Bullous pemphigoid (BP) is the most common autoimmune blistering disease. Since 2001, data from all specialized outpatient and inpatient care institutions in Sweden, have been registered with the National Patient Register (NPR), based on a unique personal identification number. Previous validations of the register have shown high accuracy for various non-dermatological autoimmune diseases. In order to validate the diagnosis of BP, all residents aged > 20 years in 2 counties in Sweden (539,000 inhabitants) diagnosed with bullous pemphigoid (ICD-10; L12.0, L12.8, L12.9) in the period 2001 to 2012 were identified in the NPR. Medical records, as well as immunopathological and histopathological data, were reviewed for this study. A total of 323 patients with BP were identified in the NPR. Of these, 178 patients had a directly confirmed diagnosis of BP from immunopathological and histopathological data, reviewed by a dermatopathologist. For the remaining 145 patients medical records were retrieved and further reviewed by 2 dermatologists. Of these, 105 patients had a confirmed diagnosis of BP. The medical records of 16 patients were missing, and 24 patients were not classified as having BP. Overall, a positive predictive value of 92% (283/307) was found for BP in the NPR. In conclusion, the present validation of medical records and immunopathological and histopathological data showed high validity for the diagnosis of BP in the Swedish NPR.

Key words: dermatology; inpatient; outpatient; healthcare registries; medical records.

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Healthcare registries are widely used for data collection and research. It is therefore of the utmost importance that they are valid and robust. The Swedish healthcare registries are recognized worldwide for their high quality and completeness. Sweden offers outstanding possibilities to perform register-based epidemiological studies, due to the structure of its healthcare system, its reliable healthcare registry, and the unique personal identity number (PIN) assigned to all Swedish residents.

Previous validation studies of the inpatient part of the Swedish National Patient Register (NPR) have shown high positive predictive values (PPVs) for most diagnoses, including a number of autoimmune diseases (85–95%) (1). One previous study validated a dermatological diagnosis (dermatomyositis), but included only the inpatient part of the register (2). There are very few studies validating the outpatient part of the NPR (3–5) and no previous study has validated a dermatological diagnosis in the NPR for both inpatient and outpatient care. In general, a review of medical records is considered the gold standard for evaluation of administrative databases (6).

Bullous pemphigoid (BP) is a chronic autoimmune disease that causes blistering on the skin surface. BP is the most common autoimmune bullous disease and typically emerges in the elderly population. Diagnosis of BP is dependent on a combination of clinical symptoms and routine histopathology and/or direct and/or indirect immunofluorescence (IF) microscopy and/or serology of BP180 or BP230 enzyme-linked immunosorbent assay (ELISA) (7, 8).

The aim of this study was to validate a specific dermatological diagnosis (BP) for both the outpatient and inpatient parts of the NPR, through an examination of medical records, in accordance with clinical and histopathological criteria.

METHODS

Swedish National Patient Register

The Swedish National Board of Health and Welfare now maintains 5 national healthcare registers, which include the entire Swedish population and enable medical research to evaluate a wide range of diseases.

The Swedish National Board of Health and Welfare has recorded data in the NPR on individual discharges since 1964 (9) and includes a complete coverage of all inpatient care in both public and private care in Sweden since 1987 (10, 11). Such reporting is mandatory and, since 2001, specialized outpatient clinics have also reported to the NPR. Inpatient coverage is almost 100% (1) and outpatient coverage is approximately 87%, with both public and private caregivers reporting to this register (12). Primary care is not covered (13, 14).

Each record contains patient data (PIN, sex, age, county of residence), hospital identification and medical data on major interventions and discharge diagnoses: diagnosis date, main diagnosis and up to 7 secondary discharge diagnoses (15). From
1997 until the present, diagnoses have been coded according to the International Classification of Diseases, 10th edition (ICD-10).

More than 98% of all diagnoses coded since 2007 have been shown to be technically correct based on the Swedish National Board of Health and Welfare’s own validation (1–2% drop-outs and 1% missing PINs) (11).

The PIN consists of a 12-digit number unique to each and every Swedish resident and is recorded for all health and census registers, which log information about date of birth and sex. These personal identifiers enable the systematic collection and linking of medical data among all national registries, resulting in a nearly 100% completion and follow-up rate, allowing for individual assessment of each patient over time (16).

