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Reference Distributions for the Negative Acute-Phase Serum Proteins, Albumin, Transferrin and Transthyretin: A Practical, Simple and Clinically Relevant Approach in a Large Cohort

Robert F. Ritchie,* Glenn E. Palomaki, Louis M. Neveux, Olga Navolotskaia, Thomas B. Ledue, and Wendy Y. Craig

Foundation for Blood Research, Scarborough, Maine

Inflammation is associated with diverse clinical conditions accompanied by characteristic changes in serum levels of the acute-phase proteins that can be used to stage the inflammatory process and evaluate the impact of treatment. Some acute-phase proteins increase during inflammation, while others, such as albumin, transferrin, and transthyretin, decrease. The current study reports reference ranges for serum levels of albumin, transferrin, and transthyretin based on a cohort of over 124,000 Caucasian individuals from northern New England, tested in our laboratory between 1986 and 1998. Measurements were standardized against CRM 470 (RPPHS) and analyzed using a previously validated statistical approach. Individuals with laboratory evidence of inflammation (C-reactive protein of 10 mg/L or higher) were excluded. The levels of all three analytes varied by age, generally rising until the second or third decade of life and then decreasing thereafter. Albumin and transthyretin levels were higher during midlife among males as compared to females; the maximum being at 25 years for albumin (5%) and 35 years for transthyretin (16%). In contrast, above the age of 10 years, transferrin levels were increasingly higher among females (7% at 20 years). When values were expressed as multiples of the age- and gender-specific median levels, the resulting distributions fitted a log-Gaussian distribution. When patient data are normalized in this manner, the distribution parameters can be used to assign a corresponding centile to an individual's measurement simplifying interpretation. The ultimate interpretation of an individual's measurement relies upon the clinical setting. J. Clin. Lab. Anal. 13:273–279, 1999.

Key words: acute-phase proteins; reference range; reference material; Caucasian; albumin; transferrin; transthyretin

INTRODUCTION

Inflammation, the physiological response to injury, foreign bodies, or endotoxin, includes a characteristic regulatory response, the acute-phase response. These effects are modulated by the multifunctional cytokines released by macrophages at the site of insult, primarily interleuken-1, interleuken-6, and, to a lesser extent, tumor necrosis factor, which control the hepatic synthesis and secretion of certain proteins. While the levels of some proteins increase as part of the acute-phase response, the levels of albumin, transferrin, and transthyretin (previously known as thyroxine-binding prealbumin) are down-regulated, hence their grouping as the ''negative'' acute-phase proteins. Measurement of these acute-phase proteins in serum is playing an increasingly important role in the clinical evaluation of the pathophysiologic process, but as with other serum proteins, effect on their levels can involve many other processes apart from inflammation.

Accurate and precise measurement of these proteins is now possible with the advent of high quality analytical instrumentation and the release of a respected reference material (CRM470/RPPHS (1)). However, their clinical utility remains hampered by a lack of age- and gender-specific reference data. Although many publications have addressed the issue of reference ranges for the acute-phase proteins, few have met the criteria of sufficiently large numbers, appropriate laboratory methodology and standardization, and assessment of relevant health status.

In the current study, comprehensive age- and gender-specific reference values were determined for the three negative acute-phase proteins: albumin, transferrin, and transthyretin. The population is primarily Caucasians that have entered the

*Correspondence to: Robert F. Ritchie, M.D., Foundation for Blood Research, Scarborough, Maine, 04074. E-mail: ritchie@fbr.org

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healthcare system. The inclusion criteria for this study was the same as that used previously to define reference ranges for the immunoglobulins (2), with the modification that subjects with laboratory evidence of inflammation were excluded (CRP of 10 mg/L or higher). A companion paper (3) presents a meta-analysis of these three negative acute-phase proteins covering the years 1962–1998 and places the current findings in that context.

