

Autoimmune Disease-Associated Reference Intervals for Routine Laboratory Tests Among Adult Outpatients

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Background: Current health-associated reference intervals (RIs) used in clinical practice are less applicable in patients with autoimmune diseases, creating the need for RIs aligned with the patient population. This study identified autoimmune disease-associated RIs and compared them to gold-standard RIs using analytical and biological variation.

Methods: Retrospective data for 16 laboratory tests were collected on outpatients with diagnosis codes for 5 autoimmune diseases (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ulcerative colitis (UC), Crohn's disease (CD), and Hashimoto's thyroiditis (HASHD)) to establish RIs, using the Clinical Laboratory Science Institute guidelines. The reference population delta was calculated between disease-associated and health-associated RIs to determine significance based on a defined critical z score.

Results: Of the 1,023 patient records reviewed, most were white (85%, n = 848) females (80%, n = 818) between the ages of 45 and 64 (44%, n = 451). Rheumatoid arthritis (RA) was the most prevalent condition (43%, n = 437). Separate RIs were established for the populations based on sex, age, and ethnicity. Statistically significant RIs included: SLE-associated changes in red blood cells (RBC's), hemoglobin, and lymphocyte counts in females; SLE-associated albumin levels in diabetic patients; RA-associated hemoglobin in black, white, and older females; RA-associated RBC counts in males and females with cardiovascular disease; UC-associated changes in RBC, hemoglobin, and chloride in males; CD-associated hemoglobin in both sexes; CD-associated platelet count in males; and HASHD-associated hemoglobin in females.

Conclusions: The autoimmune diseases impact chloride, RBC, hemoglobin, platelet, and lymphocyte RIs, suggesting the respective disease-associated RIs could be used to improve laboratory-based clinical decisions.

Keywords: Confidence interval, systemic lupus erythematosus, ulcerative colitis, white blood cell, red blood cell, Hashimoto's thyroiditis, autoimmune thyroiditis, rheumatoid arthritis, alanine transaminase, aspartate transaminase, Crohn's disease.

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Introduction

Population-based reference intervals (RIs) are the central 95% of measured values between, and including, an upper and lower cutoff value from a population with at least 120 reference individuals.¹ In accordance with the guidelines of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), RIs can either be established directly from a study of enrolled healthy participants or indirectly using statistics from patient results in a database. Additionally, the inclusion criteria of study participants can be applied either before (*a priori*), or after (*a posteriori*) specimen collection. If an RI is previously established in an alternate location or via the test manufacturer, laboratories should perform in-house verifications to ensure the adoption of the RI is applicable to the local patient population. Most laboratories opt for this approach since verifying RIs is less demanding on laboratory operations than establishing them. However, continual adoption of previously established RIs leaves the field of laboratory medicine with “studies performed decades ago, when both the analytical methods and populations were different.”^{1,2}

RIs are a hallmark in laboratory medicine, since physicians use them to compare patient data against healthy individuals, yet there are drawbacks. The definition of “healthy” is subjective and region-specific.¹ Therefore, the exclusion of truly “unhealthy” individuals cannot be achieved, risking patient misclassification from a possibly biased RI. Specimen selection, analytical variation, and biological variation can also independently impact a RI, and further amplify the error of RI comparison.¹ Depending on the literature from which the RI is adopted, such information may not be disclosed, and therefore the laboratory assumes congruency of these variables. This describes why RI adoption from previous literature is considered the lowest of the three quality model standards defined by the Stockholm Hierarchy of Models, and developed by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM).^{3,4} Because

medical comparisons using RIs can become less applicable and more elusive in patients with multiple comorbidities and medications, there is a need to interpret laboratory results to account for underlying conditions. For the most appropriate laboratory-based medical decision-making, approaches to reference intervals must be routinely revisited for improvements.

To overcome the obstacles in creating population-specific RIs, alternatives have been proposed, including common RIs, continuous RIs, and subject-based RIs. For common RIs, massive datasets from an assortment of laboratories and methodologies worldwide are compiled and analyzed to create universal intervals, consequently accounting for a majority of the analytical, geographical, and biological variation.⁵ Continuous RIs reduce pediatric patient misclassification by replacing rigid age cutoffs with dynamic ranges for each age, based on physiological stages of human development.^{5,6} Subject-based, or personalized RIs, compare one laboratory result to the previous result within a single individual for statistically significant changes.^{5,7} Other research modifies the population-specific RI approach by applying it to subgroups of reference individuals instead of using healthy participants (i.e., age-specific, disease-associated, obesity-associated, or ethnic-specific RIs). In Norway, Mikkelsen et al. performed a disease-associated RI study to assess three tumor markers reported to be elevated in chronic kidney disease patients without clinical evidence of cancer. The results revealed no statistically significant difference between RIs of the healthy population and patients with chronic kidney disease.⁸ However, another publication by the same investigators used the disease-associated RI approach to determine if patients with rheumatoid arthritis (RA), ulcerative colitis (UC), or Crohn’s disease (CD), have different reference limits of laboratory tests between healthy subjects, and those with and without major comorbidities. They discovered a significant difference between disease-associated and health-associated RIs for non-specific inflammatory markers, along

with slight differences in RIs for patients with major comorbidities compared to the healthy population.⁹ Inspired by Mikkelsen et al., this study aims to develop disease-associated RIs for RA, UC, CD, systemic lupus erythematosus (SLE), and Hashimoto's thyroiditis (HASHD) and use biological and analytical variation data to evaluate the significance between the gold-standard health-associated RIs. This data may be used to provide higher quality disease-associated reference intervals that improve the clinical classification of patients and help decipher whether the abnormal results should be attributed to an acute episode, or a chronic condition.

Methods

Sample selection

To determine which analytes to include, the effects of the 5 autoimmune diseases on different laboratory tests were assessed. Typical pathophysiologic features in autoimmune conditions involve chronic recruitment of proinflammatory cytokines; predominant infiltration of mononuclear cells; tissue necrosis; and prolonged attempts of tissue repair via fibrosis, leading to clinical signs of malnutrition, anemia, cardiovascular issues, and protein abnormalities.^{10,11} In RA and SLE, the produced autoantibodies are involved in the skin, heart, and blood vessels, and often lead to elevated positive acute phase reactants, reduced negative acute phase reactants, increased liver enzymes, underlying anemias, eosinophilia, and occasionally lymphocytosis.¹⁰⁻¹³ Platelets and neutrophils are also affected depending on the disease and drug therapy.^{11,13} Though SLE is an autoinflammatory condition, its effect on the positive acute phase reactant, C-reactive protein (CRP), is counterintuitive and only marginally increases.¹⁴ HASHD, also named chronic lymphocytic thyroiditis, or autoimmune thyroiditis, is characterized by autoantibodies to thyroid antigens and lymphocytic infiltration of the thyroid, leading to megaloblastic anemia, hyperlipidemia, and hyponatremia.¹⁵⁻¹⁸ Lastly, CD and UC are both inflammatory bowel

diseases that reveal similar extraintestinal manifestations: malnutrition, hypoalbuminemia, electrolyte deficiencies, eosinophilia, and malabsorption of Vitamin B12 due to dehydration and diarrhea.^{19,20} Based on these changes, 16 lab measurements were included that correlate with the diseases: albumin, aspartate transaminase (AST), alanine aminotransferase (ALT), sodium, chloride, total cholesterol, low density lipoprotein (LDL), CRP, red blood cell count (RBC), WBC, platelet, hemoglobin, absolute neutrophil count, absolute lymphocyte count, absolute eosinophil count, and Vitamin B12.

