From the Department of Dermatology, MetroHealth System[a]; Lerner College of Medicine, Cleveland Clinic[b]; Center for Health Care Research & Policy, MetroHealth System[c]; and School of Medicine, Case Western Reserve University, Cleveland, Ohio.[d]

Reprint requests: Thomas J. Knackstedt, MD, 2500 MetroHealth Dr, Cleveland, OH 44109

E-mail: thomas.j.knackstedt@gmail.com

REFERENCES

1. Brewer JD, Shanafelt TD, Otley CC, et al. Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol.* 2012;30(8):843-849.
2. Will B, Zhou L, Vogler TO, et al. Stem and progenitor cells in myelodysplastic syndromes show aberrant stage-specific expansion and harbor genetic and epigenetic alterations. *Blood.* 2012;120(10):2076-2086.
3. Passarelli A, Mannavola F, Stucci LS, Tucci M, Silvestris F. Immune system and melanoma biology: a balance between immunosurveillance and immune escape. *Oncotarget.* 2017; 8(62):106132-106142.

https://doi.org/10.1016/j.jaad.2020.04.148

Timing of PCR and antibody testing in patients with COVID-19−associated dermatologic manifestations

To the Editor: Increasing evidence supports a causal relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and cutaneous manifestations.[1,2] However, interpretation of SARS-CoV-2 polymerase chain reaction (PCR)/antibody results in dermatology patients with probable coronavirus disease 2019 (COVID-19) infection remains difficult because of lack of data to inform optimal test timing.

Our international registry for cutaneous manifestations of COVID-19[1,3] asked providers to report time between dermatologic symptom onset and positive or negative COVID-19 laboratory results. From April 8 to June 30, 2020, 906 laboratory-confirmed or suspected COVID-19 cases with dermatologic manifestations were reported, 534 of which were chilblains or pernio. Among PCR-tested patients, 57% (n = 208) of overall cases and 15% (n = 23) of chilblains and pernio ones were PCR positive. Antibody positivity was 37% (n = 39) overall and 19% (n = 15) for chilblains and pernio.

We evaluated the subgroup of 163 patients (representing the full spectrum of dermatologic manifestations of COVID-19)[1] with information on timing of PCR testing, antibody testing, or both (Table I, Supplemental Table I [available via Mendeley at https://data.mendeley.com/datasets/yhc38v2fk9/1]). For patients with suspected COVID-19 and any cutaneous manifestation, PCR positivity occurred a median of 6 days (interquartile range [IQR] 1-14 days) after dermatologic symptoms started, whereas PCR negativity occurred a median of 14 days later (IQR 7-24 days) (Fig 1). For patients with pernio or chilblains, PCR positivity was noted 8 days (IQR 5-14 days) after symptoms and negativity a median of 14 days later (IQR 7-28 days) (Supplemental Fig 1). Antibody testing result (immunoglobulin M or IgG) was positive a median of 30 days (IQR 19-39 days) after symptom onset for all dermatologic manifestations and 27 days (IQR 24-33 days) after chilblains or pernio.

PCR test results earlier in the disease course were more likely to be positive, even when date of onset was defined by cutaneous manifestations rather than systemic symptoms. Positive predictive values for COVID-19 nasopharyngeal swab PCR are influenced by kinetics of nasopharyngeal shedding, which are difficult to assess in nonrespiratory presentations.[4] This study highlights the low frequency of SARS-CoV-2 PCR-positive testing in COVID-19 patients with cutaneous manifestations.

Most published COVID-19 antibody data reflect systemically ill patients; kinetics of antibody production in mild to moderate COVID-19 infections remain unclear.[5] We detected positive antibodies a median of 30 days from disease onset, beyond the typical 14- to 21-day testing window. In outpatients with true infection, many factors influence the likelihood of positive antibody results: antibody production, assay sensitivity, and timing of care seeking. These variables influence interpretation of individual test results and understanding of the association between skin findings and COVID-19. Repeated serosurveys are needed to identify optimal antibody testing windows.

