# Biomarkers and patient-related factors associated with clinical outcomes in dupilumab-treated atopic dermatitis

Makiko Kido-Nakahara, MD,[a] Daisuke Onozuka, PhD,[b] Kenji Izuhara, PhD,[c] Hidehisa Saeki, MD,[c] Satoshi Nunomura, PhD,[c] Motoi Takenaka, MD,[e] Mai Matsumoto, MD,[e] Yoko Kataoka, MD,[f] Rai Fujimoto, MD,[f] Sakae Kaneko, MD,[g] Eishin Morita, MD,[g] Akio Tanaka, MD,[h] Michihiro Hide, MD,[h] Tatsuro Okano, MD,[i] Tomomitsu Miyagaki, MD,[i] Natsuko Aoki, MD,[j] Kimiko Nakajima, MD,[j] Susumu Ichiyama, MD,[d] Kyoko Tonomura, MD,[k] Yukinobu Nakagawa, MD,[k] Risa Tamagawa-Mineoka, MD,[l] Koji Masuda, MD,[l] Takuya Takeichi, MD,[m] Masashi Akiyama, MD,[m] Yozo Ishiuji, MD,[n] Michie Katsuta, MD,[n] Yuki Kinoshita, MD,[o] Chiharu Tateishi, MD,[o] Aya Yamamoto, MD,[p] Akimichi Morita, MD,[p] Haruna Matsuda-Hirose, MD,[q] Yutaka Hatano, MD,[q] Hiroshi Kawasaki, MD,[r] Keiji Tanese, MD,[r] Mamitaro Ohtsuki, MD,[s] Koji Kamiya, MD,[s] Yudai Kabata, MD,[t] Riichiro Abe, MD,[t] Hiroshi Mitsui, MD,[u] Tatsuyoshi Kawamura, MD,[u] Gaku Tsuji, MD,[a] Masutaka Furue, MD,[a] Norito Katoh, MD,[a] and Takeshi Nakahara, MD[a]

*Fukuoka, Osaka, Saga, Tokyo, Nagasaki, Shimane, Hiroshima, Kanagawa, Kochi, Aichi, Oita, Tochigi, Niigata, and Yamanashi, Japan*

**Background: Atopic dermatitis (AD) is a common chronic eczematous skin disease with severe pruritus. Several new therapeutic agents for AD such as dupilumab, an anti–IL-4Rα antibody, have been developed in recent years. We need to predict which agent is the best choice for each patient, but this remains difficult.**

**Objective: Our aim was to examine clinical background factors and baseline biomarkers that could predict the achievement of improved clinical outcomes in patients with AD treated with dupilumab.**

**Methods: A multicenter, prospective observational study was conducted on 110 patients with AD. The Eczema Area and Severity Index was used as an objective assessment, and the Patient-Oriented Eczema Measure and Numerical Rating Scale for Pruritus were used as patient-reported outcomes. In addition, some clinical background factors were evaluated.**

**Results: The achievement of an absolute Eczema Area and Severity Index of 7 or less was negatively associated with current comorbidity of food allergy and baseline serum lactate dehydrogenase (LDH) levels. There were negative associations between achievement of a Patient-Oriented Eczema Measure score of 7 or less and duration of severe AD and between achievement of an itching Numerical Rating Scale for Pruritus score of 1 or less and current comorbidity of allergic conjunctivitis or baseline serum periostin level. Furthermore, signal detection analysis showed that a baseline serum LDH level less than 328 U/L could potentially be used as a cutoff value for predicting the efficacy of dupilumab.**

**Conclusion: Baseline biomarkers such as LDH and periostin and clinical background factors such as current comorbidity of food allergy and a long period of severe disease may be useful indicators when choosing dupilumab for systemic treatment for AD, as they can predict the efficacy of dupilumab. (J Allergy Clin Immunol Global 2024;3:100317.)**

***Key words:*** *Atopic dermatitis, dupilumab, Eczema Area and Severity Index, lactate dehydrogenase, Patient-Oriented Eczema Measure, periostin, Numerical Rating Scale for Pruritus*

Atopic dermatitis (AD) is a chronic eczematous skin disease with severe pruritus. The complex interplay among skin barrier dysfunction, skin inflammation, and severe pruritus contributes to the development, progression, and chronicity of AD.[1,2] It is now recognized that AD is not a single phenotypic disease but rather a highly heterogeneous disorder influenced by a variety of genetic and environmental factors.[3,4] In recent years, novel therapeutic agents for AD based on its pathogenesis have become available,[5,6] but predicting which agent is best for which patient remains difficult.

