## Identification of cutaneous immune-related adverse events by International Classification of Diseases codes and medication administration

*To the Editor:* Cutaneous immune-related adverse events (cirAEs) are the most common toxicities of immune checkpoint inhibitor (ICI) therapy and have been found to correlate with significant survival benefits.[1,2] However, cirAEs remain largely understudied due to resource demand from manual phenotyping, limiting population-based investigations. We aim to design a rule-based approach using the International Classification of Diseases (ICD), ninth/Tenth revisions, and medications for automatic phenotyping of cirAEs.

We identified a retrospective cohort of 4409 ICI recipients between 2011 and 2020 at Mass General Hospital (MGH) (2534) and Dana-Farber Cancer Institute and Brigham and Women's Hospital (DFCI/BWH) (1875), among which 422 (16.7%) and 624 (33.3%) patients, correspondingly, visited a dermatologist within 2 years from ICI initiation. Respectively, the median follow-up after ICI initiation was 14 (IQR: 4-35) and 17 (IQR: 6-34) months; the median age at ICI initiation was 66 (IQR: 57-74) and 64 (IQR: 56-72) years old. Two independent reviewers conducted manual chart review to ascertain the presence of cirAEs, according to rash timing, morphology, absence of competing risk factors, histologic confirmation, and response to therapy. There were 373 (16%) and 450 (20%) cirAE cases within 2 years of ICI with median onset time of 58 (IQR: 20-151) and 70 (IQR: 22-176) days from ICI initiation in the 2 cohorts. We designed our rule-based algorithm using the MGH cohort and validated it on the DFCI/BWH cohort.

We extracted data from the Research Patient Data Registry[3] and then applied the following approach to identify cirAEs: (1) Include ICD codes of cutaneous events associated with ICIs in literature and expert consensus[4] and topical anti-inflammatory medications (Table I) within 2 years after ICI initiation. To reduce the false positive signals, we only included codes given by dermatologists; (2) Create a sliding time window of 3 months with a step size of 15 days. If a patient had more than 1 cutaneous event and more than 1 prescription of medications in any time window, the patient is considered as having a cirAE.

Our rule-based approach achieved an accuracy of 0.87, positive predictive value (PPV) of 0.83, and negative predictive value of 0.87 using a 3-month sliding window (Table II). We further examined the performance using windows of different sizes and validated on the DFCI/BWH cohort. The cross-institutional validation showed consistent performance with only a mild decrease in the average PPV from 0.81 to 0.69. Furthermore, the results displayed robustness with different window sizes. When also including diagnoses from oncology departments, the PPV decreased by 12% and 5% in the 2 cohorts (Table II).

In summary, we present the first rule-based algorithm for cirAEs' phenotyping. It achieved a reliable performance and can be scaled to enable further cirAE research, using claim databases with diverse populations that can improve the generalizability of research outcomes. A major restriction of this study is that it is subjected to dermatology diagnosis, which limits its generalizability. Moreover, not all cirAEs are defined by a specific ICD code, putting constraints on accuracy. However, our method can provide guidance for natural language processing pipelines that incorporate medical notes to identify cirAEs.

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**Table I.** Diagnoses and topical anti-inflammatory medications used to identify cirAEs

| Cutaneous event | Total cases[§] MGH | Total cases[§] DFCI/BWH | ICD code |
|---|---|---|---|
| Diagnosis | | | |
| Acne | 8 | 22 | ICD10: L70; ICD9: 706.1 |
| Alopecia | 0 | 0 | ICD10: L63.0; L63.1; L63.2; L63.8; ICD9: 704.01 |
| Eczema | 45 | 98 | ICD10: L20.9; L20.89; L30.8; L30.9; ICD9: 691.8; 692.9 |
| Erythema multiforme | 5 | 1 | ICD10: L51.0; L51.8; L51.9; ICD9: 695.10; 695.11; 695.12; 695.19 |
| Lichen planus | 6 | 20 | ICD10: L43; L66.1; L44.3; ICD9: 697.0 |
| Mucositis | 6 | 8 | ICD10: K12; ICD9: 528.00 |
| Sweets disease | 0 | 5 | ICD10: L98.2; L88; ICD9: 686.01 |
| Bullous dermatitis | 7 | 15 | ICD10: L12; L10; Q82.8; L13.0; L01.03; L13.8; ICD9: 694.0; 694.2; 694.5; 694.6; 694.8 |
| Pruritus | 28 | 67 | ICD10: L29.8; L29.9; ICD9: 698.8 |
| Psoriasis | 14 | 40 | ICD10: L40; L41; ICD9: 696.0; 696.1; 696.2; 696.8 |
| Rash NOS* | 86 | 280 | ICD10: R21; ICD9: 782.1 |
| SJS/TEN† | 2 | 1 | ICD10: L51.1; L51.2; L51.3; ICD9: 695.13; 695.14; 695.15 |
| Urticaria | 1 | 5 | ICD10: L50.0; L50.1; L50.8; L50.9; ICD9: 708.8 |
| Vitiligo | 15 | 32 | ICD10: L80; ICD9:709.01 |
| Maculopapular | 1 | 14 | ICD10: L27.1; ICD9: 693.0 |
| Drug hypersensitivity NOS | 30 | 99 | ICD10: L27.0; T88.7; ICD9: 693.0 |
| Panniculitis | 0 | 1 | ICD10: M79.3; M54.0; L93.2; ICD9: 729.30; 723.6 |
| DRESS‡ | 0 | 0 | ICD10: D72.12 |
| Folliculitis | 6 | 31 | ICD10: L72.9; L73.9; L11.0; L87.0 |
| Exfoliative dermatitis | 0 | 0 | ICD10: L26 |
| Dermatomyositis | 0 | 2 | ICD10: D49.9; M33.0; M33.1; M33.20; M33.90; ICD9: 710.3; 239.9 |
| Hyperpigmentation | 23 | 8 | ICD10: L81.9; ICD9: 709.00 |
| Grover's disease | 0 | 11 | ICD10: L11.1; ICD9: 702.8 |
| Photosensitivity | 1 | 13 | ICD10: L56.8; ICD9: 692.79 |
| Vasculitis | 0 | 1 | ICD10: L95.8; L95.9; D69.0; ICD9: 709.1; 287.0 |
| Sarcoidosis | 0 | 1 | ICD10: D86.3; D86.89; L92.9; ICD9: 135 |
| Scleroderma | 0 | 1 | ICD10: M34.1; M34.2; M34.9; ICD9: 710.1 |
| Rosacea | 11 | 31 | ICD10: L71.8; L71.9; ICD9: 695.3 |
| Lupus erythematosus | 0 | 2 | ICD10: L93.0; L93.1; L93.2; ICD9: 695.4 |
| Seborrheic dermatitis | 19 | 37 | ICD10: L21.9; ICD9: 690.1 |
| Erythema nodosum | 0 | 1 | ICD10: L52; ICD9: 695.2 |
| Acral erythema | 1 | 1 | ICD10: L53.8; ICD9: 695.89 |
| Erythematous condition | 2 | 1 | ICD10: L53.9; ICD9: 695.9 |
| Pityriasis rubra pilaris | 0 | 0 | ICD10: L44.0; ICD9: 696.4 |
| Granuloma annulare | 0 | 2 | ICD10: L92.0 |
| Hyperhidrosis | 2 | 0 | ICD10: R61; L74.519; L74.52; ICD9: 780.8; 705.21; 705.22 |
| Hyperkeratosis | 2 | 3 | ICD10: L85.9; ICD9: 701.9 |
| Keratoacanthoma | 1 | 8 | ICD10: L85.8; ICD9: 701.8 |
| Onycholysis | 1 | 1 | ICD10: L60.1; ICD9: 703.8 |
| Pityriasis rosea | 0 | 0 | ICD10: L42; ICD9: 696.3 |
| Actinic keratosis | 98 | 123 | ICD10: L57.0; ICD9: 702.0 |
| Other | 35 | 86 | ICD10: L85.3; K11.7; ICD9: 706.8; 527.7 |

