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ORIGINAL ARTICLE

Comorbid diseases in bullous pemphigoid: A population-based case–control study

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Abstract

Bullous pemphigoid (BP) is the most prevalent autoimmune blistering disorder, triggered by autoantibodies targeting hemidesmosome components. It is associated with substantial morbidity and increased mortality. No studies comprehensively evaluate all comorbidities before and after diagnosing patients with BP. We aimed to investigate all BP-associated comorbid diseases and their patterns of associations. This nationwide population-based study included 5066 patients with BP and 10 132 controls between 2011 and 2021. We performed an automated mass screening of 546 diagnostic codes to identify BP-associated comorbidities 5 years before and after BP diagnosis, and analyzed associations patterns of comorbidities. Patients with BP had increased odds of having pressure ulcers, intracerebral hemorrhage, scabies, neuropsychiatric disorders, psoriasis, drug eruption, and acute renal failure before BP diagnosis. After BP diagnosis, they had increased odds pneumonia, sepsis, chronic renal disease, and cardiac arrest. Strong interrelationships were observed between five neuropsychiatric conditions before BP diagnosis and a strong bidirectional association between Alzheimer's dementia and pneumonia after BP diagnosis. This large case–control study of patients with BP thoroughly identified all relevant comorbidities before and after BP diagnosis, highlighting their clinical significance as predisposing and prognostic factors in patients with BP.

KEYWORDS
association rules analysis, bullous pemphigoid, comorbidity, mass screening

1 | INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune blistering disorder, caused by autoantibodies against hemidesmosome components. It predominantly affects the older population and is associated with high morbidity and mortality. Despite early treatment, patients with BP have a 1-year mortality of up to 40%, with mortality six to seven times higher than that of healthy controls.[1,2] This may be due to patient comorbidities and immunosuppressive drugs used in BP treatments.[3] Early diagnosis and management of both BP and its comorbidities are crucial for better prognosis and reduced mortality.

Associations between BP and several conditions have been suggested through various case reports, case–control studies, and, more recently, epidemiological studies.[4–7] Initially, the links between BP and autoimmune diseases or malignancies were in the focus of interest.[8–10] Later, the associations between BP and diabetes mellitus or cardiovascular disorders including hypertension, venous thromboembolism, and pulmonary embolism were reported.[11–15] Over the past 15 years, the link to neurological and psychiatric disorders, including dementia, Parkinson's disease, stroke, multiple sclerosis, and epilepsy, has also been emphasized.[6,16–20] However, current studies are limited by small sample sizes or focus on specific comorbidities. Furthermore,

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no studies have separately investigated comorbidities before and after BP diagnosis. Recognition of these associations before and after BP diagnosis can provide insights into comorbidities that may trigger BP development and those that affect patient outcomes.

The aim of the study was to comprehensively identify BP-associated comorbidities and their patterns of associations before and after BP diagnosis.

2 | METHODS

2.1 | Study design and data source

We conducted a matched case–control study using population-based data from the Korean Health Insurance Review and Assessment Service (HIRA) from 1 October 2010 to 31 December 2021 (HIRA research data: M20220831002). Almost every Korean (97%) is enrolled in a mandatory universal single-payer national healthcare system, and the HIRA contains comprehensive information about healthcare services, including treatments, pharmaceuticals, procedures, and diagnoses, for nearly 50 million beneficiaries.[21] All hospitals in the HIRA database have accumulated person-level longitudinal data using the same patient identifier.

In 2006, the Korean National Health Insurance Service (NHI) initiated a rare intractable diseases (RID) registration program, including BP. Patients who met the diagnostic criteria and received physician certification were eligible for up to a 90% reduction in copayments after registration.[22] The diagnosis must adhere to the RID diagnostic criteria established by the NHI and be reviewed by the relevant healthcare institution before submission to the NHI. Consequently, the data concerning RIDs are verified and reliable.

The three essential diagnostic criteria for BP used by the RID program are as follows: (1) typical clinical findings, such as tense blisters and/or erosions in the skin and, rarely, mucosa, as diagnosed by a physician; (2) histological findings of subepidermal blisters with the presence of eosinophils; and (3) one of the following findings from other diagnostic tests: linear deposition of IgG and C3 along the basement membrane on direct immunofluorescence (DIF), deposition of IgG along the basement membrane on indirect immunofluorescence (IIF), or presence of BP antigen 1 (BP230) or BP antigen 2 (BP180) on enzyme-linked immunosorbent assay (ELISA).[23]

All patients with BP, regardless of severity, were included in the RID program if they met the diagnostic criteria. After RID registration, in addition to the BP-related diagnostic codes from the International Classification of Diseases, Tenth Revision (ICD-10), a specific RID code (V211) was listed in BP-related claims.

