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BRIEF REPORT

Correlation Analysis of Clinician- and Patient-Reported Outcomes Among Japanese Adults with Atopic Dermatitis

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic relapsing condition with high disease burden and impact on health-related quality of life (HRQoL). Correlations between clinician- and patient-reported outcomes tend to be poor, and limited data in Asian patients are available. ***Methods***: ADDRESS-J was a prospective, non-interventional, longitudinal study that evaluated the real-world effectiveness and safety of AD treatment in Japanese adults (aged 20–59 years) with moderate-to-severe AD. Three clinician-reported AD severity outcomes (Investigator's Global Assessment, Eczema Area and Severity Index, and body surface area affected), three dermatological patient-reported outcomes (Patient-Oriented Eczema Measure, Dermatology Life Quality Index, and Worst Itch Numerical Rating Scale), and two general HRQoL patient-reported outcomes (5-dimension EuroQoL questionnaire and EuroQol Visual Analog Scale) were collected at baseline and every 3 months throughout the 24-month observation period. Four biomarkers were also analyzed when available (thymus and activation-regulated chemokine [TARC], lactate dehydrogenase [LDH], total immunoglobulin E [IgE], and peripheral blood eosinophil counts [PB EOS]). Spearman's correlation coefficients

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were calculated using all available pooled data from baseline through 24 months.

Results: Correlations between the three clinician-reported outcomes were high/very high (Spearman's correlation coefficients 0.76–0.92); those between the three dermatological patient-reported outcomes were moderate (0.53–0.64), and those between the clinician-reported and dermatological patient-reported outcomes were low/moderate (0.37–0.51). Correlations between the general HRQoL patient-reported outcomes and the clinician-reported and dermatological patient-reported outcomes were negligible–moderate (0.26–0.60). Biomarker correlations with the clinician-reported and dermatological patient-reported outcomes were low/moderate for TARC and LDH (0.44–0.63), but negligible/low for PB EOS and total IgE (0.01–0.41).

Conclusions: These results show that clinician- and patient-reported outcomes do not necessarily correlate well in Japanese adults with AD. This highlights the importance of including patient-reported outcomes when assessing disease severity/impact, planning treatment, and assessing response to treatment.

