

Original Article

Serum B-Cell Maturation Antigen (BCMA) Levels Differentiate Primary Antibody Deficiencies

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What is already known about this topic? Diagnosis of primary antibody deficiency requiring immunoglobulin replacement often necessitates laborious testing that can be impeded by medications.

What does this article add to our knowledge? Patients with common variable immunodeficiency and X-linked agammaglobulinemia have markedly reduced serum B-cell maturation antigen levels and its measurement may improve evaluation of primary antibody deficiency.

How does this study impact current management guidelines? Low levels of serum B-cell maturation antigen can identify severe primary antibody deficiency, without requiring stoppage of immunoglobulin replacement or protracted functional antibody evaluation.

BACKGROUND: Primary antibody deficiencies (PADs) are the most prevalent primary immunodeficiencies. More severe forms of PADs—common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA)—require immunoglobulin replacement therapy (IRT) and may have serious complications. Differentiating severe PAD from milder hypogammaglobulinemia not requiring IRT can involve prolonged evaluations and treatment discontinuation. Severe PAD is defined by plasma cell deficiency, but this requires a biopsy to establish. Serum B-cell maturation antigen (sBCMA) is elevated in multiple myeloma, but levels are reduced among patients with myeloma in remission who have hypogammaglobulinemia.

OBJECTIVE: To measure the sBCMA level in 165 subjects to determine whether it differentiates severe PAD—CVID and XLA—from less severe forms not requiring IRT and those without PAD.

METHODS: sBCMA, B cells, and tissue plasma cells were measured among subjects with and without PAD, and correlated to clinical and laboratory data.

RESULTS: Subjects with an IgG level of less than 600 mg/dL had reduced sBCMA levels compared with subjects with PAD with IgG levels of greater than or equal to 600 mg/dL and controls without PAD. sBCMA level was lower in patients with CVID and XLA compared with patients with IgA or IgG deficiency and controls. sBCMA level correlated with gastrointestinal plasma cells. sBCMA level of less than 15 ng/mL had 97% positive predictive value for CVID or XLA, whereas 25 ng/mL or more had an 88% negative predictive value.

CONCLUSIONS: sBCMA level is profoundly reduced in patients with severe PAD, including those with CVID and XLA and those with IgG levels of less than 600 mg/dL. sBCMA level measurement has potential to augment clinical evaluation of PAD. Prospective studies are needed to evaluate sBCMA for new PAD diagnosis and determine the necessity of IRT. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: B-cell maturation antigen; Common variable immunodeficiency; Immunoglobulin replacement therapy; Primary antibody deficiency; X-linked agammaglobulinemia

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INTRODUCTION

The many forms of primary antibody deficiency (PAD) are the most prevalent primary immunodeficiencies.¹ Severe forms of PAD, including common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA), are associated with chronic medical complications, such as bronchiectasis, and

Abbreviations used

BCMA- B-cell maturation antigen
CVID- Common variable immunodeficiency
IgAD- Selective IgA deficiency
IgA/IgG2D- IgA and IgG2 deficiency
IgGD- IgG deficiency
IRT- Immunoglobulin replacement therapy
NPV- Negative predictive value
PAD- Primary antibody deficiency
PPV- Positive predictive value
sBCMA- Serum BCMA
XLA- X-linked agammaglobulinemia

require immunoglobulin replacement therapy (IRT).²⁻⁴ However, more restricted defects of antibody production, or those associated with immaturity or medications, may not require lifelong IRT.⁵ Differentiating patients with PAD requiring IRT from those with these less profound immunoglobulin deficiencies requires evaluation of antibody responses; this can take weeks or more and may involve repeated vaccinations.^{6,7} Moreover, such evaluation requires discontinuation of IRT in those for which such treatment is questionable and may expose the patient to a significant risk of infection.⁸ Rapid diagnostic tests to identify those with severe PAD that would not necessitate protracted vaccine challenges or stopping IRT could reduce diagnostic delay, diminish chronic pulmonary complications, and improve these patients' compromised quality of life.⁹

The hallmark of XLA and most subjects with CVID is a lack of plasma cells in bone marrow or mucosal sites, but biopsy of these tissues is required to assess plasma cell abundance.¹⁰⁻¹³ B-cell maturation antigen (BCMA) is a TNF receptor expressed largely on the surface of plasma cells and plasmablasts that promotes the survival of these cells on engagement with its ligands, a proliferation-inducing ligand and B-cell-activating factor.¹⁴ BCMA is cleaved endogenously by gamma secretase and can be quantified in a solubilized form in the blood.¹⁵ Serum B-cell maturation antigen (sBCMA) level is elevated among patients with multiple myeloma, a plasma cell malignancy in which it both predicts patients' survival and can be used to monitor the course of disease.¹⁶ However, the utility of determining sBCMA levels in PAD to evaluate the plasma cell population has not yet been investigated.

In this study, our goal was to measure sBCMA levels in a large cohort of subjects with PAD to determine whether this marker could distinguish more severe PAD (CVID and XLA) from milder forms of antibody loss. Combining sBCMA detection with measurement of peripheral B-cell subsets, immunoglobulin levels, antibody production, and plasma cells in gastrointestinal biopsies, we found that subjects with CVID and XLA, as well as subjects with PAD with IgG levels less than 600 mg/dL, were characterized by decreased sBCMA levels, in correspondence with reduced plasma cells in mucosal tissues. sBCMA levels of less than 15 ng/mL had 97% positive predictive value (PPV) for CVID or XLA, whereas a cutoff of 25 ng/mL had an 88% negative predictive value (NPV). Our results demonstrate the potential of sBCMA measurement as an informative tool to aid the diagnosis of the severe PADs, one that does not require stoppage of IRT or lengthy evaluation with vaccination challenges.

