Published in final edited form as:

Br J Dermatol. 2016 March ; 174(3): 645–648. doi:10.1111/bjd.14172.

Validation of database search strategies for the epidemiological study of pemphigus and pemphigoid

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Dear Editor

Previous studies have explored the epidemiology of autoimmune blistering disease (AIBD), but all have been limited to single centres with cohorts that typically have at most a few 100 patients.^{1–4} In order to truly understand the epidemiology of AIBD, evaluation of large-scale datasets that are representative of the broader population is needed. However, no studies to date have established the best methods for identifying patients with AIBD from such datasets.

International Classification of Diseases 9th Edition Clinical Modification (ICD-9-CM) diagnostic codes are a potential way of screening for AIBD, although their validity has yet to be established. Validation studies have been successfully performed in other fields with the intention of establishing approaches for large-scale studies.^{5,6} We hypothesized that the assigned ICD-9-CM codes of 694.4 (pemphigus) and 694.5 (pemphigoid) would demonstrate a high predictive value for the confirmed diagnosis of their respective diseases. The study protocol was approved by the institutional review board at Northwestern University.

Electronic medical record data mining was conducted with the Northwestern Medicine Electronic Data Warehouse, which includes the medical records of > 2.5 million individuals across multiple affiliated sites. Cases with a diagnosis of pemphigus and/or bullous pemphigoid between January 2001 and November 2014 were included in this study. Subjects were identified as potentially having AIBD using the ICD-9-CM codes 694.4 (pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematous, paraneoplastic pemphigus and drug-induced pemphigus) and 694.5 (bullous pemphigoid).

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Study patient characteristics.

Conflicts of interest: none declared.

Electronic medical notes were then reviewed in their entirety from the first encounter through all subsequent outpatient and inpatient records. Each note was reviewed without prior knowledge of the ICD-9-CM code. The diagnosis of pemphigus and pemphigoid was confirmed by the presence of a clinical diagnosis by a board-certified dermatologist, lesional biopsy with haematoxylin and eosin staining, perilesional biopsy with direct immunofluorescence (DIF) staining, and serum collection with indirect immunofluorescence (IIF) staining or enzyme-linked immunosorbent assay (ELISA). Not every patient had all four of these criteria documented in the chart. Therefore, a rating scale from 0 to 4 was developed to assess the strength of a diagnosis based on these confirmatory findings. One point was given for each of (i) clinical diagnosis, (ii) presence of histopathology, (iii) DIF and (iv) IIF/ELISA that was consistent with the diagnosis. A half point was assigned if the diagnosis was included in the clinical or diagnostic differential diagnosis, but the findings were not definitive. A score ≥ 2 was considered to be sufficient for confirmation of pemphigus or pemphigoid and compared against the ICD-9-CM codes 694.4 and 694.5, respectively. Sensitivity, specificity, positive and negative predictive values and kappa coefficients were estimated.

Overall, 496 patients were identified, including 273 with the ICD-9-CM diagnostic code 694.4 and 266 with the code 694.5. The mean $\pm$ SD ages at last follow-up of patients with the diagnostic codes 694.4 and 694.5 were 59.6 ± 18.4 and 66.8 ± 22.5 years, respectively. Approximately half of the patients were female, with a predominance of white individuals (Table S1; see Supporting Information). Forty-three patients (8.7%) had at least one occurrence of both diagnostic codes 694.4 and 694.5 (Table 1). Twenty-eight (5.6%) had multiple occurrences of both codes, suggesting that ICD-9-CM codes alone are not sufficient to identify pemphigus or pemphigoid.

We performed a manual review of the electronic medical records. We excluded the patients with concomitant 694.4 and 694.5 codes ($n = 43$) and stratified the results by the frequency of use of the diagnostic code of interest (never, single, multiple) (Table 2). Among patients who had a single diagnostic code of 694.4 ($n = 69$), 44 (64%) had no clinical or diagnostic information to support a diagnosis of pemphigus (score = 0). In patients who had multiple occurrences of the diagnostic code 694.4, 24 (14.9%) had no clinical or diagnostic information to support a diagnosis of pemphigus. In patients who had a single diagnostic code of 694.5 ($n = 97$), 69 (71%) had no clinical or diagnostic information to support a diagnosis of pemphigoid. In patients who had multiple occurrences of the diagnostic code 694.5, 33 (26.2%) had no clinical or diagnostic information to support a diagnosis of pemphigoid. The presence of multiple diagnostic codes of either 694.4 or 694.5 was associated with excellent specificity and positive predictive value (Table 2).

