The Development And Validation Of A Novel Ichthyosis Severity Assessment Instrument

Qisi Sun

Follow this and additional works at: https://elischolar.library.yale.edu/ymtdl

Part of the Medicine and Health Sciences Commons

Recommended Citation

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale Medicine Thesis Digital Library by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.
The Development and Validation of a Novel Ichthyosis Severity Assessment Instrument

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Mary Sun

2021
Abstract: THE DEVELOPMENT AND VALIDATION OF A NOVEL ICHTHYOSIS SEVERITY ASSESSMENT INSTRUMENT.

Qisi Sun, Amy Paller, Keith A. Choate. Department of Dermatology, Genetics & Pathology, Yale University School of Medicine, New Haven, CT.

Ichthyosis clinical trials require reliable, validated severity assessments to identify appropriate subjects and quantify treatment outcomes. There is no validated scale to measure ichthyosis severity across the entire body. We aim to create and validate a comprehensive and user-friendly instrument to measure total body ichthyosis severity in adults and children.

We divided the body into 10 regions to score special regions of interest. Likert scales (0-4) were established to quantify scale and erythema, with descriptors and photographic standards. An 83-image teaching set was created from photographs of ichthyosis patients.

Six dermatologists scored all test photographs twice to evaluate intra-rater reliability. Intra-class correlation coefficients (ICCs) determined the overall reliability of our instrument.

The ICC for combined scale and erythema scores across the entire body is 0.903 (95% CI, 0.77-0.974). ICCs for scale and erythema sub-scores are 0.911 (95% CI, 0.789-0.976) and 0.882 (95% CI, 0.723-0.968), respectively. Body sites exhibited moderate-good inter-rater reliabilities for scale, except elbows and lower extremities. Erythema reliabilities across all body sites were moderate-excellent. Intra-rater reliabilities were excellent (ICC >0.9).

The ISS is validated as a comprehensive tool for assessing ichthyosis severity across the entire body.
Acknowledgments

I would like to express my utmost gratitude to my research mentor, Dr. Keith Choate. He is a true role model, trusted advocate, unyielding detective, thoughtful healer and visionary scientist. His dedication to creating knowledge, improving patient care and advancing the field of dermatology has inspired my career path. I hope to follow his footsteps in making important contributions to the field. During my two years of research in the lab, he has opened doors to invaluable opportunities and taught me more about research, life and medicine than he can ever know. When I think back to each transformative moment in my life, I can always pinpoint at least one or two influential people who have been absolutely critical in getting me to where I am today. Dr. Choate is definitely one of these people. It has been a special honor to learn from him, and I will forever be an indebted and proud mentee.

I am also grateful to Dr. Amy Paller for her mentorship and contribution to this important work. She possesses a special triad of grit, courage and resilience that I aspire to emulate. I thank the donors of numerous research fellowship awards and the NIH T35 grant for making it possible to sustain myself during my fifth year. I thank the Office of Student Research for providing funds so that I can travel across the nation and worldwide to present my work. I thank Drs. Erica Herzog and Sarwat Chaudhry for being the fiercest champions of student well-being. Your advocacy and dedication means more than you will ever know. I am grateful to Drs. Amanda Zubek, Sarika Ramachandran and Richard Antaya for teaching me on dermatology consults during a pandemic. Thank you to the Yale Department of Dermatology and the Yale School of Medicine for supporting medical student education. Thank you to the Yale Center for Analytical Sciences for providing statistical guidance on my projects. I am also grateful to all of the raters who have devoted their time and contributions to creating the ISS: Drs. Joyce Teng, Anne Lucky, Mary Williams, John DiGiovanna, Susan Bayliss, Latanya Benjamin, Phil Fleckman, Tracy Funk, Sarah Asch, Caroline Nelson, Ingrid Polcari, Cheryl Bayart, Brandon Newell, Anna Bruckner and Amy Nopper. I thank everyone in the Choate lab for all the laughter, fun experiences and thoughtful conversations that have made my research years unforgettable.

Thank you to the F.I.R.S.T Foundation for their support and patient advocacy, our collaborators around the world for referring patients to our study and the patients who inspire our work.