METHODS**Subjects and retrospective review of medical records**

All subjects included in this study were patients at the Mount Sinai Clinical Immunology Faculty Practice. Patients with the *International Classification of Diseases Ninth or Tenth Revision* code for CVID (279.06 or D83.9), selective IgA deficiency (IgAD, 279.01 or D80.2), IgA deficiency with IgG2 subclass deficiency (IgA/IgG2D, 279.03 or D80.3), IgG deficiency (IgGD, 279.01 or D80.1), and XLA (279.04 or D80.0) were enrolled. The diagnosis of CVID was confirmed in all subjects on the basis of markedly low serum IgG and IgA and/or IgM levels (IgG < 400 mg/dL, IgA < 45 mg/dL, and IgM < 35 mg/dL), poor response to at least 1 vaccine, and exclusion of other causes of hypogammaglobulinemia.¹⁷ Patient age, sex, laboratory values (IgG, IgA, IgM, CD19⁺ B cells, isotype-switched memory B cells, and pneumococcal antibodies), and history of complications in patients with CVID (autoimmunity, interstitial lung disease, enteropathy, bronchiectasis, or pneumonia) were derived from the medical records. This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

sBCMA measurement

Serum was diluted 1:50 in reagent diluent and levels of human sBCMA were determined using an ELISA-based assay with polyclonal anti-BCMA antibodies for capture and detection (R&D Systems, Minneapolis, Minn) as done previously.¹⁶ Samples were analyzed using an EPOCH2 microplate reader (BioTek Instruments Inc, Winooski, Vt) set to 450 nm with Gen5 software (BioTek Instruments Inc) for data collection.

Quantification of plasma cells in gastrointestinal biopsies

All gastrointestinal biopsies were conducted as part of routine clinical care. Plasma cells were quantified in 17 gastrointestinal biopsies from subjects with PAD in a blinded manner by 2 independent reviewers. Plasma cells were identified by CD138 staining via immunohistochemistry and/or by distinct morphology on hematoxylin and eosin staining if no tissue was available for immunohistochemistry.

Statistical analysis

Analysis of 2 groups of continuous variables was done by Mann-Whitney test. Analysis of 3 or more groups of continuous variables was conducted using Kruskal-Wallis test followed by Dunn multiple comparisons. Comparison of categorical values was determined using χ^2 test for instances in which the sample size was large and Fisher exact test for smaller sample size. Correlation was calculated using Spearman r . Calculations were made using Prism software (GraphPad, San Diego, Calif). A P value of less than .05 was considered significant.

RESULTS**sBCMA level is reduced in severe PAD**

The level of sBCMA was determined in 145 patients with PAD who were evaluated at the Mount Sinai Clinical Immunology Practice as well as 20 controls without PAD. The subjects with PAD (Table 1) had diagnoses that varied between IgAD ($n = 10$), IgA/IgG2D ($n = 8$), IgGD ($n = 22$), CVID ($n = 93$), and XLA ($n = 12$). We found sBCMA levels to be significantly reduced in patients with CVID and XLA compared with those with IgGD, IgAD, and controls without PAD ($P < .0001$;

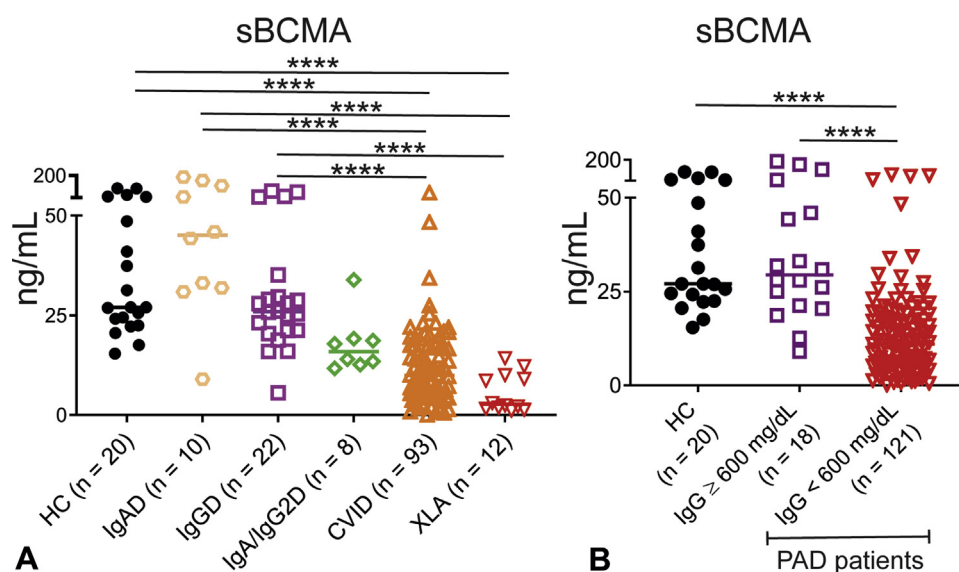
TABLE I. Characteristics of subjects with PAD in the study

