The sensitivity, specificity, and positive and negative likelihood ratios were 57.7%, 72.3%, 2.08, and 0.59, respectively. (ROC curves were not plotted for case patients aged 2 years or younger because of the small numbers.)

There was significant correlation of serum TARC levels with the SCORAD index ($r = 0.538$; 95% confidence interval [CI], 0.36-0.68), QOL indices (Infants' Dermatitis QOL: $r = 0.823$; 95% CI, 0.40-0.96; Children's Dermatology Life Quality Index: $r = .380$; 95% CI, 0.16-0.57), peripheral eosinophils, and LDH in children older than 2 years but not in the younger age groups (Table II). The correlation with IgE was not significant. In the same age group, for SCORAD index, the correlation was highest with LDH ($r = 0.582$; 95% CI, 0.40-0.72), followed by serum TARC ($r = 0.538$; 95% CI, 0.36-0.68), peripheral eosinophils ($r = 0.397$; 95% CI, 0.19-0.57), and serum IgE ($r = 0.331$; 95% CI, 0.11-0.52). In concurrence with previous studies, our results suggest that TARC correlates with the severity of AD and QOL indices.[1,5] The sensitivity and specificity were lower than those previously reported (83%-85% and 92%-96%, respectively), possibly due to choosing control individuals with diseases mimicking AD and the use of different enzyme-linked immunosorbent assay systems.[2,4] The latter may also explain the lower cutoff for TARC obtained in this study. Contrary to the report of a meta-analysis, SCORAD index correlated highest with LDH, followed by TARC.[1] Compared to LDH, a nonspecific inflammatory marker, TARC is more specific but expensive.[1] The clinical utility of TARC in distinguishing between AD and its mimics is limited by the low specificity and sensitivity. However, the study highlights its role as an objective marker for disease severity.

*Himadri, MD,[a] Renu George, MD,[a] Lydia Mathew, MD,[a] Vanitha Shanmugam, MSc,[b] Thenmozhi Mani, PhD,[c] and Lakshmanan Jeyaseelan, PhD[c]*

*From the Department of Dermatology, Venereology and Leprosy[a]; Department of Biochemistry[b]; and Department of Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India.[c]*

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*Correspondence to: Renu George, MD, Department of Dermatology, Venereology, and Leprosy, Unit 1, Christian Medical College, Vellore, Tamil Nadu, India 632004*

*E-mail: renuegeorge@gmail.com or derm1@cmcvellore.ac.in*

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## One-year real-world clinical effectiveness, safety, and laboratory safety of dupilumab in Japanese adult patients with atopic dermatitis: A single-center retrospective study

*To the Editor:* Dupilumab has demonstrated good efficacy and tolerable safety in adult patients with moderate to severe atopic dermatitis in the long term in clinical trials,[1] but real-world long-term data are limited. The Asian atopic dermatitis phenotype differs from the European American atopic dermatitis phenotype by demonstrating increased T helper cell type 17 polarization in addition to T helper cell type 2 skewing,[2] suggesting a difference in responsiveness to dupilumab. We analyzed our 1-year actual data on Japanese adult atopic dermatitis patients treated with dupilumab.

All atopic dermatitis patients who initiated dupilumab from June 2018 to August 2019 and were treated with dupilumab for more than 3 months at our hospital as of December 1, 2019, were included in this study. Dupilumab is approved in

**Table I.** Baseline demographics and clinical characteristics of atopic dermatitis patients who were treated with dupilumab at our hospital

| Characteristic | Mean ± standard deviation or no. (%) (normal range) |
|---|---|
| Age, y | 37.7 ± 11.6 |
| Sex | Men, 51; women, 10 |
| Height, cm | 166.9 ± 7.4 |
| Weight, kg | 63.3 ± 11.1 |
| BMI | 22.7 ± 20.9 |
| Disease duration, y | 29.5 ± 14.3 |
| IGA | 3.6 ± 0.5 |
| EASI score | 32.7 ± 11.5 |
| EASI score of head and face | 3.5 ± 1.9 |
| Affected BSA, % | 65.7 ± 20.9 |
| DLQI score | 11.6 ± 5.9 |
| POEM score | 18.4 ± 6.8 |
| VAS score of pruritus | 60.4 ± 25.1 |
| Serum TARC level (pg/mL) | 3783.1 ± 4811.7 (<450) |
| Serum IgE level (IU/mL) | 14,305 ± 20,530.2 (<100) |
| Serum LDH level (U/L) | 269.8 ± 89.6 (124–222) |
| No. of circulating WBCs (/$\mu$L) | 6675.4 ± 1830 (3300–8600) |
| No. of circulating eosinophils (/$\mu$L) | 527.1 ± 376 (66–344) |
| No. of circulating neutrophils (/$\mu$L) | 4325.2 ± 1662.7 (1683–5762) |
| Platelet count ($\times 10^3/\mu$L) | 278.2 ± 64.8 (158–348) |
| Presence of or a history of asthma | 30/61 (including having a childhood history of asthma) |

