Analysis of Potential Subgroups in Vaes ME/CFS Patient Clusters

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Abstract

Background: Vaes et al. (2023)[1] identified 13 symptom clusters in a large cohort of ME/CFS patients. Symptom intensity is broadly correlated with post-exertional malaise (PEM) severity, with variation across clusters that seems disorganized. Despite this research, no broadly accepted organizing principle has emerged from this paper or other attempts at phenotyping ME/CFS.

Objective: To identify and characterize potential subgroups defined by symptom domain severity relative to PEM within the original Vaes symptom clusters.

Methods: We analyzed the Vaes cluster summary data[2], calculated geometric means for each symptom domain within each cluster, and plotted these means against PEM severity to identify patterns and subgroups.

Results: Our analysis identified two groups of patient clusters with distinct symptom-domain profiles. Anchoring symptom domains to PEM collapses the 13 Vaes clusters into two reproducible families: one characterized by parallel offsets (Autonomic, Neuroendocrine, Other) and one by amplified slopes (Pain, Neurocognitive), with convergence at higher PEM levels after accounting for a single influential cluster. This subgroup's symptom trends could align with those of fibromyalgia. Further exploration with individual patient data is needed to validate these findings.

Keywords: Myalgic Encephalomyelitis, ME/CFS, patient clustering, fibromyalgia, post-exertional malaise, PEM

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1 Introduction

Dr. Anouk W. Vaes and her collaborators at CIRO performed one of the largest systematic surveys of ME/CFS symptom patterns, applying clustering methods to patient-reported outcomes to identify recurring constellations of symptoms[1]. They used symptom surveys based on the DePaul Symptom Questionnaire version 2 (DSQ-2) from 337 patients to identify a total of 45 patient clusters, of which 13 were of size ≥ 10 while the remaining were of size ≤ 2 and approximately 9.4% of the total cohort. We used the publicly available data of their final 13 clusters for most of the analysis[2] but we discuss the small clusters in Section 4.

While Vaes described each cluster, and noted some differences among symptom severity, an overall organizing principle was not proposed. Here we examine whether one might emerge from that dataset.

Our analysis suggests that the Vaes ME/CFS clusters can be organized into two overarching families defined by their relationship to PEM. This reduces the complexity of the cluster symptom intensities and highlights a subgroup within the Vaes clusters that has not been explicitly recognized in prior work. Once separated and profiled, this subgroup shows amplified PEM per symptom domain, consistent with current research on ME/CFS and fibromyalgia comorbidity. This paper invites further investigation with patient-level symptom data to validate or refute these findings and clarify their clinical and biological relevance.

Our central contribution is a PEM-referenced decomposition that reduces the Vaes clusters to two linear families (offsets vs. amplification) and explains much of the apparent heterogeneity.

2 Symptom Domains Relative to PEM

The strong weight of PEM symptoms makes the Vaes dataset tricky to interpret if you only look at raw intensity, so instead we compared overall symptom levels to PEM severity. From this comparison we identified two groups of clusters that maintain their integrity across most symptom domains. This PEM-anchored view is the organizing principle for all results that follow.

Because these analyses are exploratory and based on cluster-level data, the patterns described below should be interpreted as hypothesis-generating.

We first examine the areas of most similarity before highlighting how they differ. We add an "all" category to gauge overall symptom severity to the original symptom domains. Our use of the terms "high-intensity" and "low-intensity" does not reproduce the clusters described by Vaes or others but reflects a new organization based on how symptom domains scale with PEM. Vaes used the DePaul symptom groupings which we keep as-is.

Notes: The DSQ-2 uses a single symptom for Fatigue. Also, for the "Overall" chart we used the arithmetic mean instead of geometric mean for the Y axis. All other graphs in this study use geometric means exclusively. Shaded bands represent the 95% confidence interval of the linear models when used. While this section focuses on visual inspection, we provide more statistical descriptions in Appendix B.

2.1 Similarities

In terms of Fatigue, the two groups overlap completely, as ME/CFS patient clusters are expected to. See Figure 1, below. While the lines have a similar slope and offset we note the R^2 value is significantly weaker in the low-intensity group (0.54 vs. 0.86).