Characteristic	IgAD (n = 10)	IgGD (n = 22)	IgA/IgG2D (n = 8)	CVID (n = 93)	XLA (n = 12)	P value
Sex: female, n (%)	5 (50)	15 (68)	3 (38)	52 (56)	0 (0)	.609*
Age (y), median (95% CI)	45 (28-60)	69 (58-73)	22 (16-41)	50 (47-52)	21 (11-36)	<.0001
Laboratory value, median (95% CI)						
Diagnostic IgM (mg/dL)	162 (61-485)	81 (29-114)	42 (18-67)	15 (10-17)	0 (0-0)	<.0001
Diagnostic IgA (mg/dL)	0 (0-63)	114 (65-145)	0 (0-16)	0 (0-6)	0 (0-0)	<.0001
Diagnostic IgG (mg/dL)	1066 (779-2311)	530 (476-622)	563 (508-752)	145 (93-215)	NA	<.0001
sBCMA level (ng/mL), median (95% CI)	45.1 (30.9-167.4)	26.0 (21.2-29.7)	16.0 (11.7-33.9)	9.9 (6.8-12.1)	2.7 (1.6-10.0)	<.0001

NA, Not applicable/available.

P value was calculated by χ^2 test for categorical values and Kruskal-Wallis test for continuous values.

*P value calculation for female subjects excludes XLA.

**FIGURE 1.** sBCMA level is reduced in severe PAD. (A) sBCMA level is lower in patients with CVID and XLA compared with patients with IgAD, patients with IgGD, and HCs. (B) sBCMA level is lower in patients with PAD with IgG levels of less than 600 mg/dL compared with those with levels of greater than or equal to 600 mg/dL or HCs. Five subjects with IgAD and IgA/IgG2D did not have baseline IgG levels. HC, Healthy control. Line denotes median. **** $P < .0001$.**TABLE II.** Predictive value of sBCMA level for severe PAD

sBCMA (ng/mL)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Likelihood ratio
<15	73% (64-81)	96% (87-99)	97% (87-99)	64% (53-74)	19.1
<20	88% (80-93)	87% (75-93)	93% (86-97)	78% (65-86)	6.5
<25	95% (89-98)	69% (56-80)	86% (79-91)	88% (75-95)	3.1

Severe PAD defined as CVID or XLA.

Figure 1, A). sBCMA level was generally lower in subjects with IgA/IgG2D (median, 16.0 ng/mL) compared with those with IgAD alone (45 ng/mL), IgGD (26 ng/mL), and controls without PAD (27 ng/mL), but statistical significance was not reached. We noted that the median value for IgA/IgG2D (16.0 ng/mL) was not as low as that of either subjects with CVID (9.9 ng/mL) or subjects with XLA (2.7 ng/mL), suggesting more preserved plasma cell populations in these subjects, as would be expected. To determine whether sBCMA levels differed in those with varying degrees of hypogammaglobulinemia, we grouped subjects on the basis of whether they had a baseline serum IgG level of greater than or equal to 600 mg/dL. This IgG cutoff was derived from consensus guidelines for the diagnosis of CVID, in

which IgG levels should be at least 2 SDs below normal, or approximately 600 mg/dL.^{18,19} As expected, sBCMA level was lower in patients with PAD with a serum IgG level of less than 600 mg/dL (median, 11.1 ng/mL) compared with those with IgG levels of greater than or equal to 600 mg/dL (29.5 ng/mL) as well as healthy controls (27 ng/mL) ($P < .0001$; Figure 1, B). Together these results indicate that sBCMA levels are decreased in those with severe PAD, defined by either a clinical diagnosis of CVID or XLA or serum IgG levels less than 600 mg/dL.

Predictive value of sBCMA for severe PAD

We then determined the predictive value of sBCMA measurement for the diagnosis of severe forms of PAD (CVID or