*BMI*, Body mass index; *BSA*, body surface area; *DLQI*, Dermatology Quality of Life Index; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *IgE*, immunoglobulin E; *LDH*, lactate dehydrogenase; *POEM*, Patient-Oriented Eczema Measure; *TARC*, thymus and activation-regulated chemokine; *VAS*, visual analog scale; *WBC*, white blood cells.

Japan only for adult patients with moderate to severe atopic dermatitis who were refractory to topical corticosteroid or tacrolimus for more than 6 months. Detailed inclusion criteria, dosage, and administration have been described previously.[3] Patients whose clinical data or laboratory results were not described in their chart were excluded. Dermatologists from our department performed all assessments of patients and collected patient data.

Sixty-one Japanese patients (51 men and 10 women) were included in this study. Their mean age was 37.7 years (range 17-61 years). Only 1 patient received any form of systemic therapy (cyclosporine) before initiating dupilumab. The mean baseline Eczema Area and Severity Index score was 32.7 (standard deviation 11.5). Table I summarizes the baseline demographics and clinical characteristics of the patients. In all patients, skin eruption improved greatly after initiation of dupilumab. Fig 1 shows the percentage changes in these parameters compared with the respective baseline values. The total Eczema Area and Severity Index score significantly decreased by a mean of 47.1% at 1 month, 70.4% at 3 months, 75.6% at 6 months, and 76.5% at 12 months after initiation of dupilumab. Other clinical severity scores and quality-of-life scores improved at 1, 3, 6, and 12 months. Laboratory results showed tolerable safety and improvement of biomarkers except circulating eosinophils.

As for adverse effects, conjunctivitis was observed in 13 patients (21.3%), 5 of whom had a history of allergic conjunctivitis. Conjunctivitis was associated with higher baseline serum levels of immunoglobulin E and thymus and activation-regulated chemokine but not with clinical severity.[4] No patient discontinued dupilumab therapy because of dupilumab-associated conjunctivitis. In some patients, skin manifestation on the face was refractory to dupilumab treatment despite considerable improvement on the trunk and extremities. No other safety concerns were detected.

Our study revealed that in an actual setting, dupilumab showed effectiveness and safety with tolerable effects on laboratory parameters in Japanese adult atopic dermatitis patients in the long term. The phase 3 open-label extension study conducted in North American (50.5%), European (36.8%), and Asia-Pacific (12.7%) countries reported that the mean percentage change in Eczema Area and Severity Index score from the baseline of the parent study was −89.0% and −90.0% at weeks 52 and 76, respectively,[1] whereas it was −76.5% at 12 months in our study. This suggests the possibility of slightly poorer long-term response to dupilumab in an actual setting rather than in clinical trials, or in Japanese patients compared with North American and European ones.

*Hideaki Uchida, MD, Masahiro Kamata, MD, PhD, Aika Kato, MD, Itsumi Mizukawa, MD, Ayu Watanabe, MD, Ai Agematsu, MD, Mayumi Nagata, MD, Saki Fukaya, MD, Kotaro Hayashi, MD, PhD, Atsuko Fukuyasu, MD, Takamitsu Tanaka, MD, PhD, Takeko Ishikawa, MD, PhD, Takamitsu Ohnishi, MD, PhD, and Yayoi Tada, MD, PhD*

*From the Department of Dermatology, Teikyo University School of Medicine, Tokyo, Japan*