From [a]the Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka; [b]the Department of Oral Microbe Control, Graduate School of Medicine, Osaka University; [c]the Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School; [d]the Department of Dermatology, Nippon Medical School, Tokyo; [e]the Department of Dermatology, Graduate School of Biomedical Sciences, Nagasaki University; [f]the Department of Dermatology, Osaka Habikino Medical Center; [g]the Department of Dermatology, Shimane University Faculty of Medicine; [h]the Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University; [i]the Department of Dermatology, St. Marianna University School of Medicine, Kanagawa; [j]the Department of Dermatology, Kochi Medical School; [k]the Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University; [l]the Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine; [m]the Department of Dermatology, Nagoya University Graduate School of Medicine, Aichi; [n]the Department of Dermatology, The Jikei University School of Medicine, Tokyo; [o]the Department of Dermatology, Osaka Metropolitan University Graduate School of Medicine; [p]the Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Aichi; [q]the Department of Dermatology, Faculty of Medicine, Oita University, Hasama-machi, Oita; [r]the Department of Dermatology, School of Medicine, Keio University, Tokyo; [s]the Department of Dermatology, Jichi Medical University, Tochigi; [t]the Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences; and [u]the Department of Dermatology, Faculty of Medicine, University of Yamanashi.

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Corresponding author: Makiko Kido-Nakahara, MD, Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: nakahara.makiko.107@m.kyushu-u.ac.jp.

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*Abbreviations used*
AD: Atopic dermatitis
CCL: CC chemokine ligand
EASI: Eczema Area and Severity Index
ET-1: Endothelin-1
IGA: Investigator's Global Assessment
LDH: Lactate dehydrogenase
POEM: Patient-Oriented Eczema Measure
Pruritus-NRS: Numerical Rating Scale for Pruritus
SCCA2: Squamous cell carcinoma antigen 2
sIL-2R: Soluble IL-2 receptor
TARC: Thymus- and activation-regulated chemokine

Recently, dupilumab, an anti–IL-4Rα antibody, has been shown to be effective in improving inflammation in moderate-to-severe AD[7-9] and to firmly suppress type 2 inflammatory biomarkers.[10] However, dupilumab does not completely resolve signs and symptoms in all patients, and the degree of clinical improvement varies from patient to patient.[11] We previously conducted the B-PAD (Biomarkers to Predict Clinical Improvement of AD in Patients Treated With Dupilumab) study.[12,13] In that study, a consortium of 19 medical facilities in Japan that are actively involved in treating patients with AD was formed and 110 patients with moderate-to-severe AD were enrolled. We evaluated objective clinical outcomes using the Eczema Area and Severity Index (EASI) and assessed patient-reported outcomes using the Patient-Oriented Eczema Measure (POEM) and Numerical Rating Scale for Pruritus (Pruritus-NRS). At the same time, we measured the levels of 19 serum biomarkers at baseline. When percentage of change from baseline values of the clinical outcomes was used as the end point, no biomarkers were found to be associated with percentage of change in EASI. Meanwhile, the percentage of change in POEM score or Pruritus-NRS score was associated with levels of thymus and activation-regulated chemokine (TARC), soluble IL-2R, and lactate dehydrogenase (LDH).[13] To evaluate the effectiveness of dupilumab in real-world clinical practice, we thought that it would be better to evaluate whether improved clinical outcomes were achieved. Therefore, we decided to examine the associations of baseline biomarkers and patient background with the achievement of improved clinical outcomes and to also investigate predictive markers for the achievement of improved clinical outcomes in patients with AD treated with dupilumab by using the achievement of improved clinical outcomes as an end point.