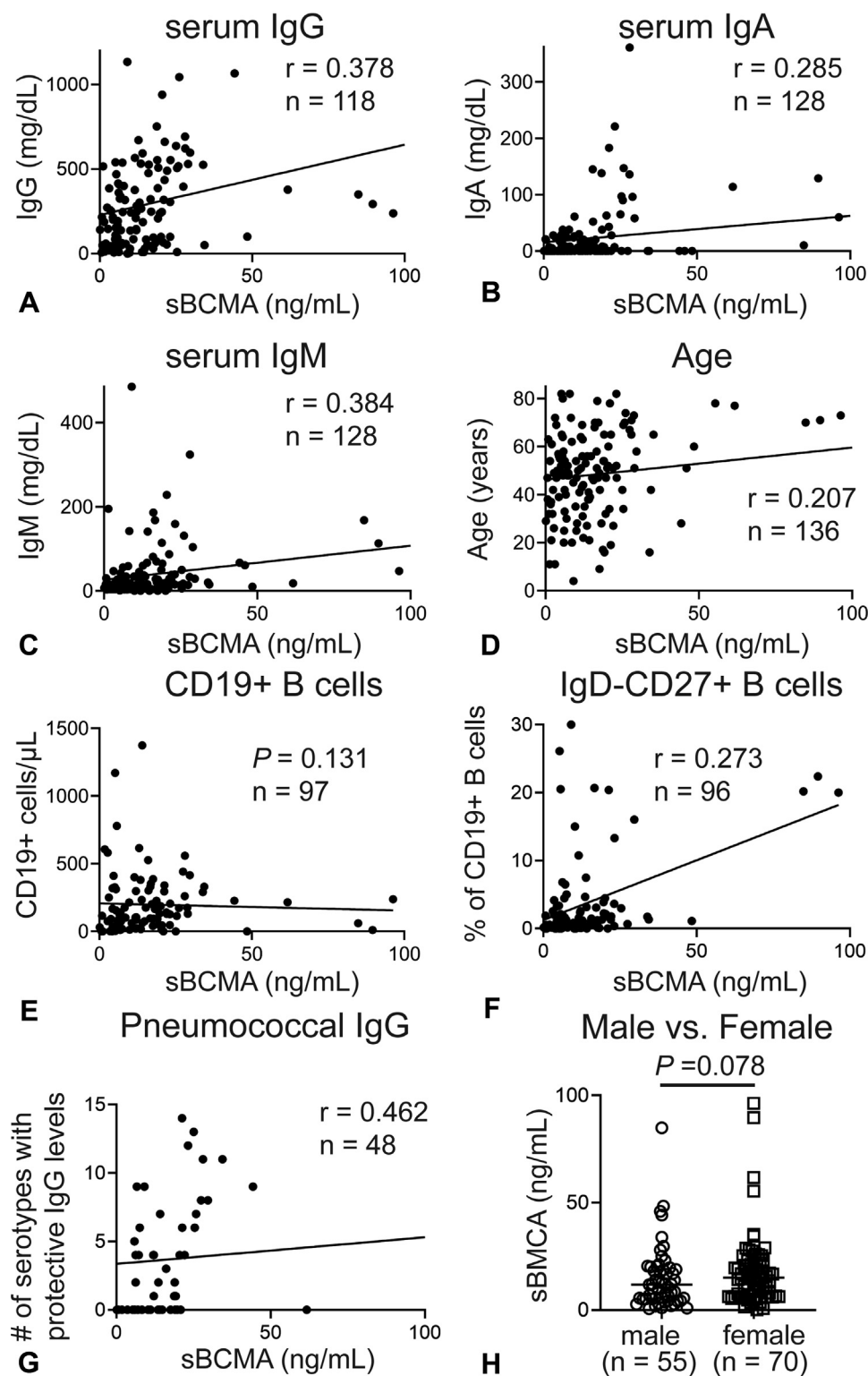


FIGURE 2. sBCMA level is independent of conventional parameters used in the evaluation of subjects with PAD with IgAD, IgA/IgG2D, IgGD, CVID, or XLA. Correlation of sBCMA level with (A) pre-IRT IgG, (B) IgA, and (C) IgM levels, (D) age, (E) CD19⁺ B cells, (F) isotype-switched memory B cells, and (G) pneumococcal serotypes with protective IgG. (H) sBCMA level comparison between males and females (XLA excluded). Lines denote median.

