

Removing the Mask of Average Treatment Effects in Chronic Lyme Disease Research Using Big Data and Sub-Group Analysis

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ABSTRACT

There is considerable controversy in the medical community surrounding chronic Lyme disease (CLD). CLD sufferers have persistent Lyme symptoms resulting from being untreated, under-treated or, having a lack of response to their antibiotic treatment protocol. Some of the past Lyme disease studies that reported on average treatment effects were unable to identify treatment successes. Using patient-reported outcome data collected by LymeDisease.org via their online registry, MyLymeData, we will show that using sub-group analysis techniques can unmask valuable information about treatment effectiveness.

INTRODUCTION

Often in medical studies the emphasis is placed on average treatment effects. As we will show, doing so masks important information that can provide insights into the range of treatment effects that are exhibited in a patient group. Using data from the MyLymeData patient registry developed by LymeDisease.org, we looked at responses to survey questions where patients reported whether they considered themselves well or sick and, also reported the degree to which their condition had changed following antibiotic treatment using a global rate of change scale, typical of those used by clinicians in practice. The scale asks whether patients report their health condition is better, worse, or unchanged since treatment (Junghard, 2007; Kamper, 2009).

Those who respond better or worse are asked to define the magnitude of change perceived by the patient on a 7-point scale. The end result is a 15-point Likert Scale, ranging from -7 to +7, with the unchanged midpoint pegged at 0. For example, compared with no change (0), those responding better select a magnitude ranging from (0) "almost the same", (1) "hardly better at all", (2) "a little better," (3) "somewhat better," (4) "moderately better," (5) "a good deal better," (6) "a great deal better," and (7) "a very great deal better." Those responding worse, choose among similar responses, ranked (0,-1 to -7) (Wang, 2011). For purposes of this analysis the category "unchanged" and both "almost the same" original categories were collapsed into the unchanged category (0).

Using this scale, we found the mean treatment effect to be 1.7 and the median treatment effect to be 2.0. We grouped responses into 3 groups: High Responders (4-7, those reporting "moderately better" to "a very great deal better"), Low Responders (1-3, those reporting "hardly better at all" to "somewhat better"), and Nonresponders (-7-0, those reporting no change to "a very great deal worse").

High Responders represented 35%; Low Responders 17% and Nonresponders 48% of the patients. More than 50% of this group of sick patients (Low and High Responders) reported some improvement in their condition. We discuss how we used JMP® Pro 13.1.0 to conduct this analysis.

We also suggest future research using the growing amount of patient-reported data and clinical data surrounding CLD to discover what illness, patient, and treatment characteristics lead to treatment success and may, in the future, guide medical professionals toward more targeted and effective treatments.

BACKGROUND

Lyme disease, which is caused by the spirochete *Borrelia burgdorferi*, has become a major worldwide epidemic. The Centers for Disease Control estimates that 300,000 people each year contract Lyme disease in the United States (Centers for Disease Control and Prevention, 2013). This incidence is 1½

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times higher than the number of women diagnosed with breast cancer and 6 times higher than the number diagnosed with HIV/AIDS each year in the United States (Centers for Disease Control and Prevention, 2013a; Centers for Disease Control and Prevention, 2013b).

As many as 36% of those diagnosed and treated for Lyme disease develop persisting debilitating symptoms following short-term antibiotic therapy (Aucott, 2013). This condition is commonly referred to as post-treatment Lyme disease (PTLD) or chronic Lyme disease (CLD).

The efficacy of retreatment or prolonged treatment of patients with CLD is controversial. Only four federally funded randomized placebo-controlled treatment trials have been conducted (Klempner, 2001; Krupp, 2003; Fallon, 2008). Some treatment guidelines characterize these trials as demonstrating that patients do not benefit from retreatment (Wormser, 2006). However, these trials, which enrolled a total of 221 combined, have been criticized due to small sample sizes and restrictive entry criteria, which precluded subgroup analysis and generalizability to other patients (Fallon, 2012; DeLong, 2012; Guyatt, 2008).

Calls for personalized treatments point to the inherent limitations of using group averaged data from randomized trials as a guide for physicians trying to determine the best treatment approach for an individual (National Research Council, 2011; Kravitz, 2004). Heterogeneity of treatment effects may be masked by using group averages that fail to use subgroup analysis to identify groups of individuals who may benefit from a treatment intervention.

DATA AND METHODS

MyLymeData is a patient registry developed by LymeDisease.org that enables pooling of longitudinal healthcare data. Participation in the registry is voluntary, and all respondent identities have remained strictly confidential. The MyLymeData registry and its surveys have been approved by the Chesapeake Institutional Review Board.