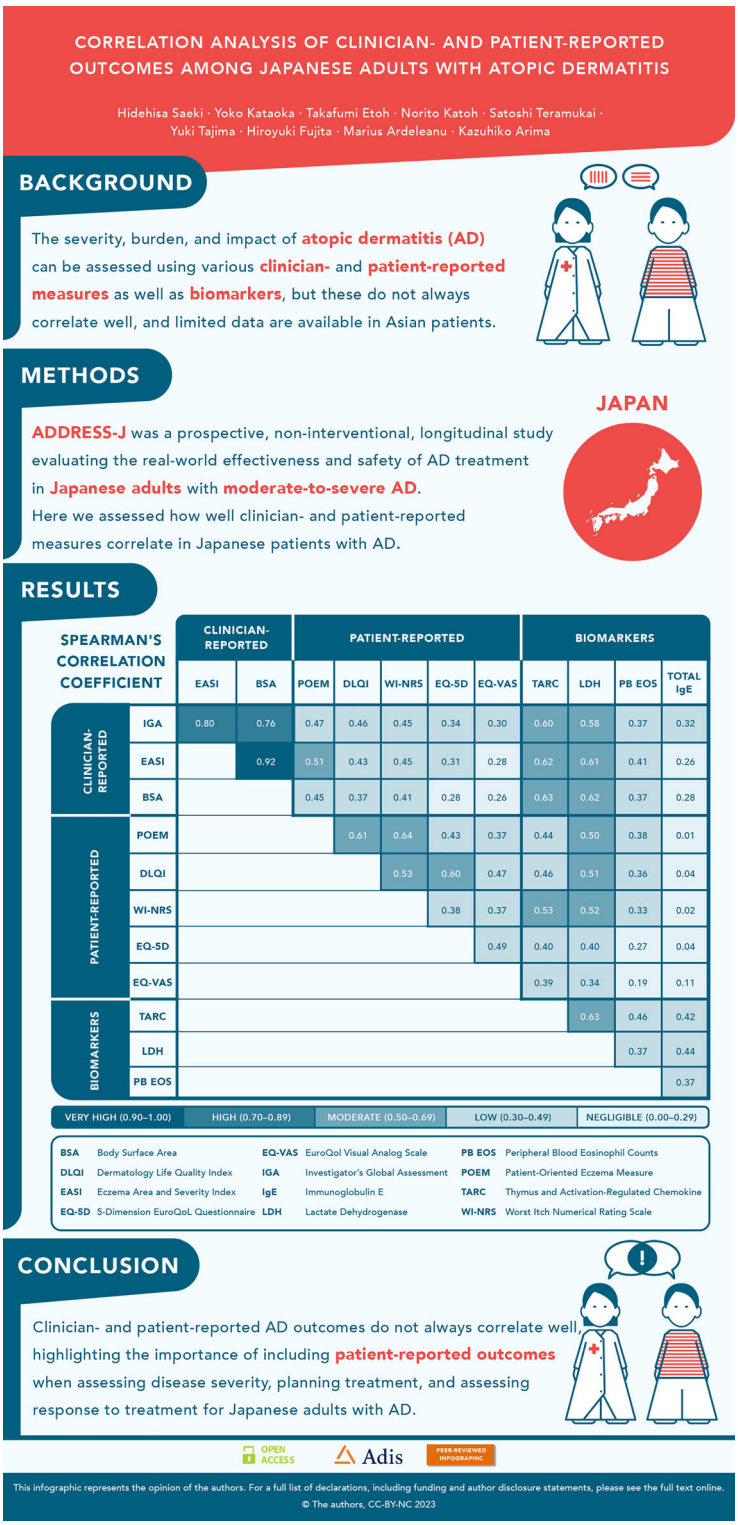
Trial Registration: UMIN Clinical Trials Registry (UMIN-CTR) Identifier UMIN000022623.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis (AD) is a long-term recurring skin disease that needs monitoring over time. Various measures (outcomes) are used to assess the severity of AD and its effect on patients. Some outcomes are based on examinations used by clinicians (doctors). Others are based on questionnaires used by patients themselves to report how severe they feel their AD is, and how it affects their lives. It is not known how well these different measures correlate with one another (how a severity score given by one outcome agrees with that given by another outcome), especially in Asian patients. This analysis used information from ADDRESS-J, a study that followed Japanese adults with moderate-to-severe AD who were treated for AD in the real world for a period of 2 years. It used a statistical method to compare three clinician-reported severity outcomes, three dermatological (skin-related) patient-reported outcomes, and two general health-related quality of life patient-reported outcomes. Agreement between the three clinician-reported outcomes was high or very high. Agreement between the three dermatological patient-reported outcomes was moderate. However, importantly, agreement between the clinician-reported outcomes and the dermatological patient-reported outcomes was low or moderate. Agreement between the general health-related quality of life outcomes and all other dermatological outcomes (whether clinician- or patient-reported) was low or moderate. The study showed that clinician-reported and patient-reported AD outcomes do not necessarily agree well in Japanese adults with AD. This highlights the importance of including patient-reported outcomes when evaluating AD, planning treatment, or judging how well patients are responding to treatment.

Keywords: Adult; Dermatitis; Atopic; Japan; Patient-reported outcomes

Infographic



Key Summary Points

Why carry out this study?

The severity, burden, and impact of atopic dermatitis (AD) can be assessed using various clinician- and patient-reported outcomes, but these do not necessarily correlate well and there are limited data in Asian patients.

The current study assessed how well clinician- and patient-reported outcomes correlate in Asian patients with AD.

What was learned from the study?

Although correlations between clinician-reported outcomes were high/very high and those between dermatological patient-reported outcomes were moderate, correlations between clinician-reported and dermatological patient-reported outcomes were low/moderate.

This highlights the importance of including patient-reported outcomes when assessing disease severity, burden, and impact to guide treatment and assess response to treatment.

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24885015.

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing condition that causes itching and impacts health-related quality of life (HRQoL) [1]. Various instruments are available for clinicians to assess disease severity and extent (e.g., Investigator's Global Assessment [IGA], Eczema Area and Severity Index [EASI], and body surface area [BSA] affected) and for patients to report their AD severity (e.g., Patient-Oriented Eczema Measure [POEM] and Worst Itch Numerical Rating Scale [WI-NRS]) and the impact of AD on their HRQoL (e.g., Dermatology Life Quality Index [DLQI]).