MATERIALS AND METHODS

Serum Protein Reagents and Instrumentation

Antisera were obtained from several sources (DiaSorin, Stillwater MN, and Midland Bioproducts, Scarborough, ME). Each batch of antiserum was compared to previous batches for value recovery and proportionality in actual assays (4). The buffer solution, antiserum characterization protocols, and instrumentation (COBAS FARA system, Roche Diagnostic Systems, Nutley, NJ) were the same as for the previous study (2). CRP was analyzed with the Behring BNA, (Dade Behring, Inc., San Diego, CA), using antisera and reagents supplied by the manufacturer. All results have been normalized to CRM 470/RPPHS (1).

Selection of Patient Results

The methodologies for selecting the referent individuals and computing the reference ranges have been described in detail elsewhere (2,5,6). Although individual health status was not collected, the diagnosis (or symptom) accompanying the sample was used as a surrogate marker of health status. This has been shown to produce immunoglobulin reference ranges consistent with those from much small studies where individual health status was evaluated (6). The current dataset differs from the earlier one in two ways: (1) data prior to 1989 were not included since CRP was not routinely measured; and (2) additional data from January, 1995, to June, 1998 was included. Overall, these two changes increased the number of records available for study from 115,017 to 124,522. As before, diagnostic strings were reviewed and assigned to one of 93 diagnostic groups. In brief, the analysis for each of the analytes included: (1) removal of 22,688 duplicate records (i.e., more than one entry for a single individual despite separation in time), 25,092 records associated with CRP measurements of 10 mg/L or higher, 1,609 records associated with missing age/gender, and 135 records with previously undiagnosed myeloma or other unusable data; (2) preliminary normalization for age and gender to ensure that differences between diagnostic groups was not due to a spurious age and/or sex association; (3) selecting diagnostic groups using an algorithm employing the population means and standard deviations found in pre-selected groups representing benign diagnoses; (4) computing observed median levels by age and sex; (5) fitting smooth curves through the observed median levels; (6) converting all assay results to multiples of the age- and gender-specific smoothed median levels (MoM); (7) fitting the reference observations (expressed in MoM) to a set of Gaussian parameters; and (8) verifying the consistency of measurements over time.

RESULTS

Selection of Diagnostic Groups to Form the Reference Population

After a preliminary adjustment for age and gender, the median albumin levels were plotted versus the variance for each of the 90 groups with at least 20 observations (Fig. 1). The circles indicate the preliminary reference population (diagnostic codes 166 and above). The rectangle is drawn at the trimmed mean ± 1.96 standard deviations for both the median levels (horizontal axis) and log variances (vertical axis) based on the preliminary reference population. The squares represent the remaining 62 diagnostic groups. Overall, the median and log variances for 71 of the 90 groups lie within the rectangle. Results from individuals within these 71 groups compose the referent population for albumin. Individuals from the 19 diagnostic groups represented by filled circles or squares were not included as part of the albumin reference population. This analysis was repeated for transferrin and transthyretin resulting in the inclusion of 67 and 61 diagnostic groups, respectively (figures available upon request).

Computation of Age- and Gender-Specific Median Values and Selected Centiles

The number of referent individuals available to calculate reference ranges for albumin, transferrin, and transthyretin

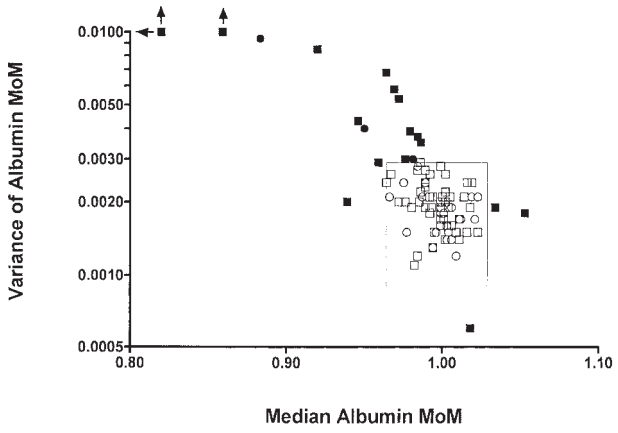

Fig. 1. Scatterplot of albumin median levels versus variance for the diagnostic categories after preliminary adjustment for age and gender. Diagnostic codes 100 through 165 are displayed as squares (□ ■), while codes 166 and above are circles (○ ●). The lower the diagnostic group number, the more severe the illness or complaint. The rectangle represents the 95 percent confidence intervals (after trimming) of the median (horizontal axis) and variance (logarithmic vertical axis) for the diagnostic categories 166 and above. Open symbols (○ □) represent those categories whose values comprise the reference population.