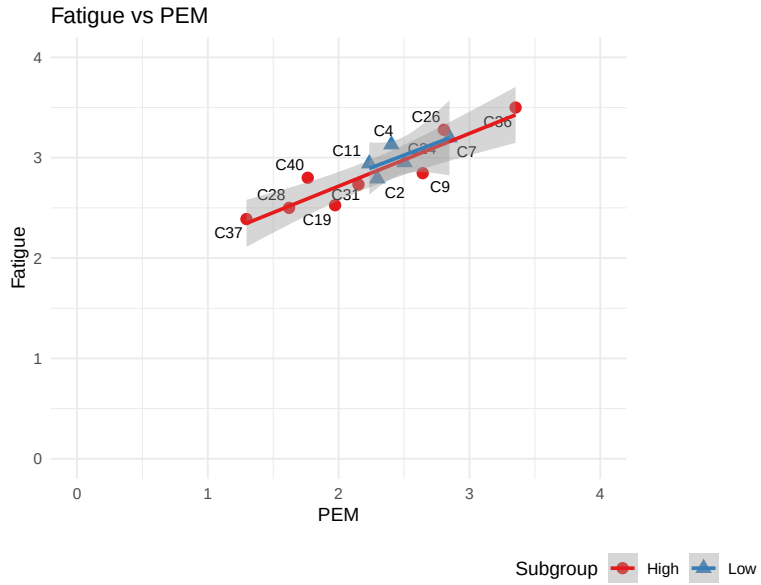

Figure 1: Fatigue vs. PEM

While Fatigue shows complete overlap in our groups the next charts (Figure 2) show how they stand out. In the first chart (top left) we compare the average of all symptoms to PEM. In this chart one can easily discern two tiers of clusters. One has a higher overall symptom burden at any given PEM level compared to the other and this relationship is where we derive the names for our groups: high and low-intensity.

Autonomic, Neuroendocrine and Other also follow a similar pattern: Parallel but lower than the high-intensity group.

We note that the limited range of PEM severity in the low-intensity group ($\approx$ 2.2 to 2.9) may have otherwise caused it to remain undetected.