Various studies have reported that although clinician-reported outcomes generally correlate well with each other [2–4], they tend to correlate less well with patient-reported outcomes [2, 3, 5–7]. For example, some patients with low clinician-reported disease severity may report a high burden, highlighting the importance of assessing patient-reported outcomes. As skin color can affect AD assessments [5, 6] and most of these studies included predominantly White patients [2, 4–7] or Japanese patients with exclusively moderate-to-severe AD [3], the objective of the current study was to assess correlations between clinician- and patient-reported outcomes in Japanese patients with a wider range of AD severity levels.

METHODS

Study Design

ADDRESS-J was a prospective, non-interventional, longitudinal study that evaluated the real-world effectiveness and safety of AD treatments in adults (aged 20–59 years) with moderate-to-severe AD (IGA 3 or 4) [3]. ADDRESS-J was conducted from 2016 to 2019, and each patient was followed for 2 years or less. Patients must have been prescribed a new AD medication or been switched to a higher potency/dose at baseline [3]. There were no restrictions on the use of concomitant medications/procedures after enrollment.

The current study analyzed anonymized data from the ADDRESS-J study. The original study was carried out at 30 Japanese medical institutions in accordance with the ethical principles derived from the 1964 Declaration of Helsinki plus subsequent amendments and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects," which was established in 2014. The protocol and other

Table 1 Scores at baseline and 6, 12, and 24 months; and all pooled (baseline through 24 months)

Tool/ biomarker	Scale	Measures	Baseline[a]	6 months	12 months	24 months	Pooled
IGA	0–4[b]	Skin lesions	3.3 (0.4)	2.4 (0.9)	2.3 (0.9)	2.2 (0.9)	2.5 (0.9)
			(*n* = 300)	(*n* = 244)	(*n* = 224)	(*n* = 193)	(*n* = 2053)
EASI	0–72[b]	Skin lesions	25.2 (15.4)	11.0 (10.9)	10.1 (10.8)	9.2 (9.6)	12.4 (12.3)
			(*n* = 300)	(*n* = 244)	(*n* = 221)	(*n* = 192)	(*n* = 2047)
BSA, %	0–100[b]	Skin lesions	50.6 (24.1)	27.0 (22.5)	25.6 (22.2)	23.2 (20.2)	28.9 (23.4)
			(*n* = 300)	(*n* = 244)	(*n* = 221)	(*n* = 192)	(*n* = 2047)
POEM	0–28[b]	Skin lesions, pruritus, sleep	16.9 (6.7)	9.9 (7.0)	10.4 (7.0)	11.1 (6.9)	11.1 (7.2)
			(*n* = 300)	(*n* = 239)	(*n* = 218)	(*n* = 179)	(*n* = 2090)
DLQI	0–30[b]	Pruritus, HRQoL	8.3 (6.3)	4.0 (3.1)	4.1 (3.6)	3.9 (3.3)	4.7 (4.3)
			(*n* = 300)	(*n* = 241)	(*n* = 216)	(*n* = 182)	(*n* = 1987)
WI-NRS	0–10[b]	Pruritus	6.5 (2.2)	4.3 (2.3)	4.6 (2.3)	4.6 (2.3)	4.7 (2.4)
			(*n* = 297)	(*n* = 239)	(*n* = 218)	(*n* = 179)	(*n* = 2088)
EQ-5D	0–1[c]	HRQoL[d]	0.79 (0.18)	0.89 (0.10)	0.88 (0.11)	0.89 (0.10)	0.87 (0.12)
			(*n* = 297)	(*n* = 241)	(*n* = 216)	(*n* = 182)	(*n* = 1988)
EQ-VAS	0–100[c]	Global HRQoL	61.4 (22.0)	71.3 (16.8)	70.4 (18.3)	72.2 (17.0)	70.0 (18.5)
			(*n* = 297)	(*n* = 240)	(*n* = 216)	(*n* = 180)	(*n* = 1977)
TARC, pg/mL	NA	NA	3157 [331, 58,677]	607 [267, 5044]	680 [235, 5241]	930 [185, 3671]	774 [142, 58,677]
			(*n* = 67)	(*n* = 40)	(*n* = 32)	(*n* = 22)	(*n* = 355)
LDH, IU/L	NA	NA	316 (116)	219 (62.9)	206 (58.7)	196 (41.3)	229 (88.0)
			(*n* = 71)	(*n* = 37)	(*n* = 34)	(*n* = 23)	(*n* = 360)
PB EOS, 10^9/L	NA	NA	0.96 (0.62)	0.43 (0.31)	0.39 (0.27)	0.34 (0.22)	0.49 (0.43)
			(*n* = 52)	(*n* = 39)	(*n* = 36)	(*n* = 24)	(*n* = 354)