Since its launch in November 2015, over 7,500 patients have enrolled. Phase 1 of the registry data collection was completed in November 2016. We began this analysis with a sample of 3,595 participants, who completed the Baseline Survey, reported residing in the US, being diagnosed with Lyme disease by a healthcare provider, having taken antibiotics, and who identified themselves as being “unwell”. We then excluded an additional 164 participants who did not provide State or Country data. The 3,431 participants (Table 1) used in this analysis included US residents clinically diagnosed with Lyme disease who completed the Phase 1 surveys and identified their health status as “unwell” when completing the survey.

Completed Baseline Survey (Unwell)	3,595
No State or Country Data	-164
Ending sample size	3,431

Table 1 Final Sample Size of Unwell used for this analysis

LIMITATIONS

Although this study includes data from over 3,000 participants in MyLymeData and has significant implications for research design and health policy, important limitations must also be recognized.

Participants had access to the Internet and were not a randomly drawn sample. Those who elect to participate may have been sick longer and more severely ill, which could lead them to seek online support and resources for their illness (Johnson L et al. 2014). Accordingly, it is unlikely that the results reported here capture the full range of illness for patients with Lyme disease.

In addition, the results are based on self-reported information without independent diagnostic confirmation. However, self-reported information has been found to have acceptable levels of reliability when compared to medical chart information and is reported to improve accuracy of patient data (Cohen, 2016; Bayliss, 2012). Moreover, self-rated health is considered to be a reliable indicator of perceived health, and personal well-being may be a more powerful predictor of mortality and morbidity than many objective measures of health (New York State Department of Health Disability and Health Program, 2007).

PARTICIPANT INCLUSION/EXCLUSION

All analysis was done using JMP® Pro 13.1.0. JMP was used for the entire analysis process, from participant exclusion (due mainly to lack of geographic information, no healthcare provider diagnosis of Lyme disease or not reporting being “unwell”) to data transformation to creating results.

We excluded participants for whom there was no State and Country data and those who indicated either residence in another country or at a US military location. Included participants were those with United States in the country field and, a valid US State in the state field, as well as participants whose country field was blank but whose state value was valid. As shown in Figure 1, we used the JMP—>Rows→Data Filter for exclusions.

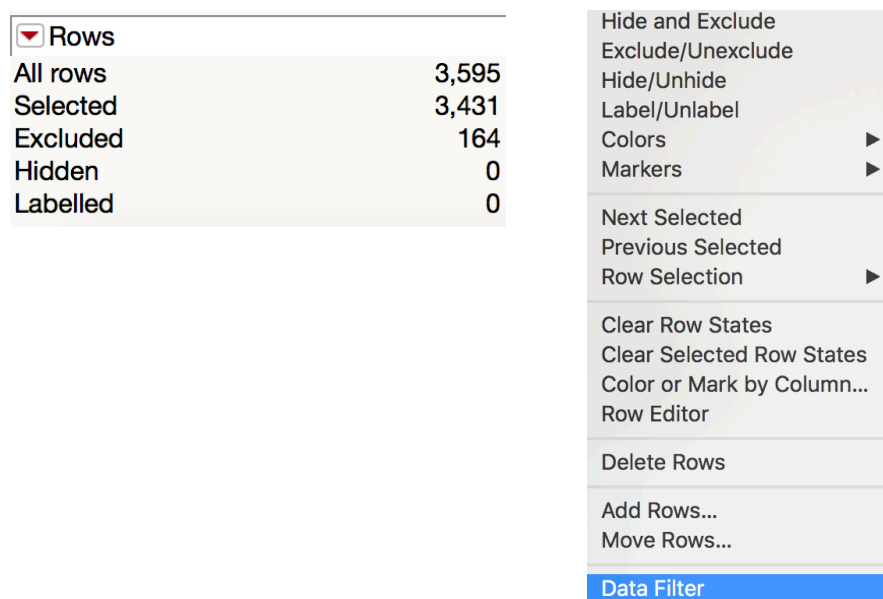


Figure 1 JMP Rows->Data Filter for exclusions

As shown in Figure 2, to include participants whose country field was blank but whose state value was valid, we created a new column and used the formula field for the new column to include the logic. Both the exclusions and transformations could be saved as a JMP script or could be written entirely in the JMP Scripting Language (JSL) and then applied to the table.