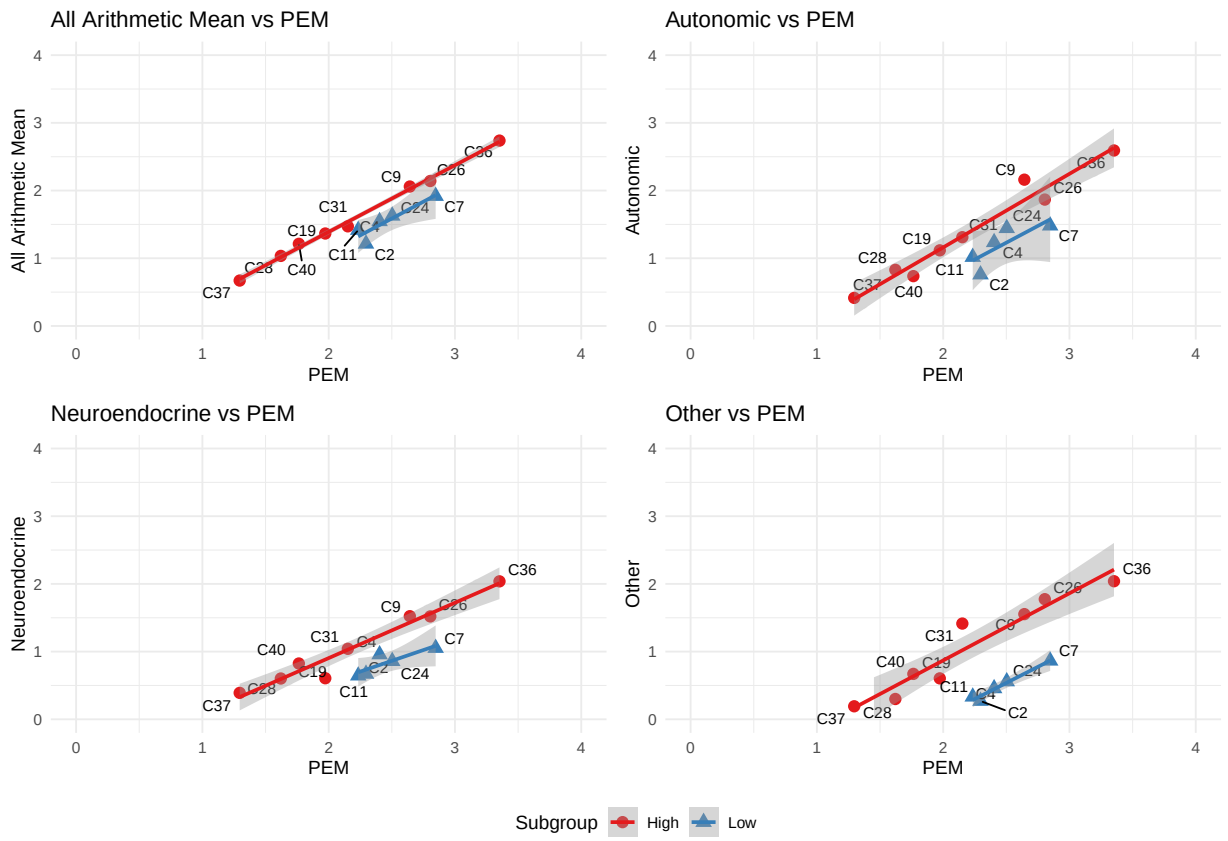

Figure 2: Similar Symptom Domains vs. PEM

Groupings: From visual inspection of the charts above we group clusters C9, C19, C26, C28, C31, C36, C37, C40 as high-intensity, C2, C4, C7, C11, C24 as low-intensity. We'll keep these groupings for all plots that follow. The high and low groups are approximately 54.5% and 45.5% of the total cohort, respectively. We further discuss our grouping choices in Leave-one-out Analysis. We group C36 with the high-intensity clusters, but it is also an outlier for the entire cohort, and discuss this further in Section 2.2.

The last chart (Other vs. PEM) shows a markedly lower offset and is perhaps the most visibly obvious difference between the two groups. Unfortunately, 'Other' only has two symptoms: sensitivity to mold and vibration which might make it a poor candidate for per-patient validation.

While the groups maintain integrity, the parallelism observed in the charts above does not hold in the next charts and suggests a more complex physiological cause for the differences.

2.2 Converging Patterns Relative to PEM

Pain and Neurocognitive domains show that while the low-intensity group remains offset, as PEM severity increases to 3, the two lines converge. Arguably, this is either increased amplification, or a reduction of differences around C26. This distinct convergence between the two cluster groups does not appear in any of the other symptom domains.