2.2 | Study population

The HIRA database identified patients with BP as those aged ≥20 years with a principal or additional diagnosis code for BP (ICD-10 code L12) at least once between October 2010 and December 2021. Patients diagnosed with BP between October 1, 2010 and September 30, 2011, were excluded to avoid bias from prevalent cases. For accurate diagnosis, the RID code related to BP (V211) was also used, resulting in 5066 incident BP cases included in this study.

The control group included participants aged ≥20 years with at least one principal diagnosis code (L82) for seborrheic keratosis (SK) from the 2010 longitudinal HIRA database. Participants with any BP diagnosis code (L12) at least once between October 2010 and December 2021 were excluded. The index date was the initial diagnosis date of BP or SK. Cases and controls were matched at a frequency of 1:2 based on age group, sex, and index date. The study participant flow chart is shown in Figure 1.

2.3 | Definition of comorbid diseases

Comorbid diseases were identified using ICD-10 codes. Among the ICD-10 codes, we excluded (1) codes differing in basic characteristics of patients with BP, such as O (pregnancy, childbirth, puerperium) and P (perinatal conditions); (2) codes difficult to classify into specific diseases, such as R (symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified), T (injury, poisoning, and certain other consequences of external causes (multiple site)), V–Y (external causes of morbidity and mortality), Z (factors influencing health status and contact with health services), and U (special purposes); and (3) the codes in which disease frequency was less than 30 in the control group.

We included 546 diagnosis codes in the analysis, separately investigating comorbidities for 5 years before and after BP diagnosis. Finally, we included 431 comorbidities before and 399 comorbidities after BP diagnosis.

2.4 | Automated mass screening and association rules analysis for comorbidities of BP

As described in a previous study, we performed a meta-analysis (random effects model) of odds ratios (ORs) for all individual comorbidities in the 5 years before and after BP diagnosis.[5] Based on the OR of the 5-year meta-analysis before and after BP diagnosis, we determined each standard OR for defining the clinical significance of BP-associated comorbid diseases in conditional logistic regression analysis. Statistical significance was calculated by multiplying 0.05/1500, a more conservative threshold than the Bonferroni method ($P < 0.00003$). We considered a comorbidity to have a significant association with BP only when both clinical and statistical significance were satisfied. To analyze patterns of association between comorbidities, we performed an association rules analysis limited to comorbidities with a positive association before and after BP diagnosis.[24]