were 57, 556, 56, 793, and 51,310, respectively. Figure 2 shows selected albumin centiles for males (**a**) and females (**b**). The logarithmic horizontal axis shows the average age for each interval while the logarithmic vertical axis shows the median albumin value (filled circles) along with the 5th and 95th centiles (lower and upper open circles, respectively). The observed centiles for individuals under age 10, 10–30, 30–80, and over 80 years old are based on about 50, 200–400, 1,000–1,500, and less than 300 observations for males, and about 50, 300–3,000, 3,000–1,000, and less than 500 observations for females, respectively. The solid line indicates the predicted median levels for albumin in males and the dashed line indicating the predicted medians for females. Figures 3 and 4 display similar data for transferrin and transthyretin, respectively. For all three analytes, the increase in median levels in both younger males and females is fitted by a straight line. Although median levels of the analytes do change during this time period, little difference is seen by gender for any of the three analytes. The pattern becomes more complicated in older individuals. It should be noted that the complexity of the curves is partially the result of the logarithmic nature of the x-axis. Beyond age 10, complex changes reflect physiologic maturation and aging not unlike other parameters, such as anthropomorphic features and more familiar biochemical measurements. There is significant difference in the albumin and transthyretin median levels for males and females beginning at about 10 years of age; males have, on average, higher levels. At about age 70, the differences between males and females have disappeared. Transferrin values are relatively constant during the first four decades of life, and for later ages, females have consistently higher levels. For each analyte, the distances from the median to the 95th centile and from the median to the 5th centile are approximately equal across the entire age range. This indicates that each of the distributions are symmetric after a logarithmic transformation, and that the variances of the distributions do not change appreciably by age. Table 1 contains the gen-

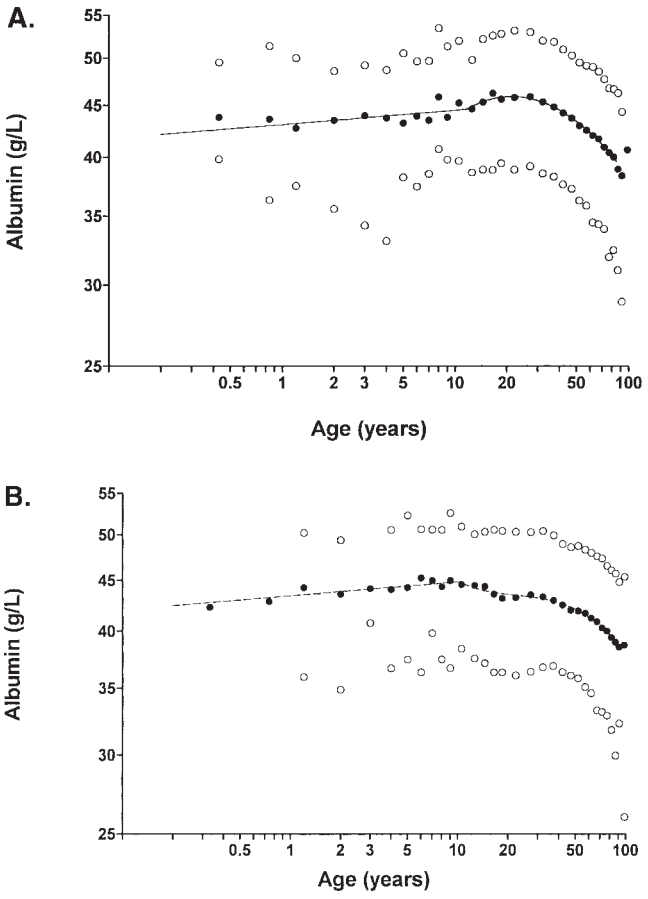

Fig. 2. Albumin centiles and medians versus age. The individual's age is displayed on the horizontal logarithmic axis versus the albumin level on the vertical logarithmic axis. The closed circles (●) represent the observed median level; the lower and upper open circles (○) represent the observed 5th and 95th centiles, respectively. The lines represent the predicted median values. **A** and **B** show the albumin results for males and females, respectively.