## METHODS

### Study patients

Details of the methods of this exploratory study have already been reported.[12,13] It is a multicenter, prospective, observational study in which samples and information were obtained from 19 medical facilities joining a consortium in Japan between October 10, 2019, and March 31, 2022. The study was carried out under real-world standard treatment guidelines.[5] We enrolled 131 Japanese subjects from the 19 medical facilities. The subjects were required to be at least 18 years of age, have moderate-to-severe AD with an EASI of 16 or more, have an Investigator's Global Assessment (IGA) score of 3 or more, and have eczema on at least 10% of their body surface area, and have had chronic AD for at least 3 years before the start of this study. They were also required to have stopped receiving cyclosporine, oral steroids, or phototherapy at least 4 weeks before the start of injections of dupilumab. Subjects were set to receive subcutaneous injections of dupilumab biweekly for 16 weeks (an initial dose of 600 mg followed by doses of 300 mg thereafter). Use of systemic steroids, systemic calcineurin inhibitors, and phototherapy after the initiation of dupilumab was not allowed. Continued use of any topical steroids, topical calcineurin inhibitors, topical moisturizers, and oral antihistamines being used at baseline was allowed. A change of topical drugs to more potent ones was not allowed. The use of ocular, intranasal, or inhalant steroids and calcineurin inhibitors was allowed throughout the study, as was the use of antihistamine drugs. Additional information about eligibility criteria is available (for the eligibility criteria, see the Supplementary Methods in the Online Repository at www.jaci-global.org). All investigators involved in this study carried out the work in accordance with the Declaration of Helsinki (as revised in 2013) and the latest edition of the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Japanese Ministry of Health, Labor, and Welfare. The study protocol has been approved by the Clinical Research Network Fukuoka Certified Review Board (approval no. CRB7180004). This study has been registered with the University Hospital Medical Information Network Clinical Trials Registry (registration no. UMIN000037307).

### Assessment of clinical background, laboratory parameters, and clinical outcome

We examined patient background factors, including age, sex, body mass index, duration of severe AD, current comorbidity of allergic disease (bronchial asthma, allergic rhinitis, allergic conjunctivitis, food allergy), current ocular comorbidity (blepharitis, keratoconjunctivitis, cataract), and family history of allergic diseases (bronchial asthma, allergic rhinitis, allergic conjunctivitis, AD). In addition, the levels of 19 serum biomarkers were measured at the beginning of treatment. Objective clinical findings were evaluated by using the EASI.[14-16] Subjective symptoms were assessed by using patient-reported outcomes such as the POEM[16,17] and the Pruritus-NRS.[18,19] We also measured the levels of the following 19 biomarkers: eosinophil count, LDH, soluble IL-2 receptor (sIL-2R), CC chemokine ligand (CCL)17/TARC, CCL18, CCL22, CCL26, CCL27, IL-13, IL-22, IL-24, IL-25, IL-31, IL-33, thymic stromal lymphopoietin, periostin, squamous cell carcinoma antigen 2 (SCCA2), and endothelin-1 (ET-1). We also examined whether the following clinical outcomes had been achieved: (1) an EASI of 75 or EASI of 90; (2) improvement of AD in the form of achievement of an absolute EASI of 7 or less, an absolute POEM score of 7 or less, and an absolute Pruritus-NRS score of 4 or less; or (3) marked improvement of AD (achievement of an absolute EASI of 1 or less, absolute POEM score of 2 or less, and absolute Pruritus-NRS score of 1 or less) at 16 weeks.[15,17,18] Furthermore, we analyzed the associations of the achievement of improved clinical outcomes with patient background and levels of 19 serum biomarkers at baseline.

### Statistical analysis

We used logistic regression models to investigate the associations of each baseline biomarker and patient background with

**TABLE I.** Association between patient background and improvements in clinical score (achievement of an EASI of 7 or less, POEM score of 7 or less, or itch NRS score of 4 or less)

| | EASI ≤ 7 | | | POEM score ≤ 7 | | | Itch NRS score ≤ 4 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient background** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** |
| Sex (male) | 0.658 | (0.247-1.755) | .403 | 0.388 | (0.140-1.079) | .070 | 0.655 | (0.208-2.066) | .471 |
| Age | 0.999 | (0.962-1.037) | .958 | 0.982 | (0.943-1.023) | .391 | 0.975 | (0.931-1.022) | .301 |
| Body mass index | 1.001 | (0.896-1.118) | .989 | 1.026 | (0.907-1.162) | .680 | 1.038 | (0.903-1.192) | .602 |
| Duration of severe AD | 1.001 | (0.968-1.034) | .972 | **0.966** | **(0.935-0.998)** | **.036** | 0.976 | (0.942-1.011) | .175 |
| Bronchial asthma | 0.841 | (0.074-9.620) | .157 | 1.063 | (0.320-3.533) | .921 | 1.149 | (0.293-4.509) | .842 |
| Allergic rhinitis | 0.488 | (0.180-1.319) | .788 | 0.715 | (0.238-2.147) | .549 | 0.492 | (0.158-1.534) | .221 |
| Allergic conjunctivitis | 0.875 | (0.332-2.307) | .370 | 0.361 | (0.117-1.114) | .076 | 0.564 | (0.170-1.870) | .349 |
| Food allergy | **0.635** | **(0.236-1.713)** | **.016** | 0.513 | (0.142-1.854) | .309 | 0.285 | (0.074-1.098) | .068 |
| Blepharitis | 0.240 | (0.075-0.770) | .894 | 0.515 | (0.165-1.608) | .253 | 0.431 | (0.128-1.452) | .174 |
| Keratoconjunctivitis | 0.926 | (0.299-2.870) | .561 | 0.284 | (0.048-1.671) | .164 | 1.124 | (0.128-9.900) | .916 |
| Cataract | 0.928 | (0.249-3.463) | .911 | 0.395 | (0.104-1.502) | .173 | 0.947 | (0.188-4.765) | .947 |
| Family history of bronchial asthma | 0.939 | (0.313-2.818) | .911 | 0.172 | (0.007-4.188) | .093 | 0.643 | (0.181-2.289) | .495 |
| Family history of allergic rhinitis | 1.037 | (0.345-3.112) | .948 | 0.377 | (0.120-1.178) | 112 | 1.009 | (0.256-3.987) | .989 |
| Family history of allergic conjunctivitis | 1.203 | (0.215-6.735) | .833 | 0.409 | (0.136-1.232) | .851 | 1.124 | (0.128-9.903) | .916 |
| Family history of atopic dermatitis | 1.464 | (0.539-3.974) | .455 | 0.845 | (0.145-4.938) | .381 | 0.369 | (0.117-1.162) | .088 |