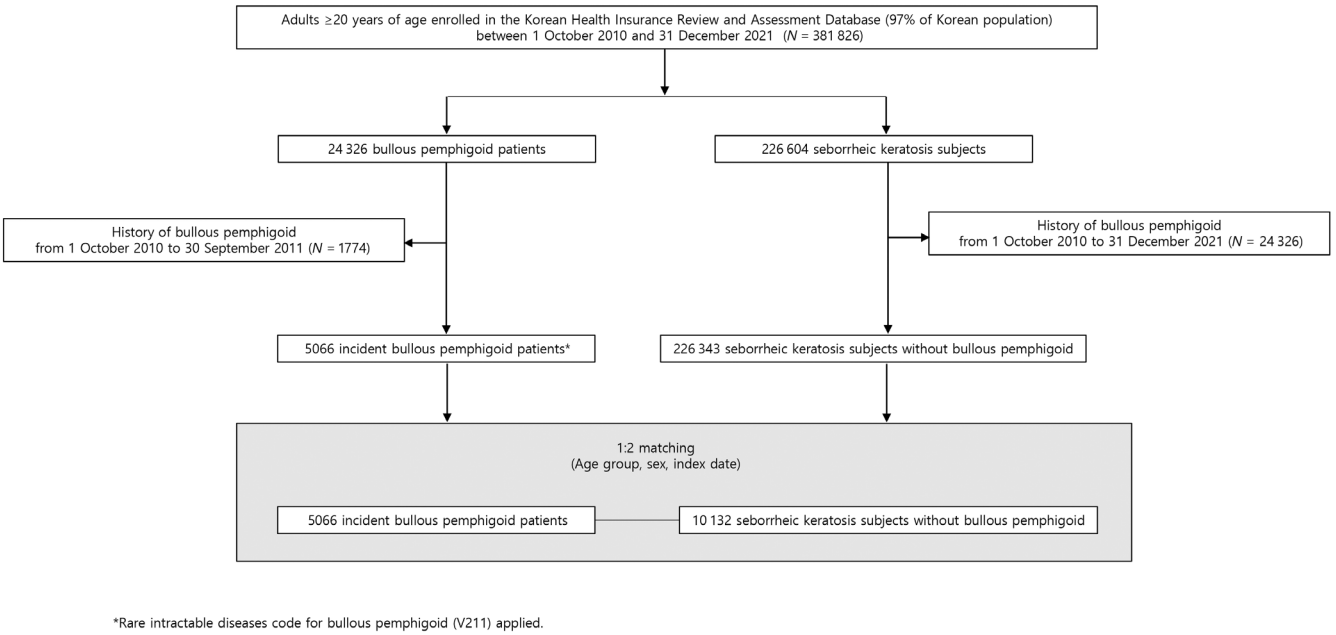

FIGURE 1 Flow chart of study population selection.

2.5 | Statistical analyses

We compared the occurrence of each comorbid disease in patients with BP and matched control participants using conditional logistic regression analysis. Data were analyzed using SAS version 9.4.2 (SAS Institute, Cary, NC, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Association rules analysis was conducted in R (version 3.5.1, R Development Core Team, 2014) using the arules library (version 1.6–2). To reduce and simplify analysis, we set minimum thresholds for support, confidence, and lift at 5%, 10%, and >1%, respectively.

3 | RESULTS

3.1 | Baseline characteristics of the study population

We identified 5066 incident patients with BP >20 years old from October 2011 to December 2021 and 10 132 matched controls without BP. Among patients with BP, 89.4% were >60 years old and 54.2% were women (Table 1).

TABLE 1 Clinical characteristics of the study population.

Characteristic	Bullous pemphigoid	Control	*P* value
Total number	5066	10 132	
Age, years			
20–29	24 (0.5)	49 (0.5)	1.000
30–39	56 (1.1)	111 (1.1)	
40–49	126 (2.5)	254 (2.5)	
50–59	332 (6.6)	660 (6.5)	
60–69	635 (12.5)	1272 (12.6)	
70–79	1604 (31.7)	3208 (31.7)	
≥80	2289 (45.2)	4578 (45.2)	
Sex			
Male	2318 (45.8)	4629 (45.7)	0.950
Female	2748 (54.2)	5503 (54.3)	
Insurance type			
Health insurance	4651 (91.8)	9510 (93.9)	<0.001
Medical aid	415 (8.2)	622 (6.1)	

Note: Data are presented as number (%). 1:2 matching: age group, sex, and index date.

3.2 | Overall disease association in the 5 years before and after BP diagnosis

We obtained 431 ORs for 431 comorbid diseases in the 5 years before BP diagnosis, and a meta-analysis OR of 0.8376 (95% confidence interval [CI] 0.7904–0.8876, $I^2 = 97.8\%$). We set OR <0.3 as the criterion of a negative association, which was more conservative than 0.8376, and OR >2.8 for a high relevance with BP, which was a counterpart of 0.3 (0.8376/0.3). Thirty-one diseases satisfied both clinical and statistical significance: 24 diseases showed an increased association and seven showed a decreased association in the 5 years before BP diagnosis (Table 2 and Supporting Information Table S1).

For the 5 years after BP diagnosis, we obtained 399 ORs for 399 comorbid diseases, with a meta-analysis OR of 0.5123 (95%

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TABLE 2 Increased comorbidities in patients with BP 5 years before and after diagnosis.