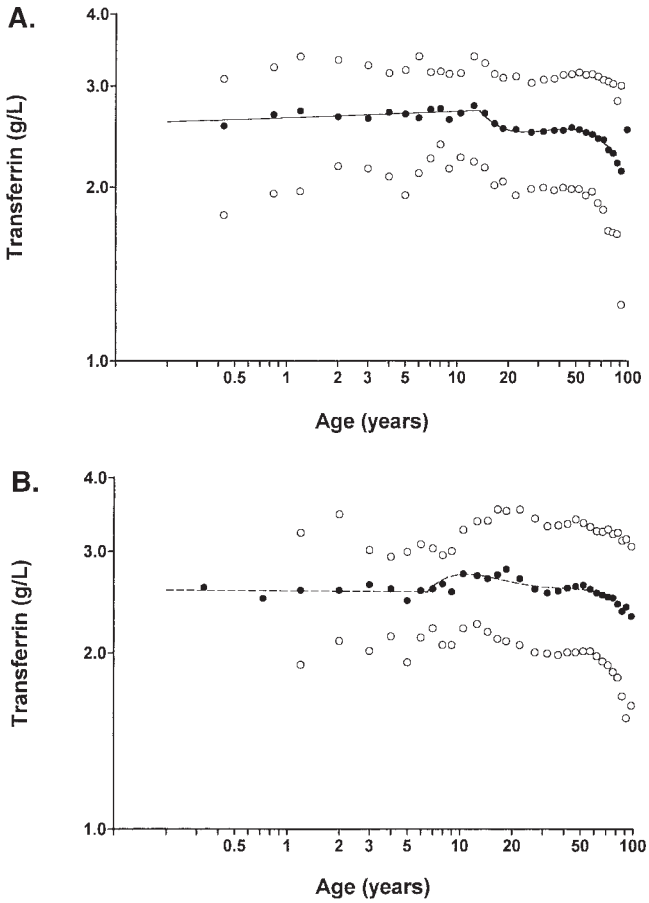

Fig. 3. Transferrin centiles and medians versus age. The data is presented in the same format as Figure 2. **A** and **B** show the transferrin results for males and females, respectively.

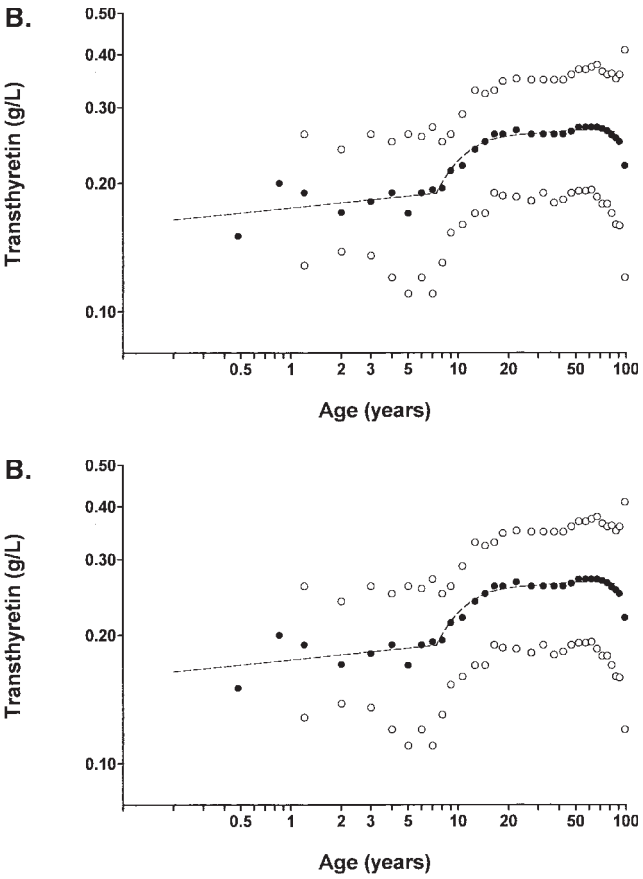

Fig. 4. Transthyretin centiles and medians versus age. The data is presented in the same format as Figure 2. **A** and **B** show the transthyretin results for males and females, respectively.

