Blood Type Distribution in Autoimmune Diseases: An Anonymous, Large-Scale, Self-Report Pilot Study

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Abstract

Background: Recent research has verified that blood group or Rh factor can influence susceptibility to various cardiovascular, neoplastic and infectious diseases including COVID-19. While a number of studies have looked at correlations between blood group and various rheumatological diseases, findings have been inconsistent, often because many of these studies suffered from small sample size issues. In order to better understand the potential relationships between blood group/Rh factor and rheumatological diseases, we performed a large-scale self-report pilot study of blood type distributions in five autoimmune diseases.

Methods: Five autoimmune diseases were included in the study: systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and ankylosing spondylitis. We also included a control group in which participants did not have any autoimmune diseases. The participants were recruited through social media and organizations such as the Lupus Foundation and the National Psoriasis Foundation. Respondents who met the inclusion criteria were asked only two questions by anonymous survey: blood type and country of birth.

Results: Each autoimmune disorder group included between 570 and 951 US participants. While there was little difference in blood type distribution patterns among the five diseases, unexpectedly, all five disease groups showed a consistent pattern where Rh negative was almost twice as high as US population norms. A *post-hoc* non-autoimmune control group was added in order to determine if this anomalous finding was an artifact of the study design. The control group displayed a similar unexpected increase in the Rh-negative blood type prevalence, suggesting that the very high Rh-negative frequency among the tested disease groups was likely to be an artifact of the study design.

Conclusions: Overall, our preliminary study results show no meaningful differences between the disease groups and the *post-hoc* control group**,** suggesting that neither ABO type nor Rh factor affects susceptibility to the development of any of the five studied autoimmune diseases. Nevertheless, the unexpected observed difference in Rh factor distribution between the studied groups/control group and the corresponding US population norms has important implications for any research study using self-selected subjects. Our results suggest that such studies may be subject to unanticipated biases, requiring meticulous controls to confirm impartiality and exclude any artifacts of the study design.

Background

Over the past 100 years, hundreds of studies have been done looking at statistical relationships between blood groups and medical conditions or traits such as personality and even criminality. While many of these early studies were controversial and suffered from numerous methodological flaws, including small sample size and incorrect analysis, more recent research has demonstrated that there are clear associations between blood groups or Rh factor and susceptibility to various diseases, including infectious and, cardiovascular diseases, certain cancers, and most recently, COVID-19. (1–6)

A number of studies have looked at distribution patterns of ABO group and Rh factor in multiple autoimmune diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren's syndrome (SjS). (7–11) In general, most of these studies found little or no difference in ABO group distribution patterns in the various studied diseases, but several studies did report differences in Rh factor between study groups and control groups in several autoimmune diseases, but even there, findings were inconsistent in the various studies. A likely reason for the disparity in results is that in several of these studies, group sizes were quite small.

There is a perception in the popular press and in patient support groups that patients with Rh negative blood are more susceptible to autoimmune diseases. In 2016, the Scleroderma Education Project (a 501c3 non-profit organization focused on systemic scleroderma education and research) conducted a large-scale, self-report online survey of SSc patients to see if there was a basis for conducting a formal study to investigate blood type distribution patterns in patients with SSc. This initial survey of 743 respondents found that Rh-negative SSc patients were significantly more common than was expected. Unfortunately, this survey failed to assess country of birth, making it impossible to do a valid statistical analysis since different countries have significantly different blood-type distribution norms.

In April 2017, we decided to do a formal large-scale self-report pilot study of blood type distributions in five separate autoimmune diseases in order to see if a formal follow-up study using patient records could potentially be justified. There is inherent concern with self-report data because of potential issues like self-selection biases and self-report accuracy. However, previous research has shown that there is good to very good agreement between self-report and medical records for both diagnosis and symptoms (12–14), suggesting that a self-report study is an appropriate first step before initiating a more expensive formal study using medical records.

The five diseases chosen for the study are listed below:

- SSc
- SLE
- RA
- Psoriasis
- AS

SSc, SLE, and RA are strongly female dominant connective tissue diseases that are usually positive for anti-nuclear antibodies (ANA). Psoriasis is also female dominant but is ANA negative. AS is one of the rare autoimmune diseases that is male dominant.