Boldface indicates statistical significance.

**TABLE II.** Association between patient background and significant improvement in clinical scores (achievement of an EASI of ≤1, POEM score of ≤2, or itch NRS score of ≤1)

| | EASI ≤ 1 | | | POEM score ≤ 2 | | | Itch NRS score ≤1 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient background** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** |
| Sex (male) | 2.174 | (0.625-7.568) | .222 | **0.328** | **(0.108-0.998)** | **.049** | 0.684 | (0.292-1.598) | .380 |
| Age | 0.974 | (0.920-1.032) | .375 | 0.989 | (0.952-1.028) | .574 | 1.010 | (0.978-1.044) | .536 |
| Body mass index | 0.946 | (0.809-1.105) | .481 | 1.077 | (0.968-1.198) | .176 | 1.010 | (0.921-1.108) | .832 |
| Duration of severe AD | 0.976 | (0.928-1.027) | .350 | 0.980 | (0.947-1.015) | .253 | 0.983 | (0.955-1.011) | .230 |
| Bronchial asthma | 0.456 | (0.081-2.559) | .373 | 1.655 | (0.601-4.562) | .330 | 0.862 | (0.336-2.211) | .758 |
| Allergic rhinitis | 1.470 | (0.395-5.472) | .566 | 0.964 | (0.370-2.510) | .940 | 0.638 | (0.274-1.487) | .298 |
| Allergic conjunctivitis | 0.565 | (0.124-2.571) | .460 | 0.688 | (0.234-2.026) | .498 | **0.351** | **(0.127-0.972)** | **.044** |
| Food allergy | 0.567 | (0.057-5.662) | .629 | 0.682 | (0.169-2.754) | .591 | 0.624 | (0.179-2.182) | .461 |
| Blepharitis | 0.542 | (0.088-3.351) | .510 | 0.562 | (0.162-1.945) | .363 | 0.631 | (0.232-1.717) | .368 |
| Keratoconjunctivitis | 1.293 | (0.107-15.682) | .840 | 0.655 | (0.105-4.110) | .652 | 0.470 | (0.090-2.453) | .370 |
| Cataract | 0.845 | (0.131-5.463) | .860 | 0.530 | (0.123-2.292) | .395 | 0.551 | (0.160-1.894) | .344 |
| Family history of bronchial asthma | 1.327 | (0.326-5.405) | .693 | 0.452 | (0.133-1.536) | .203 | 0.631 | (0.232-1.717) | .368 |
| Family history of allergic rhinitis | 0.961 | (0.211-4.372) | .959 | 1.070 | (0.366-3.131) | .901 | 0.814 | (0.307-2.160) | .679 |
| Family history of allergic conjunctivitis | 1.930 | (0.275-13.524) | .508 | 2.273 | (0.499-10.342) | .288 | 0.884 | (0.199-3.922) | .871 |
| Family history of atopic dermatitis | 0.628 | (0.154-2.564) | .517 | 1.609 | (0.626-4.139) | .324 | 1.023 | (0.449-2.329) | .957 |

Boldface indicates statistical significance.