der-specific regression equations along with the age range over which each equation is valid for albumin, transferrin, and transthyretin median values. A sample equation can be found as a footnote to Figure 1.

Fitting the Reference Data Expressed in Multiples of the Median (MoM) to a Population Distribution

Figure 5 shows probability plots of approximately 2,000 albumin, transferrin, and transthyretin measurements (expressed in MoM). The samples were randomly selected to equally represent each year of age. The albumin measurements (Fig. 5a) fitted the distribution well between the 4th and 99th centiles **(**logarithmic mean and standard deviation of 0.0000 and 0.0408, respectively). The transferrin (Fig. 5b) measurements fitted well between the 2nd and 99th centiles (logarithmic mean and standard deviation of 0.0000 and 0.0651, respectively). The transthyretin (Fig. 5c) measurements fitted well between the 5th and 99th centiles (logarithmic mean and standard deviation of 0.0000 and 0.0838, respectively). When this analysis was restricted to individuals less than 10 years of age or between 70 and 85 years of age, the logarithmic means were similar to the overall values (within ± 0.006). The log standard deviations were fairly consistent among the youngest group (within ± 10 percent) except for transferrin (20 percent lower). For the oldest age group, the log standard deviations for the three proteins were consistently higher by 15–18 percent.

Predicting Age- and Gender-Specific Centiles

Because the parameters summarize the distributions well (at least between about the 5th and 99th centiles and for those under age 70), any result within this range can be assigned an age- and gender-specific centile. Table 2 contains the predicted 2.5th, 50th and 97.5th centiles for selected age and gender categories using the log-Gaussian parameters. As a further example, consider a transthyretin measurement of 0.30 g/L. If this value were to be reported for a 40-year-old male, it would be considered relatively normal (multiple of the median of 0.97 [0.30/0.31] and would be assigned the 44th centile [z-score of –0.16 ((log(0.97)–log(1.00))/0.0838)].

TABLE 1. Regression models and coefficients for median albumin, transferrin, and transthyretin measurements by age and gender

		Age range (years)		Constant	Coefficients[a]			
Analyte	Sex	From	To	A0	A1	A2	A3	A4
Albumin	Males	0.5	11	1.63478606	0.014205592	0	0	0
		12	85	1.35054741	0.46941064	–0.17664158	0	0
	Females	0.5	10	1.63800583	0.014213492	0	0	0
		11	85	2.27913852	–1.49907809	1.25780763	–0.42745149	0.042963302
Transferrin	Males	0.5	13	0.42295661	0.011456115	0	0	0
		14	85	3.29141786	–5.78912162	3.84087508	–0.84415289	0
	Females	0.5	6	0.40938625	–0.00191626	0	0	0
		7	85	–1.64206324	6.26478635	–6.90771775	3.30738655	–0.58440182
Transthyretin	Males	0.5	7	–0.75675111	0.026760158	0	0	0
		8	85	–1.62176424	1.41808057	–0.45322732	0	0
	Females	0.5	7	–0.75677126	0.039536114	0	0	0
		8	85	–4.06809704	8.98762426	–8.72870207	3.77332336	–0.61048899

[a]The general form of the equation is Median = $10^{(A0 + A1 * \log(age) + A2 * Log(age)\hat{}2 + A3 * \log(age)\hat{}3 + A4 * \log(age)\hat{}4.}$ The median albumin level for a 20-year-old male is $10^{(1.35054741 + 0.46941064 * \log(20) - 0.17664158 * \log(20) * \log(20)}$ or 45.9 g/L.