Initial goals for the study were to determine 1) if there were any significant differences in blood type distribution patterns among the five surveyed diseases, and 2) if the blood type distribution patterns for any of these diseases differed from the US population norms. Our primary focus was to determine if clear patterns were evident that would justify a more formal follow-up study rather than on detailed quantitative analyses of the data. This study was determined to qualify as an exempt study by the University of Wisconsin (Madison) Institutional Review Board (Project No: 2017-0545).

Methods

Autoimmune Disease Blood Type Survey Design

The survey was restricted to just two questions:

- **What is your blood type?**

Response choices were: A-, A+, B-, B+, AB-, AB+, O-, O+, in that order.

- **What is your country of birth?**

Response choices consisted of a list of 100 countries. The first three were United States, United Kingdom, and Canada. Following these three countries, additional countries listed were alphabetical. There was also an “Other (please

specify)" option that allowed someone to enter the name of any country that was not on the list.

The surveys were done using a common online survey tool called SurveyMonkey. The surveys were configured so that only one survey was allowed per IP address. While technically, anyone could take the survey more than once, this would require them to take the survey again from a different physical location or to use a software tool like a Virtual Private Network to alter the normal IP address, which we believe to be unlikely to occur given the nature of the surveys.

Table 1 shows the specific inclusion/exclusion criteria listed for each of the five individual surveys. Patients need to know their blood type to participate in the surveys.

Table 1: Autoimmune Disease Survey Inclusion/Exclusion Criteria

Disease	Inclusion Criteria	Exclusion Criteria
Systemic Sclerosis (SSc)	· **Formally diagnosed with SSc (limited or diffuse) or** Mixed Connective Tissue Disease (MCTD)	· **Tentative diagnosis such as Undifferentiated Connective Tissue Disease (UCTD)** · **Localized (not systemic) scleroderma, for example morphea or linear scleroderma**
Systemic Lupus Erythematosus (SLE)	· Formally diagnosed with SLE	· Tentative diagnosis such as UCTD · **Diagnosis of lupus/scleroderma overlap syndrome such as MCTD**
Rheumatoid Arthritis (RA)	· **Formally diagnosed with RA**	· **Tentative diagnosis such as UCTD** · **Diagnosis of osteoarthritis (OA) instead of RA**
Psoriasis	· Formally diagnosed with psoriasis	· **Suspected or confirmed psoriatic arthritis instead of or in addition to psoriasis**
Ankylosing Spondylitis (AS)	· Formally diagnosed with AS	· **Diagnosed with enteropathic arthritis, psoriatic arthritis, reactive arthritis, or undifferentiated spondyloarthritis**

Autoimmune Disease Respondent Recruitment

Our target goal was a minimum of 500 respondents per disease with the US as country of birth. Recruitment was done primarily through social media, for example through postings in individual disease-focused patient support groups on Facebook or other organizations. The surveys were also announced in online news websites such as *Scleroderma News* and *Lupus News*. Several organizations, including the Lupus Foundation and the National Psoriasis Foundation, also publicized the study. The first survey was launched in February 2017 and the final survey was closed in November 2017.

Non-Autoimmune Control Group*

In order to properly analyze the results of our survey of patients with autoimmune diseases, we included a control group of people that did not have any type of autoimmune disease. Control group participants could not be either: 1) formally diagnosed with, or 2) in the process of being evaluated for any autoimmune disease, not limited to the five diseases we were studying, but also including other autoimmune diseases such as multiple sclerosis, Hashimoto's disease, or SjS. Control group survey participants were recruited through groups and methods that had no disease association, including non-medical Facebook groups and also through Amazon MTurk.

*Note: the control group was added *post-hoc* after a preliminary analysis of the data showed unexpected distribution patterns.

US Blood Type Distribution

Blood type distribution norms for the US are set out in Table 2.

Table 2: US Blood Type Distributions

Blood Type	Estimated %
A-	6.3%
A+	35.7%
B-	1.5%
B+	8.5%
AB-	.6%
AB+	3.4%
O-	6.6%
O+	37.4%

Source: Stanford School of Medicine Blood Center
(originally sourced from the *AABB Technical Manual 18th Edition)*

Results

We were able to easily achieve our overall goal of a minimum of 500 US survey participants per disease. Table 3 below shows the total number of survey responses per disease and the number of surveys where the selected country of birth was the US.