the achievement of improved clinical outcomes. Because our study had a single primary outcome and findings for secondary outcomes were considered subsidiary and exploratory, there was no need to adjust for multiplicity.[20] Statistical analysis for 6 biomarkers, IL-13, IL-24, IL-25, IL-31, IL-33, and thymic stromal lymphopoietin, was not possible because their levels were below the detection limit in many samples. Ultimately, 13 biomarkers were examined. A signal detection analysis was performed to explore which cutoff values for each biomarker were most strongly associated with achievement of improved clinical outcomes.[21] A signal detection analysis focuses on the sensitivity and specificity of the biomarkers and identifies unknown combinations of certain biomarkers to maximize the sensitivity and specificity in predicting the model for the achievement of each clinical outcome. The optimally efficient biomarker or cutoff point is determined by the maximum weighted κ coefficient. All of the 13 biomarkers were included in the model, along with their minimal and maximal values and intermediate cutoff points. On the basis of this analysis, we checked each variable and its possible cutoff points to determine the optimally efficient variable as well as its cutoff point with respect to the probability of achievement for each clinical outcome. All statistical analyses were performed using Stata 18.0 (Stata Corp, College Station, Tex). The 2-sided significance level for all tests was $P < .05$.

## RESULTS

### Association between patient background and achievement of improved clinical outcomes

Of the 131 enrolled subjects,7 were excluded because of withdrawal of their consent to participate was withdrawn and or ineligibility for inclusion, leaving a final sample size of 124. Of those subjects, 110 (74 of whom were male) were included in the efficacy analysis (see Fig E1 in the Online Repository at www.jaci-global.org). First, the association between patient background factors and improvement of various clinical outcomes was analyzed (Tables I and II and see Table E1 in the Online Repository at www.jaci-global.org). There was no association between patient

**TABLE III.** Association between baseline biomarkers and clinical score improvements (achievement of an EASI of ≤7, POEM score of ≤7, or itch NRS score of ≤4)

| | EASI ≤ 7 | | | POEM score ≤ 7 | | | Itch NRS score ≤ 4 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient background** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** |
| LDH | **0.99392** | **(0.98791-0.99997)** | **.049** | 1.00182 | (0.99466-1.00903) | .620 | 0.99917 | (0.99151-1.00688) | .832 |
| Eosinophils | 1.00034 | (0.99926-1.00142) | .534 | 1.00009 | (0.99901-1.00117) | .868 | 1.00000 | (0.99891-1.00108) | .999 |
| WBC | 0.99997 | (0.99990-1.00004) | .421 | 0.99998 | (0.99990-1.00005) | .563 | 1.00003 | (0.99994-1.00010) | .546 |
| sIL-2R | 0.99947 | (0.99722-1.00171) | .643 | 1.00255 | (0.99924-1.00586) | .131 | 1.00201 | (0.99844-1.00558) | 269 |
| TARC | 0.99990 | (0.99979-1.00001) | .081 | 1.00010 | (0.99990-1.00029) | .310 | 1.00009 | (0.99987-1.00031) | .404 |
| CCL22 | 0.99985 | (0.99940-1.00030) | .529 | 1.00007 | (0.99940-1.00063) | .814 | 1.00010 | (0.99950-1.00069) | .736 |
| CCL26 | 0.99881 | (0.98732-1.01042) | .840 | 1.00045 | (0.98840-1.01262) | .942 | 1.00588 | (0.98600-1.02615) | .565 |
| IL-22 | 0.97183 | (0.94219-1.00239) | .070 | 1.01681 | (0.96945-1.06640) | .493 | 1.00441 | (0.96510-1.04532) | .829 |
| CCL27 | 1.00022 | (0.99909-1.00134) | .703 | 0.99986 | (0.99862-1.00110) | .829 | 0.99949 | (0.99822-1.00070) | 426 |
| CCL18 | 1.00000 | (0.99999-1.00000) | .965 | 1.00000 | (0.99999-1.00000) | .841 | 1.00000 | (0.99999-1.00000) | .835 |
| ET-1 | 1.19737 | (0.38996-3.67648) | .753 | 0.95612 | (0.33750-2.70856) | .933 | 1.04517 | (0.29131-3.74987) | .946 |
| Periostin | 1.00129 | (0.99239-1.01020) | .777 | 0.99590 | (0.98679-1.00509) | .381 | 0.99772 | (0.98760-1.00793) | .660 |
| SCCA2 | 0.97094 | (0.93421-1.00911) | .134 | 1.01491 | (0.96011-1.07280) | .601 | 1.01636 | (0.95360-1.08313) | .617 |

Boldface indicates statistical significance.