After exclusion of patients with concomitant diagnostic codes 694.4 and 694.5, 16 patients had a primary inpatient diagnosis of code 694.4. Only one patient (6%) had no clinical or diagnostic information to support a diagnosis of pemphigus. Thirteen patients had a primary inpatient diagnosis of 694.5. Only two (15%) had no clinical or diagnostic information to support a diagnosis of pemphigoid.

There are a multitude of factors that can account for erroneous ICD-9 coding. Firstly, typographical error or ‘human error’ is a real possibility given the similar sounding names of the diagnoses and similar ICD-9 codes (694.4 vs. 694.5). Moreover, providers who do not routinely see patients with pemphigus and pemphigoid may have a gap in their knowledge about how to distinguish between different AIBDs. Finally, patients may have been diagnosed elsewhere and presented with an established history of self-reported disease. This introduces the possibility of misclassification bias, as patients are likely not aware of the differences between pemphigus and pemphigoid. In addition, there may be incomplete documentation of biopsies and diagnostic testing if they were performed at another institution. Future studies are needed to understand the reasons for ICD miscoding in electronic medical records.

Strengths of this study include the structured data abstraction to confirm the diagnosis of pemphigus and pemphigoid based on histopathology, immunofluorescence and clinical findings. Another strength is that both outpatient and inpatient records were reviewed at a large quaternary care hospital in a major metropolitan city. A limitation of this study is that it was carried out at a single academic centre that may not necessarily be generalizable to all medical centres. On the other hand, if selection of pemphigus and pemphigoid based on a single ICD-9-CM diagnosis code is not reliable in this setting, it is likely not reliable in many other settings.

In conclusion, the results of this study do not support the hypothesis that a single ICD-9-CM code for pemphigus and pemphigoid is sufficient to identify these disorders in large-scale epidemiological studies. Exclusion of patients with conflicting diagnostic codes and only a single occurrence of the ICD-9-CM codes 694.4 and 694.5, or limitation to inpatient records appear to be better approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources: This publication was made possible with support from the Agency for Healthcare Research and Quality (AHRQ), grant number K12HS023011. Northwestern Medicine Enterprise Data Warehouse (NMEDW) is supported by NUCATS grant 8UL1TR000150.

References

1. Ambiel MV, Roselino AM. Prevalence of metabolic syndrome and its components in a Brazilian sample of pemphigus patients. *An Bras Dermatol*. 2014; 89:752–756. [PubMed: 25184914]
2. Cai S, Allen J, Lim Y, et al. Association of bullous pemphigoid and malignant neoplasms. *JAMA Dermatol*. 2015; 151:665–667. [PubMed: 25671805]
3. Ruocco E, Wolf R, Caccavale S, et al. Bullous pemphigoid: associations and management guidelines: facts and controversies. *Clin Dermatol*. 2013; 31:400–412. [PubMed: 23806157]
4. Heelan K, Mahar AL, Walsh S, Shear NH. Pemphigus and associated comorbidities: a cross-sectional study. *Clin Exp Dermatol*. 2015; 40:593–599. [PubMed: 25786337]

5. Bartels CM, Singh JA, Parperis K, et al. Validation of administrative codes for calcium pyrophosphate deposition: a Veterans Administration study. *J Clin Rheumatol*. 2015; 21:189–192. [PubMed: 26010181]
6. Greenberg JK, Ladner TR, Olsen MA, et al. Validation of an International Classification of Diseases, Ninth Revision Code algorithm for identifying Chiari malformation type 1 surgery in adults. *Neurosurgery*. 2015; 77:269–273. [PubMed: 25924208]