Table 3
Survey Counts by Disease

	SSc	RA	SLE	AS	Psoriasis	Control
Total Count	924	1448	1802	1483	1083	893
US Only	570	951	773	938	793	893

Table 4 shows the detailed breakdown of blood types for each of the five diseases as well as the US population norms from the Stanford School of Medicine Blood Center (Table 2). Table 5 shows the result breakdown by ABO Type. Table 6 shows the result breakdown by Rh Factor.

Table 4
US Blood Type Distributions by Disease

Blood	US	Control		SSc		RA		SLE		AS		Psoriasis	
Type	%	%	N	%	N	%	N	%	N	%	N	%	N
A-	6.3%	6.7%	60	8.8%	50	9.3%	88	8.9%	69	7.8%	73	9.8%	78
A+	35.7%	24.6%	220	33.0%	188	27.1%	258	24.7%	191	33.8%	317	27.5%	218
B-	1.5%	3.5%	31	3.0%	17	4.6%	44	2.7%	21	4.3%	40	2.9%	23
B+	8.5%	13.3%	119	8.2%	47	8.4%	80	10.5%	81	9.1%	85	9.3%	74
AB-	.6%	2.8%	25	1.4%	8	2.3%	22	1.8%	14	1.8%	17	2.0%	16
AB+	3.4%	6.6%	59	4.2%	24	4.2%	40	5.2%	40	4.3%	40	6.2%	49
O-	6.6%	14.0%	125	13.7%	78	11.8%	112	14.9%	115	11.7%	110	14.5%	115
O+	37.4%	28.4%	254	27.7%	158	32.3%	307	31.3%	242	27.3%	256	27.7%	220
Count		893		570		951		773		938		793	

Table 5
US Blood Type Distributions – ABO Type Summary

Blood	US	Control		SSc		RA		SLE		AS		Psoriasis	
Type	%	%	N	%	N	%	N	%	N	%	N	%	N
A	42.0%	31.4%	280	41.8%	238	36.4%	346	33.6%	260	41.6%	390	37.3%	296
B	10.0%	16.8%	150	11.2%	64	13.0%	124	13.2%	102	13.3%	125	12.2%	97
AB	4.0%	9.4%	84	5.6%	32	6.5%	62	7.0%	54	6.1%	57	8.2%	65
O	44.0%	42.4%	379	41.4%	236	44.1%	419	46.2%	260	39.0%	366	42.2%	335
Count		893		570		951		773		938		793	

Table 6
US Blood Type Distributions – Rh Factor Summary

Blood	US	Control		SSc		RA		SLE		AS		Psoriasis	
Type	%	%	N	%	N	%	N	%	N	%	N	%	N
Rh +	85.0%	72.9%	652	73.2%	417	72.0%	685	71.7%	554	74.4%	698	70.7%	561
Rh -	15.0%	27.1%	241	26.8%	153	28.0%	266	28.3%	219	25.6%	240	29.3%	232
Count		893		570		951		773		938		793	

Figures 1, 2, and 3 show these distributions graphically.

Statistical Analysis

There were two questions these questionnaires were designed to address:

1) Does blood type distribution differ among these different autoimmune diseases?

Answer: Yes: $X^2(28) = 48.1$, $p < 0.01$

2) Is the distribution of blood types in each of these five autoimmune diseases the same as in the general population?

The answer to this question is more complicated. When we saw that the results were vastly different from the general population, we added a control group to determine if the unexpected results were an artifact of the experimental design or an actual reflection of blood type distributions in our studied disease populations.

As is readily visible in Fig. 1, all five of the disease groups and the control group are highly significantly different than published population norms ($p < 0.0001$). In looking at differences between individual diseases and the control group (Table 7), only SSc, RA, and AS do show statistically significant differences between these diseases and the control group.

Table 7
Disease Groups Compared to Control Group

SSc	RA	SLE	AS	Psoriasis
$X^2(7) = 25.4$	$X2(7) = 26.0$	$X^2(7) = 10.7$	$X^2(7) = 30.6$	$X^2(7) = 13.9$
$p < 0.001$	$p < 0.001$	$p = 0.153$	$p < 0.001$	$p = 0.053$

Discussion

While the main goals for this preliminary study were to look at blood type distribution patterns in five different autoimmune diseases compared to US population norms and each other, our most striking finding was that the blood-type distribution pattern in our control group of people without any association with any autoimmune disease was substantially different from the expected population norms. While there are some statistically significant differences in distribution patterns among the five diseases, overall, the five diseases showed similar distribution patterns, and all five diseases were very similar to the control group.