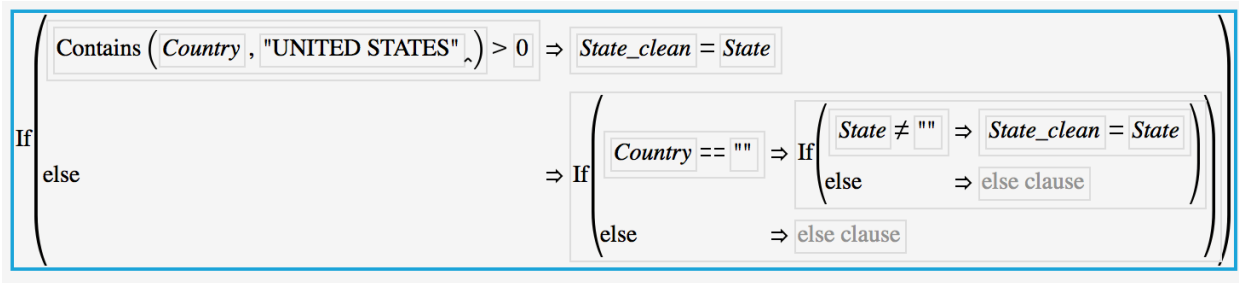


Figure 2 Create a New Column State_Clean

CREATION OF A LIKERT SCALE VARIABLE FROM RESPONSES

The participants were asked a series of questions. They were asked “In general overall, I would say that with antibiotic therapy, my Lyme symptoms are” and responded: worse, unchanged, or better. Based on their response, they were asked a question concerning how much worse or better they felt following treatment as described previously. (See Attachment A.) As shown in Figure 3, using these responses and the JMP column formula feature, we developed a 15-point Likert Scale for use in this analysis. An additional column created, using the JMP column formula, grouped these responses as High Responders (4 to 7), Low Responders (1 to 3), and Nonresponders (-7 to 0). The JMP “Match” function will fill in the values of the left side of the column dynamically from the data. If it is important for readability, as is the case here, for the values to appear in the expression in order, use the Column Properties→Value Ordering feature to control the order in the expression.

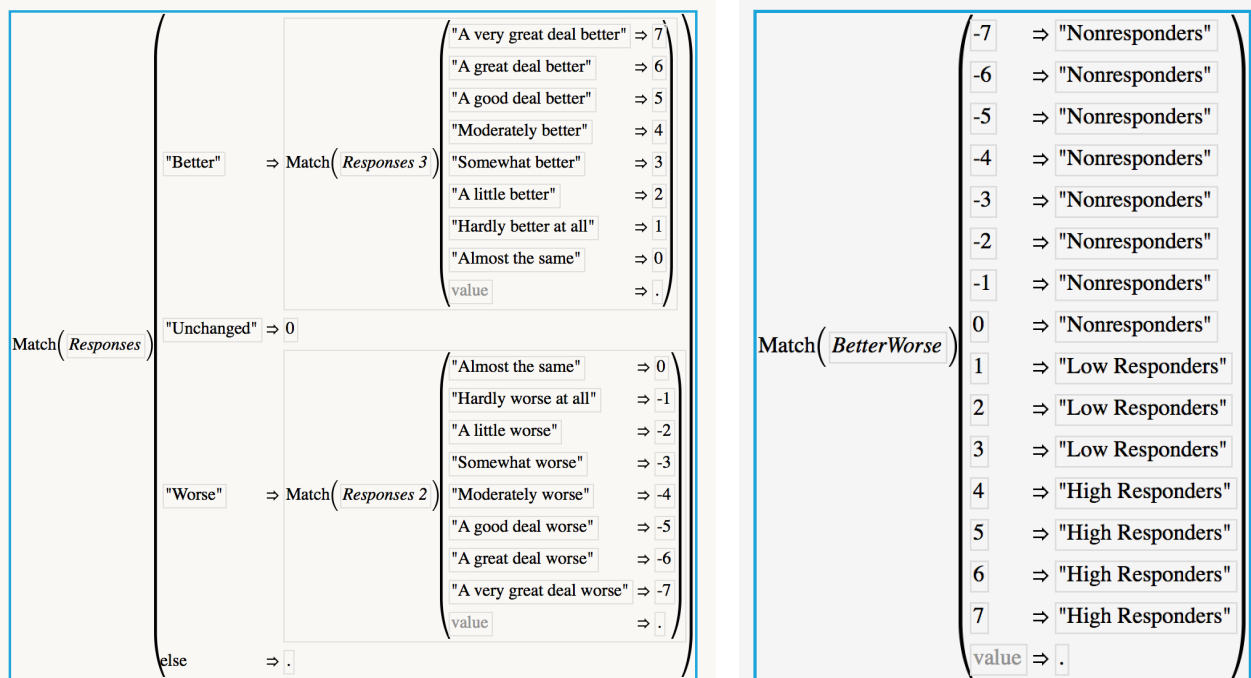


Figure 3 Grouping of Likert Scores into High Responders, Low Responders and Nonresponders