We acknowledge limitations inherent to a provider-reported registry. There is selection bias because providers likely preferentially entered laboratory-confirmed cases. Test timing could be influenced by type of symptoms (patients with systemic symptoms might have been tested earlier than those with skin-only manifestations), inpatient versus outpatient care, and geographic location. We relied on providers' judgment that the dermatologic manifestation was related to COVID-19, so the laboratory-result-negative group may have included

Table I. Distribution and timing of severe acute respiratory syndrome coronavirus 2 polymerase chain reaction and coronavirus disease 2019 antibody test results in relation to dermatologic manifestations

Testing characteristic	Chilblains/pernio			Nonchilblains/pernio			All dermatologic conditions, including pernio and nonpernio		
	No. of pernio patients	No. of pernio patients with timing data	Pernio onset to testing interval, median (IQR), days	No. of nonpernio patients	No. of nonpernio patients with timing data	Nonpernio dermatologic symptom onset to testing interval, median (IQR), days	No. of patients	No. of patients with timing data	Dermatologic symptom onset to testing interval, median (IQR), days
PCR testing									
PCR+	23	5	8 (5–14)	185	62	6 (1–15)	208	67	6 (1–14)
PCR−	134	58	14 (7–28)	27	10	9 (5–13)	161	68	14 (7–24)
SARS-CoV-2–positive antibody testing									
IgM+/IgG+	—	—	—	1	1	14	1	1	14
IgM+/IgG−	7	7	24 (23–28)	—	—	—	7	7	24 (23–28)
IgM−/IgG+	1	1	99	5	5	31 (14–32)	6	6	32 (14–35)
IgM unknown/IgG+	3	3	35 (25–40)	10	7	38 (14–46)	12	10	37 (25–40)
Ig+ (isotype unknown)	1	1	10	3	3	60 (30–107)	5	4	45 (20–84)
SARS-CoV-2–negative antibody testing									
IgM−/IgG−	17	5	37 (21–42)	1	—	—	18	5	37 (21–42)
IgM unknown/IgG−	35	16	38 (33–50)	2	2	14 (0–27)	37	18	36 (28–49)
Ig- (isotype unknown)	11	6	34 (21–60)	—	—	—	11	6	34 (21–60)

IgM, Immunoglobulin M; *IQR*, interquartile range; *PCR*, polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; +, positive; −, negative; —, no cases reported.

patients without SARS-CoV2 infection. Complicating the interpretation of negative test results are reports of PCR/antibody-negative patients whose skin biopsies contain detectable SARS-CoV-2 RNA (Supplemental references).

More population-level testing data are needed to fully understand the expected timing between disease symptoms and test positivity or negativity. Positive identification of COVID-19 in minimally symptomatic patients, including patients with skin findings, remains critical to the public health effort.

Esther E. Freeman, MD, PhD,[a,b] Devon E. McMahon, BA,[a] George J. Hruza, MD, MBA,[c] Jules B. Lipoff, MD,[d] Lars E. French, MD,[e] Lindy P. Fox, MD,[f] and Marlys S. Fassett, MD, PhD[f,g]

From the Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston[a]; Medical Practice Evaluation Center, Mongan Institute, Massachusetts General Hospital, Boston[b]; Department of Dermatology, St. Louis University, Missouri[c]; Department of Dermatology, University of Pennsylvania, Philadelphia[d]; Department of Dermatology, University Hospital, Munich University of Ludwig Maximilian, Germany[e]; and the Department of Dermatology[f] and Department of Immunology and Microbiology,[g] University of California–San Francisco

Correspondence to: Esther E. Freeman, MD, PhD, Department of Dermatology, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114