Data from the main laboratory were retrieved retrospectively from electronic medical records between January 2016 and August 2023. Adults (≥ 18 years of age) from a university hospital's outpatient clinics were selected by ICD-10-CM codes corresponding to their autoimmune disease. Pregnant individuals, patients with documented alcohol or drug abuse, prisoners, and patients with medical histories of cancers were excluded. Confounding variables such as self-reported race, ethnicity, and sex; age; body mass index (BMI); disease-modifying antirheumatic drugs (DMARDs); and triiodothyronine/thyroxine hormone replacement were collected, and assessed for significance to either stratify the RI, or remove it from the RI calculation. Comorbidity data for diabetes mellitus, chronic obstructive pulmonary disorder (COPD), cardiovascular disease (CVD), and chronic kidney disease were also analyzed for statistical differences. Supplemental Table 1 details the operational definitions for each variable collected. Ethical approval was obtained from the Institutional Review Board (IRB# 23-0238) with waived patient consent prior to data collection.

Data analysis

Results from the last documented patient encounter were collected based on the inclusion criteria, and any duplicates, results with incomplete information, or results analytically indicating acute inflammation or infection were excluded from further calculations. The

Table 1. Description of Sample Patient Population by Autoimmune Disease.

		No. (%) of patients by disease				
		Rheumatoid arthritis (n = 437)	Systemic lupus erythematosus (n = 153)	Ulcerative colitis (n = 126)	Crohn's disease (n = 111)	Hashimoto's thyroiditis (n = 196)
Sex						
	Female	361 (83)	141 (92)	70 (56)	71 (64)	175 (89)
	Male	76 (17)	12 (8)	56 (44)	40 (36)	21 (11)
Race						
	White/Caucasian	366 (84)	109 (71)	109 (87)	92 (83)	172 (88)
	Black/African American	65 (15)	38 (25)	13 (10)	13 (12)	19 (10)
	Asian	5 (1)	4 (3)	4 (3)	3 (3)	5 (3)
	Alaskan/American Indian	1 (<1)	1 (1)	0 (0)	3 (3)	0 (0)
	Unknown	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Ethnicity						
	Hispanic/Latino Not	88 (20)	37 (24)	19 (15)	19 (17)	29 (15)
	Hispanic/Latino	341 (78)	112 (73)	105 (83)	91 (82)	163 (83)
	Patient Refused	1 (2)	2 (1)	0 (0)	0 (0)	1 (1)
	Unknown	7 (<1)	2 (1)	2 (2)	1 (1)	3 (2)
Age Group						
	18-24	11 (3)	10 (7)	10 (8)	17 (15)	11 (6)
	25-34	32 (7)	28 (18)	17 (14)	20 (18)	39 (20)
	35-44	66 (15)	36 (24)	22 (18)	10 (9)	47 (24)
	45-54	90 (21)	37 (24)	24 (19)	21 (19)	52 (27)
	55-64	132 (30)	22 (14)	27 (21)	23 (21)	23 (12)
	65+	106 (24)	20 (13)	26 (21)	20 (18)	24 (12)
Cardiovascular Disease		199 (46)	69 (45)	43 (34)	40 (36)	69 (35)
COPD		32 (73)	8 (5)	6 (5)	4 (4)	4 (2)
Diabetes Mellitus		9 (2)	5 (3)	0 (0)	2 (2)	2 (1)

Percentages may not equate to 100 due to rounding.

Analyse-It Software, Version 6.15.4, Ltd (Leeds, United Kingdom) was used for descriptive and inferential statistics. Normality was reviewed using a frequency density plot and the Shapiro-Wilk test.²¹ Any non-Gaussian distributions were transformed using the logarithmic, or the Box-Cox method, then back-transformed to establish the parametric RIs. Outliers were identified using the Tukey detection method, and then removed based on clinical indication, effects from comorbidities

or medications, and visual inspection. Covariates were then nonparametrically assessed for either removal, or partitioning. The Mann-Whitney U test was used to assess the significance of age (adults and geriatric adults), and sex variables. The Kruskal-Wallis test was used to assess race and ethnicity. RIs for each test were established in triplicate using the parametric, simple nonparametric, and Harrell-Davis nonparametric technique. In cases of

sample size ($n \leq 120$ and ≥ 40), the simple non-parametric method was bootstrapped with 1,000 repetitions. For $20 \leq n < 40$, the Robust method was used, and for $n < 20$, an RI was not established, as this can be impractical.¹ Once derived, the RI method producing the narrowest 90% confidence interval (CI) for the limit of interest was selected for further data analysis. The widths of the 90% CIs were then compared to the widths of the RIs themselves (width ratio, w) to assess the RI relevance. If $w \geq 0.20$, the CI is too wide for the RI to be practical, and additional samples are recommended.¹

Statistical significance between RIs of the established disease-associated reference limits (RL_E), and the published health-associated reference limits (RL_P) was determined using the reference population delta ($RP\Delta$) (Equation 1) – a rearranged version of the reference change value (RCV) formula with the addition of between-subject biological variation.²² Historically, the RCV determines significance between two consecutive laboratory results within a single patient. The RCV equation also requires dispersion expressed as Standard Deviation (SD) for calculation, but since the ratio and the sum of normally distributed variables are not equal, a transformation is required from coefficient of variation (CV) to SD based on Equation 2, then calculated using an alternate RCV equation.²² The university laboratory provided analytical variation (CV_A), and the EFLM database houses ample data for within-subject biological variation (CV_I), and between-subject biological variation (CV_G).

$$\text{Equation 1: } RP\Delta_{\text{decimal}} = \exp\left(\pm z \times \sqrt{2} \times \sqrt{SD_A^2 + SD_I^2 + SD_G^2}\right) - 1$$

$$\text{Equation 2: } SD^2 = \ln[(\%CV/100)^2 + 1]$$

An autoimmune disease-associated RI was considered significantly different from the health-associated RI if the RL_E was not producible from the $RP\Delta$ applied to the RL_P (i.e., the reference limit of the autoimmune disease falls beyond the allowable variation of

the healthy population reference limit). This is empirically expressed as $RL_E = RL_P \cdot (1 + RP\Delta)$, then rearranged to determine the z score (Equation 3).

$$\text{Equation 3: } \pm z = \frac{\ln(RL_E / RL_P)}{\sqrt{2} \times \sqrt{SD_A^2 + SD_I^2 + SD_G^2}}$$

The computed z scores from Equation 3 were compared to the defined critical z values for each analyte (Supplemental Table 2). Since autoimmune diseases affect each analyte differently, a positive, or negative unidirectional change per analyte was expected; therefore, critical z values at $\alpha = 0.05$ were defined at +1.65, or -1.65. Only neutrophil and platelet in RA have been reported to be bidirectional; thus, $\alpha = 0.05$ was defined at ± 1.96 . Statistical significance was defined as the observed $|z| \geq$ critical $|z|$ for each RI.

The index of individuality (Iol) for each analyte was calculated using the same analytical and biological variation data to assess the usefulness of the population-based RI. An Iol < 0.6 , has more variation between subjects than within subjects and the analytical system; therefore, results could be abnormal for an individual, yet still found within the normal interval.^{22,23} In this case, a subject-based (personalized) RI is more appropriate. An Iol > 1.4 , has more variation within subjects and analytical system than between subjects, suggesting the population-based RI is more clinically useful.^{22,23}

Results

Population demographics

A total of 1,023 outpatient medical records were evaluated, after excluding 74 records of moderate to end-stage chronic kidney disease, and two records of hemoglobin less than 7 mg/dL. The sample population was 80% (818/1,023) female, 83% (848/1,023) White, and 44% (451/1,023) between the ages of 45 to 64. The most prevalent diseases were RA at 43% (437/1,023), and HASHD at 19% (196/1,023). Outpatients with diagnosis codes related to cardiovascular disease (CVD) included 41% (420/1,023) of the overall sample, followed by

Table 2. Autoimmune Disease-Associated Reference Intervals by Analyte and Statistical Method