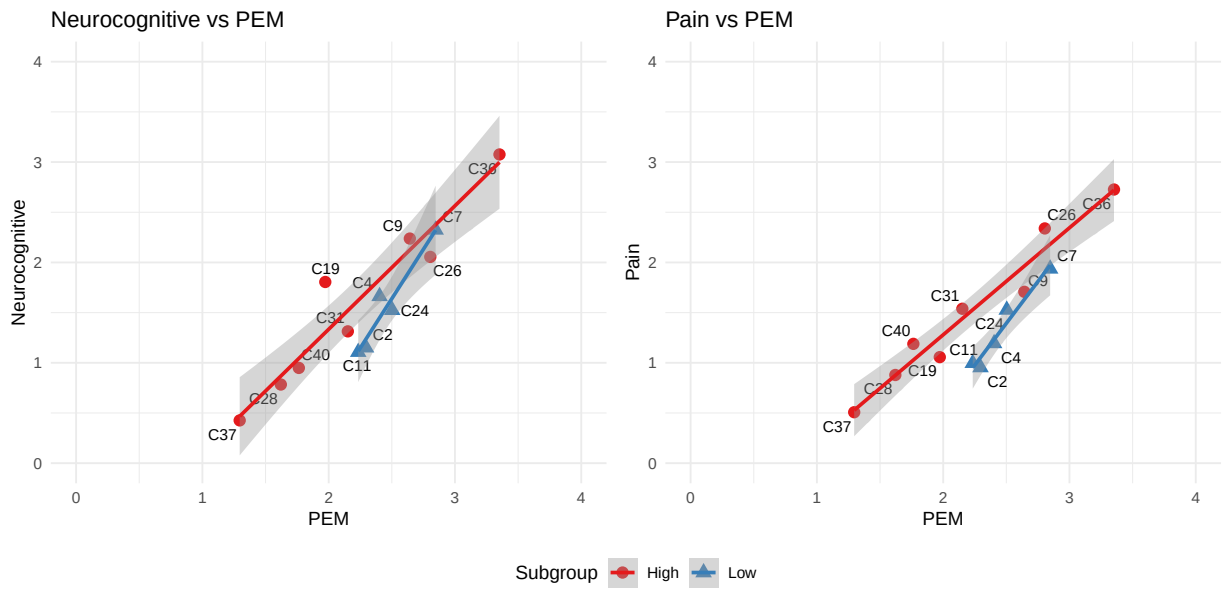

Figure 3: Pain and Neurocognitive vs. PEM

Without C36, the cohort outlier, the upper limits of PEM, Neurocognitive and Pain would converge around where C7 (low-intensity) and C26 (high-intensity) meet. Vaes et al. note that the participants in C36 "had the highest symptom burden (i.e. highest frequency and severity of symptoms)"[1] and all of the charts in this study are consistent with that observation.

2.3 Weak Correlations Relative to PEM

In all of the previous charts we've shown that both groups maintain a strong but distinct relationship to PEM. By contrast, the Immune and Sleep domains show little to no correlation with PEM severity in the low-intensity group. Notably, despite this lack of correlation, sleep disturbance can be pronounced in the low-intensity group.

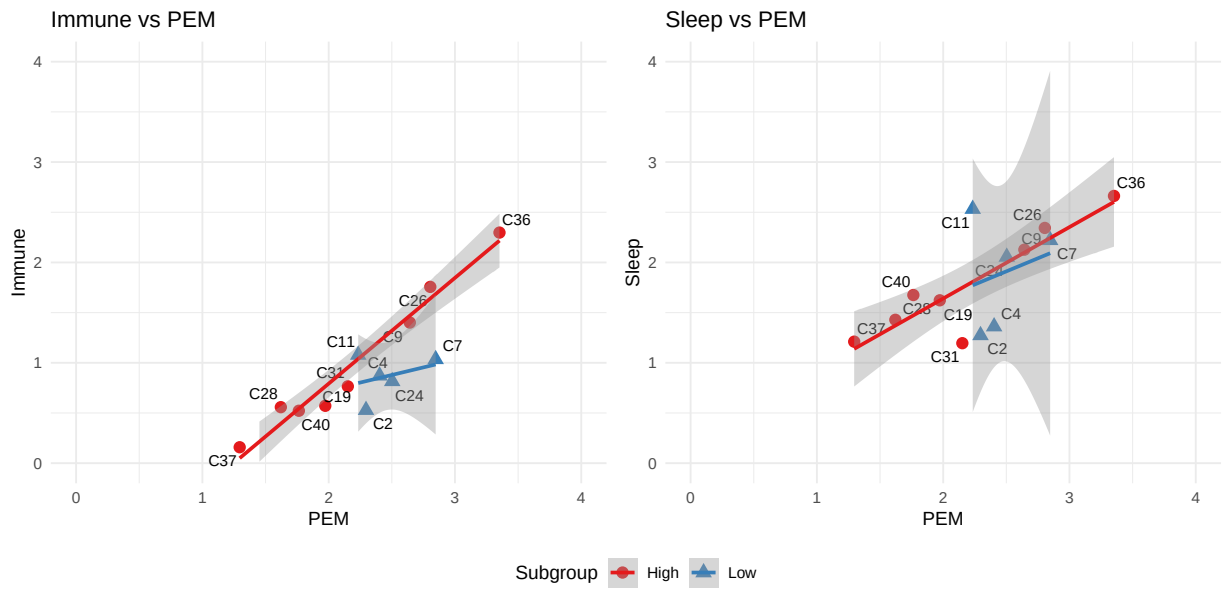

Figure 4: Immune and Sleep vs. PEM

2.4 Summary of Differences

High-intensity: Has a consistent amplification pattern: as PEM increases, all other symptom domains rise together.