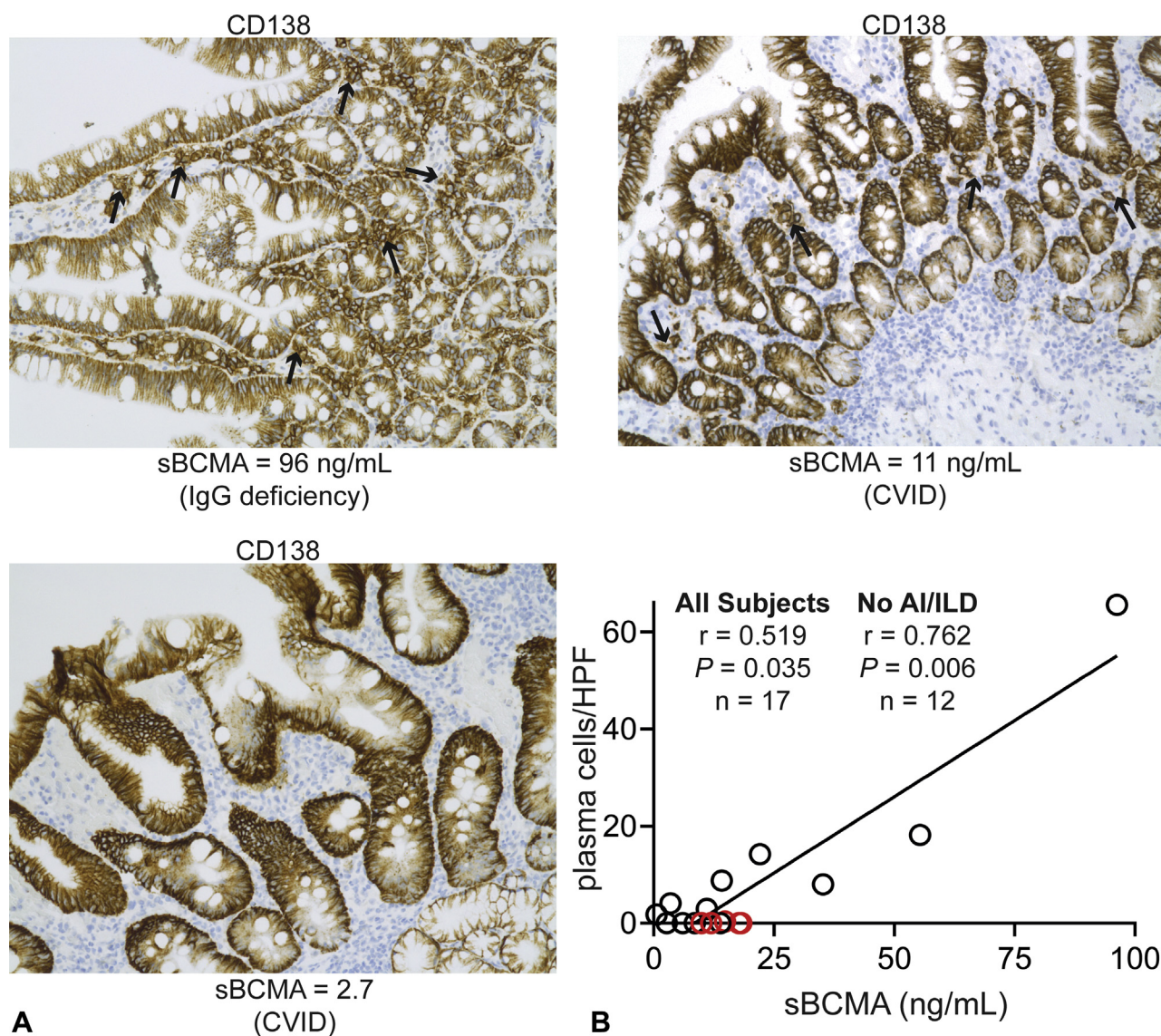


FIGURE 3. sBCMA level correlates with plasma cell counts in the gastrointestinal tract. (A) Representative gastrointestinal biopsies from patients with PAD. CD138⁺ plasma cells denoted by black arrows. (B) Correlation of sBCMA level with number of plasma cells per hpf. Subjects with autoimmunity (AI) or interstitial lung disease (ILD) marked as red circles. Spearman *r* calculated for subjects with and without AI/ILD.

XLA) within this study cohort. Subjects with IgA/IgG2D were excluded from this analysis because an unclear number of these patients may progress to CVID.²⁰ The receiver-operating characteristic curve for sBCMA demonstrated excellent discrimination of severe forms of PAD (CVID and XLA) from other subjects with and without PAD, with an area under the curve of 0.9448 (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The fifth percentile for sBCMA level in controls without PAD was 15.6 ng/mL. Using an sBCMA level of less than 15 ng/mL for identifying CVID or XLA among subjects with and without PAD, sensitivity was 73% (95% CI, 64-81), specificity 96% (95% CI, 87-99), and PPV 97% (95% CI, 87-99) (Table II). We did not find a notable improvement in specificity or PPV when a cutoff level of 10 ng/mL for sBCMA was used. Sensitivity and NPV did improve with increases in

sBCMA levels, and a cutoff level of 20 ng/mL had 88% sensitivity and 78% NPV, whereas 25 ng/mL (approximately the median of controls without PAD) had 95% sensitivity and 88% NPV. Our findings suggest that sBCMA measurement has potential to aid in the evaluation of patients suspected of having CVID or XLA.

sBCMA correlates poorly with conventional parameters used to evaluate patients with PAD

Because there were significant differences in age and immunoglobulins among the distinct PAD diagnoses included (Table I), we tested the correlation of sBCMA level with these variables as well as with other common clinical measurements from the medical records. Using data from all subjects with PAD analyzed together, we calculated Spearman correlation

TABLE III. Characteristics of subjects with CVID in the study

Characteristic	Value
No. of subjects	93
Sex: female, n (%)	51 (55)
Age (y), median (95% CI)	50 (47-52)
Laboratory value, median (95% CI)	
Diagnostic IgG (mg/dL)	145 (93-215)
Diagnostic IgA (mg/dL)	0 (0-6)
Diagnostic IgM (mg/dL)	15 (10-17)
CD19 ⁺ B cells (#/μL)	99.5 (76-140)
Isotype-switched memory B cells (% of CD19 ⁺)	1.19 (0.75-1.55)
Complication history, n (%)	
Autoimmunity	29 (31)
Interstitial lung disease	27 (29)
Enteropathy	14 (15)
Bronchiectasis	17 (18)
Pneumonia	60 (65)

coefficients (r) and for those that were significant ($P < .05$) used conventional interpretations for strength of correlation, with r less than 0.4 signifying poor correlation, $r = 0.4$ to 0.7 as moderate correlation, and $r = 0.7$ to 1.0 as strongly correlated.^{21,22} sBCMA level correlated poorly with serum IgG ($r = 0.38$), IgA ($r = 0.285$), IgM ($r = 0.384$), and age ($r = 0.207$) (Figure 2, A–D). Thus, despite immunoglobulin levels and age, which were significantly variable among our subject groups, these characteristics were not correlated to sBCMA levels. We found that circulating B-cell counts were also not correlated with sBCMA levels ($P = .131$) and levels of isotype-switched memory B cells in the blood were only poorly correlated ($r = 0.273$) (Figure 2, E and F). Postvaccination pneumococcal antibodies were tested in 48 subjects with PAD and found to moderately correlate with sBCMA level ($r = 0.462$) (Figure 2, G). Female subjects with PAD trended toward higher sBCMA levels, but this difference was short of statistical significance ($P = .078$). Together these results indicate that sBCMA levels are not strongly associated with the typical clinical and laboratory parameters measured during PAD evaluation.

sBCMA correlates with plasma cell counts in the gastrointestinal tract

Because BCMA is largely expressed by plasma cells, we correlated sBCMA measurement with quantification of plasma cells in the gastrointestinal tract mucosa, where these cells are typically numerous. Gastrointestinal biopsies from 17 subjects with PAD performed as part of routine medical care were used. Plasma cells were quantified in the duodenum whenever possible ($n = 14$), the terminal ileum if no tissue from the duodenum was available ($n = 1$), and right colon in the instances where no tissue from the duodenum or terminal ileum was available ($n = 2$). Plasma cells are often profoundly reduced in CVID but maintained at near-normal levels in those with less severe forms of PAD (Figure 3, A).²³ We found that the level of sBCMA was correlated with the number of plasma cells per hpf ($r = 0.519$; Figure 3, B). Because we have shown that subjects with CVID with autoimmunity and interstitial lung disease have IgM-producing plasmablasts (which may also express BCMA), but still lack gastrointestinal plasma cells, we also evaluated

correlation without the 5 subjects with this phenotype.²⁴ On removing these subjects, we again analyzed the data and found even stronger correlation between sBCMA levels and gastrointestinal plasma cells ($r = 0.762$). Thus, sBCMA level correlates with plasma cell count more strongly than with any of the conventional laboratory tests used during PAD evaluation.

