 2020 [6]. All eligible iMCD patients were identified using a previously validated claims-based algorithm that in addition to CD-specific ICD-10 diagnosis code (D47.Z2), required negative HHV-8 and HIV status, and presence of corresponding diagnostic or laboratory claims for ≥2 minor criteria, consistent with published diagnostic criteria recommendations for iMCD [7, 8]. A patient’s index diagnosis date (IDD) was defined as the first date of the D47.Z2 diagnosis claims code when available or the previous nonspecific ICD-9-CM code for enlargement of lymph nodes previously used for CD (785.6), whichever appeared first. Morbidities occurring in iMCD patients were grouped in three categories and identified using ICD9/10 diagnosis codes: (1) Organ dysfunction and thrombotic events including heart failure, liver dysfunction, renal dysfunction, respiratory dysfunction or interstitial lung disease, drug-induced diabetes mellitus, and thrombotic events (stroke, transient ischemic attack, extremity deep vein thrombosis, pulmonary embolism, and portal vein thrombosis); (2) Myeloid malignancies including acute myeloid leukemia, chronic myeloid leukemia, myelodysplastic syndromes (MDS), and Philadelphia chromosome-negative myeloproliferative neoplasm (MPN); (3) Solid malignancies including colon, lung, skin (melanoma), breast, prostate, thyroid, head and neck, and carcinoma of unknown primary.

To better understand important features in the longitudinal histories of these patients, we performed a mutual information (MI) analysis of the iMCD population relative to controls. This allowed us to quantify binary features that are statistically most relevant for discriminating between iMCD and non-iMCD patients. The top 15 diagnosis codes by mean MI value across all 6-month periods are provided in Table 1A.

To analyze disease burden over time, we calculated cumulative proportions of individual morbidities across the group over a 4-year period (±2 years from IDD). To control for confounding, we matched all iMCD patients to non-iMCD controls at a frequency of 1:50 on age group (0–17, 18–44, 45–54, 55–64, >65 years), sex, insurance type, length of claims history in database, and region (Northeast, South, Midwest, West).

The number of ER visits and inpatient hospitalization days per patient, defined by specific place of service codes, were calculated for each patient in 12 months prior to (1 year before) and 12 months following (1 year after) IDD. When available, ER visits and hospitalizations were also calculated for 13–24 months prior to or following (±2 years) IDD. Multiple ER claims on a single day were counted as a single visit. All significance tests for continuous variables were calculated using Welch’s Unequal Variance T-Test with a significance level of 0.05. A chi-square test without Yates correction was used to identify significance between features described by binary variables.

Of 30.7 million eligible individuals in the Truven MarketScan® database, 487 patients had a Castleman disease (CD) diagnosis—
of which 271 were identified as IMCD based on our algorithm [7]. Compared to the base population (non-CD enrollees), the IMCD cohort had a higher proportion of females (59.4%), higher proportion of private insurance coverage (66.4%) and lower proportion of Medicaid (24.7%), with an average continuous enrolment of 6.7 years (data not shown). Approximately, 90% of IMCD patients in this dataset did not have claims corresponding with IL-6 directed therapies.

We performed an unbiased MI analysis to identify the most common morbidities between IMCD and a non-IMCD control population (Table 1A). The top three morbidities with the highest mean MI value in IMCD patients were localized enlarged lymph nodes.

| ICD-10 Code | Morbidity | Mean MI Value | IMCD patients | Control patients | p* |
|-------------|-----------|---------------|---------------|------------------|----|
| R59.0 | Localized enlarged lymph nodes | 0.023 | 47.2% | 0.8% | <0.001 |
| R59.9 | Enlarged lymph nodes, unspecified | 0.020 | 48.0% | 0.3% | <0.001 |
| R59.1 | Generalized enlarged lymph nodes | 0.019 | 35.8% | 0.3% | <0.001 |
| D47.Z9 | Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue | 0.011 | 24.7% | 0.0% | <0.001 |
| I10 | Essential (primary) hypertension | 0.009 | 49.4% | 14.8% | <0.001 |
| D64.9 | Anemia, unspecified | 0.009 | 38.4% | 3.5% | <0.001 |
| Z79.899 | Other long term (current) drug therapy | 0.008 | 43.5% | 7.9% | <0.001 |
| D50.9 | Iron deficiency anemia, unspecified | 0.007 | 23.6% | 1.6% | <0.001 |
| R91.8 | Other nonspecific abnormal finding of lung field | 0.007 | 31.7% | 2.2% | <0.001 |
| K21.9 | Gastro-esophageal reflux disease without esophagitis | 0.006 | 33.9% | 7.0% | <0.001 |
| R10.9 | Unspecified abdominal pain | 0.006 | 33.2% | 5.5% | <0.001 |
| R50.9 | Fever, unspecified | 0.005 | 26.6% | 3.2% | <0.001 |
| R06.02 | Shortness of breath | 0.005 | 32.1% | 5.0% | <0.001 |
| R07.9 | Chest pain, unspecified | 0.005 | 35.8% | 5.8% | <0.001 |
| G47.33 | Obstructive sleep apnea (adult) (pediatric) | 0.004 | 18.5% | 3.1% | <0.001 |