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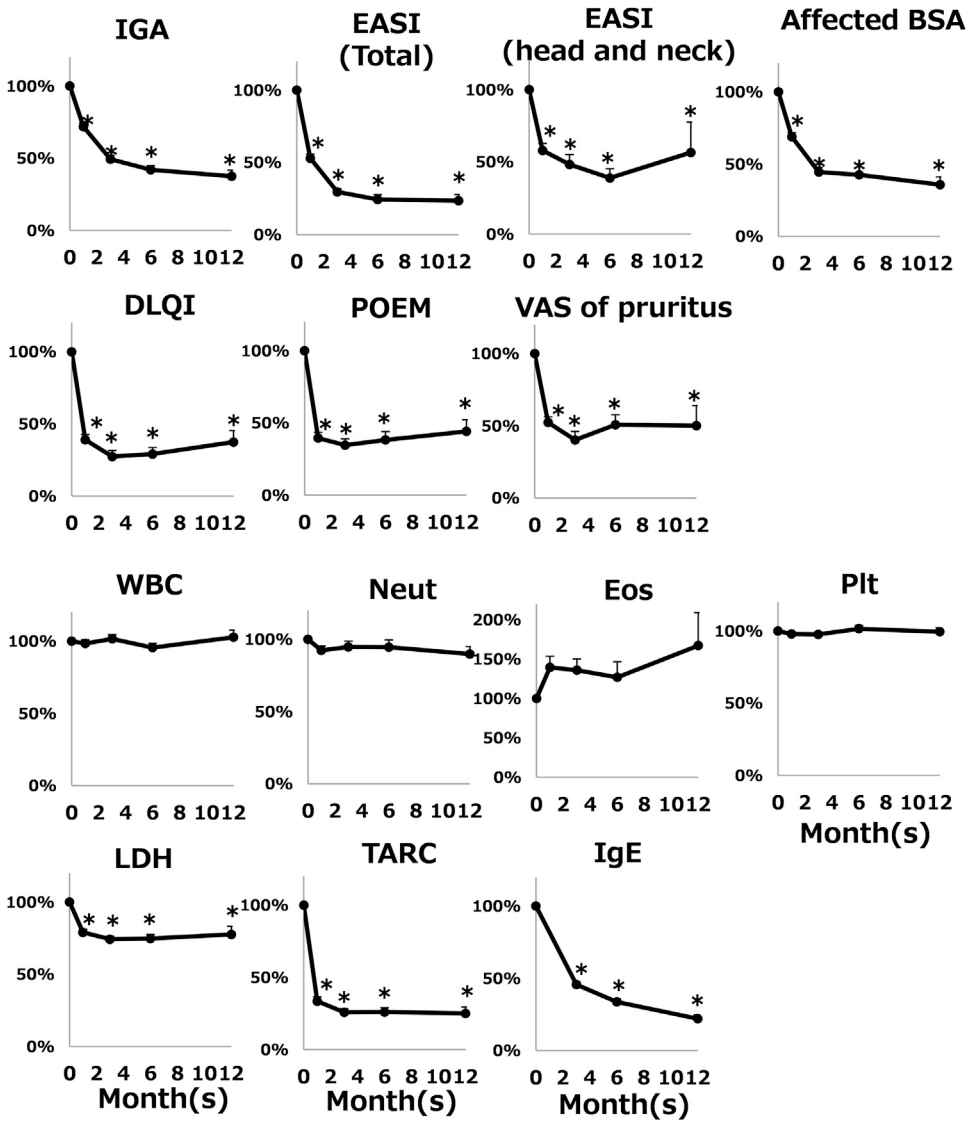


**Fig 1.** Percentage changes in clinical severity scores, quality-of-life scores, and laboratory results compared with the respective baseline values over time. Patients started treatment with dupilumab at 0 months. Data are shown as mean ± standard error. *$P < .05$ compared with the respective baseline value at time 0. *BSA*, Body surface area; *DLQI*, Dermatology Quality of Life Index; *EASI*, Eczema Area and Severity Index; *Eos*, number of circulating eosinophils; *IGA*, Investigator's Global Assessment; *IgE*, immunoglobulin E; *LDH*, lactate dehydrogenase; *Neut*, number of circulating neutrophils; *Plt*, platelet count; *POEM*, Patient-Oriented Eczema Measure; *TARC*, thymus and activation-regulated chemokine; *VAS*, visual analog scale; *WBC*, white blood cells.

*Conflicts of interest: Drs Kamata and Tada have received honoraria for lectures from Sanofi. Drs Uchida, Kato, Mizukawa, Watanabe, Agematsu, Nagata, Fukaya, Hayashi, Fukuyasu, Tanaka, Ishikawa, and Ohnishi have no conflicts of interest to declare.*

*Reprints not available from the authors.*

*Correspondence to: Masahiro Kamata, MD, PhD, Department of Dermatology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan*

*E-mail: mkamata-tky@umin.ac.jp*

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## Large nuclear size correlated with better overall survival, Merkel cell polyomavirus positivity, and terminal deoxynucleotidyl transferase expression in Merkel cell carcinoma

*To the Editor:* The histologic appearance of Merkel cell polyomavirus (MCPyV)-positive Merkel cell carcinoma (MCC) has been reported to be distinctive: more uniform, round nuclei and less cytoplasm than cells in MCPyV-negative tumors.[1,2] In most of these studies, however, the described morphologic differences were identified by light microscopy, and morphometric analysis was done on a limited number of cases.[1,3] Extraction of nuclear features by computational methods from high-resolution whole-slide digital scans of histologic slides has been shown to improve accuracy and consistency.