sBCMA levels in patients with CVID with or without a history of complications

sBCMA levels were quite variable in CVID, not unexpected, because this PAD is noted for its heterogeneous clinical presentations.²⁵ However, because BCMA levels exert controls on autoimmunity in murine models,^{26–28} we investigated whether these levels may be influenced by the presence of autoimmunity and/or interstitial lung disease in CVID. Although the clinical and laboratory characteristics of the 93 patients with CVID included in this study were similar to those of other cohorts (Table III),^{29,30} there was no statistical difference in sBCMA levels between those with or without histories of autoimmunity, interstitial lung disease, enteropathy, bronchiectasis, or pneumonia (Figure 4, A–F).

sBCMA and other characteristics of subjects with IgA/IgG2D and IgGD receiving IRT

Although IRT is the standard of care for those with CVID or XLA, usage of this therapy is at the discretion of the treating physician in those with IgA/IgG2D or IgGD. We examined whether sBCMA levels, as well as other specific parameters, differed between the patients with IgA/IgG2D and IgGD who were or were not prescribed IRT by their treating physician. There was no difference in sBCMA levels between patients with IgA/IgG2D and IgGD on IRT compared with those not on IRT (Figure 5, A). Likewise, there was no difference in pre-IRT IgG, IgA, and IgM levels, pneumococcal antibodies, circulating CD19⁺ B cells, age, or sex between patients with IgA/IgG2D and IgGD who were or were not prescribed this treatment (Figure 5, B–H).

We also determined sBCMA levels in 2 subjects with persistent hypogammaglobulinemia as a consequence of rituximab given for autoimmunity more than 5 years ago. Both subjects had been prescribed IRT because of their severe antibody deficiency. Interestingly, the sBCMA levels for these subjects were 4.92 and 5.0 ng/mL, well below the fifth percentile (15 ng/mL) of controls without PAD, which had a PPV of 97%. These illustrative examples suggest the potential for using sBCMA measurement to identify individuals requiring IRT because of persistent antibody deficiency from secondary causes.

DISCUSSION

B-cell-activating factor receptor, transmembrane activator and calcium modulating ligand interactor, and BCMA comprise a group of TNF superfamily receptors that share ligands (B-cell-activating factor and/or a proliferation-inducing ligand) to promote activation, maturation, and survival of B cells.¹⁴ These receptors are differentially expressed during B-cell maturation, with BCMA largely restricted to plasma cells.^{31–34} sBCMA levels are elevated among patients with the plasma cell malignancy multiple myeloma; in addition, the RNA expression of the gene encoding BCMA is much reduced in the blood of patients with CVID who show an absence of plasma cells, suggesting that sBCMA levels may be reduced among patients with severe forms