Study design and participants

Today Sweden is divided into 21 counties and, for 2 of these counties, Örebro and Västerbotten, all residents > 20 years of age who were diagnosed with BP as a primary or secondary diagnosis (ICD-10: L12.0, L12.8, L12.9) between 2001 and 2012 were retrieved from the population-based NPR, including both inpatient and outpatient care. These 2 counties have a total population of 539,000. The age limit was set at 20 years, since BP is extremely rare in subjects under 20 years of age, and to avoid risk of confusion with other childhood blistering diseases.

Örebro and Västerbotten counties were chosen because they represent different parts of Sweden with regards to geographical location and population density. Also, both of these counties use only one specific pathology laboratory and one dermatology department.

A diagnosis of BP (BP+) was defined according to relevant ICD-10 code in the NPR (L12.0, L12.8, L12.9; Table I).

First, those residents over 20 years of age diagnosed with BP were retrieved from the NPR of Örebro and Västerbotten counties for 2001 to 2012. Simultaneously, a search in the immunopathological and histopathological registries from the pathology department in each county was performed. All histopathological records coded for SNOMED codes D3618 and D36180 (BP) were collected. Each record was then matched to the individual PINs from the NPR search. All immunopathological and histopathological records found this way were reviewed by a dermatopathologist and, if these data were consistent with BP, those patients were true BP+ and correctly coded in the NPR. The typical histopathological pattern included subepidermal blistering with an inflammatory infiltrate of eosinophils in the superficial dermis and linear deposits of immunoglobulin G (IgG) and/or C3 along the basement membrane zone by direct immunofluorescence (17, 18). In order to verify the remaining patients, medical and histopathological records were gathered from the 2 dermatology and pathology departments in each county via each patients’ PIN. Here, 2 dermatologists performed a manual review of each case in a structured and standardized manner to evaluate whether they were correctly coded regarding BP diagnosis (true BP+). To meet criteria for BP diagnosis in these cases a clear clinical history and physical examination status in the medical records, together with positive enzyme-linked immunosorbent assay (ELISA) or a histopathological or immunopathological pattern consistent with BP was necessary.

The study was approved by the Regional Ethics Review Board in Stockholm, Sweden.

Statistical analysis

All data were analysed using the statistical package STATA® Statistical Software (release 11.1; Stata-Corp, College Station, TX, USA) or Microsoft Excel®.

RESULTS

A total of 323 patients with a diagnosis of BP from the 2 counties, Örebro and Västerbotten were identified from the NPR between 2001 and 2012 (Fig. 1). A majority of these were diagnosed in outpatient care (77.4%, n = 250) and 86.1% (n = 278) were diagnosed with BP as the primary diagnosis.

A total of 178 patients had immunopathological and/or histopathological findings consistent with BP confirmed directly from pathology department records in each county.

For the remaining 145 patients, medical and histopathological records from the 2 dermatology departments in each county were retrieved manually through the PIN and reviewed by 2 dermatologists. Chart review of the remaining patients indicated that 84 patients fulfilled 2 or more criteria for BP and 21 patients were confirmed as having BP only through the clinical judgement of a dermatologist. Twenty-four patients did not fulfill the criteria for BP according to the review. Sixteen patients could not be validated because of missing medical records, hence they were excluded.

Of the 307 patients, 283 had received a correct diagnosis of BP in the NPR when validated against histo-

Table I. International Classification of Diseases, 10th edition (ICD-10) diagnostic codes for bullous pemphigoid selected for this study

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>L12.0</td>
<td>Bullous pemphigoid</td>
</tr>
<tr>
<td>L12.0A</td>
<td>Generalized bullous pemphigoid</td>
</tr>
<tr>
<td>L12.0B</td>
<td>Localized bullous pemphigoid</td>
</tr>
<tr>
<td>L12.0W</td>
<td>Other bullous pemphigoid</td>
</tr>
<tr>
<td>L12.8</td>
<td>Other pemphigoid</td>
</tr>
<tr>
<td>L12.9</td>
<td>Pemphigoid, unspecified</td>
</tr>
</tbody>
</table>

Table 1. International Classification of Diseases, 10th edition (ICD-10) diagnostic codes for bullous pemphigoid selected for this study
pathological and/or immunopathological records and/or medical records, resulting in a PPV of 92%.