Analyte (unit)	Disease	n	Mdn	Reference Interval			
				Parametric	Simple nonparametric	Harrell-Davis nonparametric	
				LRL (90% CI) URL (90% CI)	LRL (90% CI) URL (90% CI)	LRL (90% CI) URL (90% CI)	
Albumin (g/dL)	RA	Female	258	4.2	3.3 (3.2-3.4)	3.2 (2.7-3.5)	3.2 (2.8-3.4)
					4.8 (4.8-4.9)	4.9 (4.7-5.1)	4.9 (4.7-5.0)
		Male	55	4.3	3.7 (3.6-3.8)	3.8 (3.7-3.8) ^b	3.8 (3.7-3.9)
					4.9 (4.8-5.0)	5.1 (4.8-5.3) ^b	5.1 (4.8-5.3)
	SLE	w/o Diabetes	88	4.3	Fails normality	3.3 (3.2-3.5) ^b	3.3 (3.3-3.5)
					Fails normality	5.1 (4.8-5.2) ^b	5.1 (4.9-5.2)
		with Diabetes	21	4.1	2.9 (2.6-3.4) ^a	Not established	3.0 (3.0-3.2)
					5.1 (4.8-5.3) ^a	Not established	4.6 (4.5-4.6)
	UC		93	4.4	3.5 (3.3-3.6)	3.2 (2.7-3.7) ^b	3.2 (2.8-3.7)
					5.0 (4.9-5.1)	5.0 (4.9-5.1) ^b	5.0 (4.9-5.1)
CD		91	4.4	3.4 (3.2-3.5)	3.2 (2.9-3.6) ^b	3.2 (3.0-3.6)	
				5.0 (4.9-5.0)	5.0 (4.9-5.2) ^b	5.0 (4.9-5.2)	
ALT (U/L)	RA	Adult	161	22	11 (10-12)	11 (8-13)	11 (10-13)
					71 (60-86)	81 (60-92)	78 (62-88)
		Geriatric	59	18	9 (8-10)	9 (8-11) ^b	9 (8-11)
					60 (45-86)	76 (41-97) ^b	77 (40-93)
	SLE		81	19	10 (9-11)	10 (8-11) ^b	10 (9-11)
					50 (42-60)	58 (40-71) ^b	57 (42-68)
	HASHD ^c		117	22	10 (10-11)	11 (9-12) ^b	11 (10-12)
					68 (55-85)	70 (53-88) ^b	70 (55-81)
		Female	104	21	10 (10-11)	10 (9-12) ^b	10 (10-12)
					61 (50-78)	61 (51-88) ^b	61 (52-78)
	Male	13	33	Not established	Not established	Not established	
				Not established	Not established	Not established	
AST (U/L)	RA		220	29	18 (17-18)	18 (16-19)	18 (17-19)
					59 (54-66)	63 (56-76)	63 (56-70)
	SLE		81	26	18 (17-19)	18 (17-19)	18 (17-19)
					55 (47-66)	57 (46-63)	57 (46-62)
	HASHD ^c		117	26	18 (17-18)	17 (16-18) ^b	17 (16-18)
					57 (49-69)	62 (52-68) ^b	62 (53-66)
	Female	104	26	8 (6-11)	17 (16-18) ^b	17 (16-18)	
				48 (45-50)	62 (51-68) ^b	62 (50-66)	
	Male	13	31	Not established	Not established	Not established	
				Not established	Not established	Not established	
Chloride (mmol/L)	UC	Female	55	104	96 (94-98)	95 (94-97) ^b	95 (94-99)
					108 (108-109)	108 (108-109) ^b	108 (108-109)
		Male	44	102	93 (88-96)	89 (87-96) ^b	90 (87-97)
					107 (106-108)	107 (107-107) ^b	107 (106-107)

	CD		94	103	97 (97-98) 108 (107-109)	96 (95-98) ^b 109 (107-111) ^b	96 (95-98) 109 (107-110)	
Cholesterol, total (mg/dL)	HASHD		54	200	121 (102-139) 262 (251-273)	107 (91-138) 269 (251-281)	107 (94-146) 269 (246-279)	
CRP (mg/dL)	RA		204	0.5	Not applicable Fails normality	Not applicable 3.0 (2.1-7.3)	Not applicable 3.3 (2.3-5.5)	
	SLE ^c		45	0.6	Not applicable 4.4 (2.6-7.6)	Not applicable 4.5 (3.2-5.4) ^b	Not applicable 4.5 (2.7-5.3)	
	UC		34	0.4	Not applicable 2.1 (1.3-3.2) ^a	Not applicable Not established	Not applicable 2.2 (1.6-2.4)	
	CD		35	0.4	Not applicable 3.3 (2.6-8.2) ^a	Not applicable Not established	Not applicable 2.5 (1.8-2.7)	
Eosinophil, absolute (10 ³ /μL)	RA	Female	253	0.14	Fails normality Fails normality	0.03 (0.03-0.03) 0.49 (0.39-0.54)	0.03 (0.03-0.03) 0.49 (0.41-0.54)	
		Male ^c	56	0.20	0.00 (0.00-0.02) 0.43 (0.39-0.48)	0.03 (0.03-0.04) ^b 0.48 (0.39-0.51) ^b	0.03 (0.03-0.05) 0.48 (0.37-0.51)	
	UC	Female	41	0.15	0.02 (0.01-0.04) 0.46 (0.38-0.56)	0.02 (0.01-0.03) ^b 0.50 (0.37-0.54) ^b	0.02 (0.01-0.04) 0.50 (0.34-0.53)	
		Male	38	0.14	0.04 (0.03-0.05) ^a 0.42 (0.36-1.07) ^a	Not established Not established	0.04 (0.03-0.07) 0.42 (0.28-0.46)	
	CD	Female	53	0.15	0.05 (0.04-0.06) 0.55 (0.43-0.72)	0.05 (0.04-0.06) ^b 0.51 (0.43-0.56) ^b	0.05 (0.04-0.06) 0.51 (0.42-0.55)	
		Male	32	0.14	0.04 (0.02-0.04) ^a 0.51 (0.39-0.82) ^a	Not established Not established	0.04 (0.04-0.05) 0.52 (0.27-0.57)	
	Hemoglobin (g/dL)	RA	Female	265	13.0	9.1 (8.6-9.5) 15.4 (15.2-15.6)	9.0 (8.0-9.5) 15.3 (14.9-16.2)	9.0 (8.4-9.4) 15.3 (14.9-15.9)
			Black, F	40	12.4	9.3 (8.6-10.0) 15.5 (14.8-16.2)	9.1 (8.7-10.0) ^b 15.7 (14.3-16.2) ^b	9.1 (8.8-10.3) 15.7 (14.2-16.1)
White, F			214	13.1	9.2 (8.6-9.7) 15.5 (15.2-15.7)	9.2 (7.9-9.6) 15.4 (14.9-16.2)	9.1 (8.4-9.5) 15.3 (15.0-15.8)	
Adult, F			207	13.1	9.5 (9.0-9.9) 15.5 (15.3-15.7)	9.4 (8.0-10.0) 15.5 (14.9-16.2)	9.3 (8.6-9.9) 15.5 (15.0-16.1)	
Geriatric, F			58	12.3	8.7 (8.0-9.3) 15.5 (14.8-16.1)	8.4 (7.9-9.1) ^b 14.9 (14.5-15.2) ^b	8.4 (8.0-9.2) 14.9 (14.4-15.1)	
Male ^c			55	14.8	10.9 (10.3-11.6) 17.9 (17.2-18.5)	9.9 (9.0-11.2) ^b 17.4 (16.4-18.0) ^b	9.9 (9.2-11.4) 17.4 (16.3-17.9)	
SLE		Female ^c	113	13.2	7.7 (5.8-9.0) 15.3 (15.1-15.5)	7.9 (7.1-9.3) ^b 15.2 (14.9-15.5) ^b	7.8 (7.3-9.1) 15.2 (14.9-15.4)	
		Male	9	12.9	Not established Not established	Not established Not established	Not established Not established	