Table 1 continued

Tool/ biomarker	Scale	Measures	Baseline[a]	6 months	12 months	24 months	Pooled
Total IgE, IU/mL	NA	NA	6568 [45, 66,200] (n = 66)	8166 [160, 56,925] (n = 7)	6374 [806, 9462] (n = 8)	4134 [1821, 7590] (n = 3)	6086 [27, 119,972] (n = 140)

Data are presented as mean (SD) or median [minimum, maximum] (number of patients with data)
BSA body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *EQ-5D* 5-dimension EuroQoL questionnaire, *EQ-VAS* EuroQol Visual Analog Scale, *HRQoL* health-related quality of life, *IGA* Investigator's Global Assessment, *IgE* immunoglobulin E, *LDH* lactate dehydrogenase, *NA* not applicable, *PB EOS* peripheral blood eosinophil counts, *POEM* Patient-Oriented Eczema Measure, *SD* standard deviation, *TARC* thymus and activation-regulated chemokine, *WI-NRS* Worst Itch Numerical Rating Scale
[a]Baseline data were previously reported as median and range [3]
[b]Higher scores indicate more severe disease
[c]Higher scores indicate better health
[d]Dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression

documents were approved by institutional review boards/ethics committees, details of which can be found in the Ethical Approval section. All patients provided written informed consent before any study procedures [3].

Outcomes

Clinician- and patient-reported outcomes were collected at baseline and every 3 months throughout the 24-month observation period. Clinician-reported outcomes were IGA (0–4), EASI (0–72), and BSA (0–100%), and dermatological patient-reported outcomes were POEM (0–28), DLQI (0–30), and WI-NRS (0–10); higher scores indicate more severe disease. We also studied two general HRQoL outcomes: the 5-dimension EuroQoL questionnaire (EQ-5D) (0–1) and EuroQol Visual Analog Scale (EQ-VAS) (0–100); higher scores indicate better health. Various biomarkers were analyzed when these were available in routine clinical practice: serum levels of thymus and activation-regulated chemokine (TARC), lactate dehydrogenase (LDH), total immunoglobulin E (IgE), and peripheral blood eosinophil counts (PB EOS).

Statistical Analysis

Analyses of correlation between outcomes were performed, with scores ranked from least to most severe disease, regardless of the direction of the numeric scores. Spearman's correlation coefficients were calculated using all available pooled data from baseline through 24 months. Values of 0.90–1.00 were interpreted to show very high correlations; 0.70–0.89, high; 0.50–0.69, moderate; 0.30–0.49, low; and 0.00–0.29, negligible [8]. The statistical package SAS® (version 9.2 or later; SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

Of the 300 patients included in ADDRESS-J (60.7% male; median age 34 years) [3], 288 had at least one post-baseline evaluation [9]. At baseline, most of these 288 patients (80.2%) were only receiving topical AD treatment (corticosteroid and/or calcineurin inhibitor), 14.6% systemic treatment, and 5.6% ultraviolet phototherapy [9]. By 24 months, the corresponding