5 years before BP diagnosis					5 years after BP diagnosis				
ICD-10 code	Comorbidity	BP Events *n*, (%)	Control Events *n*, (%)	Odds ratio (95% CI)	ICD-10 code	Comorbidity	BP Events *n*, (%)	Control Events *n*, (%)	Odds ratio (95% CI)
B86	Scabies	326 (6.44)	54 (0.53)	12.83 (9.6, 17.15)	A41	Other sepsis	445 (8.78)	130 (1.28)	7.41 (6.08, 9.04)
					B86	Scabies	81 (1.60)	52 (0.51)	3.15 (2.22, 4.47)
E87	Other disorders of fluid, electrolyte, and acid–base balance	217 (4.28)	110 (1.09)	4.07 (3.23, 5.14)	E16	Other disorders of pancreatic internal secretion	65 (1.28)	54 (0.53)	2.43 (1.69, 3.49)
					E87	Other disorders of fluid, electrolyte, and acid–base balance	179 (3.53)	150 (1.48)	2.44 (1.96, 3.04)
F00	Dementia in Alzheimer's disease	1527 (30.14)	807 (7.96)	4.98 (4.54, 5.47)	F00	Dementia in Alzheimer's disease	1231 (24.30)	1469 (14.50)	1.89 (1.74, 2.06)
F01	Vascular dementia	356 (7.03)	135 (1.33)	5.59 (4.57, 6.84)	F01	Vascular dementia	147 (2.90)	147 (1.45)	2.03 (1.61, 2.56)
F03	Unspecified dementia	493 (9.73)	233 (2.30)	4.58 (3.9, 5.37)					
F31	Bipolar affective disorder	113 (2.23)	47 (0.46)	4.89 (3.48, 6.89)					
G20	Parkinson's disease	437 (8.63)	181 (1.79)	5.19 (4.35, 6.19)	G20	Parkinson's disease	370 (7.30)	230 (2.27)	3.39 (2.87, 4.01)
G21	Secondary parkinsonism	75 (1.48)	52 (0.51)	2.91 (2.04, 4.15)	G40	Epilepsy	88 (1.74)	65 (0.64)	2.74 (1.98, 3.78)
G22	Parkinsonism in diseases classified elsewhere	64 (1.26)	34 (0.34)	3.8 (2.5, 5.76)	G81	Hemiplegia	249 (4.92)	85 (0.84)	6.11 (4.77, 7.84)
G30	Alzheimer's disease	265 (5.23)	151 (1.49)	3.65 (2.98, 4.47)					
G40	Epilepsy	131 (2.59)	85 (0.84)	3.14 (2.38, 4.13)					
G81	Hemiplegia	450 (8.88)	63 (0.62)	15.57 (11.94, 20.32)					
I61	Intracerebral hemorrhage	227 (4.48)	41 (0.40)	11.54 (8.26, 16.12)	I46	Cardiac arrest	94 (1.86)	51 (0.50)	3.74 (2.65, 5.26)
I63	Cerebral infarction	1134 (22.38)	885 (8.73)	3.01 (2.74, 3.31)	I61	Intracerebral hemorrhage	132 (2.61)	69 (0.68)	3.9 (2.91, 5.23)
I69	Sequelae of cerebrovascular disease	472 (9.32)	223 (2.20)	4.56 (3.88, 5.37)	I69	Sequelae of cerebrovascular disease	184 (3.63)	146 (1.44)	2.58 (2.07, 3.21)
J90	Pleural effusion	58 (1.14)	89 (0.38)	3 (1.99, 4.5)	J15	Bacterial pneumonia	327 (6.45)	298 (2.94)	2.28 (1.94, 2.67)
					J18	Pneumonia, organism unspecified	891 (17.59)	849 (8.38)	2.33 (2.11, 2.58)
					J69	Pneumonitis due to solids and liquids	262 (5.17)	63 (0.62)	8.72 (6.61, 11.5)
L01	Impetigo	380 (7.50)	214 (2.11)	3.76 (3.17, 4.46)	L89	Decubitus ulcer and pressure area	320 (6.32)	105 (1.04)	6.44 (5.15, 8.05)

TABLE 2 (Continued)

5 years before BP diagnosis					5 years after BP diagnosis				
		BP	Control				BP	Control	
ICD-10 code	Comorbidity	Events *n*, (%)	Events *n*, (%)	Odds ratio (95% CI)	ICD-10 code	Comorbidity	Events *n*, (%)	Events *n*, (%)	Odds ratio (95% CI)
L27	Dermatitis due to substances taken internally	201 (3.97)	115 (1.14)	3.6 (2.85, 4.53)					
L30	Other dermatitis	2038 (40.23)	1898 (18.73)	2.92 (2.71, 3.15)					
L40	Psoriasis	250 (4.93)	164 (1.62)	3.15 (2.58, 3.85)					
L89	Decubitus ulcer and pressure area	356 (7.03)	48 (0.47)	15.87 (11.72, 21.5)					
L98	Other disorders of skin and subcutaneous tissue	301 (5.94)	180 (1.78)	3.49 (2.89, 4.21)					
N17	Acute renal failure	123 (2.43)	71 (0.70)	3.52 (2.63, 4.73)	N17	Acute renal failure	127 (2.51)	100 (0.99)	2.58 (1.98, 3.36)
					N18	Chronic kidney disease	457 (9.02)	498 (4.92)	1.92 (1.68, 2.19)
S72	Fracture of femur	354 (6.99)	209 (2.06)	3.56 (2.99, 4.24)					

Abbreviation: BP, bullous pemphigoid; CI, confidence level; ICD-10, International Classification of Diseases, Tenth Revision.