	UC						
	Female	48	13.5	10.8 (10.3-11.4) 15.9 (15.4-16.4)	10.8 (10.7-11.1) ^b 15.9 (15.2-16.1) ^b	10.8 (10.7-11.2) 15.9 (15.1-16.1)	
	Male	38	14.4	9.1 (5.6-10.2) ^a 17.0 (16.8- 17.4) ^a	Not established Not established	9.4 (9.2-10.8) 16.8 (16.3-17.0)	
	CD						
	Female	56	12.9	Fails normality Fails normality	9.1 (8.1-10.5) ^b 16.2 (14.7-16.8) ^b	9.1 (8.3-10.7) 16.3 (14.6-16.7)	
	Male	32	14.0	9.5 (7.3-10.2) ^a 17.2 (16.8- 18.1) ^a	Not established Not established	10.2 (9.9-11.2) 16.8 (16.2-16.9)	
	Adult, M	26	14.4	10.1 (8.3-11.6) 17.0 (16.4-17.6)	Not established Not established	10.2 (9.9-12.2) 16.8 (16.2-16.9)	
	HASHD						
	Female ^c	125	13.4	10.1 (9.5-10.6) 15.5 (15.3-15.8)	9.5 (9.3-10.6) 15.6 (15.1-16.2)	9.8 (9.5-10.5) 15.6 (15.2-16.0)	
	Male	17	14.9	Not established Not established	Not established Not established	Not established Not established	
LDL (mg/dL)	HASHD		51	115	Not applicable 163 (153-173)	Not applicable 167 (157-183)	Not applicable 166 (154-177)
Lymphocyte, absolute (10 ³ /μL)	RA						
	Female	254	1.9	0.7 (0.6-0.8) 3.8 (3.6-4.0)	0.6 (0.4-0.8) 3.9 (3.5-4.6)	0.6 (0.5-0.8) 3.9 (3.5-4.4)	
	Adult, F	198	2.0	0.7 (0.6-0.8) 4.0 (3.7-4.2)	0.5 (0.4-0.8) 4.0 (3.7-5.4)	0.6 (0.4-0.8) 4.1 (3.7-4.8)	
	Geriatric, F	53	1.6	0.4 (0.2-0.7) 2.9 (2.6-3.1)	0.7 (0.6-0.8) ^b 3.0 (2.8-3.1) ^b	0.7 (0.6-0.8) 3.0 (2.7-3.0)	
	Male	56	1.8	0.5 (0.2-0.7) 3.2 (3.0-3.5)	0.6 (0.4-0.9) ^b 3.3 (3.1-3.5) ^b	0.6 (0.4-0.9) 3.3 (3.0-3.4)	
	SLE						
	Female	103	1.9	0.7 (0.6-0.8) 3.7 (3.4-4.0)	0.6 (0.5-0.7) ^b 3.8 (3.3-4.5) ^b	0.6 (0.5-0.8) 3.8 (3.3-4.2)	
Neutrophil, absolute (10 ³ /μL)	RA						
	Female	252	4.20	1.74 (1.61-1.89) 10.14 (9.38- 10.96)	1.64 (1.35-2.00) 10.82 (9.13-11.30)	1.67 (1.46-1.95) 10.61 (9.47- 11.32)	
	Black, F	46	3.33	1.44 (1.23-1.69) 10.39 (7.96- 13.86)	1.44 (1.30-1.69) ^b 10.34 (8.09- 10.87) ^b	1.43 (1.32-1.77) 10.34 (7.61- 10.81)	
	White, F	202	4.33	1.90 (1.74-2.07) 9.92 (9.16- 10.73)	1.88 (1.35-2.22) 10.45 (8.64-11.3)	1.87 (1.56-2.21) 10.31 (9.18- 11.23)	
	Male	50	4.72	2.03 (1.69-2.44) 10.91 (9.33- 12.74)	1.90 (1.66-2.47) ^b 11.08 (9.66- 11.91) ^b	1.88 (1.70-2.67) 11.07 (9.16- 11.77)	

	SLE						
	Female	109	4.22	1.64 (1.43-1.87) 9.49 (8.51-10.57)	1.51 (1.22-2.01) ^b 9.92 (8.17-12.21) ^b	1.51 (1.30-1.99) 9.94 (8.18-11.28)	
	Male	9	3.78	Not established Not established	Not established Not established	Not established Not established	
Platelet (10 ³ /μL)	RA						
	Female						
	w/o CVD, F	89	280	134 (111-157) 437 (414-460)	154 (127-171) ^b 462 (437-483) ^b	153 (135-176) 462 (430-477)	
	with CVD, F	168	255	109 (92-126) 417 (400-434)	110 (62-137) 450 (406-498)	111 (95-129) 448 (411-479)	
	Male	58	238	126 (102-150) 380 (356-404)	134 (115-162) ^b 399 (364-420) ^b	134 (118-165) 399 (363-416)	
	SLE						
	Female	111	265	135 (121-150) 461 (431-493)	121 (97-157) ^b 499 (421-560) ^b	121 (103-154) 499 (424-544)	
	Male	9	215	Not established Not established	Not established Not established	Not established Not established	
	UC						
	Female	52	279	142 (116-167) 403 (377-429)	153 (134-180) ^b 388 (380-391) ^b	153 (137-181) 388 (374-390)	
	Male	37	235	117 (93-130) ^a 425 (398-500) ^a	Not established Not established	118 (108-148) 419 (354-432)	
	CD						
	Female	61	292	169 (153-186) 493 (445-545)	167 (163-184) ^b 521 (424-557) ^b	167 (163-188) 521 (423-549)	
	Male	32	269	154 (135-165) ^a 624 (517-879) ^a	Not established Not established	160 (151-190) 571 (446-587)	
HASHD							
Female	124	264	144 (127-160) 400 (383-416)	156 (135-170) 433 (383-447)	157 (145-168) 426 (391-439)		
Male	17	229	Not established Not established	Not established Not established	Not established Not established		
RBC (10 ⁶ /μL)	RA						
	Female						
	w/o CVD, F	97	4.40	3.33 (3.10-3.53) 5.23 (5.13-5.33)	3.20 (3.03-3.53) ^b 5.22 (5.13-5.31) ^b	3.19 (3.09-3.53) 5.22 (5.12-5.29)	
	with CVD, F	155	4.28	3.24 (3.12-3.37) 5.38 (5.26-5.50)	3.00 (2.56-3.32) 5.25 (5.15-5.54)	3.08 (2.86-3.50) 5.27 (5.15-5.40)	
	Male	55	4.82	3.55 (3.31-3.79) 6.02 (5.78-6.26)	3.45 (3.26-3.74) ^b 6.13 (5.86-6.34) ^b	3.45 (3.29-3.82) 6.13 (5.78-6.30)	
	SLE						
Female	103	4.46	3.25 (3.01-3.47) 5.22 (5.12-5.31)	3.00 (2.07-3.67) ^b 5.26 (5.01-5.60) ^b	3.01 (2.39-3.59) 5.25 (5.01-5.49)		
Male	9	4.43	Not established Not established	Not established Not established	Not established Not established		