In this study, we analyzed the whole-slide digital images of tissue microarrays stained with hematoxylin from 134 MCCs of 134 patients with the QuPath program,[4] a free and open-source quantitative whole-slide imaging software (Fig 1, *A*). Nuclear features, including nuclear area (NA), maximum (maxD) and minimum (minD) nuclear distance (longest and shortest axes along a 2-dimensional cut of a cell, respectively), and nuclear circularity (1.0 for a perfect circle and close to 0 for an increasingly elongated polygon) were extracted for each nucleus and aggregated per patient by mean, median, and SD and divided into 90-centile/50-centile/10-centile of the values using the R statistical package.[5] The extracted nuclear features, conventional histologic and clinical features, stage, MCPyV status, and terminal deoxynucleotidyl transferase (TdT) expression were correlated with patient outcome. Statistical methods included Kaplan-Meier curves and Cox proportional hazard modeling for survival analyses. $P < .05$ was considered statistically significant.

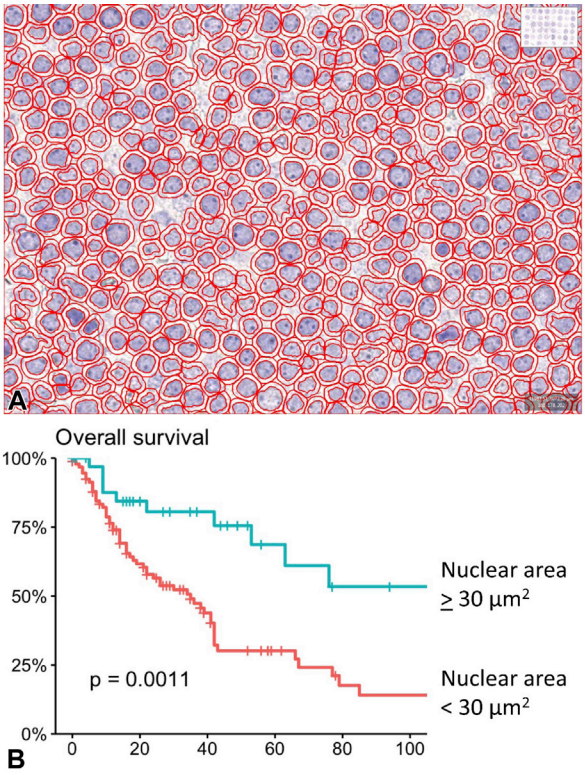


**Fig 1.** **A**, Representative image from tissue microarray in QuPath with cell detection and classification. **B**, Kaplan-Meier curves demonstrate significant correlation between better overall survival and larger nucleus area. The *y*-axis depicts percentage survival, and the *x*-axis depicts months.

The median number of evaluated nuclei for each tumor was 35,036 (range, 1817-94,401). The optimal cutoff or median for NA, minD, maxD, and nuclear circularity were 30 $\mu m^2$, 5.32 $\mu m$, 8.2 $\mu m$, and 0.7798, respectively. By box plots, large nuclear features significantly correlated with MCPyV positivity and TdT expression. By univariate Cox proportional hazard models and Kaplan-Meier curves, older age ($P < .0001$), higher stage (stages III and IV) at presentation ($P = .0066$), and ulceration ($P = .0051$) correlated with poorer overall survival (OS). There was no correlation between receipt of adjuvant therapy, including immunotherapy, and prognosis. Larger nuclear features (NA [$P = .0017$], minD [$P = .0057$], and maxD [$P = .048$]), MCPyV positivity ($P = .0061$), and high TdT expression ($P = .0019$) correlated with improved OS (Fig 1, *B*) (Table I).

Four multivariate models were evaluated—each for NA, minD, maxD, and nuclear circularity (Table I). Smaller NA ($P = .012$), older age ($P = .0017$), higher stage ($P = .032$), and low TdT expression ($P = .045$) remained independent