RESULTS

The Likert Scale approach was used to evaluate the patients' self-reported treatment effects. As described above, the values ranged from -7 ("a very great deal worse") to 7 ("a very great deal better"). The value for each patient was determined by their response to a series of survey questions. The mean and median for these patient values were 1.7 and 2.0, respectively. If the patient responses were evaluated by looking at the mean only, one might conclude that there is very little improvement in the health of this group of patients; using only the median would lead to a similar conclusion. However, examining the distribution of the values for this group of patients unmasks the fact that more than 50% showed some degree of improvement.

As shown in Table 2 and Figure 3, 34% of patient responses translate to a Likert Scale value of 4 or higher ("Moderately better", "A good deal better", "A great deal better", "A very great deal better"), 16% of the responses were 1, 2, or 3 ("Hardly better at all", "A little better", "Somewhat better"), and the remaining 49% of responses were 0 or lower ("Unchanged", "Almost the same", or from "Hardly worse at all" to "A very great deal worse").

As shown in Figure 3, we created three groups representing High Responders (from 4 up to 7), Low Responders (1, 2, 3) and Nonresponders (from 0 down to -7). By grouping these responses in this way (Figure 5), we can identify more than 50% of these patients as improving with treatment: 34% were High Responders, and 16% were Low Responders.

By looking at the gradations of participant responses to their treatment using the Likert Scale, we have thus shown that more than 50% of them reported some level of improvement with treatment. The use of this approach rather than merely calculating measures of central tendency suggests that both in patient-reported studies and other clinical studies, using larger sample sizes and finer granularity of patient response enhances subgroup identification that may lead to a faster path to identifying valuable treatment options.