	UC	Female ^c	51	4.53	3.72 (3.56-3.88) 5.30 (5.14-5.46)	3.70 (3.60-3.86) ^b 5.44 (5.29-5.54) ^b	3.70 (3.62-3.91) 5.44 (5.19-5.52)	
		Male	38	4.66	3.42 (3.10-3.77) ^a 6.07 (5.76-6.33) ^a	Not established Not established	3.17 (3.09-3.66) 5.72 (5.50-5.76)	
	CD	Female	63	4.42	3.67 (3.54-3.81) 5.21 (5.07-5.34)	3.62 (3.49-3.89) ^b 5.36 (5.04-5.52) ^b	3.62 (3.52-3.89) 5.36 (5.03-5.49)	
		Male ^c	33	4.66	3.54 (3.24-3.66) ^a 6.17 (5.89-6.90) ^a	Not established Not established	3.71 (3.68-3.88) 5.94 (5.50-5.98)	
	HASHD	Female	124	4.51	3.52 (3.36-3.66) 5.32 (5.22-5.41)	3.26 (3.11-3.66) 5.33 (5.08-5.85)	3.37 (3.19-3.62) 5.37 (5.12-5.65)	
		Hispanic, F	22	4.79	3.62 (3.29-4.05) ^a 5.88 (5.55-6.18) ^a	Not established Not established	3.73 (3.70-4.07) 5.79 (5.28-5.84)	
		Non-Hispanic, F	71	4.44	3.49 (3.28-3.69) 5.07 (4.97-5.16)	3.33 (3.18-3.64) ^b 5.09 (4.91-5.27) ^b	3.34 (3.21-3.65) 5.09 (4.92-5.23)	
		Male	17	4.98	Not established Not established	Not established Not established	Not established Not established	
	Sodium (mmol/L)	UC	Female	56	140	135 (134-136) 145 (144-145)	133 (131-136) ^b 144 (144-144) ^b	133 (131-136) 144 (143-144)
			Male	41	138	132 (131-134) 143 (142-144)	132 (131-133) ^b 143 (141-143) ^b	132 (131-133) 143 (141-143)
	CD		94	139	134 (133-135) 144 (143-145)	134 (132-135) ^b 145 (143-146) ^b	134 (133-135) 145 (143-146)	
	HASHD		152	139	135 (134-135) 143 (143-143)	134 (134-135) 144 (142-144)	134 (134-135) 144 (142-144)	
Vitamin B12 (pg/mL)	UC		40	539	184 (97-272) 961 (874-1049)	278 (261-336) ^b 984 (882-1000) ^b	277 (263-345) 983 (868-998)	
	CD		31	520	Fails normality Fails normality	Not established Not established	294 (292-307) 971 (885-984)	
WBC (10 ³ /μL)	RA	Female	261	7.1	3.8 (3.5-4.0) 13.8 (13.0-14.6)	4.1 (3.8-4.2) 14.9 (12.8-16.5)	4.1 (3.8-4.2) 14.8 (13.3-16.0)	
		Black, F	40	5.7	3.1 (2.8-3.5) 12.4 (10.2-15.4)	3.1 (2.9-4.0) ^b 11.6 (11.1-11.8) ^b	3.1 (2.9-4.1) 11.6 (10.6-11.8)	
		White, F	210	7.2	4.2 (4.0-4.5) 14.4 (13.2-15.9)	4.2 (4.1-4.7) 15.1 (12.8-16.5)	4.3 (4.1-4.6) 14.7 (12.8-15.9)	
		Male	56	7.4	4.1 (3.6-4.5) 15.3 (13.3-17.7)	4.1 (3.9-4.6) ^b 14.6 (13.4-15.0) ^b	4.1 (3.9-4.7) 14.6 (13.1-15.0)	
	SLE	Female	112	6.7	3.0 (2.7-3.4) 13.2 (12.2-14.2)	2.9 (2.1-3.4) ^b 13.8 (12.3-15.8) ^b	2.9 (2.4-3.4) 13.8 (12.3-15.0)	

	UC	Male	9	5.9	Not established Not established	Not established Not established	Not established Not established
		Female	52	7.1	4.2 (3.9-4.6) 14.0 (12.0-16.6)	4.2 (4.0-4.6) ^b 14.4 (11.5-15.9) ^b	4.2 (4.1-4.7) 14.4 (11.2-15.6)
	CD	Male ^c	33	6.4	3.2 (2.6-3.9) ^a 9.6 (8.9-10.5) ^a	Not established Not established	3.7 (3.7-4.2) 8.9 (8.3-9.0)
		Female	62	6.7	3.7 (3.3-4.1) 13.0 (11.5-14.6)	3.7 (3.4-4.3) ^b 12.7 (11.2-13.9) ^b	3.7 (3.5-4.4) 12.7 (11.1-13.6)
		Male	32	7.2	3.8 (3.2-4.1) ^a 12.6 (11.8- 14.5) ^a	Not established Not established	4.1 (4.1-4.7) 11.7 (10.9-11.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; F, female; HASHD, Hashimoto's thyroiditis; LDL, low density lipoprotein; LRL, lower reference limit; M, male; Mdn, median; n, sample size; RA, rheumatoid arthritis; RBC, red blood cell; SLE, systemic lupus erythematosus; UC, ulcerative colitis; URL, upper reference limit; WBC, white blood cell.

^aDerived using the Robust method described in CLSI-EP28-A3c, and using 1000 bootstrap replications.

^bDerived using the Bootstrapped method, based on 1000 replications.

^cA subpopulation within this sample was found to be significant, but could not be partitioned because of too small sample sizes; the subpopulation may have an over- or under-estimated reference limit.

chronic obstructive pulmonary disease comprising 5% (54/1,023). 14% (147/1,023) of outpatients had at least two comorbidities, and about 1% (14/1,023) of outpatients had all three comorbidities. The most prevalent age groups were 35 to 54 for SLE; 45 to 54 for HASHD; 55 to 64 for RA and CD; and above 54 for UC. Table 1 summarizes the population demographics for each autoimmune disease.

Autoimmune disease-associated RIs

Table 2 depicts the RIs established in triplicate for each disease, analyte, and any partitioned demographic. In RA, albumin was significant by sex, $z = 2.42$, $P = .015$, with an effect size of 0.14, and males having an increased lower limit than females. ALT by age demographic was significant, $z = -2.87$, $P = .004$, and a small effect size of -0.19; adults had a lower ALT median than geriatric outpatients. Eosinophils in males by age demographic was significant, $z = -2.09$; $P = .04$, and small effect size of -0.28. However, the RI for geriatric males could not be established due to $n < 20$. The eosinophil median for geriatric males was $0.15 \times 10^3/\mu\text{L}$, and for adult males was $0.21 \times 10^3/\mu\text{L}$. Hemoglobin was partitioned by race and age in

females, and significant by age in males. Black and White females were found to be different with $\chi^2_2 = 11.86$, $P = .005$. Despite these RIs having almost identical limits, the median for Black females was lower than the median for White females. Hemoglobin in females by age was significant, $z = -3.20$, $P = .001$ with a small effect size of -0.20. Males by age was significant, $z = -2.01$, $P = 0.045$ with a small effect size of -0.27, yet an RI for geriatric males was not established because of low sample sizes; adult males had a hemoglobin median of 15.1 g/dL, and geriatric males had a median of 14.0 g/dL. Lymphocyte was significant in females by age group, $z = -2.95$, $P = .003$, and effect size of -0.19; the median for geriatric females was lower than the median for adult females. Platelet in females diagnosed with CVD compared to those not diagnosed with CVD was significant, $z = -2.00$, $P = .046$, and a small effect size of -0.13. Neutrophils in females was also partitioned by race, $\chi^2_2 = 10.2$, $P = .006$, and Black females had a decreased, lower reference limit and median than White females. WBC in females was significant, $\chi^2_2 = 10.4$, $P = .006$, with Black female patients having a wider RI.

In SLE, CRP by ethnicity was significant, $x^2_2 = 6.16$, $P = 0.04$. The median for non-Hispanics was 0.8 mg/dL and the median for Hispanics was 0.3 mg/dL, but an RI for the latter could not be established due to $n < 20$. Hemoglobin was also significant by age in females, $z = 2.12$, $P = .034$, with a small effect size of 0.20, but due to a low sample size, the geriatric RI was not established. Geriatric females had a higher median, 13.9 g/dL, than adult females, 13.0 g/dL. Albumin was partitioned for diabetics, $z = -2.74$, $P = .006$, and a small effect size of -0.26; the median for diabetes-diagnosed patients was higher than in those not diagnosed with diabetes.

In UC, chloride was partitioned by sex, $z = -2.60$, $P = .009$, with a small effect size of -0.26; the lower reference limit for males was lower compared to females. RBC in females was significant by ethnicity, $x^2_2 = 9.63$, $P = .016$; however, due to low sample sizes for each ethnic group, separate RIs could not be established. Hispanic females had a higher median at $4.78 \times 10^6/\mu\text{L}$, than non-Hispanics at $4.49 \times 10^6/\mu\text{L}$. Sodium by sex was significant, $z = -3.14$, $P = .002$, and a moderate effect size of -0.31, despite the RI being almost identical between sexes. WBC in males was significant by ethnicity, $z = -2.15$, $P = .032$ with a moderate effect size of -0.37; however, a separate RI could not be established. Hispanic males had a higher median of $8.12 \times 10^3/\mu\text{L}$, compared to non-Hispanic males with a median of $6.18 \times 10^3/\mu\text{L}$.