CI 0.4790–0.5479, $I^2 = 97.0\%$). We set OR <0.3 as the negative association standard and OR >1.8 as the positive association standard. Fifty-eight diseases satisfied both clinical and statistical significance: 18 diseases showed an increased association and 40 showed decreased association in the 5 years after BP diagnosis.

3.2.1 | Certain infectious and parasitic diseases

We found a significant association between BP and scabies both before and after BP diagnosis (B86: OR 12.83, 95% CI 9.6–17.15 and OR 3.15, 95% CI 2.22–4.47, respectively), and an increased association with sepsis after BP diagnosis (A41: OR 7.41, 95% CI 6.08–9.04), which was the second most common comorbidity in patients with BP post-diagnosis. However, BP showed a decreased correlation with viral warts both before and after BP diagnosis (B07: OR 0.16, 95% CI 0.12–0.22 and OR 0.12, 95% CI 0.08–0.18, respectively), and viral conjunctivitis significantly decreased after BP diagnosis compared to controls (B30: OR 0.28, 95% CI 0.17–0.46).

3.2.2 | Neoplasms

Certain benign and malignant tumors showed a decreased correlation with BP. Malignant skin tumors (C44: OR 0.15, 95% CI 0.09–0.25 and OR 0.09, 95% CI 0.06–0.14) and benign thyroid neoplasms (D34: OR 0.26, 95% CI 0.17–0.4 and OR 0.26, 95% CI 0.16–0.44) showed decreased association with BP both before and after BP diagnosis. Additionally, melanocytic nevi showed decreased association with BP before BP diagnosis, whereas carcinoma in situ of the skin and benign tumors of skin, connective, and soft tissue showed decreased association after BP diagnosis.

3.2.3 | Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

No clinically or statistically significant associations with BP were observed in this group, including lymphoproliferative disorders.

3.2.4 | Endocrine, nutritional, and metabolic diseases

Disorders of fluid, electrolyte, and acid–base balance showed a positive correlation with BP both before and after the BP diagnosis (E87: OR 4.07, 95% CI 3.23–5.14 and OR 2.44, 95% CI 1.96–3.04, respectively). Pancreatic internal secretion disorders also showed a positive association after BP diagnosis (E16: OR 2.43, 95% CI 1.69–3.49).

3.2.5 | Mental and behavioral disorders

Alzheimer's dementia (F00: OR 4.98, 95% CI 4.54–5.47 and OR 1.89, 95% CI 1.74–2.06) and vascular dementia (F01: OR 5.59, 95% CI 4.57–6.84 and OR 2.03, 95% CI 1.61–2.56) showed increased association with BP both before and after BP diagnosis. Bipolar affective disorder showed a positive correlation before BP diagnosis, whereas anxiety and somatoform disorders showed a negative association with BP after BP diagnosis.

3.2.6 | Diseases of the nervous system

Parkinson's disease (G20: OR 5.19, 95% CI 4.35–6.19 and OR 3.39, 95% CI 2.87–4.01), epilepsy (G40: OR 3.14, 95% CI 2.38–4.13 and OR 2.74, 95% CI 1.98–3.78), and hemiplegia (G81: OR 15.57, 95% CI 11.94–20.32) showed significant association with BP both before and after BP diagnosis. Conversely, headache syndromes (G44: OR 0.28, 95% CI 0.23–0.35) and facial nerve disorders (G51: OR 0.2, 95% CI 0.1–0.39) showed low association with BP after BP diagnosis.

3.2.7 | Disease of the eye and ear

Some eye and ear diseases were observed less frequently in patients with BP after diagnosis, including diseases of the eyelid (H02) and lacrimal system (H04), retinal vascular occlusions (H34), Eustachian salpingitis and obstruction (H68), vestibular function disorders (H81), and conductive and sensorineural hearing loss (H90).