**TABLE IV.** Association between baseline biomarkers and significant improvement in clinical scores (achievement of an EASI of ≤1, POEM score of ≤2, or itch NRS score of ≤1)

| | EASI ≤ 1 | | | POEM score ≤ 2 | | | Itch NRS score ≤1 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient background** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** | **Odds ratio** | **95% CI** | ***P* value** |
| LDH | 0.995 | (0.986-1.004) | .279 | 1.000 | (0.986-1.014) | .999 | 0.998 | (0.992-1.004) | .472 |
| Eosinophils | 0.999 | (0.998-1.001) | .407 | 1.001 | (0.998-1.003) | .628 | 0.999 | (0.998-1.000) | .067 |
| WBC | 1.000 | (1.000-1.000) | .524 | 1.000 | (1.000-1.000) | .639 | 1.000 | (1.000-1.000) | .463 |
| sIL-2R | 0.997 | (0.992-1.001) | .165 | 1.004 | (0.998-1.009) | .219 | 1.001 | (0.999-1.003) | .298 |
| TARC | 1.000 | (1.000-1.000) | .624 | 1.000 | (1.000-1.000) | .383 | 1.000 | (1.000-1.000) | .871 |
| CCL22 | 1.000 | (1.000-1.001) | .393 | 1.000 | (0.999-1.002) | .414 | 1.000 | (1.000-1.000) | .724 |
| CCL26 | 0.997 | (0.977-1.018) | .800 | 0.973 | (0.925-1.023) | .288 | 0.988 | (0.972-1.003) | .118 |
| IL-22 | 0.995 | (0.959-1.031) | .770 | 1.001 | (0.881-1.139) | .985 | 1.006 | (0.982-1.031) | .630 |
| CCL27 | 1.000 | (0.999-1.002) | .852 | 0.999 | (0.997-1.002) | .606 | 1.000 | (0.999-1.001) | .550 |
| CCL18 | 1.000 | (0.999-1.000) | .607 | 1.000 | (1.000-1.000) | .583 | 1.000 | (1.000-1.000) | .817 |
| ET-1 | 1.320 | (0.408-4.272) | .643 | 1.653 | (0.239-11.411) | .610 | 1.028 | (0.430-2.456) | .951 |
| Periostin | 1.006 | (0.995-1.017) | .307 | 0.992 | (0.974-1.011) | .410 | **0.990** | **(0.982-0.999)** | **.036** |
| SCCA2 | 0.982 | (0.933-1.033) | .483 | 0.955 | (0.810-1.127) | .590 | 1.007 | (0.981-1.034) | .589 |

Boldface indicates statistical significance.

background factors and the achievement of an EASI of 75 or EASI of 90 (see Table E1). Regarding improvement of AD (ie, achievement of an EASI of ≤7, POEM score of ≤7, or itch NRS score of ≤4), there were negative associations between current food allergy comorbidity and achievement of an EASI of 7 or less and between duration of severe AD and achievement of a POEM score of 7 or less. No patient background factors were associated with achieving a Pruritus-NRS score of 4 or less (Table I). Regarding substantial improvement of AD (as demonstrated by an EASI of 1 or less, POEM level of 2 or less, or Pruritus-NRS level of 1 or less), none was associated with achievement of an EASI of 1 or less. Meanwhile, there were negative associations between male sex and achievement of a POEM score of 2 or less and between current comorbidity of conjunctivitis and achievement of a Pruritus-NRS score of 1 or less (Table II).

## Association between levels of 13 serum baseline biomarkers and achievement of improved clinical outcomes

The association between serum baseline markers and the improvement of various clinical outcomes was analyzed (Tables III and IV and see Table E2 in the Online Repository at www.jaci-global.org). No association between baseline biomarkers and the achievement of an EASI of 75 or achievement of EASI of 90 was identified (see Table E2). Regarding improvement of AD (EASI ≤ 7, POEM score ≤ 7, and Pruritus-NRS score ≤ 4), there was a negative association between LDH and achievement of an EASI of 7 or less; no serum baseline biomarkers were associated with achievement of a POEM score of 7 or less or a Pruritus-NRS score of 4 or less (Table III). Regarding substantial improvement (EASI ≤ 1, POEM score ≤2, and pruritus-NRS score ≤ 1), no serum baseline biomarkers were associated with the achievement of an EASI of 1 less or POEM score of 2 or less. There was a negative association between periostin level and achievement of a Pruritus-NRS score of 1 or less (Table IV).