In CD, hemoglobin in males was significant by age group, $z = -2.17$, $P = .030$, with a moderate effect size of -0.38. Low sample sizes in geriatric males prevented RI establishment; therefore, they may be overestimated with median of 11.7 g/dL, compared to adult males, median of 14.4 g/dL. RBC in males by ethnicity was significant, $z = -2.01$, $P = .044$, with a moderate effect size of -0.35. Similarly, Hispanic males had a low sample size preventing the establishment of this RI; therefore, this subpopulation was underestimated. The median for Hispanic males was $5.20 \times 10^6/\mu\text{L}$, but for non-Hispanic males was $4.58 \times 10^6/\mu\text{L}$.

In HASHD, ALT and AST by sex was significant, $z = 3.50$, $P < .001$, and a moderate effect size of 0.32 for ALT; and $z = 2.61$, $P = .009$, and a small effect size of 0.24 for AST. Hemoglobin in females was significant by race; $x^2_2 = 10.77$, $P = .003$; however, the RI for Black females was not established because $n < 20$. The median for Black females was 12.1 g/dL, and the median for White females was 13.5 g/dL. Lastly, RBC in females was partitioned by ethnicity, $x^2_2 = 8.38$, $P = .015$, and Hispanic females had slightly higher medians and reference limits than non-Hispanic females.

Significance of autoimmune disease-associated RIs

Table 3 lists the established RIs, the selected establishment technique, calculated z scores, respective P values, and width ratios. The sources of published RIs with their respective analytical and biological variation data are found in Supplemental Table 3. Comparisons of the disease-associated to health-associated RIs revealed $P < .001$ for hemoglobin RIs in females with SLE, and in geriatric females with RA. Results with $P < .01$ included the RBC RI in males with UC; and the hemoglobin RIs in Black and White females with RA, males with UC, and females with CD. Significance with $P < .05$ was found for the albumin RI for diabetic patients with SLE; chloride RI in males with UC; platelet RI in males with CD; lymphocyte RI in females with SLE; hemoglobin RIs in both males with CD and females with HASHD; and RBC RIs in females with SLE, males with RA, and females with CVD. Ethnicity was significant in RIs for RBC, CRP, and WBC; however, they could not be established for Hispanics due to insufficient data.

Of the significant RIs, the RA-associated hemoglobin RIs had $w < 0.20$, suggesting narrow enough CIs to attest to the significances. For females in both the HASHD-associated hemoglobin RI, and the SLE-associated lymphocyte RI, the width ratios are low at $w = 0.172$ and $w = 0.067$ respectively. The RA-associated RBC RI in males was also significant and contained a satisfactory width ratio, $w =$

0.194. Conversely, the SLE-associated hemoglobin RI in females was the most statistically significant finding, yet it had an unsatisfactory width ratio, $w = 0.243$, despite having $n = 113$. Of the remaining significant RIs, CD-associated

hemoglobin, CD-associated platelets in males, SLE-associated RBCs in females, UC-associated RBCs in males, and UC-associated chloride in males similarly had unsatisfactory width ratios.

Table 3. Statistical Significance of Autoimmune Disease-Associated Reference Intervals by Analyte

Analyte (unit)	Disease, demographic	Established RI	Selected technique	z	P	w
Albumin (g/dL)	RA					
	Female	<u>3.3</u> -4.8	Parametric	-0.74	.23	0.133
	Male	<u>3.8</u> -5.1	Nonparametric (Simple)	1.03	.85	0.077
	SLE					
	w/o Diabetes	<u>3.3</u> -5.1	Nonparametric (Harrell-Davis)	-0.74	.23	0.111
	with Diabetes	<u>3.0</u> -4.6	Nonparametric (Harrell-Davis)	-1.93*	.03	0.125
	UC	<u>3.5</u> -5.0	Parametric	0.00	.50	0.200
CD	<u>3.4</u> -5.0	Parametric	-0.36	.36	0.188	
ALT (U/L)	RA					
	Adult	11- <u>71</u>	Parametric	0.65	.26	0.433
	Geriatric	9- <u>60</u>	Parametric	0.32	.38	0.804
	SLE	10- <u>50</u>	Parametric	-0.04	.52	0.450
	HASHD ^a	10- <u>70</u>	Nonparametric (Harrell-Davis)	0.62	.27	0.458
Female	10- <u>61</u>	Nonparametric (Harrell-Davis)	0.35	.36	0.510	
AST (U/L)	RA	18- <u>59</u>	Parametric	1.29	.10	0.293
	SLE	18- <u>57</u>	Nonparametric (Harrell-Davis)	1.18	.12	0.410
	HASHD ^a	17- <u>62</u>	Nonparametric (Harrell-Davis)	1.46	.07	0.289
	Female	8- <u>48</u>	Parametric	0.61	.27	0.356
Chloride (mmol/L)	UC					
	Female	<u>95</u> -108	Nonparametric (Simple)	-0.99	.16	0.231
	Male	<u>93</u> -108	Parametric	-1.67*	.048	0.571
CD	<u>97</u> -108	Parametric	-0.33	.37	0.091	
Cholesterol, total (mg/dL)	HASHD	121- <u>262</u>	Parametric	1.17	.12	0.156

CRP (mg/dL)	RA		<3.3	Nonparametric (Harrell-Davis)	1.23	.11	n/a
	SLE ^a		<4.5	Nonparametric (Simple)	1.49	.07	n/a
	UC		<2.2	Nonparametric (Harrell-Davis)	0.88	.19	n/a
	CD		<2.5	Nonparametric (Harrell-Davis)	0.99	.16	n/a
Eosinophil, absolute (10 ³ /μL)	RA						
		Female	<u>0.03-0.49</u>	Nonparametric (Harrell-Davis)	0.27	.39	0.28 3
		Male ^a	<u>0.03-0.48</u>	Nonparametric (Simple)	-0.12	.55	0.26 7
	UC						
		Female	<u>0.02-0.50</u>	Nonparametric (Simple)	0.30	.38	0.35 4
		Male	<u>0.04-0.42</u>	Nonparametric (Harrell-Davis)	-0.28	.61	0.47 4
	CD						
	Female	<u>0.05-0.51</u>	Nonparametric (Harrell-Davis)	0.32	.38	0.28 3	
	Male	<u>0.04-0.52</u>	Nonparametric (Harrell-Davis)	-0.02	.51	0.62 5	
Hemoglobin (g/dL)	RA						
		Female	<u>9.1-15.4</u>	Parametric	-2.51**	.006	0.14 3
		Black, F	<u>9.1-15.7</u>	Nonparametric (Simple)	-2.51**	.006	0.19 7
		White, F	<u>9.2-15.5</u>	Parametric	-2.40**	.008	0.17 5
		Adult, F	<u>9.5-15.5</u>	Parametric	-2.08*	.02	0.15 0
		Geriatric, F	<u>8.4-14.9</u>	Nonparametric (Harrell-Davis)	-3.34***	<.001	0.18 5
		Male ^a	<u>10.9-17.9</u>	Parametric	-1.17	.12	0.18 6
	SLE						
		Female ^a	<u>7.8-15.2</u>	Nonparametric (Harrell-Davis)	-4.11***	<.001	0.24 3
	UC						
		Female	<u>10.8-15.9</u>	Nonparametric (Simple)	-0.74	.23	0.07 8
		Male	<u>9.4-16.8</u>	Nonparametric (Harrell-Davis)	-2.70**	.003	0.21 6
	CD						
		Female	<u>9.1-16.3</u>	Nonparametric (Harrell-Davis)	-2.51**	.006	0.33 3
	Male	<u>10.2-16.8</u>	Nonparametric (Harrell-Davis)	-1.85*	.03	0.19 7	
	Adult, M	<u>10.2-16.8</u>	Nonparametric (Harrell-Davis)	-1.85*	.03	0.34 8	
HASHD							
	Female ^a	<u>9.8-15.6</u>	Nonparametric (Harrell-Davis)	-1.75*	.04	0.17 2	