3.2.8 | Diseases of the circulatory system

After pressure sores, intracerebral hemorrhage (I61: OR 11.54, 95% CI 8.26–16.12) was the second most frequent comorbidity in patients before BP diagnosis. Additionally, cerebral infarction (I63) and sequelae of cerebrovascular disease (I69) were positively associated with BP before BP diagnosis. Intracerebral hemorrhage and sequelae of cerebrovascular disease continued to show a positive correlation after BP diagnosis, and cardiac arrest showed a newly increased correlation after BP diagnosis.

3.2.9 | Diseases of the respiratory system

Pleural effusion (J90: OR 3, 95% CI 1.99–4.5) showed an increased correlation with BP before diagnosis, and bacterial pneumonia (J15: OR 2.28, 95% CI 1.94–2.67) and pneumonia with an unspecified organism (J18: OR 2.33, 95% CI 2.11–2.58) showed increased association with BP after diagnosis. Notably, pneumonitis due to solids and liquids (J69: OR 8.72, 95% CI 6.61–11.5) was the most common comorbidity after BP diagnosis.

3.2.10 | Diseases of the digestive system

Gastro-esophageal reflux disease (K21) and diseases of the gallbladder (K82) were negatively associated with BP after diagnosis.

3.2.11 | Diseases of the skin and subcutaneous tissue

Pressure sores were the most common comorbidity in patients with BP before diagnosis and also showed a significantly increased association after diagnosis (L89: OR 15.87, 95% CI 11.72–21.5 and OR 6.44, 95% CI 5.15–8.05). Moreover, impetigo (L01: OR 3.76, 95% CI 3.17–4.46), dermatitis due to substances taken internally (drug eruption) (L27: OR 3.6, 95% CI 2.85–4.53), other dermatitis (L30: OR 2.92, 95% CI 2.71–3.15), and psoriasis (L40: OR 3.15, 95% CI 2.58–3.85) were positively associated with BP before diagnosis.

In contrast, skin changes due to chronic exposure to nonionizing radiation (L57: OR 0.23, 95% CI 0.16–0.32 and OR 0.03, 95% CI 0.01–0.06) and pigmentation disorders (L81: OR 0.14, 95% CI 0.08–0.25 and OR 0.09, 95% CI 0.04–0.2) showed a decreased association with BP both before and after diagnosis. Follicular cysts (L72), corns and callosities (L84), and hypertrophic disorders of the skin (L91) showed a decreased association with BP after diagnosis.

3.2.12 | Diseases of the musculoskeletal system and connective tissue

Among systemic diseases, musculoskeletal diseases showed the most frequent decreased association in patients with BP. This negative correlation was observed only after BP diagnosis and included arthritis, spondylopathies, dorsopathies, disorders of synovium, tendon, and enthesis.

3.2.13 | Diseases of the genitourinary system

Compared with control participants, patients with BP were associated with acute renal failure both before and after BP diagnosis (N17: OR 3.52, 95% CI 2.63–4.73). Additionally, chronic kidney disease (N18: OR 1.92, 95% CI 1.68–2.19) showed a positive association after BP diagnosis, whereas benign mammary dysplasia (N60: OR 0.22, 95% CI 0.12–0.38) showed a negative association before BP diagnosis.

3.2.14 | Injury, poisoning, and certain other consequences of external causes

A high frequency of femur fracture (S72: OR 3.56, 95% CI 2.99–4.24) was observed in patients with BP compared with controls before BP diagnosis, whereas a lower frequency of dislocation, sprain, and

strain of joints and ligaments at neck level (S13: OR 0.29, 95% CI 0.23–0.37) was observed in patients with BP compared with controls after diagnosis.

3.3 | Association rules analysis among comorbidities with increased association with BP

Although association rules analysis was initially developed for retail marketing, its concept is applicable to various informational investigations aimed at uncovering relationships between seemingly unrelated data.[25] This study assessed hidden patterns and interactions among comorbidities of BP using association rules analysis and network graph structures. From analyzing 42 diseases positively associated with BP before and after diagnosis in 5066 patients with BP, we identified 25 association rules with support, confidence, and lift of at least 5%, 10%, and >1%, respectively (Table 3). Support values (%) ranged from 5.19% to 17.45%, suggesting that the probability of having both antecedent and consequent comorbidities simultaneously in patients with BP was 5.19%–17.45%. Confidence was 21.36%–78.65%, indicating that patients with BP diagnosed with antecedent comorbidities had a 21.36%–78.65% probability of having consequent comorbidities. Lift was a measure used to determine the strength and significance of the discovered association rules. A lift value greater than 1 indicated a positive association, and a higher lift value indicated a more significant association rule. Chronic comorbidities before BP diagnosis typically persisted after diagnosis, leading to subsequent complications. Several association rules among different comorbidities were also discovered and visualized in the network graph (Figure 2).