### Days admitted to ER/Days of Inpatient stays (n) ER visits n (%) Inpatient length of stay in days n (%)

| Year | Days admitted to ER/Days of Inpatient stays (n) | ER visits n (%) | Inpatient length of stay in days n (%) |
|------|-----------------------------------------------|-----------------|--------------------------------------|
| 2 years before | 0 | 154 (79.8) | 174 (90.2) |
| | 1 | 17 (8.8) | 1 (0.5) |
| | 2 | 14 (7.2) | 1 (0.5) |
| | 3 | 0 (0) | 1 (0.5) |
| | 4 | 2 (1) | 4 (2.1) |
| | 5+ | 6 (3.1%) | 12 (6.2) |
| 1 year before | 0 | 123 (52.1) | 117 (49.6) |
| | 1 | 47 (19.9) | 1 (0.4) |
| | 2 | 31 (13.1) | 9 (3.8) |
| | 3 | 13 (5.5) | 15 (6.4) |
| | 4 | 5 (2.1) | 13 (5.5) |
| | 5+ | 17 (7.2) | 81 (34.3) |
| Year 1 | 0 | 136 (57.4) | 168 (70.9) |
| | 1 | 44 (18.6) | 2 (0.8) |
| | 2 | 23 (9.7) | 8 (3.4) |
| | 3 | 10 (4.2) | 16 (6.8) |
| | 4 | 6 (2.5) | 6 (2.5) |
| | 5+ | 18 (7.6) | 37 (15.6) |
| Year 2 | 0 | 134 (86.5) | 143 (92.3) |
| | 1 | 15 (9.7) | 1 (0.7) |
| | 2 | 3 (1.9) | 1 (0.7) |
| | 3 | 1 (0.7) | 1 (0.7) |
| | 4 | 1 (0.7) | 1 (0.7) |
| | 5+ | 1 (0.7) | 8 (5.2) |

Percentage of patients calculated at 24 months. 
ICD International Classification of Diseases, MI mutual information, ER emergency room visit, n number of patients, % percentage. 
*p values calculated from Chi-squared test and p < 0.001 considered significant.
nodes (mean MI value 0.023), enlarged lymph nodes (mean MI value 0.020), and generalized enlarged lymph nodes (mean MI value 0.019). These findings are consistent with what we anticipated and support the clinical validity of additional morbidities that were found. Three additional important findings of clinical interest in iMCD patients over 2 years on either side of diagnosis were hypertension, anemia and neoplasms.

Our analysis of iMCD burden over time as a function of ER visits and hospitalization days revealed increased healthcare utilization in the year immediately before and after IDD compared to 2 years before and 2 years after diagnosis (Table 1B). A higher proportion of iMCD patients required an ER visit (47.8% and 42.6% in the year before and after IDD, respectively) before dropping to 13.5% in the second year after diagnosis. The proportion of patients with greater than five ER visits increased from 3.1% 2 years prior to diagnosis to 7.2% and 7.6% in the 2 years around IDD. The same pattern was observed with inpatient stays with the most marked increase observed in those who were hospitalized for at least 5 days, increasing from 6.2% 2 years prior to diagnosis to 34.3% and 15.6% in the subsequent 2 years.

Fig. 1 Development of morbidities over time in iMCD patients before and after diagnosis relative to non-disease controls. A Cumulative proportion of various organ dysfunction and thrombotic events over time between iMCD patients and non-disease controls, B Cumulative proportion of myeloid malignancies over time between iMCD patients and non-disease controls, C Cumulative proportion of solid malignancies over time between iMCD patients and non-disease controls.
The cumulative proportion of myeloid malignancies, organ dysfunction, thrombotic events, and solid malignancies were significantly higher in iMCD patients compared to the control patients ($p < 0.001$) (Fig. 1). Among all organ dysfunction-related morbidities, there was a substantially higher proportion of iMCD patients with renal, respiratory dysfunction, and thrombotic events compared to controls ($p < 0.001$) (Fig. 1A). Overall, the cumulative proportion of myeloid and solid malignancies were higher in iMCD patients compared to controls (10.0% vs 0.6%, 18.1% vs 7.4%, respectively; $p < 0.001$). Among all myeloid malignancies, MDS and MPN accounted for the highest proportion of cases, whereas carcinoma of unknown primary accounted for the most cases of solid malignancies in iMCD patients (Fig. 1B, C). We additionally undertook analysis of lymphoid malignancies, which revealed higher cumulative proportions of non-Hodgkin’s lymphoma in iMCD patients following IDD compared to control (19.2% vs 0.4% at 24 months post-index) (data not shown). Of note, we observed similar patterns of increasing proportions of morbidity with age across all morbidity categories in both the non-disease and iMCD cohorts.

To the best of our knowledge, this is the first population level study to comprehensively characterize the pattern and evolution of morbidity in iMCD patients leading up to and following iMCD diagnosis. The key findings of this study indicate a high proportion of iMCD patients experiencing renal and pulmonary dysfunction, thrombotic events, myeloid malignancies particularly MDS and MPN, and solid tumors particularly carcinoma of unknown primary. We observed an increase in morbidities leading up to the iMCD diagnosis and continued rise (either persistence or emergence of new morbidities) post diagnosis even in the short follow-up period (2 years). This correlated with increased healthcare utilization, potentially reflecting difficulties in establishing the diagnosis and contributing to increasing severity at the time of treatment initiation.

Earlier studies have reported an increased prevalence of certain morbidities including a three-fold increased prevalence of malignancy (19%) compared to age-matched controls (6%) in iMCD patients [4, 5, 8, 9]. Our larger comparative analyses using a matched cohort corroborate these earlier observations. However, it is unclear how to interpret the increased lymphoid malignancies as they are iMCD mimics and may represent misdiagnoses or miscoding.

A major strength of this study was reliance on a validated claims-based methodology to identify iMCD cases from a large dataset, therefore, the data use agreement.
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ADDITIONAL INFORMATION

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