E-mail: efreeman@mgh.harvard.edu

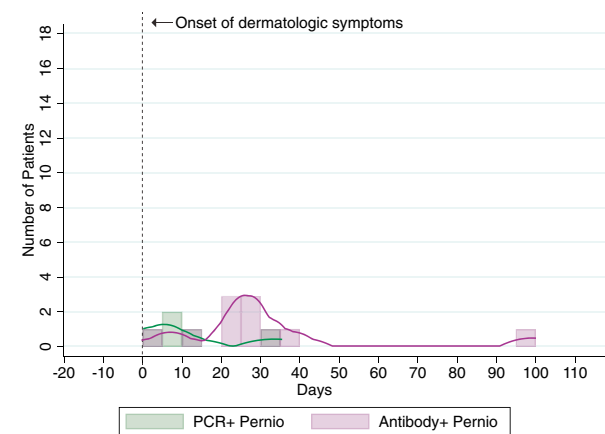## All dermatologic manifestations
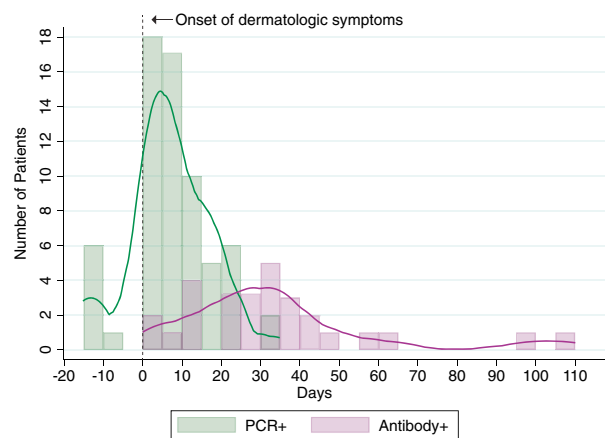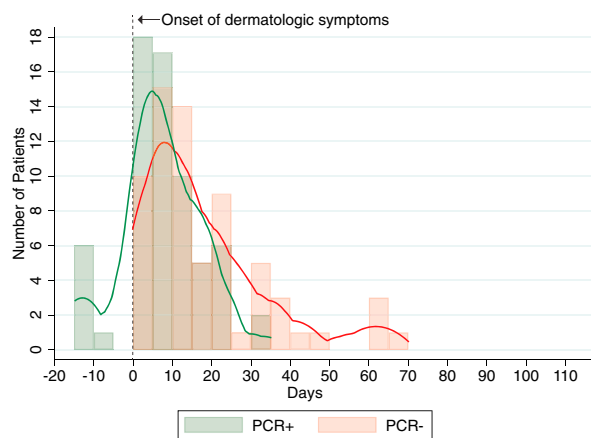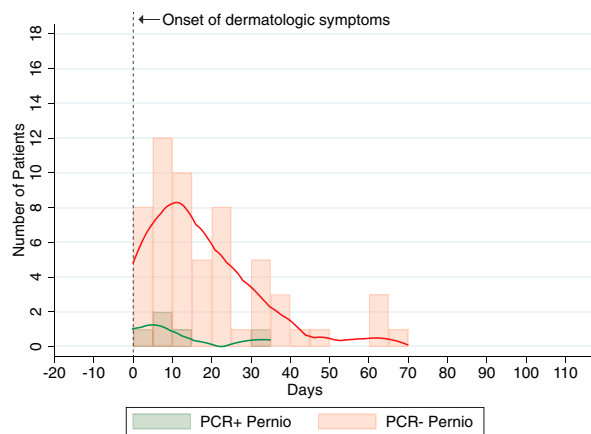

Pernio only

Fig 1. Distribution of positive and negative coronavirus disease 2019 test results in relation to onset of dermatologic symptoms, including polymerase chain reaction—positive/negative test results and polymerase chain reaction—positive/antibody-positive test results. Individual cases graphed as 5-day bins, defined by date of laboratory testing. *PCR*, Polymerase chain reaction.

REFERENCES

1. Freeman EE, McMahon DE, Lipoff JB, et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. *J Am Acad Dermatol.* 2020;83(4):1118-1129.
2. Hubiche T, Le Duff F, Chiaverini C, Giordanengo V, Passeron T. Negative SARS-CoV-2 PCR in patients with chilblain-like lesions. *Lancet Infect Dis.* https://doi.org/10.1016/S1473-3099(20)30518-1.
3. Freeman EE, McMahon DE, Fitzgerald ME, et al. The AAD COVID-19 Registry: crowdsourcing dermatology in the age of COVID-19. *J Am Acad Dermatol.* 2020;83(2):509-510.
4. Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. *JAMA.* 2020;323(22):2249-2251.
5. Robbiani DF, Gaebler C, Muecksch F, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature.* 2020;584(7821):437-442.

Chilblain-like lesions and COVID-19 infection: A prospective observational study at Spain's ground zero

To the Editor: Chilblain-like lesions (CBLL) have been related to severe acute respiratory coronavirus 2 (SARS-CoV-2) infection,[1] although solid microbiological confirmation is still lacking.

We present a prospective cohort study of 37 patients (median age, 14 years) presenting new-onset CBLL during the COVID-19 outbreak in Spain that included (1) SARS-CoV-2 testing (nasopharyngeal polymerase chain reaction [PCR] and serologies) and immunologic profiles for all patients, (2) custom recall antigen experiments and