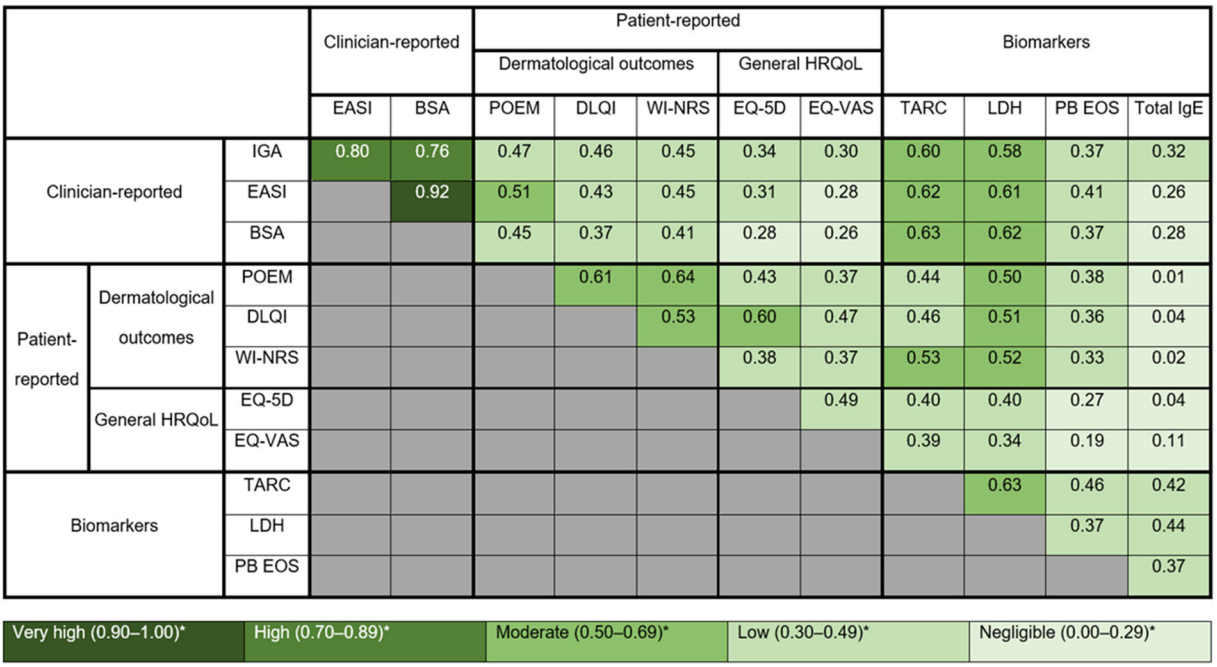


Fig. 1 Spearman's correlation coefficients between outcomes using the pooled data. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index; *EQ-5D* 5-dimension EuroQoL questionnaire, *EQ-VAS* EuroQol Visual Analog Scale, *HRQoL* health-related quality of life, *IGA* Investigator's Global Assessment, *IgE* immunoglobulin E, *LDH* lactate dehydrogenase, *PB EOS* peripheral blood eosinophil counts, *POEM* Patient-Oriented Eczema Measure, *TARC* thymus and activation-regulated chemokine, *WI-NRS* Worst Itch Numerical Rating Scale. *Cutoffs from Mukaka [8]

figures were 59.7%, 29.9%, and 12.2%, respectively, and 2.1% had received biologics [9].

Mean clinician- and patient-reported outcomes improved from baseline to 6 months and were then maintained for the remainder of the study (Table 1). The proportion of patients with IGA 3 or 4 fell from 100% at baseline to 50.4%, 44.6%, and 42.0% at 6, 12, and 24 months, respectively, providing data for a range of AD severities.

Correlations between the three clinician-reported outcomes (IGA, EASI, BSA) were high/very high (Spearman's correlation coefficients 0.76–0.92), while those between the three dermatological patient-reported outcomes (POEM, DLQI, WI-NRS) were moderate (0.53–0.64), and those between clinician- and patient-reported outcomes were mainly low (0.37–0.51) (Fig. 1). Correlations between the general patient-reported HRQoL outcomes (EQ-5D, EQ-VAS) and the other six outcomes were negligible to moderate (0.26–0.60) (Fig. 1).

Correlations between clinician- or dermatological patient-reported outcomes were low/moderate for TARC or LDH (Spearman's correlation coefficients 0.44–0.63), low for PB EOS (0.33–0.41), and generally negligible for total IgE (0.01–0.32), with better correlations with biomarkers for clinician- vs. dermatological patient-reported outcomes overall (Fig. 1). Correlations between biomarkers were low/moderate (0.37–0.63) (Fig. 1).

Figure 2 shows how the individual scores were correlated. For example, the EASI/BSA correlation shows a strong linear relationship, but the EASI/POEM and EASI/WI-NRS correlations had many datapoints with low EASI but high POEM or WI-NRS, indicating a potential discrepancy between clinician- and patient-reported outcomes.