If only the ABO distribution is analyzed (with no consideration of Rh factor), the five diseases and the control group were relatively close to the expected US population norms for ABO type distribution, with the exception of the rarest ABO type – AB. While this may be an anomaly due to relatively small numbers of this least frequent blood type, there may be another explanation for this consistent finding across all disease groups plus the control group. This is discussed below.

However, the most striking finding was the unexpected difference between the Rh-positive and Rh-negative individuals in all studied groups. While there were few significant differences among the five disease groups or between the control group and the disease groups, there was a very large difference in Rh factor distribution (positive *versus* negative) between the Stanford US population data and both the disease group data and the control group data, with the percentage of respondents who were Rh-negative being 70% to 95% higher than expected depending on the specific disease.

Understanding the Results

There are two factors that need to be considered that might account for some or all of the anomalous survey results:

Random Guessing

Some of the people taking the survey are probably wrong about their blood type. If we assume that the incorrect blood type "guesses" are evenly distributed among the eight possibilities, the effect of random guessing is to increase the

expected frequencies of any rare blood type (*e.g.*, O-) and decrease the expected frequency of any common blood type (*e.g.*, A+). While this type of error may potentially account for a small portion of the anomalous results, it does not explain why the Rh-, and in particular O-, observed results are much higher than expected.

A "Red Cross Effect"?

A second, and much more likely explanation for the unexpected results is a well-documented phenomenon called the "availability heuristic" or "availability bias" (15). An availability heuristic is a type of mental shortcut that involves basing judgements on information and examples that immediately spring to mind.

Most people in the US learn their blood type either as part of a medical procedure or when donating blood or blood products. When people desire to donate blood or blood products at the Red Cross or other organization, their blood is screened at the initial visit for potential transmissible diseases, and it is also typed. If it turns out that they are O-negative in particular, they will be informed that they are "universal donors" and that their blood is highly sought after by organizations like the Red Cross.

While this needs to be confirmed by research comparing known blood types through medical records *versus* self-recall of blood type, it is possible that being told that one's blood type is in high demand may substantially increase the likelihood of remembering correctly the directly-determined blood type. Also, blood drives often emphasize getting blood donations from people who are Rh-negative since Rh-negative blood can be transfused into many more people than Rh-positive blood.

Note: In looking at the blood type distribution patterns for each disease group and in comparison to the control, there are a few statistically significant differences that may be worth examining in future research. Figures 2 and 3 suggest that these differences stem from ABO blood group rather than Rh factor considerations.

Conclusion

Our self-report pilot study suggests that there are no significant differences in blood type distribution among the five surveyed autoimmune disease groups or between the disease groups and a *post-hoc* control group. This suggests that at least for these five surveyed autoimmune diseases, there is no indication that either ABO type or Rh factor increases or decreases the likelihood of patients being diagnosed with any of these diseases. Based on this, there does not appear to be any justification for doing a follow-up study using actual patient records for any of these diseases. Certainly, our findings do not exclude the possibility that the ABO type or Rh factor may play a role in some other autoimmune disease and any future research of this nature should consider the methodology limitations observed in our study.

Nevertheless, the large difference in Rh factor distribution (positive/negative) between the disease and control groups *versus* the Stanford US data norms is definitely worthy of further investigation. Although there is no reason to doubt the accuracy of the Stanford data or similar charts from the American Association of Blood Banking, obviously there is some cause leading to a self-selection bias effect. While this could be from the availability heuristic such as our hypothesized "Red Cross Effect" or from random error, as discussed earlier, it could be due to some other, completely unknown, factor(s). Further research is needed to determine the reason for the anomalous results observed in our study.

As noted earlier, research studies suggest that self-reporting of diagnosis is usually in good agreement with the patient's medical record. However, it is likely that patients may be less accurate in determining whether or not they meet the exclusion criteria for each disease. This raises the question of whether or not some patients should have been excluded from participating in the survey, although this issues may be somewhat mitigated by the very large number of subjects surveyed in each disease group. Obviously, there are clear limitations in a preliminary study of this nature, some of

which were also noted earlier. Nonetheless, this study demonstrates that when interpreting the results of studies using self-selected subjects, it is important to consider carefully the potential influence of unconscious factors that may lead to self-selection biases that may critically confound the interpretation of the study results.