Low-intensity: Presents a more selective profile. Pain, and Neurocognitive symptoms start low but converge with the high-intensity group, while Sleep and Immune symptoms show low correlation. Additionally, the low-intensity group is notably nestled in the middle of the overall PEM range which could allow it to hide among the other clusters if not actively searched for.

We summarize these differences in the table below.

Table 1: Summary of Group Differences

Feature	High group	Low group
Overall vs. PEM	Higher	Lower - esp. "Other"
Fatigue	R^2 - 0.86	Weaker R^2 - 0.54
PEM range	$\approx 1.3 - 3.4$	Narrower $\approx 2.2 - 2.9$
Neurocognitive	Tracks PEM	Elevated amplification
Pain	Tracks PEM	Elevated amplification
Immune	Tracks PEM	Flat at ≈ 1
Sleep	Tracks PEM	$\approx 1.4 - 2.5$, but uncorrelated

Symptom Severity: In terms of overall symptom range the two groups largely overlap. The high-intensity group, by symptom intensity alone, could be considered a superset of the low-intensity group. It is the differing relationships to PEM and the selective amplification of Pain and Neurocognitive symptom domains in the low-intensity group that set the two groups apart. We discuss this further in Section 3, below.

3 Exploring the Low-intensity Subgroup

Based on the trends noted in Section 2, a discussion of whether the low-intensity group could relate to fibromyalgia is warranted. We note that Vaes et al.[1] did not model fibromyalgia diagnoses, nor did they report excluding patients with fibromyalgia from their cohort. We cannot assert that the subgroup is clinically fibromyalgia, only that its domain profile aligns with what would be expected if fibromyalgia were present within this cohort.

Patterns in the low-intensity group have higher PEM burdens for all symptom domains except Immune and Sleep, which are uncorrelated with PEM. Further, Neurocognitive and Pain regression lines are amplified.

Vaes et al.[1] recruited participants who self-reported ME/CFS and later mapped them to multiple case definitions, yielding a broad spectrum of clinical presentations:

> Almost 90% of the participants fulfilled the Fukuda case definition, compared to 80%, 59% and 39% fulfilling the IOM, CCC and ME-ICC case definitions, respectively. More than a quarter of the participants met the criteria for all four different case definitions, whilst 5% of the participants met none of the abovementioned case definitions,...

This breadth makes mixed phenotypes plausible. Independent evidence also indicates that fibromyalgia frequently co-occurs with ME/CFS[3,4], and comorbidity has been associated with more frequent and severe PEM in ME/CFS patients[5], which could explain the subgroup's right-shift along the PEM axis.

Because the Vaes analysis used cluster-level summaries and did not model comorbidities, we cannot identify fibromyalgia directly here. Confirmation would require patient-level data we do not have access to.

4 Characteristics of the Smallest Clusters

Vaes et al.[1] identified 13 large[2] and 32 small clusters[6]. These were mostly of size 1, with 4 clusters of size 2 and represent approximately 9.4% of the cohort. We used similar charts to those in Section 2 with the addition of the small cluster data. Our goal was to examine if the small clusters could illuminate or challenge our two-group hypothesis.

We re-use the Neuroendocrine vs. PEM chart we showed above in Figure 2 as an example of how per-patient data could alter our findings. In Figure 5 we overlay the original plot with small clusters. They sit mostly above the high-intensity trend, while several align closely with it. The low-intensity groups however remain apart from the small clusters. Other symptom domains show a variety of differing patterns.

We cannot draw strong conclusions from the small clusters alone, but they illustrate the importance of further research with per-patient analysis which could alter or refute our hypotheses.