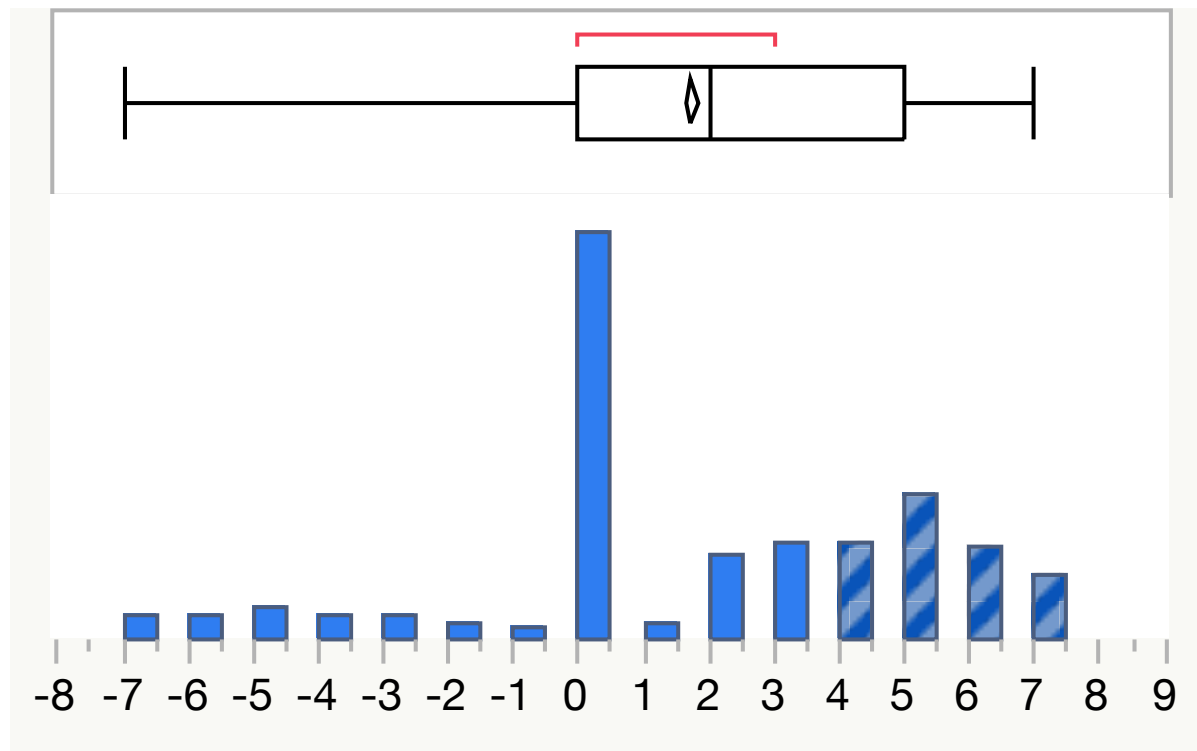


Figure 4 Frequency of Likert Scale Values: 35% High 17 % Low, 48% Nonresponders

Better Worse	Scale-Grouped	N	% of Total
-1	Nonresponders	23	1%
-2	Nonresponders	32	1%
-3	Nonresponders	65	2%
-4	Nonresponders	68	2%
-5	Nonresponders	82	2%
-6	Nonresponders	61	2%
-7	Nonresponders	61	2%
0	Nonresponders	1241	37%
1	Low Responders	43	1%
2	Low Responders	251	7%
3	Low Responders	286	8%
4	High Responders	283	8%
5	High Responders	430	13%
6	High Responders	272	8%
7	High Responders	184	5%

164 rows have been excluded.

Table 2 Frequency and Percentages of Unwell High Responders, Low Responders and Nonresponders

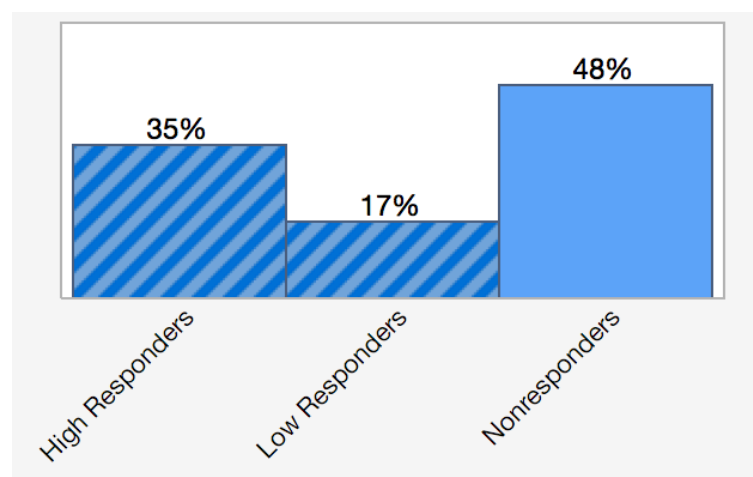


Figure 5 Distribution of High, Low and Nonresponders

(Note: 49 of the participants left one of the key follow-up questions unanswered which resulted in a missing value for this grouping.)

CONCLUSION

With the increase in the number of cases of CLD, there is a growing urgency to discover how best to treat these patients. The analysis discussed in this paper, the combination of using a larger sample size and a 15-point Likert Scale to provide a more granular view of treatment response, demonstrates the benefit of going beyond examination of average treatment effects. With the increased availability of big data, both patient-generated and clinician-generated, a highly granular approach is becoming more feasible, not only in meta-analysis but for individual studies.

This approach paves the way for analyzing patient characteristics to understand why a treatment is more effective with certain patients. Possible approaches to teasing out treatment effects may include examination of the following: disease duration, disease severity at diagnosis, number of co-infections, patient demographics, and treatment delivery mechanism as well as treatment regimen and duration. A deeper understanding of treatment response may help identify potential biomarkers for this disease and aid in developing more targeted and innovative treatments for CLD.

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RECOMMENDED READING

For further information visit: LymeDisease.org

CONTACT INFORMATION

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Attachment A: Global Rate of Change Scale and Scoring Baseline Survey Phase 1 Unwell

In general overall, I would say that with antibiotic therapy my Lyme symptoms are...

Worse [Branch to Worsening Symptoms]

0 Unchanged

Better [Branch to Symptom Improvement]]

Worsening Symptoms

More specifically, I would say my degree of health decline since I began treatment is...

- 0 Almost the same
- 1 Hardly worse at all
- 2 A little worse
- 3 Somewhat worse
- 4 Moderately worse
- 5 A good deal worse
- 6 A great deal worse
- 7 A very great deal worse

Symptom Improvement

More specifically, I would say my degree of health improvement since I began treatment is...

- 0 Almost the same
- 1 Hardly better at all
- 2 A little better
- 3 Somewhat better
- 4 Moderately better
- 5 A good deal better
- 6 A great deal better
- 7 A very great deal better