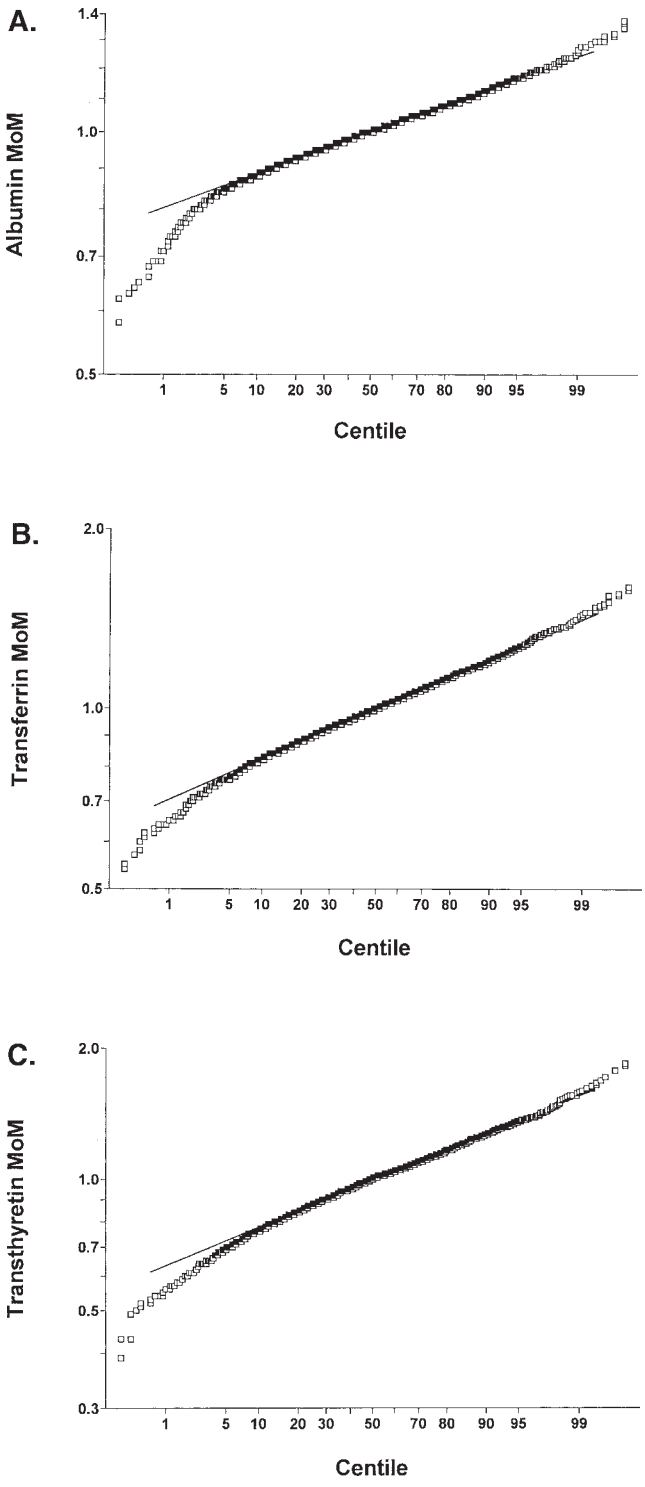

Fig. 5. Probability Plots of Negative Acute-Phase Protein Measurements Expressed as Multiples of the Median (MoM). Approximately 2,000 observed MoM values uniformly selected by age from both males and females age 1 to 85 years old are plotted vertically on a logarithmic axis and horizontally on the Gaussian centile scale. The latter is based on the rank of the observation. If the points fit a straight line, the distribution is log-Gaussian. **A**, **B**, and **C** show results for albumin, transferrin, and transthyretin, respectively.

However, if the value were from a 7-year-old female, the clinical implication would be quite different (1.58 multiples of the median [0.30/0.19] and would be assigned the 99th centile [z-score of 2.37 ((log(1.58)–log(1.00))/0.0838].