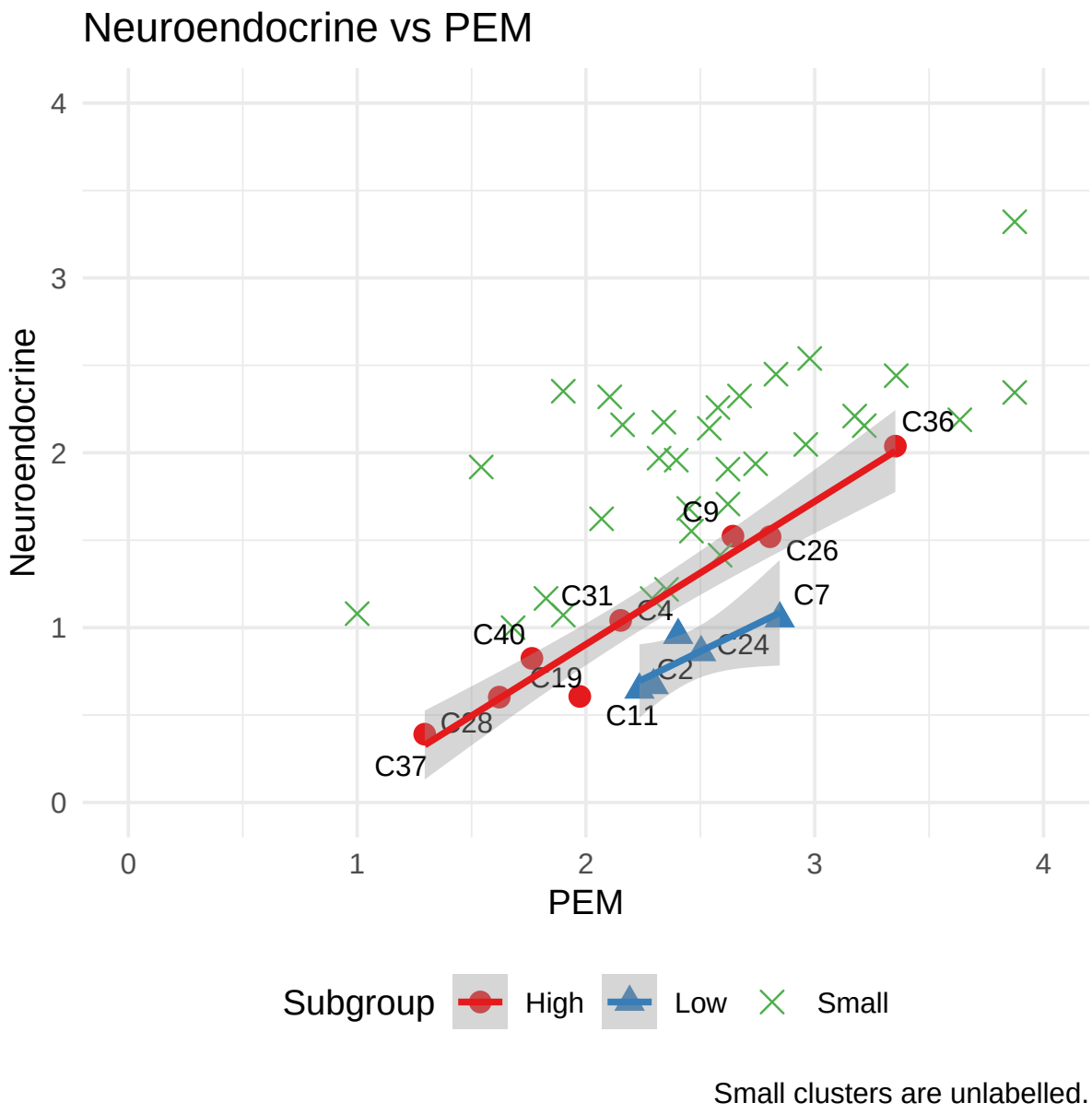

Figure 5: Neuroendocrine vs. PEM with Small Clusters

5 Discussion

We have shown that the Vaes clusters can be organized into two subgroups defined by symptom domains relative to PEM, and that these subgroups remain consistent across most domains. Grouping them by their relationship to PEM simplifies the original complexity at both the domain and cluster levels. From this perspective, the 13 Vaes clusters can be reduced to two groups of linear models, where membership in one group combined with PEM intensity allows inference of the intensity of other symptom domains. We view this PEM-referenced, two-family reduction (offsets vs. amplification, with C36 sensitivity at the high end) as the main conceptual advance over prior descriptions of the Vaes clusters.