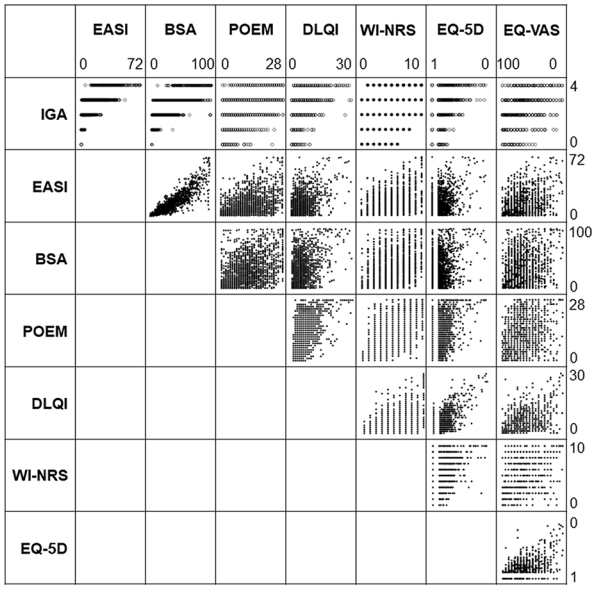


Fig. 2 Correlations for clinician- and patient-reported outcomes using the pooled data. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *EQ-5D* 5-dimension EuroQoL questionnaire, *EQ-VAS* EuroQol Visual Analog Scale, *IGA* Investigator's Global Assessment, *POEM* Patient-Oriented Eczema Measure, *WI-NRS* Worst Itch Numerical Rating Scale

DISCUSSION

In this analysis of approximately 2000 datapoints, correlations between clinician-reported outcomes were high/very high (Spearman's correlation coefficients 0.76–0.92), with moderate correlations (0.53–0.64) between dermatological patient-reported outcomes. However, correlations between clinician- and dermatological patient-reported outcomes were mainly low (0.37–0.51), indicating a discrepancy in disease assessment and perception between clinicians and patients. This highlights the importance of including patient-reported outcomes when assessing disease severity for treatment selection and response [10, 11] (as is recommended for dupilumab in the UK [12]). In Japan, newer systemic treatment options have recently been approved for patients with AD [1, 13]. These are only indicated for patients who have IGA $\geq$ 3 and BSA $\geq$ 10% and EASI $\geq$ 16 (or head and neck EASI $\geq$ 2.4) [1, 13], which are all clinician-reported. The addition of patient-reported outcomes might be clinically meaningful for identifying patients not otherwise considered to have high disease burden.

The current results are well aligned with correlation analyses performed in predominantly White patients [2, 4–7]. Overall, POEM and WI-NRS appear to be suitable for assessing disease improvement, whereas EASI and DLQI seem to be appropriate for assessing more severe disease. This is because lower POEM or WI-NRS scores are associated with milder skin lesions and better HRQoL, while higher scores may not always indicate severe skin lesions or poor HRQoL.

Although there was a moderate correlation between DLQI and EQ-5D (Spearman's correlation coefficient 0.60), correlations between the other outcomes and EQ-5D or EQ-VAS were negligible/low (0.26–0.49), showing the limited clinical relevance of these outcomes for Japanese patients with AD. The limitation (ceiling effect) of EQ-5D as a tool for HRQoL assessment has previously been demonstrated [14].

Although the biomarker results should be interpreted with caution because of the limited data available, correlations between PB EOS or total IgE and clinician-/patient-reported outcomes were negligible/low (0.01–0.41), showing that these are poor indicators of AD severity, although total IgE is generally higher in patients with atopic predisposition [1]. TARC and LDH showed moderate correlations with clinician-reported outcomes (Spearman's correlation coefficients 0.58–0.63) and low/moderate correlations with dermatological patient-reported outcomes (0.44–0.53). Japanese guidelines recognize that serum TARC levels correlate more strongly with disease severity and progression than with the other three biomarkers [1], although we found similar correlations for TARC and LDH. Recent data have suggested that interpretation of the levels of each biomarker depends on the treatments used [15].