Table 1

Co-occurrence of International Classification of Diseases 9th Edition Clinical Modification (ICD-9-CM) codes 694.4 and 694.5

Code 694.5	Code 694.4		
	None	Single	Multiple
None	0 (0)	69 (13.9)	161 (32.5)
Single	97 (19.6)	5 (1.0)	5 (1.0)
Multiple	126 (25.4)	5 (1.0)	28 (5.6)

Values are n (%) of the total cohort of 496. Among the 43 patients with both ICD-9-CM codes 694.4 and 694.5, the final clinical diagnosis was bullous pemphigoid in 17 (40%), pemphigus vulgaris in 13 (30%), pemphigus foliaceus in one (2%), cicatricial pemphigoid in two (5%), contact dermatitis in one (2%), Hailey–Hailey disease in four (9%), lichen planus pemphigoides in one (2%), nephrogenic fibrosing dermopathy in one (2%) and unknown in three (6%).

Table 2

Br J Dermatol. Author manuscript; available in PMC 2017 March 01.

ICD-9-CM code									
Variable	694-4			694-5			Inpatient 694-4 (n = 16)		Inpatient 694-5 (n = 13)
	None (n = 223)	Single (n = 69)	Multiple (n = 161)	None (n = 230)	Single (n = 97)	Multiple (n = 126)			
Dsg1	1 (2-1)	0	35 (35-0)	0	0	0	5 (38)	0	0
Dsg3	1 (2-1)	0	61 (61-0)	0	0	0	9 (64)	0	0
Dsg1 or Dsg3	1 (0-5)	0	76 (47-2)	0	0	0	9 (56)	0	0
BP180	0	0	0	0	1 (10)	21 (55)	0	6 (86)	
BP230	0	0	0	0	2 (20)	12 (32)	0	5 (71)	
BP180 or BP230	0	0	0	0	3 (3)	26 (20-6)	0	7 (54)	
Score									
0	190 (85-2)	44 (64)	24 (14-9)	152 (66-1)	69 (71)	33 (26-2)	1 (6)	2 (15)	
0-5	0	0	2 (1-2)	0	0	2 (1-6)	0	0	
1	33 (14-8)	17 (25)	33 (20-5)	77 (33-5)	19 (20)	19 (15-1)	3 (19)	1 (8)	
1-5	0	1 (1)	1 (0-6)	0	0	0	0	0	
2	0	5 (7)	26 (16-2)	1 (0-4)	4 (4)	16 (12-7)	3 (19)	3 (23)	
2-5	0	0	1 (0-6)	0	0	2 (1-6)	0	0	
3	0	2 (3)	32 (19-9)	0	4 (4)	39 (31-0)	3 (19)	4 (31)	
3-5	0	0	1 (0-6)	0	0	0	0	0	
4	0	0	41 (25-5)	0	1 (1)	15 (11-9)	6 (38)	3 (23)	
Statistics for score									
Sensitivity			0-47 (0-40-0-54)			0-37 (0-31-0-44)	0-72 (0-46-0-89)	0-75 (0-51-0-90)	
Specificity			1-00 (0-98-1-00)			0-99 (0-97-0-99)	0-95 (0-73-0-99)	0-94 (0-71-0-99)	
PPV			1-00 (0-96-1-00)			0-99 (0-93-0-99)	0-93 (0-64-0-99)	0-94 (0-68-0-99)	
NPV			0-35 (0-30-0-41)			0-38 (0-33-0-43)	0-79 (0-57-0-92)	0-77 (0-54-0-91)	
Kappa			0-47 (0-40-0-53)			0-37 (0-30-0-43)	0-68 (0-45-0-91)	0-69 (0-46-0-91)	

BP, bullous pemphigoid antigen; DIF, direct immunofluorescence staining; Dsg, desmoglein; IIF/ELISA, indirect immunofluorescence staining/enzyme-linked immunosorbent assay; H&E, haematoxylin and eosin stain; NPV, negative predictive value; PPV, positive predictive value.

^aThe results exclude any patients with concomitant diagnostic codes 694-4 and 694-5.

^b95% confidence intervals given in brackets. All other values are n (%).