## Signal detection analysis of the association between baseline biomarkers and achievement of an EASI of 7 or less

Next, a signal detection analysis was performed to explore which cutoff values for each biomarker were most strongly associated with achieving improved clinical outcomes. The results of

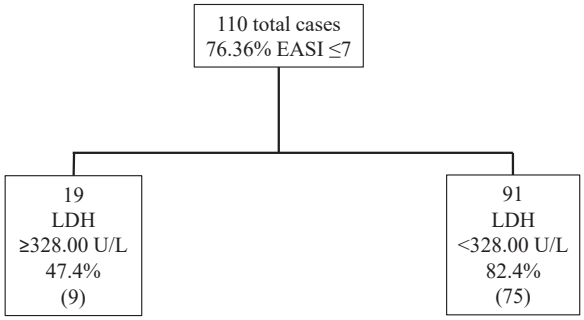


**FIG 1.** The biomarker that most efficiently distinguished between those who did and did not achieve an EASI of 7 or less was baseline serum LDH level. Of those patients with an LDH level less than 328 U/L, 82.4% achieved an EASI level less than 7, whereas only 47.4% of those with an LDH level of 328 U/L or more achieved EASI an of 7 or less, thus indicating a statistically significant difference between the 2 groups ($P = .001$).

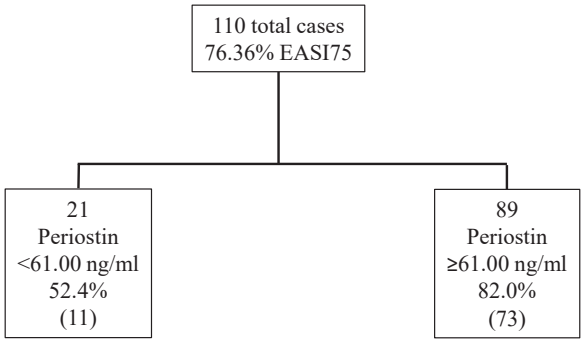


**FIG 2.** The biomarker that most efficiently distinguished between those patients who did and did not achieve an EASI of 75 was baseline serum periostin level. Of those patients with a periostin level of 61.0 ng/mL or more, 82.0% achieved an EASI of 75, whereas 52.4% of those with a periostin level less than 61.0 ng/mL achieved an EASI of 75, indicating a statistically significant difference ($P = .004$).

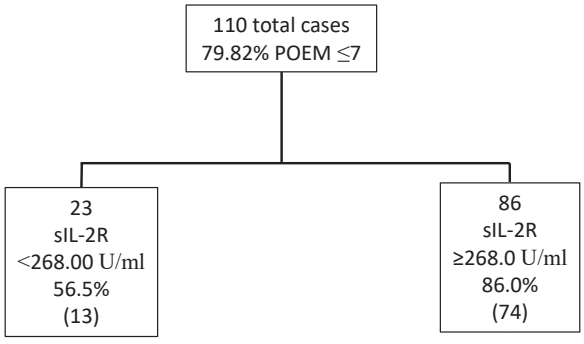


**FIG 3.** The biomarker that most efficiently distinguished between those who did and did not achieve a POEM score of 7 or less was baseline serum sIL-2R level. Of those patients with an sIL-2R level of 268.0 U/mL or more, 86.0% achieved a POEM score of 7 or lower, whereas 56.5% of those with an sIL-2R level less than 268.0 U/mL achieved a POEM score of 7 or less, indicating a statistically significant difference ($P = .002$).

signal detection analysis are shown in Figs 1 to 3 and Figs E2 and E3 (available in the Online Repository at www.jaci-global.org). The biomarker that most efficiently distinguished between those who achieved an EASI of 7 or less and those who did not was LDH ($P = .001$). Of the patients with an LDH level of 328 U/L, 82.4% achieved an EASI of 7 or less, whereas only 47.4% of those with an LDH level of 328 U/L or more achieved an EASI of 7 or less (Fig 1). The biomarkers that proved most efficient at distinguishing patients who achieved an EASI of 75, an EASI of 90, a POEM score of 7 or less, and a POEM score of 2 or less from those who did not were periostin, CLL22, sIL-2R, and ET-1 ($P = .004$, .006, .002, and .009), respectively (Figs 2 and 3 and see Figs E2 and E3). No significant cutoff values were detected for the association between baseline biomarkers and achievement of an EASI of 1 or less, Pruritus-NRS score of 4 or less, or Pruritus-NRS score of 1 or less.