Last but not least, words cannot do justice to how grateful I am to my parents for providing wisdom, advice and non-judgmental guidance whenever I need it. I thank my siblings for their patience with and support of me in times of stress. To the close friends I have met at the Yale School of Medicine—thank you for staying by my side in times of need, for adding color to these past five years and for making medical school an incredibly enriching and treasured experience!
# Table of Contents

1. Introduction ........................................................................................................................................1  
2. Statement of purpose .......................................................................................................................31  
3. Methods ...........................................................................................................................................31  
4. Results ............................................................................................................................................35  
5. Discussion .....................................................................................................................................40  
6. References ....................................................................................................................................57
Introduction

The ichthyoses are a heterogeneous group of genetic skin disorders featuring scale and erythema with or without associated systemic findings. Mutations in over 50 genes cause ichthyosis, and their common pathogenesis is abnormal barrier function and increased transepidermal water loss with ensuing compensatory hyperproliferation. Most are inherited, but acquired ichthyosis can arise from malignancy, autoimmune or inflammatory disease, nutritional deficiency and medications.\textsuperscript{1} Inherited ichthyoses are classified into syndromic and non-syndromic forms.

In Dr. Keith Choate’s laboratory, we seek to understand the fundamental mechanisms of rare genodermatoses using tools of human genetics. In addition, we manage the National Registry for Ichthyosis and Related Disorders in collaboration with the Foundation for Ichthyosis and Related Skin Types (F.I.R.S.T). Over the years, we have served as the major national and international referral center for rare genodermatoses and have recruited over 1400 kindreds with disorders of keratinization. We utilized whole exome sequencing for novel gene discovery and sequenced parent-child trios to identify de novo mutations and paired genomic and affected tissue DNA samples when somatic mosaicism is suspected. Our work has led to significant discoveries that have enhanced our understanding of the pathogenesis of skin disease and transformed patient care.

In the following sections, we will focus on the non-syndromic ichthyoses, first providing a brief overview of the different types before identifying an important need in the field that served as the motivation behind this thesis project.
Phenotypic features of subjects with this genotype are shown in Fig. 1. 87% of the subjects surveyed with TGM1 mutations were born with a collodion presentation, a tight, shiny, parchment-like membrane that encases the neonate, resulting in ectropion and ecallion. The characteristic appearance of ichthyosis caused by TGM1 mutations is flat, dark, plate-like scale in lamellar ichthyosis and fine, white, superficial scales with mild to moderate degrees of erythema and ectropion in congenital ichthyosiform erythroderma.

Figure 1. Phenotypes of ichthyosis due to TGM1 mutations. (a-e) The characteristic appearance of subjects with TGM1 mutations include flat, plate-like scales in a mosaic pattern and mild to moderate erythema. Phenotypes range from discontinuous smoothening (diminished fine skin markings, shininess) (f), confluent scales with pink erythema (g), and confluent, primarily large (>1cm) plate-like thick scales (h).
Figure 2. Phenotypes of ichthyosis due to ABCA12 mutations

(a-e) The characteristic appearance of ichthyosis caused by ABCA12 mutations include significant and often severe erythema with fine white or thick lamellar scale and palmoplantar keratoderma. (d-g) Distinguishing features include tapered digits, hyperconvex nails, and pyknotic ears. Clinical manifestations range from mild erythema and discontinuous smoothening with small scales (h) to severe erythema with confluent smoothening and large scales (i).

Distinguishing features identified in all of these subjects and only rarely in other subjects with autosomal recessive congenital ichthyosis include tapered digits, hyperconvex nails and malformation of the auricle (Fig. 2d-g).
Additional characteristic features include pruritus (87%), anhidrosis (87%), skin pain (76%) and skin infections (62%) (Table 1a). The presence of collodion membrane at birth (OR 0.31, p=0.006) and alopecia (OR 0.24, p=0.007) are negatively associated with NIPAL4 mutations (Table 1a).

PNPLA1

PNPLA1 encodes patatin-like phospholipase domain containing 1, which forms the epidermal lipid barrier. We identified 27 kindreds with mutations in PNPLA1. 14 are compound heterozygous, 13 are homozygous and 13 mutations are novel.
extensor surfaces of joints, particularly knees and elbows. (a-f) Distinguishing features include thick, often functionally limiting, palmoplantar keratoderma. Skin findings range from columnar hyperkeratosis most prominent in the intertriginous areas with mild erythema (g) to confluent, organized or geometric exaggeration of coarse skin markings with pink erythema and marked skin fragility (h and i). There is significant palmoplantar keratoderma in all cases, ranging from moderate and smooth (j), moderate and patchy (panel k), to severe and smooth palmoplantar keratoderma (panel l).