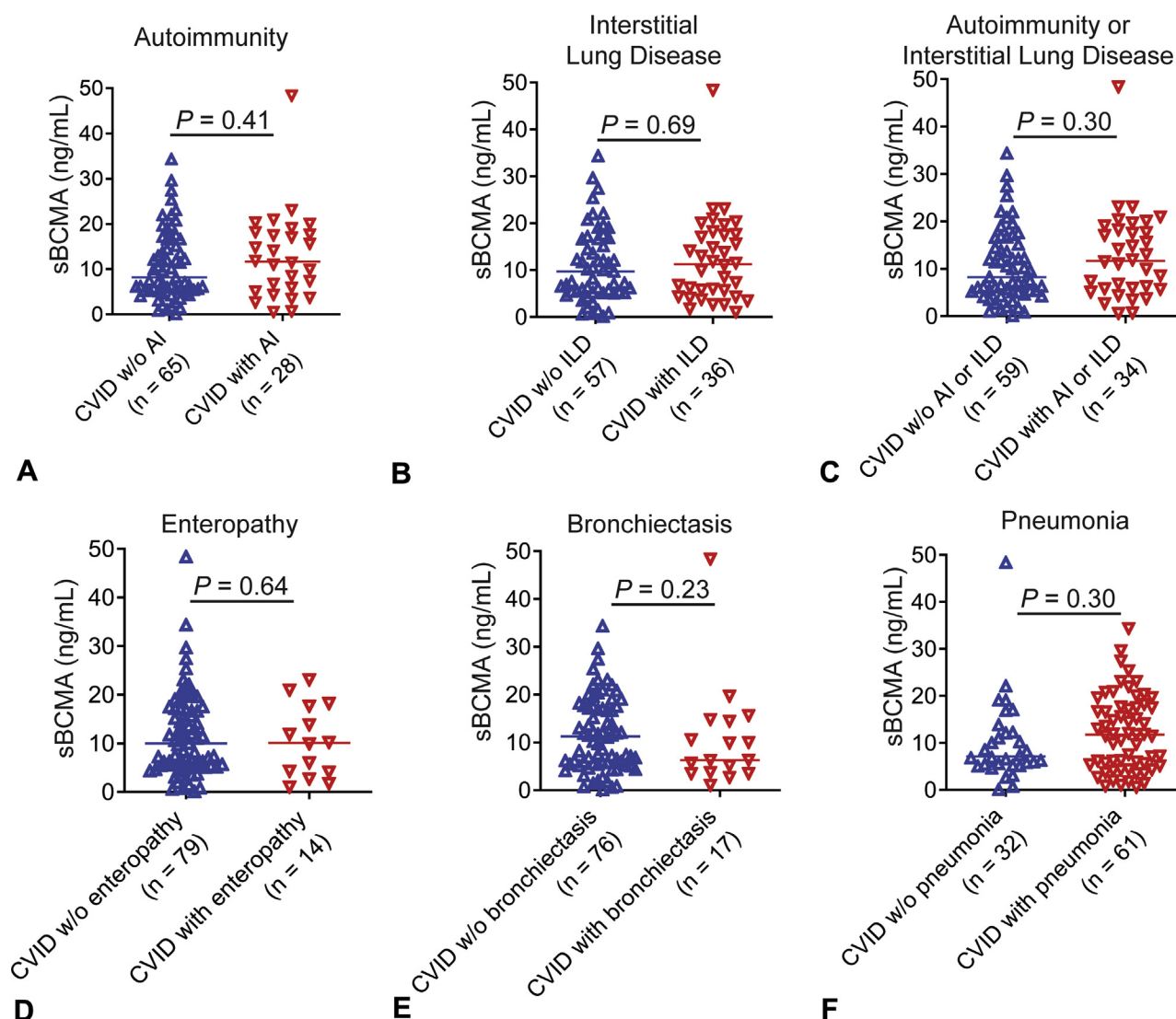


FIGURE 4. sBCMA level in patients with CVID with or without a history of complications. There is no significant difference in sBCMA level between patients with CVID with or without a history of (A) autoimmunity (AI), (B) interstitial lung disease (ILD), (C) AI or ILD grouped together, (D) enteropathy, (E) bronchiectasis, and (F) pneumonia.

of PAD.²⁴ Despite its utility as a noninvasive means to monitor plasma cell abundance, sBCMA measurement has, to our knowledge, not been reported in the evaluation of PAD. In this study, we assessed sBCMA measurement for the identification of individuals with PAD, particularly those with more severe forms in which plasma cells are profoundly reduced or absent.

Because patients with CVID and XLA have a marked deficiency of plasma cells, many develop chronic respiratory complications and all require IRT. As expected, sBCMA level was markedly reduced in subjects with CVID and XLA relative to subjects with IgAD and IgGD or normal controls. sBCMA level was correlated more strongly with plasma cell abundance in gastrointestinal tissues than with immunoglobulin levels, age, CD19⁺ and isotype-switched memory B cells in the blood, and antibody responses to pneumococcal vaccination. Notably, an sBCMA value at the fifth percentile (15 ng/mL) had a high PPV (97%) and the NPV of the median sBCMA level in controls

without PAD (25 ng/mL) was 88%. Thus, sBCMA measurement has the potential to be a useful diagnostic tool in the evaluation of PAD.

Consistent with its expression predominantly by plasma cells, we found sBCMA levels in the blood to be positively correlated with plasma cell abundance in tissues, as quantified in gastrointestinal biopsies. This approach was limited by the number of gastrointestinal tissue used for plasma cell quantification, because only biopsies done as part of regular medical care were available. Plasma cells were quantified in the duodenum preferentially, but the terminal ileum or right colon was used in a few instances. Also potentially affecting the correlation between sBCMA level and gastrointestinal plasma cells is the likelihood that plasma cells in other tissues are a source of sBCMA. Plasma cells are abundant in the bone marrow; however, biopsies of this tissue are infrequently obtained in PAD and were not available in these subjects. However,