| Medication type | | | Medication |
|---|---|---|---|
| Topical medication | | | |
| Corticosteroids | 672 | 994 | Hydrocortisone, fluticasone, fluocinolone; fluocinonide, mometasone, alclometasone, desoximetasone, halobetasol, betamethasone, clobetasol, triamcinolone, desonide, amcinonide, diflorasone |

Continued

**Table I.** Cont'd

| Medication type | | | Medication |
|---|---|---|---|
| Calcineurin inhibitors | 0 | 0 | Pimecrolimus, tacrolimus |
| Vitamin D analogs | 9 | 14 | Calcitriol, calcipotriene |

*cirAEs*, Cutaneous immune-related adverse events; *ICD*, International Classification of Diseases.
*NOS: not otherwise specified.
†SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.
‡DRESS: Drug reaction with eosinophilia and systemic symptoms.
§Total cases collected from dermatology diagnosis.

**Table II.** Cross-institutional validation performance of the rule-based cirAE phenotyping

| Department* | Sliding window size | Institution | Accuracy† | PPV‡ | NPV§ |
|---|---|---|---|---|---|
| Dermatology only | 1 mo | MGH | 0.86 | 0.79 | 0.86 |
| | | DFCI/BWH | 0.83 | 0.73 | 0.83 |
| | 2 mo | MGH | 0.87 | 0.80 | 0.87 |
| | | DFCI/BWH | 0.83 | 0.67 | 0.84 |
| | 3 mo | MGH | **0.87** | **0.83** | **0.87** |
| | | DFCI/BWH | 0.83 | 0.68 | 0.84 |
| | 6 mo | MGH | 0.87 | 0.83 | 0.87 |
| | | DFCI/BWH | 0.83 | 0.66 | 0.85 |
| | Average | MGH | 0.87 | 0.81 | 0.87 |
| | | DFCI/BWH | 0.83 | 0.69 | 0.84 |
| Dermatology or oncology | 1 mo | MGH | 0.87 | 0.70 | 0.88 |
| | | DFCI/BWH | 0.83 | 0.68 | 0.84 |
| | 2 mo | MGH | 0.87 | 0.70 | 0.88 |
| | | DFCI/BWH | 0.83 | 0.63 | 0.85 |
| | 3 mo | MGH | 0.87 | 0.70 | 0.88 |
| | | DFCI/BWH | 0.83 | 0.63 | 0.85 |
| | 6 mo | MGH | 0.87 | 0.66 | 0.88 |
| | | DFCI/BWH | 0.83 | 0.61 | 0.86 |
| | Average | MGH | 0.87 | 0.69 | 0.88 |
| | | DFCI/BWH | 0.83 | 0.64 | 0.85 |

The bold values highlight the best performance we achieved using different sliding window size.
*cirAE*, Cutaneous immune-related adverse event; *DFCI/BWH*, Dana-Farber Cancer Institute and Brigham and Women's Hospital.
*Department: The diagnosis department that our rule included.
†Accuracy: the number of patients with cirAE status identified correctly divided by the number of patients in the cohort.
‡PPV: positive predictive value.
§NPV: negative predictive value.

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**Conflicts of interest**

Y.R.S. is an advisory board member/consultant and has received honoraria from Incyte Corporation, Castle Biosciences, Galderma, and Sanofi outside of the submitted work.

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