Figure 2 shows strong correlations among eight comorbidities before and after BP diagnosis: Alzheimer's dementia (F00), unspecified dementia (F03), Parkinson's disease (G20), hemiplegia (G81), cerebral infarction (I63), sequelae of cerebrovascular disease (I69), pneumonia (J18), and other dermatitis (L30). A strong association pattern was observed among five diseases before BP diagnosis, and a strong relationship between two diseases after BP diagnosis. Before BP diagnosis, patients with BP had a 7.68% (rule 5, 6) probability of having both cerebral infarction and Alzheimer's dementia, and among patients with BP and cerebral infarction, the probability of having Alzheimer's dementia is 34.3% (rule 5). Before a diagnosis of BP, patients had a 7.38% probability (rule 7, 8) of having both unspecified dementia and Alzheimer's dementia. Among patients with BP and unspecified dementia, the probability of having Alzheimer's dementia was 75.86% (rule 7). Additionally, before BP diagnosis, there was a 6.2% probability (rule 14, 15) of having both cerebral infarction and hemiplegia, with a 27.69% probability (rule 15) of having hemiplegia among patients with BP and cerebral infarction. Furthermore, patients with BP had a 5.53% probability (rule 20, 21) of having both cerebral infarction and sequelae of cerebrovascular disease, and among those with BP and cerebral infarction, the probability of having sequelae of cerebrovascular disease was 24.69% (rule 21).

After BP diagnosis, patients with BP had a 5.55% (rule 18, 19) probability of having both pneumonia and Alzheimer's dementia, and among patients with BP and pneumonia, the probability of having Alzheimer's dementia is 31.54% (rule 18).

4 | DISCUSSION

Although the association of BP with various comorbidities has been described, previous studies are constrained by small sample sizes and narrow focus, lacking comprehensive analysis of comorbidities before and after BP diagnosis. In this nationwide population-based case–control study, we evaluated overall comorbidities associated with BP. Patients with BP had increased odds of developing pressure ulcers, intracerebral hemorrhage, scabies, and neuropsychiatric disorders (Alzheimer's dementia and Parkinson's disease) before BP diagnosis. After BP diagnosis, they were more likely to develop pneumonia and sepsis. The study revealed strong interrelationships among Alzheimer's disease, dementia, cerebral infarction, hemiplegia, and sequelae of cerebrovascular disease before BP diagnosis, and a strong bidirectional association between Alzheimer's dementia and pneumonia after BP diagnosis. This study has a large sample size (5066 BP patients) with a comprehensive investigation of comorbidities before and after BP diagnosis. This provides insights into comorbidities that may trigger BP development and those that affect patient outcomes.

Identifying differences in associated diseases before and after a diagnosis of BP could have practical implications for diagnosing and managing the condition. Comorbidities present before the diagnosis of BP may be linked to genetic predisposition or risk factors that influence the development of BP, offering insights into the etiopathogenetic mechanisms and potential prevention strategies. Conversely, comorbidities arising after the diagnosis of BP may indicate complications or progression related to BP, necessitating concurrent management and targeted prevention efforts. Our findings underscore the importance for clinicians to remain vigilant about the potential for various comorbidities both before and after a BP diagnosis. They suggest that optimal care plans for patients with BP should incorporate an assessment of other comorbidities.

Our results of an association between BP and neuropsychiatric disorders (Alzheimer's dementia, vascular dementia, Parkinson's disease, and epilepsy) and stroke (intracerebral hemorrhage and cerebral infarction) align with previous studies, which reported an approximate 2- to 5-fold increased risk of these disorders in patients with BP.[6,7] However, we found that the risk of intracerebral hemorrhage before BP diagnosis was 11.54 times higher than that in the control group, the highest reported to date. In particular, the possibility of having pressure sores and scabies before BP diagnosis was also high at 15.87 and 12.83 times, respectively, suggesting these comorbidities may trigger BP development.

Several biologic mechanisms may explain the association between BP and the aforementioned diseases. The association

TABLE 3 Association rules between comorbidities with increased association with BP 5 years before and after diagnosis.