Additional characteristic features include skin pain (91%), skin odor (79%), pruritus (70%), skin infections (57%) and anhidrosis (55%). Distinguishing features identified in all subjects with KRT1 mutations and only rarely in others include thick, often
functionally limiting palmoplantar keratoderma. The range of palmoplantar keratoderma typically includes moderate and confluent scale with yellow thickening, moderate and focal piled scale with yellow thickening, and thick, confluent yellow piled scale (Fig. 11 j-l).

To further expand the phenotypic spectrum, 26% of the IWC subjects in our cohort have KRT1 mutations. All result in a frameshift, with 8% having a splice site mutation. In contrast to those with IWC and KRT10 mutations, every IWC subject with KRT1 mutations had moderate or severe palmoplantar keratoderma. In addition, typical IWC-I features such as malformed ears, hypoplastic nipples, ectropion and hypertrichosis were absent among subjects with IWC and KRT1 mutations.

Overall, subjects with KRT1 mutations are less likely to be born with a collodion membrane (OR 0.25, p=0.02) and experience eye problems (OR 0.22, p=0.02) or alopecia (OR 0.13, p=0.02) compared to those without KRT1 mutations (Table 1b).

Palmoplantar keratoderma due to KRT1 and KRT10 mutations

It is widely accepted that palmoplantar keratoderma, when present in those with KRT10 mutations, is mild and smooth with occasional focal accentuation because KRT10 has limited expression in the palmoplantar suprabasal epidermis. Prior studies have suggested that KRT1 mutations lead to a limited cutaneous phenotype with predominant palmoplantar presentation, while KRT10 mutations result in a more widespread cutaneous involvement. Our findings show that while palmoplantar keratoderma tends to be more
chosen because they are usually less aggressively groomed and are thus more representative. Given the phenotypic variability of scales in ichthyosis, we proceeded to create two different types of scale standards: lamellar for flat scale and keratoderma for columnar scale. A five-point Likert scale was used to represent severity.

Validation was conducted in two stages. First, 60 test photographs were sent to 10 dermatologists who independently scored all photographs for scale and erythema. Four weeks later, the photographs were re-sent to the same raters to determine intra-rater reliability. The second stage involved in-person validation at the annual June 2016 F.I.R.S.T. family conference in San Diego. 85 subjects were enrolled in the study. Participants were seen in one of three clinical exam rooms with four dermatologists in each room. 12 dermatologists participated as raters and independently scored the ichthyosis severity of each participant in their room. All raters for both stages were experts in ichthyosis.

The inter-rater and intra-rater reliabilities were calculated with ICCs for absolute agreement. In contrast to the Congenital Ichthyosis Severity Index study, we used more stringent criteria to determine reliability. ICCs less than 0.7 were unacceptable, 0.7-0.9 was fair, 0.8-0.89 was good, and 0.9 or greater was excellent.

For both rounds of photographic scoring, scale scores were significantly correlated (ICCs near 0.7 or greater) although the reliabilities for erythema were poor (ICCs <0.7). The inter-rater reliability of choosing either lamellar or keratoderma scale type across all
raters was determined by the Kuder-Richardson Formula 20 to be greater than 0.9 across all four body sites. For the live validation stage, ICCs for both scale and erythema were near or greater than 0.7. ICCs for combined and total scores for the four representative sites were consistently above 0.7. These results validate the Visual Index for Ichthyosis Severity as a reliable tool for scoring severity in all types of ichthyosis.

Remaining challenges and gaps

Although there are two validated ichthyoses severity assessment tools, each has its own limitations. For instance, the Congenital Ichthyoses Severity Index only focuses on four types of ichthyoses and does not represent the full spectrum of severity. The Visual Index for Ichthyosis Severity has only been validated for four body sites and does not adequately address the nuances of ichthyosis in darker-skinned patients. For example, one of the limitations we discussed was that our photographic standards were chosen from subjects with lighter, Fitzpatrick I-III skin types; ideally standards should include a range of skin colors.

There are additional unaddressed challenges. For instance, to date, no scale has been validated to measure ichthyosis severity across the entire body. In addition, there is a demand for a more comprehensive and user-friendly instrument that not only measures ichthyosis severity in both adults and children but is also more representative of the diverse community we serve.
Given minimal regional variation in scale features among most body regions, photographic scale standards were created for five body sites: elbows, knees, palms, soles and torso (which can be applied to all other body regions) (Supplemental Figs. 3, 4, 5, 6, 7). Each standard included representations of all severity levels and all skin colors were represented whenever possible. Professional photographers took the photographs of ichthyosis patients at the Foundation for Ichthyosis and Related Skin Types (FIRST) family conferences. The images were of uniform focus, magnification, positioning, lighting and background, and represented subjects from all Fitzpatrick skin types.