LDL (mg/dL)	HASHD	≤163	Parametric	0.06	.48	n/a
Lymphocyte, absolute (10 ³ /μL)	RA					
	Female	0.7- <u>3.8</u>	Parametric	0.40	.34	0.129
	Adult, F	0.7- <u>4.0</u>	Parametric	0.55	.29	0.152
	Geriatric, F	0.7- <u>3.0</u>	Nonparametric (Simple)	-0.27	.61	0.130
	Male	0.6- <u>3.3</u>	Nonparametric (Simple)	0.09	.46	0.148
	SLE					
Female	<u>0.7</u> -3.7	Parametric	-1.78*	.04	0.067	
Neutrophil, absolute (10 ³ /μL)	RA					
	Female	<u>1.74-10.14</u>	Parametric	-0.21 1.00	.83 .32	0.03 0.19
	Black, F	<u>1.44-10.34</u>	Nonparametric (Simple)	-0.74 1.05	.46 .29	0.04 0.31
	White, F	<u>1.90-9.92</u>	Parametric	0.03 0.93	.98 .35	0.04 0.20
	Male	<u>1.90-11.08</u>	Nonparametric (Simple)	-0.13 1.30	.90 .19	0.09 0.25
	SLE					
Female	<u>1.64-9.49</u>	Parametric	-0.38	.35	0.056	
Platelet (10 ³ /μL)	RA					
	Female					
	w/o CVD, F	<u>153-462</u>	Nonparametric (Harrell-Davis)	-0.32 1.01	.75 .31	0.13 0.15
	with CVD, F	<u>109-417</u>	Parametric	-1.65 0.60	.10 .55	0.11 0.11
	Male	<u>134-399</u>	Nonparametric (Harrell-Davis)	-0.44 0.78	.66 .44	0.18 0.20
	SLE					
	Female	<u>135-461</u>	Parametric	-0.81	.21	0.089
	UC					
	Female ^a	<u>153-388</u>	Nonparametric (Simple)	0.32	.37	0.068
	Male	<u>118-419</u>	Nonparametric (Harrell-Davis)	0.97	.17	0.259
	CD					
	Female	<u>169-493</u>	Parametric	1.27	.10	0.309
Male	<u>160-571</u>	Nonparametric (Harrell-Davis)	2.20*	.014	0.343	
HASHD						
Female	<u>144-400</u>	Parametric	0.44	.33	0.129	

RBC (10 ⁶ /μL)	RA	Female					
		w/o CVD, F	<u>3.33</u> -5.23	Parametric	-1.54	.06	0.22 6
		with CVD, F	<u>3.24</u> -5.38	Parametric	-1.80*	0.04*	0.11 7
		Male	<u>3.55</u> -6.02	Parametric	-1.70*	.045	0.19 4
	SLE	Female	<u>3.25</u> -5.22	Parametric	-1.77*	.04	0.23 4
		UC					
		Female ^a	<u>3.70</u> -5.44	Nonparametric (Harrell-Davis)	-0.56	.29	0.16 7
		Male	<u>3.17</u> -5.72	Nonparametric (Harrell-Davis)	-2.76**	.003	0.22 4
	CD	Female	<u>3.67</u> -5.21	Parametric	-0.64	.26	0.17 5
		Male ^a	<u>3.71</u> -5.94	Nonparametric (Harrell-Davis)	-1.29	.10	0.09 0
	HASHD	Female	<u>3.52</u> -5.32	Parametric	-1.03	.15	0.16 7
		Hispanic, F	<u>3.73</u> -5.79	Nonparametric (Harrell-Davis)	-0.49	.31	0.18 0
		Non-Hispanic, F	<u>3.49</u> -5.07	Parametric	-1.11	.13	0.25 9
Sodium (mmol/L)	UC	Female	<u>135</u> -145	Parametric	0.00	.50	0.20 0
		Male	<u>132</u> -143	Nonparametric (Harrell-Davis)	-0.92	.18	0.18 2
	CD	<u>134</u> -144	Parametric	-0.30	.38	0.20 0	
	HASHD	<u>135</u> -143	Parametric	0.00	.50	0.12 5	
Vitamin B12 (pg/mL)	UC	<u>278</u> -984	Nonparametric (Simple)	0.28	.61	0.10 6	
	CD	<u>294</u> -971	Nonparametric (Harrell-Davis)	0.39	.65	0.02 2	
WBC (10 ⁹ /μL)	RA	Female	3.8- <u>13.8</u>	Parametric	0.76	.23	0.16 0
		Black, F	3.1- <u>11.6</u>	Nonparametric (Simple)	0.15	.44	0.08 2
		White, F	4.2- <u>14.4</u>	Parametric	0.90	.18	0.26 5
		Male	4.1- <u>14.6</u>	Nonparametric (Simple)	1.08	.14	0.15 2
	SLE	Female	<u>3.0</u> -13.2	Parametric	-1.25	.11	0.06 9

	UC						
		Female	4.2- <u>14.4</u>	Nonparametric (Harrell-Davis)	0.90	.18	0.431
		Male ^a	3.7- <u>8.9</u>	Nonparametric (Harrell-Davis)	-0.64	.74	0.135
	CD						
		Female	3.7- <u>12.7</u>	Nonparametric (Harrell-Davis)	0.47	.32	0.278
		Male	4.1- <u>11.7</u>	Nonparametric (Harrell-Davis)	0.31	.38	0.118

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; F, female; HASHD, Hashimoto's thyroiditis; LDL, low density lipoprotein; M, male; n/a, not applicable; RA, rheumatoid arthritis; RBC, red blood cell; RI, reference interval; SLE, systemic lupus erythematosus; UC, ulcerative colitis; w, width ratio; WBC, white blood cell.

^aA subpopulation within this sample was found to be significant, but could not be partitioned because of too small sample sizes; the subpopulation may have an over- or under-estimated reference limit.

*P < .05, **P < .01, ***P < .001

Underlined limits were the reference limits used in the RCV equations to determine significance between published and established RIs; only limits in RIs comprised of two limits are underlined.

Discussion

The study population mostly consisted of white, non-Hispanic females between the ages of 45-64, which echoes the national prevalence data.^{24,25} Sex was the most influential covariate, as females had a reduction in reference limits compared to males, thus, sex-specific RIs were established within RA-associated albumin, and HASHD-associated ALT and AST. Conversely, for UC- and CD-associated sodium and chloride, males had reduced lower limits compared to females. This agrees with heavily studied trends of females having lower values of albumin than males; however, the higher electrolyte values in UC and CD for females is unexpected and may be from hormone differences playing a role in the regulation of the intestinal microenvironment.^{26,27} Race also influenced many hematological parameters, depicting decreased reference limits in the Black population compared to the White population for hemoglobin, neutrophil, and WBC RIs in female patients with RA. This, too, matches with the literature, as studies reveal the Black population as having reduced values for the parameters.²⁶ Age group was another major factor in the RIs as ALT, hemoglobin, and lymphocyte limits were lower in the geriatric

population, as expected.²⁶ Ethnicity also affected RIs, as the self-reported Hispanic population showed higher medians for WBCs in males with UC; and RBCs in females with UC and males with CD, compared to Non-Hispanics. Research supports this finding and describes the Hispanic population as having higher hematological values than Non-Hispanics, despite this study's inability to establish many RIs for this population due to low sample sizes.^{28,29} Only HASHD-associated RBCs for Hispanic females had a sufficient sample size to establish an RI, and the lower limit was still higher than the Non-Hispanic lower limits. To further substantiate the influence of ethnicity, additional samples would be required. Though, some studies examining inflammatory bowel disease in various ethnicities have noted the Hispanic population as having higher values for WBCs and less phenotypical complications, citing low incidences of risk alleles as an attributing factor.²⁸⁻³⁰