While these patterns are striking, our analysis is a secondary exploration based on symptom-domain summaries of the Vaes patient data. The small subgroup sizes (eight and five clusters) together with the original clustering approach and our own visualizations may have produced trends that are purely artifacts of layering our visualizations on top. These concerns highlight the need for validation before our findings can be clinically relevant.

We see challenges in at least three areas: whether the groupings hold when tested with individual patient data; whether symptom-domain analysis can reliably identify the group to which a given patient belongs; and how these subgroups relate—or fail to relate—to fibromyalgia. As an example, Vaes[1] includes cluster-specific summaries of standout symptoms; some of those align with our domain-based charts while others show a different emphasis, demonstrating the challenge of reconciling symptom-level observations with domain-level analyses.

Despite these limitations, we believe further investigation could clarify whether these axes yield clinically useful patient groupings. A simplified narrative that organizes patients on a few axes could help clinicians and researchers better understand the heterogeneity of ME/CFS.

6 Conclusion

Our secondary analysis suggests that the 13 clusters identified by Vaes et al. can be organized into two broader structures defined by overall symptom intensity relative to PEM severity. These two groups remain coherent across symptom domains and display distinct, largely linear relationships with PEM. Although exploratory and limited to cluster-level data, these findings offer a reproducible framework for further research, specifically for validating these potential subgroups and exploring their clinical and biological relevance.

7 Appendices

Appendix A: Cluster Summary Data

We use the Vaes cluster spreadsheet[2] exclusively as our data source. We use R for significant cleaning and transformation from Excel to CSV. After removing everything but the mean severity of the symptoms in the 13 clusters we:

- Rename symptom groups to use consistent capitalization and abbreviations
- Group each cluster by symptom domain and calculate geometric means for each symptom domain within each cluster.
- Rotate the table
- Add a new column, "all_mean" which is the arithmetic mean of all symptoms within each cluster.
- Save this file as cluster_grouped_tidy.csv

This file is what we then used for our analysis, and the plots. We present the final data used below. Values were rounded for formatting. See the Code Availability section for links to the code used to generate this file.

Table 2: Cluster Summary Data with Geometric Means by Symptom Domain

Cluster	All	Auto	Fatigue	Immune	NC	NE	Other	PEM	Pain
C2	1.21	0.76	2.79	0.53	1.15	0.67	0.27	2.30	0.95
C4	1.55	1.24	3.13	0.87	1.66	0.96	0.46	2.40	1.19
C7	1.92	1.48	3.20	1.03	2.32	1.05	0.86	2.85	1.94
C9	2.06	2.16	2.85	1.40	2.24	1.52	1.55	2.64	1.71
C11	1.42	1.02	2.94	1.08	1.11	0.64	0.33	2.23	1.00
C19	1.37	1.12	2.53	0.57	1.81	0.61	0.60	1.97	1.06
C24	1.63	1.44	2.95	0.82	1.52	0.86	0.56	2.50	1.53
C26	2.14	1.87	3.28	1.76	2.06	1.52	1.77	2.80	2.34
C28	1.03	0.83	2.50	0.56	0.78	0.60	0.30	1.62	0.88
C31	1.47	1.31	2.73	0.77	1.31	1.04	1.41	2.15	1.54
C36	2.74	2.59	3.50	2.30	3.08	2.04	2.04	3.35	2.73
C37	0.67	0.41	2.39	0.16	0.43	0.39	0.19	1.30	0.51
C40	1.21	0.74	2.80	0.52	0.95	0.82	0.67	1.76	1.19

Appendix B: Statistical Descriptions

In the body of the text, we used visual analysis to identify two subgroups of ME/CFS patient clusters defined by their symptom domain profiles relative to PEM severity. Here we present statistics that may help clarify the data in the plots. Given the exploratory nature of this study and the small number of clusters, these results should be interpreted as descriptive rather than confirmatory.