We developed written descriptors characteristic of each severity level for erythema and scale. Recognizing that scale features vary minimally among the various regions except for palms and soles, we created two different sets of written scale descriptors: standards for body regions excluding palms and soles and standards for palms and soles only (Supplemental Fig. 8). Two ichthyosis experts (KC and AP) ensured that the descriptions adequately captured the wide spectrum of scale features seen among the ichthyoses, following FDA recommendations by employing morphological descriptors that emphasized clear, non-overlapping and non-comparative categories.

The extent of ichthyosis, as measured by body region involvement, is also critical for quantifying the baseline clinical disease burden and treatment efficacy. Since each body region contributes uniquely to the total body surface area, the “rule of nines” was used to assign each site a constant weighted value. These values varied for patients younger than 8 years and those 8 years and older. The final score is calculated by first multiplying the
sum of scale (0-4) and erythema (0-4) by the multiplier for each body region, and then adding the scores for all 10 regions. The final score ranges from 0 to 8 (Supplemental Fig. 9).

**ISS application**

To aid in ease-of-use, we created iOS and Android ISS applications to assist researchers and dermatologists in rapidly calculating site-specific and/or total-body severity scores for both adults and children. It is available for download from the Apple application store and the Google Play store.

**Validation of the ISS**

ISS validation was performed using scoring of test photographs, a different set of images from the photographic standards. Six ichthyosis experts were each provided with detailed scoring instructions, a score sheet and a hardcopy booklet of high-resolution photographs of standards, test photos and accompanying descriptors. They then independently used the ISS to score scale and erythema for 83 photographs (9 patients). The photographs were then sent to the same dermatologists 4 weeks later to determine intra-rater reliability. The 4-week period for the test-retest approach was chosen to reduce rater recall of previous scoring.

**Participants**

This study was approved by the Yale Human Investigation Committee, consistent with the Declaration of Helsinki guidelines. Written informed consent was obtained from all
When analyzed according to body region, all inter-rater reliabilities for scale were in the moderate-good category, with ICCs ranging from 0.503-0.898, except for elbows in round 1 and lower extremities (excluding knees and soles) in round 2. Inter-rater reliabilities for erythema were in the moderate-excellent category, with ICCs ranging from 0.587-0.902. Complete descriptive statistics for ICC agreement and consistency values during both rounds of testing are shown in Figures 14 and 15, respectively.
Figure 14. ICCs for agreement for round 1 and 2 of photographic testing.
Figure 15. ICCs for consistency for round 1 and 2 of photographic testing.
**Intra-rater reliability**

Raters exhibited excellent intra-rater reliability, with an ICC of 0.954 (95% CI, 0.918-0.974), 0.956 (95% CI, 0.925-0.974) and 0.913 (95% CI, 0.855-0.949) for the total, scale and erythema scores, respectively.

When analyzed according to body region, all intra-rater reliabilities fell in the moderate-excellent category, with ICCs ranging from 0.642-0.952 for scale and 0.742-0.915 for erythema.

**Discussion**

We have created a validated ISS for the comprehensive assessment of ichthyosis severity in clinical trials and during patient treatment. Although several tools have been developed and evaluated, none have been validated for use across the whole body. Our grading system was designed with the goal of becoming the most reliable, comprehensive and globally-adopted ichthyosis assessment tool. It needed to accurately measure severity across ichthyoses of all genetic subtypes yet be simple to implement.

The ISS assesses scale and erythema over 10 body regions. In contrast, the VIIS is limited to four body regions: upper arm, upper back, lower leg and dorsal foot. In developing our grading system, it was evident these four sites alone do not sufficiently capture a patient’s overall ichthyosis severity. Certain subtypes such as epidermolytic ichthyosis exhibit only mild, generalized ichthyosis with scale mostly limited to the palms and soles, sites that were not included in the VIIS. We also discovered that the
palms and soles display unique scale morphology, including yellow thickening, desquamative scale and fissuring. Therefore, these regions should be included when assessing ichthyosis severity and deserve their own set of scale descriptors.