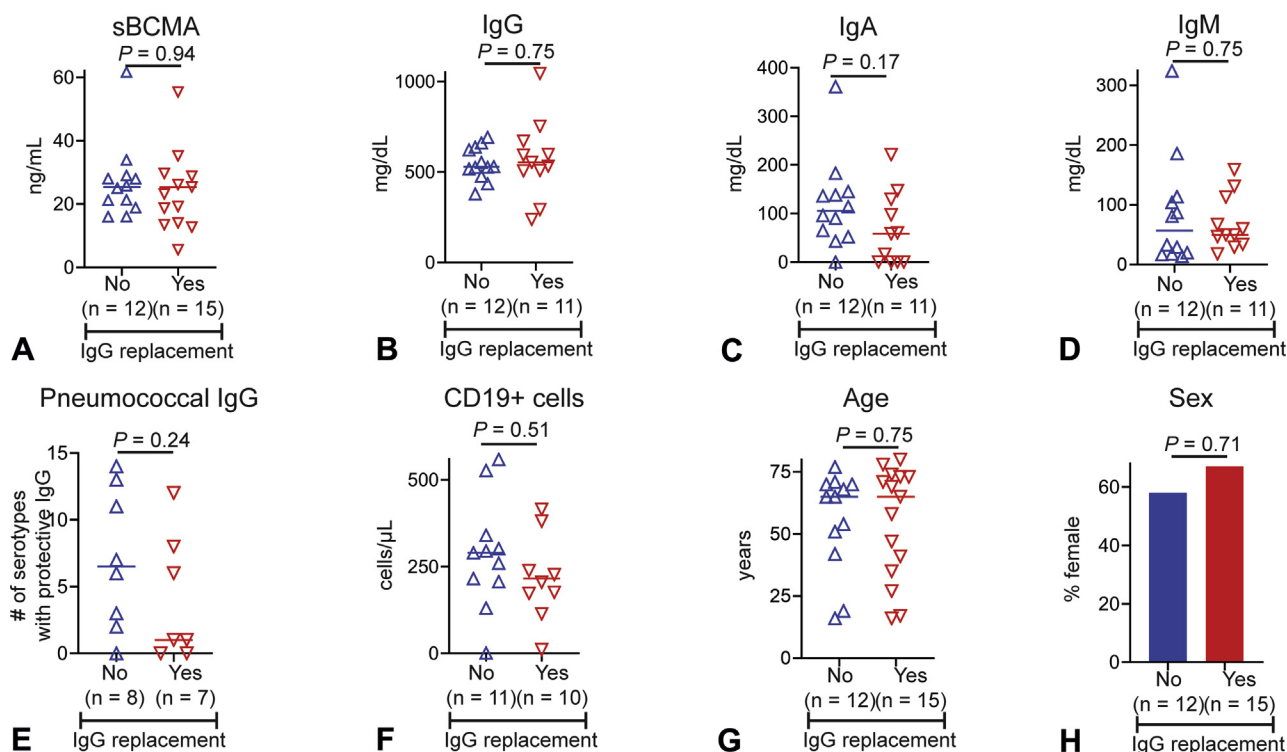


FIGURE 5. sBCMA level and other characteristics of subjects with IgA/IgG2D and IgGD receiving IRT. (A) sBCMA, (B) diagnostic IgG, (C) IgA, (D) IgM, (E) pneumococcal IgG, (F) CD19⁺ B cells, (G) age, and (H) sex did not differ on the basis of IgG replacement. *P* value was calculated by Mann-Whitney test for continuous variables and Fisher exact test for categorical variables.

because 94% of subjects with CVID have highly reduced or no plasma cells in the bone marrow, it is unlikely to be a significant source of sBCMA in these patients.¹¹ Plasmablasts are another potential source of sBCMA and appear to be increased in patients with CVID with autoimmunity and interstitial lung disease.^{24,35} Indeed, on exclusion of patients with CVID with autoimmunity or interstitial lung disease, correlation between sBCMA level and gastrointestinal plasma cells strengthened. Yet, we did not find significant differences in sBCMA levels between patients with CVID on the basis of specific complications, including autoimmunity or interstitial lung disease. Thus, sBCMA levels may be influenced by factors we have yet to define, such as current state of autoimmune and interstitial lung disease activity or alternative sources of sBCMA, such as plasmacytoid dendritic cells.^{36,37} Thus, although largely specific for plasma cells, sBCMA measurement may be complicated by its expression by short-lived plasmablasts in certain patients with CVID as well as its shedding from other cell types.

Although our results are encouraging, prospective studies are needed to validate the utility of sBCMA in PAD diagnosis. Moreover, we must determine whether sBCMA can help identify individuals requiring IRT, particularly those with immunoglobulin deficiency but who do not have a diagnosis of CVID or XLA. This would include those in which evaluation is complicated by usage of immunosuppressive medications or malignancy. sBCMA measurement could be quicker and not have painful localized immunization reactions some experience as a consequence of vaccination challenges currently used for

the evaluation of patients with PAD. sBCMA level was very low in 2 subjects who had persistent hypogammaglobulinemia after receiving rituximab treatment that left them requiring IRT. These illustrative examples, though preliminary, indicate that larger studies of sBCMA measurement in patients for whom the use of IRT is unclear may be informative.

BCMA has previously been shown to have utility as a biomarker and therapeutic target in plasma cell malignancy.^{16,38-40} In addition, sBCMA levels are very low among patients with multiple myeloma in complete remission with reduced nonmalignant plasma cells and associated hypogammaglobulinemia.⁴¹ Thus, we explored whether BCMA levels could be useful for the diagnosis of PAD in whom plasma cells are deficient. Our work demonstrates that sBCMA level is profoundly reduced in patients with PAD with IgG levels of less than 600 mg/dL as well as in those with diagnoses of CVID and XLA, specifically, relative to less severe forms of PAD and those without PAD. These results indicate that sBCMA level may help identify individuals with forms of PAD that require IRT and are associated with chronic complications, that is, specific types of PAD in which earlier diagnosis is particularly crucial. Importantly, sBCMA level measurement can help identify severe PAD without laborious vaccination challenges or the infection risks of stopping IRT in those for which its benefit is in question. Future studies are needed to validate the utility of sBCMA level as a diagnostic tool for clinically significant antibody deficiency and determine whether it can aid in the identification of patients for whom IRT is most appropriate.

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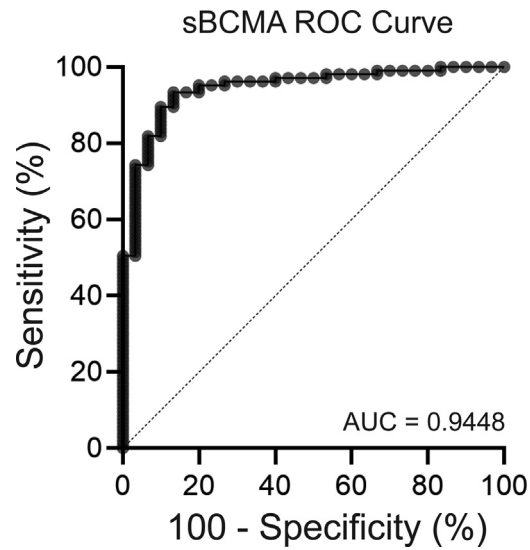


FIGURE E1. Receiver-operating characteristic (ROC) curve for sBCMA level demonstrates excellent discrimination of severe forms of PAD (CVID and XLA) from other PADs and subjects without PAD. Area under the curve (AUC) is 0.9448.