Verification of Results Over the Course of the Study

The median MoM level was reasonably consistent for all three analytes over time (1.00 with an observed 95 percent confidence of ± 0.06, ± 0.06, ± 0.04 for albumin, transferrin, and transthyretin, respectively). With the large numbers available for each quarter (approximately 1,500), these confidence intervals are wider than expected based on the population variances, but likely represent the best control over pre- and intra-analytical assay conditions that can be achieved in routine practice. The average age of patients rose slightly during the study from 49 to 51 years of age while the percentage of males decreased from 34 to 31 percent.

DISCUSSION

Recent evidence has underscored the value of assessing the acute-phase response in a wide range of conditions (7,8). Now that the technology for serum protein measurement has reached a high level of automated precision and accuracy, and that a widely accepted reference material is available (1,9), the remaining barrier preventing more effective use of acute-phase protein measurements is the availability of a robust set of age- and gender-specific reference ranges. Until the approach to personal, life-long medical care advances to the point that individual reference intervals are practical and affordable, reference ranges such as those reported here are the best we can achieve.

The present study is a sequel to the development of reference ranges for the three major immunoglobulins from a single laboratory (2,10). An additional feature of this study was the removal from analysis all referent individuals with a CRP value of 10 mg/L or higher—a clinical cut-point usually accepted in the United States as an indicator of active inflammation. This step is an effort to simplify the introduction of useful reference ranges for three of the negative acute-phase proteins. Inflammation, or the acute-phase response, is a ubiquitous condition present in all animals at all times. It represents a normal, curative process for the repair of tissue damage due to injury, necrosis, or microbial invasion. Common problems such as minimal periodontal disease, local infection of the genito-urinary and respiratory tracts likely stimulate the acute-phase response, but to levels not presently considered abnormal. A recent publication, however, has shown that even relatively low levels of the acute-phase proteins can act as harbingers of significant disease (11).

The negative acute-phase proteins, albumin, transferrin, and transthyretin, while less dramatic in their response to acute inflammation then the positive acute-phase proteins, are, nev-

TABLE 2. Predicted albumin, transferrin, and transthyretin medians and selected centilies stratified by age and gender

Decimal	Albumin (g/L)			Transferrin (g/L)			Transthyretin (g/L)		
age (years)	2.5th	50th	97.5th	2.5th	50th	97.5th	2.5th	50th	97.5th
				Males					
1.0	35.9	43.1	51.9	1.86	2.65	3.77	0.12	0.18	0.26
4.0	36.6	44.0	52.9	1.89	2.69	3.83	0.12	0.18	0.27
7.0	36.9	44.3	53.3	1.90	2.71	3.86	0.13	0.18	0.27
10.0	37.1	44.6	53.8	1.91	2.72	3.88	0.15	0.22	0.32
14.0	37.7	45.3	54.5	1.89	2.70	3.84	0.18	0.26	0.37
18.0	38.1	45.9	55.1	1.79	2.55	3.64	0.19	0.28	0.41
20.0	38.2	45.9	55.2	1.77	2.52	3.60	0.20	0.29	0.42
30.0	37.9	45.5	54.8	1.76	2.51	3.58	0.21	0.30	0.44
40.0	37.0	44.6	53.6	1.78	2.53	3.61	0.21	0.31	0.45
50.0	36.1	43.6	52.3	1.77	2.53	3.60	0.21	0.30	0.44
60.0	35.2	42.3	50.9	1.74	2.49	3.54	0.20	0.29	0.43
70.0	34.3	41.2	49.6	1.70	2.42	3.44	0.19	0.28	0.41
80.0	33.4	40.2	48.3	1.63	2.33	3.31	0.19	0.27	0.40
				Females					
1.0	36.1	43.5	52.2	1.80	2.57	3.66	0.12	0.18	0.26
4.0	36.9	44.3	53.3	1.80	2.56	3.65	0.13	0.18	0.27
7.0	37.2	44.7	53.7	1.83	2.61	3.72	0.13	0.19	0.28
10.0	37.3	44.9	54.0	1.92	2.74	3.91	0.15	0.23	0.33
14.0	36.6	44.0	52.9	1.91	2.72	3.88	0.17	0.25	0.36
18.0	36.3	43.7	52.5	1.88	2.68	3.82	0.18	0.26	0.37
20.0	36.3	43.6	42.4	1.87	2.66	3.79	0.18	0.26	0.38
30.0	35.0	43.3	52.0	1.83	2.61	3.72	0.18	0.26	0.38
40.0	35.6	42.8	51.4	1.82	2.60	3.71	0.18	0.26	0.39
50.0	35.1	42.1	50.7	1.82	2.59	3.69	0.18	0.27	0.39
60.0	34.4	41.4	49.7	1.80	2.57	3.66	0.18	0.27	0.39
70.0	33.7	40.6	48.8	1.77	2.53	3.60	0.18	0.27	0.39
80.0	33.0	39.7	47.8	1.73	2.47	3.52	0.18	0.26	0.39