During both rounds of testing, soles exhibited the highest ICCs for scale. Palms had the second and third highest ICCs for scale in round 1 and 2, respectively. The high inter-rater agreement is likely a reflection of the prominence of distinct scale features across these sites and an indication that the descriptors adequately captures scale severity. Elbows and lower extremities had the lowest ICCs for scale in round 1 and 2, respectively. Scale on the elbows may have been challenging to assess because elbow wrinkles may sometimes be difficult to distinguish from flat scale, especially in elderly patients with increased skin laxity. The lower extremities saw poor-moderate inter-rater agreement. One probable explanation for this finding is that the lower extremities represent one of the largest surface areas and some raters may have scored the large region based on the worst score for that site rather than an average, despite our instructions indicating otherwise. Furthermore, some raters may have included the knees in their assessment of lower extremities, despite written instructions indicating that the lower extremities exclude the knees and soles. It is therefore not unreasonable to assume that with prior completion of a training course, agreement among raters for these sites would increase. Erythema ICCs for both rounds were all within the moderate-excellent range.
Overall, the ISS demonstrated excellent agreement among physicians. This is notable given the heterogeneity of subjects analyzed. The inter-rater reliabilities for total score and aggregate scale scores were near perfect (ICC>0.9). Inter-rater reliabilities for aggregate erythema scores were also high (ICC>0.85). Importantly, individual evaluators were consistent in their assessments of overall severity even after one month, a time span not only long enough to reduce memory of prior scoring but also reflective of the time-frame for routine clinic follow-up. This consistency over time is essential for assessing ichthyosis improvement and therapeutic efficacy.

Although there was excellent agreement among raters using the ISS, one limitation of our study is that we validated the grading system using photographs, which may limit physicians’ assessments of physical characteristics such as scale thickness and erythema. The next step is to test the ISS in live settings. Another limitation is that only three of our nine test patients had bald scalp photos. Scalp is a challenging site to assess given that most patients have hair that can obscure scale and erythema. One way to circumvent this challenge is to take advantage of the physical exam during in-person evaluations, which if necessary, would also allow for the assessment of groin and buttocks—sites for which we did not have test photos.

Even though two regions showed poor ICCs, the substantial inter-rater reliabilities for the other eight body sites and the near-perfect agreement for total score demonstrate that the ISS is a reliable tool for scoring ichthyosis severity across the entire body. It should also be noted that the substantial inter-rater reliabilities were achieved without training the
**Elbows and knees**

- **Elbows:** Includes attachment of the humerus to the proximal radius and ulna. It excludes antecubital fossa.

- **Knees:** Includes attachment of the femur to the tibia and patella. It excludes the popliteal fossa.

**Palms:** extends from the tip of the phalanges to the carpal bones (wrist joint) and includes the area between the five phalanges. It includes glabrous skin.

**Soles:** extends from the tip of the toes to the calcaneus (heel). It includes glabrous skin.

By contrast, because erythema can be obscured by scale, the erythema score for a particular region should be the worst score for that region.
Severity score 1: Mild: Barely perceptible pink
Severity score 2: Moderate: Pink to red
Severity score 3: Severe: Bright red
Severity score 4: Very severe: Deep red-purple
Supplemental Figure 3. Elbows photographic standards

Supplemental Figure 4. Knees photographic standards
Supplemental Figure 5. Palms photographic standards

Minimal, confluent or focal thickening with continued visibility of normal skin lines may have minimal desquamative scale.
Supplemental Figure 6. Soles photographic standards.
Several areas of scaling upon a background of mildly thickened skin often with some loss of normal skin markings.
Supplemental Figure 8. Written descriptions of each severity level for all sites except palms and soles and for palms and soles only

<table>
<thead>
<tr>
<th>Scale descriptors for all sites except the palms and soles</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal skin; no perceptible scale, and no loss of normal skin markings</td>
<td>No normal skin intermixed with small scales or areas of minimally thickened skin and/or partial loss of normal skin markings</td>
<td>Several areas of scaling upon a background of mildly thickened skin often with some loss of normal skin markings</td>
<td>Confluent scales with or without focal areas of thick, piled scales and moderately thickened skin</td>
<td>Extensive areas of confluent primarily thick, piled scale and severely thickened skin</td>
</tr>
</tbody>
</table>
Supplemental Figure 9. Final score calculations for individuals younger than 8 years (top) and those 8 years and older (bottom).

<table>
<thead>
<tr>
<th>Body Region</th>
<th>Start PA</th>
<th>Min/mid</th>
<th>Ext/med</th>
<th>Min/mid</th>
<th>Size/rendch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torso</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest/breast</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palm</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms (including shoulder)</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower extremities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legs (including toes)</td>
<td>X00RR</td>
<td>+</td>
<td>X00RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Score</td>
<td>_ _ _ _ _</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