List Of Abbreviations

RA: rheumatoid arthritis

AS: ankylosing spondylitis

SLE: systemic lupus erythematosus

SSc: systemic sclerosis

SjS: Sjögren's syndrome

ANA: anti-nuclear antibodies

MCTD: mixed connective tissue disease

UCTD: Undifferentiated Connective Tissue Disease

OA: osteoarthritis

Declarations

Ethics approval and consent to participate

This study was determined to qualify as an exempt study by the University of Wisconsin (Madison) Institutional Review Board (Project No: 2017-0545).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's Contributions

ESH designed the research study with the assistance of MM. HDH performed all statistical analysis. ESH was the primary author of the paper with significant additional contributions from HDH and MM. All authors have reviewed and

edited the final manuscript.

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Figures

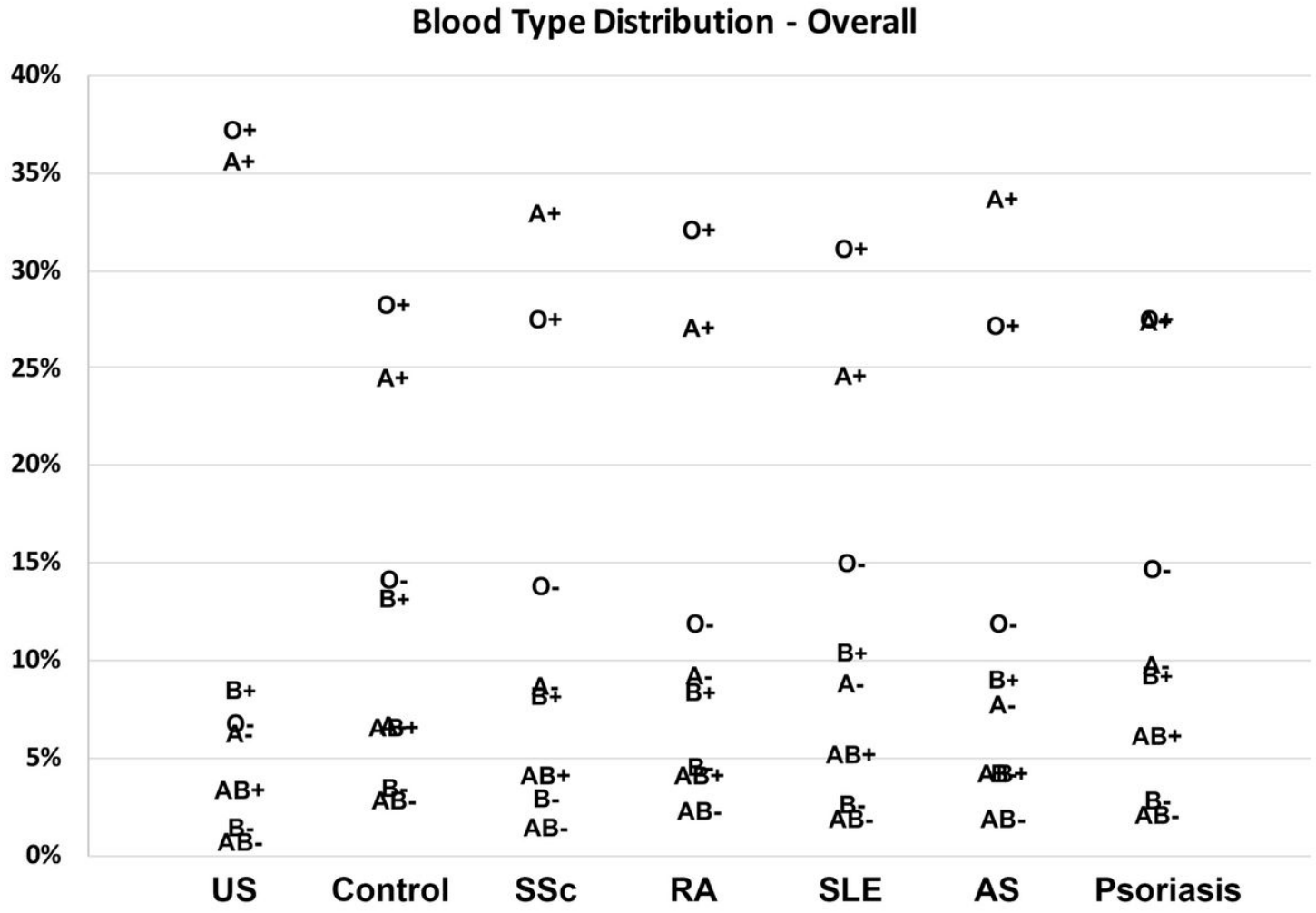

Figure 1

US Blood Type Distributions Overall

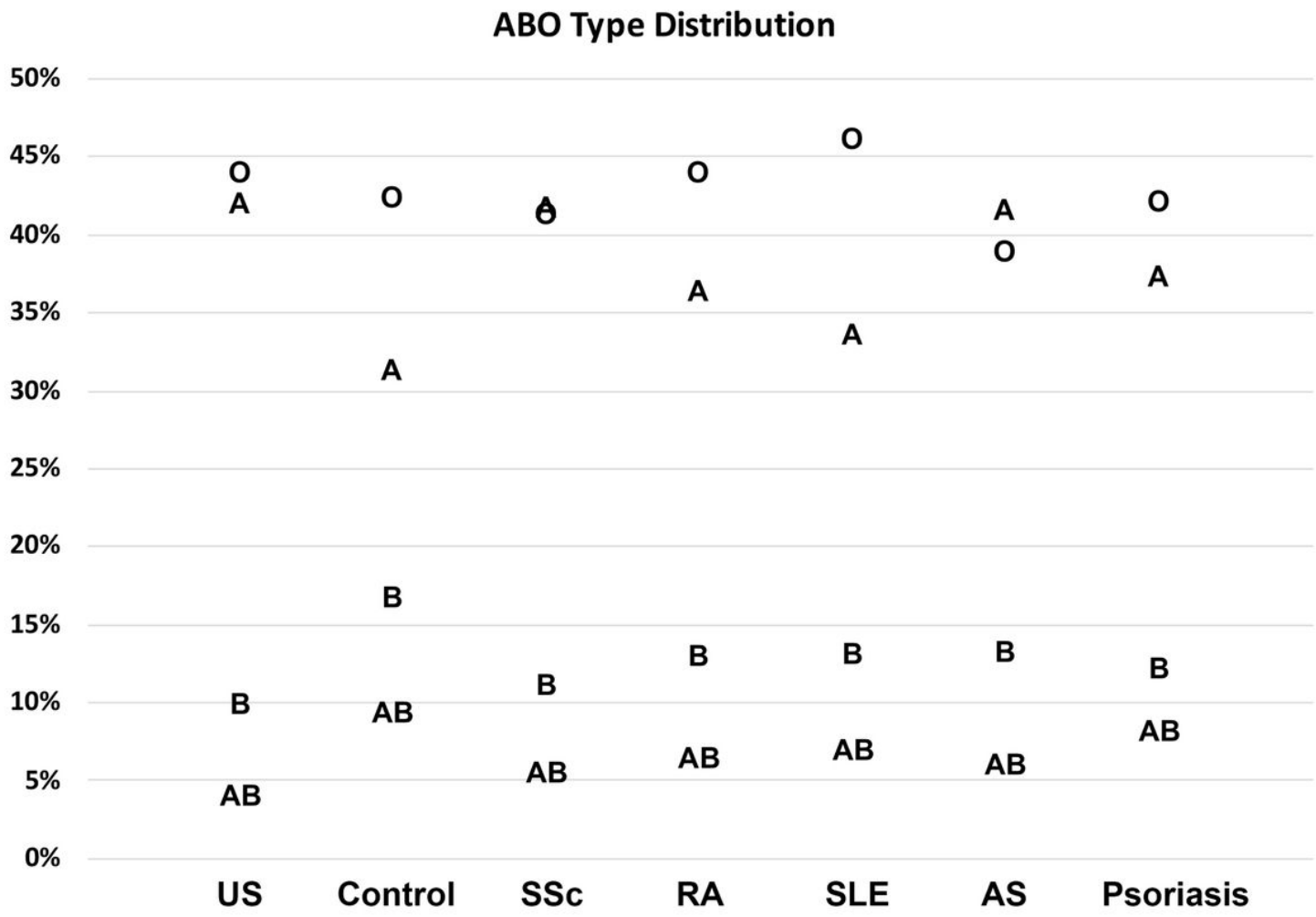

Figure 2

US Blood Type Distributions by ABO Type

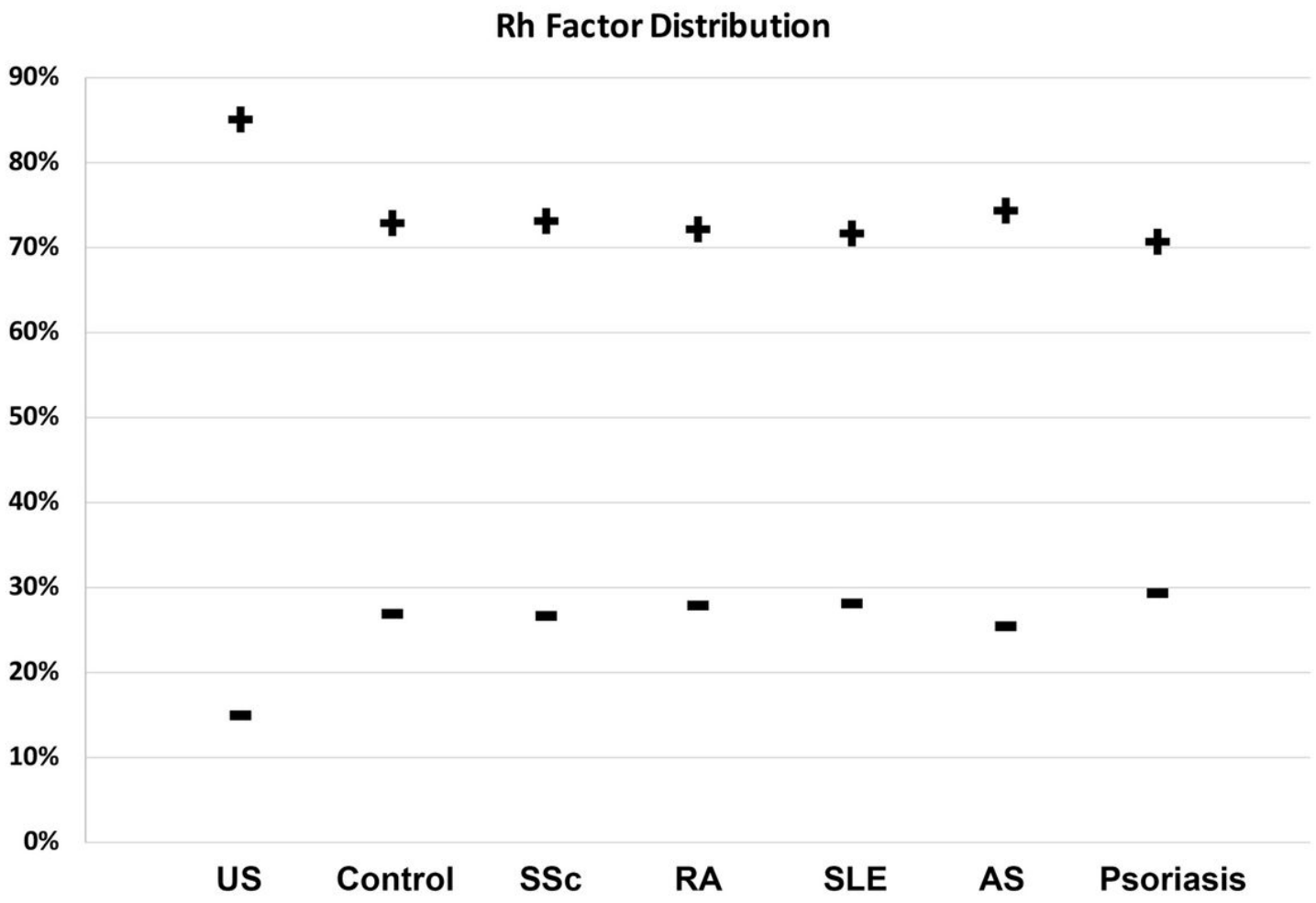

Figure 3

US Blood Type Distributions by Rh Factor