ertheless, responsive to chronic illness due to inflammation, necrosis, malnutrition, and even subclinical malignancy (12). In particular, albumin is used worldwide as an indication of nutritional status without consideration or knowledge of the inflammatory status of the subject. Transferrin, in its role as the transport protein for ferric iron in vivo, is more responsive to synthesis-reducing pathology than is albumin, while transthyretin is the most sensitive of the three to down-regulatory signals. Conversely, transferrin and transthyretin syntheses are stimulated by commonplace situations whereas albumin is not. Transferrin and transthyretin syntheses change as the result of decreased iron stores and as the result of estrogen stimulation (13,14) endogenous or exogenous, while transthyretin levels rise with anti-inflammatory medications including over-the-counter products (15,16). It is particularly important, therefore, to make available reference ranges that cover individuals without perceivable inflammatory condition. Hence the step of removing from consideration individuals with laboratory evidence of significant inflammatory drive.

The current study is sufficiently large to reliably estimate the effects of age and gender from a cohort of Caucasians tested in a single laboratory using one methodology that was calibrated against a single reference material. This study has the limitation that it is presently applicable only to a relatively homogeneous Caucasian population. It was also not possible to take into account individual usage of tobacco products, over the counter anti-inflammatory medications, contraceptives, or hormone supplementation. Since the half-life of these drugs is short, only carefully designed studies could take their usage into account. As shown in the companion paper (3) our data compares favorably with previous small studies which employed formal guidelines defining health status (5,6).

Although the observed data fit a Gaussian distribution fairly well after logarithmic transformation, there was some deviation, especially in the lower tails of the distribution (Fig. 5). It is possible that a small percentage of our reference population is not healthy or has some condition that causes abnormally low levels of these three analytes that would not be found in a truly healthy population. The fitted line on Figure 5 may represent the ''true'' population better than the observed data does. In support of this possibility, we found the fit of all three analytes to be improved when the values with elevated CRP were removed (data not shown).

Converting laboratory results to a multiple of the age- and gender-specific medians (MoM) has several advantages. Once the conversion has been accomplished, the resulting values for each analyte fit a logarithmic Gaussian distribution rea-

sonably well, allowing each MoM level to be assigned a centile. Thus, a laboratory measurement can be reported not only in mass units, but also, through conversion to MoM, by the associated centile based on that individual's age and sex. This process greatly simplifies the clinical interpretation of these serum protein values

CONCLUSION

For the first time, a large homogeneous cohort has been examined to determine the reference distributions for albumin, transferrin, and transthyretin in the absence of significant active inflammation. The values are consistent with a review of much smaller studies in the world's literature which often verify the health status of each participant (6). For these analytes, both age and gender are important covariates to the normal ranges and therefore necessitate separate reference ranges. Converting the analyte measurements to multiples of the age- and gender-specific medians simplifies interpretation and enhances the clinical utility of their measurements. After verification of the appropriateness of medians presented in the current study, the finding should be considered for use by laboratorians or clinicians making interpretations of albumin, transferrin, and transthyretin.

With these reference ranges in place it becomes appropriate to examine other ethnic or geographically diverse populations or subjects with defined diseases.

ACKNOWLEDGMENTS

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