Most diseases altered the laboratory tests as predicted by the z scores, including the duality of neutrophil and platelet limits in RA, suggesting the assigned critical z values were appropriate and reliable. Additionally, many of the RI limits established in this study were

comparable to those reported for the non-comorbidity (“Included”) population in Mikkelsen et al. 2021, despite differences in inclusion criteria and study methodology.⁹

For example, in RA-associated albumin among females, the lower reference limit decreased to the same value in both studies (3.3 g/dL; 3.3 g/L) (Figure 1). Similarly, the upper reference limit for RA-associated platelet counts in females increased to $462 \times 10^3/\mu\text{L}$ in this study and to $486 \times 10^9/\text{L}$ in the comparison study (Figure 2). For RA-associated WBC counts in females, the upper reference limit was approximately 1.2 times the health-associated limit, whereas the comparison study reported an upper limit that is nearly double. Despite these differences, both studies identified similar upper limits of approximately $14 \times 10^3/\mu\text{L}$ ($10^9/\text{L}$) (Figure 3). Across all RIs, the 90% CIs were comparable to or narrower than those reported, despite smaller sample sizes for WBCs and platelet measurements in this study. RA-associated CRP values increased similarly between both studies. Notably, the combined RA CRP upper reference limit in this study matched the reported male RA reference limit (Figure 4). However, the comparison study stratified CRP reference intervals by sex and observed substantially higher limits in females, whereas this study found no significant sex-based differences in CRP values among RA outpatients. RA-associated hemoglobin reference limits were reduced in both studies (Figure 5). In this study, the lower hemoglobin reference limit aligned with the other study’s comorbidity and anemia of chronic disease (“Sick”) population. Although this finding suggests that further refinement of inclusion criteria may be necessary to better exclude patients with comorbidities, the comparison study similarly questioned this result, proposing that adequate treatment among patients may explain the observed overlap. Lastly, UC-associated CRP limits increased modestly in this study (2.75-fold) compared with the markedly higher increase (12.2-fold) reported in the compared study (Figure 6).

Contrary to the assigned z-scores, limits for albumin in males with RA, and for absolute eosinophils in males with UC or CD shifted in the opposing direction. Males had higher results for albumin, and lower results for eosinophils compared to the health-associated RIs. For albumin, this may be because the disease-associated RI is stratified by sex, and females have a lower albumin limit while males have a higher albumin limit. If these two populations were not stratified, they would average out and match the combined health-associated RI. In SLE, CRP limits showed a drastic increase from the health-associated limit. This differs from research as SLE would likely have a dampened effect on CRP from overproduced type I interferons inhibiting its production, or CRP-autoantibodies causing its destruction.¹⁴ This drastic increase may be further evidence to refine the sample population, as it suggests the inclusion of outpatients with underlying acute conditions, such as infections, in the population. In females with UC, the WBC upper limit unexpectedly decreased by 1.2 times the health-associated limit; contrary to the Mikkelsen study, which the upper limit increased about 1.5 times the health-associated limit (Figure 7). Though reasoning has not been fully studied, there is some evidence that UC patients with complete mucosal healing can have substantially lower WBC values than expected, and some of the reference individuals could be included in the population.³¹ Another contributing factor might be the low sample size affecting the RI.

When assessing significance of the established disease-specific RIs, 22% (19/88) were statistically significant, 25% (22/88) had $n \geq 120$, and 50% (44/88) had a satisfactory $w < 0.20$. Of the significant RIs, 58% (11/19) had a satisfactory $w < 0.20$. Overall, the hemoglobin and RBC RIs showed statistical significance across autoimmune diseases, while platelet, lymphocyte, and chloride RIs were significant for at least one disease. The RA-associated hemoglobin RIs in females had the strongest significance (i.e., a combination of the highest z score with the lowest w). RIs

for SLE-associated albumin in diabetic patients, and RA-associated RBCs in females with CVD were both significant; however, these were only secondary findings, as diabetes and CVD consisted of clusters of ICD-10-CM codes used to “purify” the RIs. Additional steps are needed to further evaluate the comorbidities for the impact on the RIs in these populations. When reviewing analyte IOLs, sodium and chloride produced an IOL close to, or above 1.4, followed by albumin at IOL = 0.95. The remaining analytes produced IOLs close to, or below 0.6; therefore, subject-based RIs for these analytes would be the higher quality approach.

Limitations

One major limitation of the study were the unverifiable ICD-10-CM codes, as reviewing a thousand patients for agreement with medical criterion of their respective disease was not feasible. Trust was placed in healthcare providers to accurately report diagnosis codes and in the correct location. Additionally, despite other studies developing precise methods for improved participant selection based on ICD codes, access to such technology and time constraints were limiting factors in this study. The other major limitation of this study was small sample sizes, which directly affects the strength of established RIs. However, the CLSI endorses techniques to develop RIs with sample sizes as low as 40, and RIs in this study were determined based on those standards. Another limitation is the certainty of biological variation data. Though EFLM provides quality data from meta-analyses of appraised evidence, many analytes still have vastly wide 90% CI for variation. This weakens the application of the RPA in this study and could alter significances of established RIs. Moreover, biological variations for the “healthy” population and the autoimmune disease-specific population are likely different, introducing further uncertainty in the RPA. Other limitations associated with this study includes the differences in drug mechanisms of action, dosages, and patient compliance prior to sample collection, and the

lack of BMI data to account for the effects on certain analytes.

Overall, additional prospective studies should focus on refining inclusion criterion, increasing generalizability, and strengthening statistical power—especially in the geriatric, Black, and Hispanic female populations. Clinical utility studies should also be included to measure outcomes of applying the disease-associated RIs in a real-world setting. However, since many analytes have low IOLs, research should pivot towards implementing the next highest quality model of subject-based RIs in medicine.

Conclusion

This study demonstrates that RIs in patients with autoimmune diseases are different than the RIs currently used in healthcare. Based on the collective strength of RI significance, 90% CIs, width ratios, and IOLs, clinical validation for appropriateness is needed. The nonsignificant RIs, though informative, may be optional since available data suggests the health- and disease-associated RIs were equivalent. The UC-associated chloride RI in males was statistically significant and is mathematically the most clinically useful RI but cautiously recommend it for clinical validation because of the wide 90% CI. RA-, SLE-, and UC-associated hemoglobin; RA-associated RBC; CD-associated platelet; and SLE-associated lymphocyte RIs were all significant with satisfactory confidence, thus clinical validation is strongly recommended.

In addition to clinical validation, the integration of the autoimmune disease-associated RIs must be considered. Most LIS systems store RIs based on age and sex, and physicians should not have to memorize RIs. Though the established RIs could be thought of as clinical decision limits for easier adoption, they technically do not equate to actionable laboratory values, because they only serve as a reference. The best approach is to upgrade electronic health records with the logic to provide guidance on laboratory interpretation based on the entirety of the patient’s chart.

With the advancement of artificial Intelligence, implementation of more advanced diagnostic algorithms may improve the calculation and application of RIs.

Overall, considering the findings and the limitations, this study provides a method and starting point for further research on the interpretation of laboratory tests based on underlying disease. These findings provide insight into the interpretation of routine laboratory results in patients with underlying autoimmune diseases, based on the university hospital's serving population. However, if the autoimmune disease-associated RIs are utilized at other facilities with different analyzers and patient populations, verifications are necessary. More appropriately, population-specific interval studies are needed to support the specific patient population.

Ultimately, each of the established autoimmune disease-associated RIs provide a higher quality standard, as they reflect the patient population and improve laboratory-based patient management.

Along with the downstream effects of morbidity and mortality, the United States Renal

Data System (USRDS) also reports that the healthcare cost burden of CKD to be approximately 114 billion dollars annually in the United States.⁵ The early detection, management, and slowing of progression of CKD to later stages and end-stage renal disease (ESRD) have large economic implications for potential cost savings in the amount spent annually towards treating this disease. Approximately one third of the total cost of CKD treatments is focused on patients with ESRD.⁶

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Ethical Approval

This study was reviewed by the UTMB institutional IRB and considered a quality assessment/quality improvement study.

Conflict of interest statements

All authors declare no conflicts of interest.

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