ANCOVA

We performed an analysis of covariance (ANCOVA) to identify the domains which could be most statistically significant and discriminatory. We compare our two groups for each symptom domain. We arrange the results by descending F-statistic and show the p-value rounded to three decimal places.

Table 3: ANCOVA Analysis

Domain	F statistic	p-value	Significance
Other	33.3	< 0.001	***
NE	11.6	0.007	**
Fatigue	5.2	0.046	*
Autonomic	3.8	0.08	.
Pain	3.1	0.108	NA
Immune	1.4	0.268	NA
all_mean	1.0	0.33	NA
Sleep	0.2	0.647	NA
NC	0.0	0.849	NA

Table 3 shows agreement with the charts that Other, Neuroendocrine and Autonomic domains show the most significant offsets between the two groups. The high F-statistic and low p-value for Fatigue, however, do not agree with the regression lines. As we note earlier in Section 2.1, the lines in Figure 1 are nearly identical but R^2 is significantly weaker in the low-intensity group. The high F-statistic and low p-value in the ANCOVA analysis for fatigue is most likely an artifact of the wide spread and small sample count in the low-intensity group.

Leave-one-out Analysis

We discovered our two groups by visual analysis, but we can re-identify the set using leave-one-out analysis. In this analysis we go through each domain and examine what happens when we remove one cluster at a time. The goal is to identify which clusters, when removed, improve R^2 the most.

We summarize the mean R^2 differences, in order of greatest improvement, in Table 4.

Table 4: Leave-one-out Analysis

Cluster	Group	Domains Improved	Mean ΔR^2
C2	low	9	0.0379
C11	low	9	0.0271
C4	low	8	0.0191
C31	high	7	0.0163
C7	low	5	0.0129
C24	low	8	0.0126

Of the top 6 clusters only C31 is not part of the low-intensity group. While this does not prove the existence of two subgroups it does support the idea that the members of the low-intensity group are, overall, responsible for most of the R^2 degradation in the combined group.

C31 does exhibit variability but it varies around the high-intensity group trend lines, which is why we include it with the high group despite this result.

R^2 by Group

We compare the coefficient of determination (R^2) of the symptom domains in three levels:

- Combined (all clusters)
- High-intensity group
- Low-intensity group

Table 5: R^2 by Domain

Domain	Combined R^2	High-intensity R^2	Low-intensity R^2
Autonomic	0.79	0.96	0.62
Fatigue	0.84	0.86	0.54
Immune	0.78	0.96	0.11
NC	0.85	0.92	0.93
NE	0.73	0.95	0.75
Other	0.52	0.92	0.96
Pain	0.81	0.95	0.95
Sleep	0.53	0.82	0.05
all_mean	0.91	1.00	0.84

Table 5 shows that for almost every symptom domain, the high-intensity group has a higher R^2 than the combined group, which in turn has a higher R^2 than the low-intensity group. In some cases – such as Neurocognitive, Neuroendocrine, and Other – the combined R^2 is significantly weaker than either of the subgroups.

Code Availability

All data manipulation and analysis scripts are available at
https://github.com/eriksquires/VaesSubgroups

Data Availability

A copy of the original Vaes spreadsheets are available in the GitHub repository, above, and from the original Vaes publication[1] at https://doi.org/10.1186/s12967-023-03946-6.

All other data files are created from the original Vaes spreadsheets using the code in the GitHub repository, above.

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Dr. Vaes had no role in the writing of this paper, and all errors or misinterpretations are the responsibility of the author.

Author Contributions

Erik K. Squires conceived the study, performed the analysis, and wrote the manuscript. This work presents an original investigative method and resulting framework which were both developed and first reported by the author in this preprint.

Competing Interests

The author declares no competing interests.

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Ethics Statement

This study reanalyzed publicly available reports and published symptom cluster data (Vaes 2023). No new patient data were collected.

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