The 24 patients with an incorrect diagnosis of BP were initially coded in the NPR as BP because of clinical symptoms consistent with BP. However, after further skin biopsies and blood tests, these patients were identified as having pemphigus vulgaris \( (n=6) \), eczema \( (n=2) \), dermatitis herpetiformis, streptococcal infection, purigo nodularis, porphyria cutanea tarda, pyoderma gangrenosum, erythema multiforme, leg ulcer, herpes infection, lower leg oedema, or morbus Grover’s disease \( (n=2) \), or had an unclear diagnosis \( (n=5) \).

**DISCUSSION**

This study found a high PPV for BP (92%) when comparing the Swedish NPR with histopathological and medical records for both inpatient and outpatient care.

Such validations with medical records for inpatient care registered by NPR have shown different PPVs for different diagnoses, varying between 85% and 95% (1, 10, 19). High PPVs (87–99%) have also been found in other Swedish studies validating the inpatient NPR for other autoimmune diseases (rheumatoid arthritis (5, 20) and diabetes mellitus type 1 and 2 in combination with foot ulcers (21)) from the use of medical records as the gold standard. Patients diagnosed with rheumatoid arthritis in the inpatient register are correctly coded in 87–95% of cases (1), and patients with dermatomyositis have shown an accurate diagnosis in 72% of patients and a probable diagnosis in 20% (2).

Several studies with diverse diagnoses have used data from the outpatient register (3, 22–25), yet, to the best of our knowledge, only 3 studies have previously validated the outpatient care of the NPR. They have also found similar high PPVs as in the present study for rheumatoid arthritis (91%), atrial flutter (96.5%) and spondyloarthritis (98% both inpatient and outpatient care) (3–5).

A recent study by Hsu et al. (26) validated an electronic medical record database for pemphigus and pemphigoid using ICD-9-CM codes. The authors found low PPVs when codes for both pemphigoid and pemphigus were present and if only one diagnostic code occurred in the medical records, and suggested excluding these cases. It is difficult to compare this study with our results, as Hsu et al. (26) used ICD-9 codes, and their data covered only one academic centre, which may not necessarily be generalizable to all medical centres.

The high PPV found in this study seems to be related to the fact that BP is a severe skin disease, in which highly specific tests are performed in order to ascertain a diagnosis to ensure proper treatment. PPV is probably higher in patients with a severe skin disease than in those with a milder disease outbreak, since, as a rule, further examinations and specific testing are routinely performed on severely ill patients. Thus, it is important to bear in mind that all dermatological diagnosis cannot be presumed to have the same high percentage of PPV.

A limitation of this study was that not all medical records could be reviewed. This was probably due to new systems for filing medical records and their storage in a separate archive for all deceased patients. Including all missing records as non-confirmed cases (worst-case scenario) results in a PPV of 87.6% \( (283/323) \). Including all missing records as confirmed cases (best-case scenario) results in a PPV of 92.6% \( (299/323) \). To minimize the risk of underestimating the PPV and to avoid uncertain calculations on the missing cases, we suggest excluding the missing cases from the calculation of PPV.

A total of 262 patients (93%) of the 283 patients with true BP+ had at least 2 criteria for being diagnosed as BP (clinical, histopathological, direct and/or indirect immunofluorescence and/or ELISA). The diagnosis of BP for the remaining 21 patients (7%) was based only on a clinical judgement by a dermatologist. This could have been due to patient age or unwillingness to undergo treatment or further diagnostic tests. We believe that in order to validate the NPR in the most correct way these cases should be regarded true BP+.

The present study has a number of strengths; it was population-based, and a large number of medical and histopathological records were manually reviewed in a structured manner by the 2 dermatologists and the dermatopathologist in order to best ascertain a correct diagnosis of BP. In order to avoid selection bias, 2 distinct counties in Sweden were selected for validation that had a divergent population density and differing access to healthcare. In addition, inclusion of both outpatient and inpatient care enabled all subjects with BP to be covered. Due to unique aspects of Sweden’s healthcare system, with easy and fast access to specialist care, it is more likely that dermatologists make the diagnosis of BP. The results of this study may not be generalized to countries with healthcare systems with reduced access to specialist care.

In conclusion, diagnosis of BP was shown to be accurate in the Swedish NPR. Moreover, the NPR was found to be a useful and reliable data source for future studies of BP.

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