## DISCUSSION

In this study, we investigated the associations of clinical improvement with patient background and baseline biomarkers in patients with AD treated with dupilumab by using the achievement of clinical outcomes as an end point. Logistic regression analysis showed that the clinical background factors of duration of severe AD, current comorbidity of food allergy or allergic conjunctivitis, and sex (male), and as well as the baseline levels of the biomarkers LDH and periostin, were negatively correlated with the achievement of improved clinical outcomes. Signal detection analysis indicated cutoff values for baseline serum LDH, periostin, CCL22, sIL-2R, and endothelin levels as possible factors that could predict improvement. The observations from this study suggest hypotheses that could be tested in future clinical trials.

This report is consistent with previous reports in that high baseline serum LDH level was associated with poor efficacy of dupilumab.[22,23] Furthermore, this is the first report to present cutoff values of LDH level for predicting dupilumab efficacy for AD. Serum LDH level is a clinically measurable laboratory parameter and is thus expected to become a practical indicator of the clinical response to dupilumab therapy.

The prevalence of food allergies has been reported to increase with AD severity.[24] In the present analysis, even after adjustment for the baseline EASI values, a negative association between current food allergy comorbidity and achievement of an EASI of 7 or less was observed, suggesting that this difference was not due simply to the increased severity of AD. This suggests that mediators other than IL-4 and IL-13 may be more involved than in patients with AD with current comorbid food allergy.

POEM score is assessed by the patients themselves and includes not only skin rash but also pruritus and sleep disturbances. Therefore, the negative association between the duration of severe AD and achievement of a POEM score of 7 or less might suggest that even after the improvement of skin symptoms of AD with dupilumab, patients with long-term severe AD might still have pruritus and sleep disturbances. This may also be related to the strong association of prolonged pruritus with sleep disturbances and cognitive dysfunction.[25,26]

This study also identified negative associations between sex (male) and the achievement of a POEM score of 2 or lower and between current conjunctivitis comorbidity and the achievement of a Pruritus-NRS score of 1 or less. However, differences between the sexes among patients with AD have hardly been elucidated, and the relationship between POEM score and sex will need to be investigated in further studies. As for allergic conjunctivitis, it has been reported that neuropathic pruritus may underlie its pathogenic mechanisms[27] and that the itching

might not be completely suppressed with the IL-4/IL-13 inhibitor dupilumab.

Baseline serum periostin levels were negatively associated with achievement of a Pruritus-NRS score of 1 or less in this present study. Periostin is one of the itch mediators of AD and has been reported to cause itching directly[28] or promote itching in AD, such as by releasing various itch mediators.[29-31] Therefore, it is suggested that periostin-mediated pruritus might not be completely resolved by treatment with dupilumab. On the other hand, a signal detection analysis revealed that those patients with a baseline periostin level of 61 ng/mL or more had a significantly higher rate of achievement of an EASI of 75. For skin inflammation, periostin levels have also been reported to correlate with AD severity,[32] and they might predict good efficacy of dupilumab treatment.

The patients with baseline sIL-2R ≥268 U/mL significantly achieved POEM ≤7, which was consistent with previous reports describing that high baseline levels of sIL-2R, IL-31, and IL-36β might predict good efficacy of dupilumab treatment.[33] However, AD was reported to be immunopathologically heterogeneous,[34] and further investigation is needed to clarify the association between the clinical background factors and baseline markers identified in the present study and the differences in subtypes and clusters of AD.

Many reports of psoriasis induced by dupilumab have been published.[35,36] In this study, IL-22 level was measured because it is associated with the AD pathogenesis of epidermal thickening; unfortunately, however, $T_H17/T_H1$ cytokines such as IL-17, IL-23, and TNFα were not examined. It is important to examine whether differences in $T_H17/T_H1$ cytokine levels before dupilumab treatment alter the effect of dupilumab or how $T_H17/T_H1$ cytokine expression is altered by dupilumab treatment, but these issues are to be analyzed in future work.

In conclusion, we found negative associations between the achievement of an absolute EASI of 7 or less with current food allergy comorbidity and baseline serum LDH levels. We also found a negative association between achievement of a POEM score of 7 or less and the duration of severe AD, as well as negative associations between achievement of a Pruritus-NRS score of 1 or lower with current allergic conjunctivitis comorbidity and baseline serum periostin level. Furthermore, we showed that a serum LDH level of 328 U/L has potential as a cutoff value for predicting the efficacy of dupilumab. These factors may be useful indicators when selecting dupilumab for systemic treatment for AD. Further studies are needed to reveal the significance of these biomarkers in the pathogenesis of AD and their relevance to treatment with dupilumab.

## DISCLOSURE STATEMENT

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**Clinical implications: Several baseline biomarkers and clinical background factors were associated with the achievement of improved clinical outcomes. The cutoff values for baseline serum LDH level could be used as predictors of improvement.**

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