Strengths and Limitations

To our knowledge, this is the largest Japanese dataset that has been analyzed for correlations

between outcomes among patients with a range of AD severities. It expands upon our previous correlation analysis (which included only data at baseline, when all patients had IGA 3 or 4) [3]. However, there are some limitations: some data were missing for some patients (particularly biomarker data), the number of patients diminished over time, and there were fewer patients with low IGA scores. The low number of patients with biomarker data was due to the observational nature of ADDRESS-J and available data tended to be in patients with more severe disease. Hence, the biomarker correlation results should be interpreted with caution. Also, although we included three clinician-reported outcomes and five patient-reported outcomes, we did not include other scores, e.g., Atopic Dermatitis Control Test or Recap of Atopic Eczema, which have recently been recommended for the evaluation of long-term disease control [11].

CONCLUSIONS

The results of this study confirm that clinician- and patient-reported outcomes are not necessarily correlated among Japanese adults with AD. This highlights the importance of including patient-reported outcomes when assessing disease severity/impact, planning treatment, and assessing treatment response.

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Author Contributions. Hidehisa Saeki, Yoko Kataoka, Takafumi Etoh, Norito Katoh, Satoshi Teramukai, Yuki Tajima, Hiroyuki Fujita, Marius Ardeleanu, and Kazuhiko Arima contributed to the study concept and design. Hidehisa Saeki, Yoko Kataoka, Takafumi Etoh and Norito Katoh acquired the data. All authors had access to the data, contributed to the data analysis or interpretation, and participated in the development, review, approval, and decision to submit this publication. All authors read and approved the final version. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Data Availability. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

Declarations

Conflict of Interest. Hidehisa Saeki has received lecture fees from AbbVie, Eli Lilly Japan, Japan Tobacco, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Novartis, Otsuka, Sanofi, Taiho, and Torii Pharmaceutical; and scholarship donations from Esai, Maruho, Taiho Pharma, and Tokiwa. Yoko Kataoka reports honoraria for lectures and contract research grants from Sanofi; and research grants from AbbVie, Eli Lilly, LEO Pharma, Maruho, Otsuka, and Pfizer. Takafumi Etoh has received honoraria for lectures from Kyowa Kirin and Maruho. Norito Katoh has received honoraria for lectures from AbbVie, Celgene Japan, Eli Lilly Japan, Janssen Pharmaceuticals, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Sanofi, and Taiho Pharma; and research grants from AbbVie, Eli Lilly Japan, Kyowa Kirin, LEO Pharma, Maruho,

Mitsubishi Tanabe Pharma, Sanofi, Sun Pharma, and Taiho Pharma. Satoshi Teramukai has received honoraria for lectures from Bayer, Chugai Pharmaceutical, and Nipro; a research grant from Nippon Boehringer Ingelheim and Sun Contact Lens; and consultant fees from Atworking, Daiichi Sankyo, Gunze, Kaneka, Kringle Pharma, NapaJen Pharma, Sanofi, Solasia Pharma, Sysmex, and Takeda. Yuki Tajima, Hiroyuki Fujita, and Kazuhiko Arima are Sanofi K.K. employees, and may hold stock and/or stock options in the company. Marius Ardeleanu is an employee and shareholder of Regeneron Pharmaceuticals Inc.

Ethical Approval. The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice (ICH GCP) guideline, and applicable regulatory requirements. The protocol was reviewed and approved by the following institutional review boards/ethics committees: Asai Dermatology Clinic Institutional Review Board (Central IRB); Kyoto Prefectural University of Medicine Medical Ethics Review Committee; Nippon Medical School Ethics Committee; Medical Research Ethics Committee/Commissioned Research Review Committee, Osaka Habikino Medical Center; Medical Ethics Committee, Tokyo Teishin Hospital; Epidemiological Research Ethics Review Committee, Graduate School of Biomedical and Health Sciences, Hiroshima University; Ethics Committee, Tokyo Women's Medical University; Epidemiology and Observational Research Ethics Review Committee, The University of Tokyo Graduate School of Medicine; Intervention and Observational Research Ethics Review Committee, Osaka University Graduate School of Medicine; University of Yamanashi School of Medicine Ethics Committee; Clinical Research Ethics Review Committee, Dokkyo Medical University Saitama Medical Center. All patients provided written informed consent.

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