No.	Antecedent	Consequence	Support (%)	Confidence (%)	Lift
1	F00 after (dementia in Alzheimer's disease)	F00-before (dementia in Alzheimer's disease)	17.45	71.81	2.38
2	F00 before (dementia in Alzheimer's disease)	F00-after (dementia in Alzheimer's disease)	17.45	57.89	2.38
3	F00 after (dementia in Alzheimer's disease)	L30 before (other dermatitis)	10.15	41.75	1.04
4	L30 before (other dermatitis)	F00 after (dementia in Alzheimer's disease)	10.15	25.22	1.04
5	I63 before (cerebral infarction)	F00 before (dementia in Alzheimer's disease)	7.68	34.30	1.14
6	F00 before (dementia in Alzheimer's disease)	I63 before (cerebral infarction)	7.68	25.47	1.14
7	F03 before (unspecified dementia)	F00 before (dementia in Alzheimer's disease)	7.38	75.86	2.52
8	F00 before (dementia in Alzheimer's disease)	F03 before (unspecified dementia)	7.38	24.49	2.52
9	F00 before (dementia in Alzheimer's disease), F00 after (dementia in Alzheimer's disease)	L30 before (other dermatitis)	7.03	40.27	1.00
10	L30 before (other dermatitis), F00 after (dementia in Alzheimer's disease)	F00 before (dementia in Alzheimer's disease)	7.03	69.26	2.30
11	F00 before (dementia in Alzheimer's disease), L30 before (other dermatitis)	F00 after (dementia in Alzheimer's disease)	7.03	61.17	2.52
12	J18 after (pneumonia, organism unspecified)	F00 before (dementia in Alzheimer's disease)	6.77	38.50	1.28
13	F00 before (dementia in Alzheimer's disease)	J18 after (pneumonia, organism unspecified)	6.77	22.46	1.28
14	G81 before (hemiplegia)	I63 before (cerebral infarction)	6.20	69.78	3.12
15	I63 before (cerebral infarction)	G81 before (hemiplegia)	6.20	27.69	3.12
16	G20 after (Parkinson's disease)	G20 before (Parkinson's disease)	5.74	78.65	9.12
17	G20 before (Parkinson's disease)	G20 after (Parkinson's disease)	5.74	66.59	9.12
18	J18 after (pneumonia, organism unspecified)	F00 after (dementia in Alzheimer's disease)	5.55	31.54	1.30
19	F00 after (dementia in Alzheimer's disease)	J18 after (pneumonia, organism unspecified)	5.55	22.83	1.30
20	I69 before (sequelae of cerebrovascular disease)	I63 before (cerebral infarction)	5.53	59.32	2.65
21	I63 before (cerebral infarction)	I69 before (sequelae of cerebrovascular disease)	5.53	24.69	2.65
22	I63 before (cerebral infarction)	F00 after (dementia in Alzheimer's disease)	5.53	24.69	1.02
23	F00 after (dementia in Alzheimer's disease)	I63 before (cerebral infarction)	5.53	22.75	1.02
24	F03 before (unspecified dementia)	F00 after (dementia in Alzheimer's disease)	5.19	53.35	2.20
25	F00 after (dementia in Alzheimer's disease)	F03 before (unspecified dementia)	5.19	21.36	2.20

Abbreviation: BP, bullous pemphigoid.

between BP and neuropsychiatric disorders may be due to neuroinflammation exposing neuronal antigens,[26,27] leading to the production of cross-reactive autoantibodies against skin basement membrane antigens, as both skin and neurons originate from the ectoderm and share hemidesmosomal protein antigens (BP230, BP180).[28–30] Additionally, physical factors such as radiation, wounds (pressure ulcers), and scabies can trigger BP. It is hypothesized that patients with BP have low titers of anti-basement membrane autoantibodies preclinically, which become pathogenic when evoked by an innate immune response following cutaneous tissue damage.[31–33] Our findings suggest that physicians should monitor the skin condition of patients with neuropsychiatric disorders and stroke, especially those with pressure ulcers or scabies infestations, as these may be early signs or triggers of BP.

Notably, as shown in the network graph, a strong correlation was observed among five neuropsychiatric conditions, including Alzheimer's dementia and cerebral infarction, in patients with BP before diagnosis. However, no association was observed between Parkinson's disease and other neuropsychiatric diseases. This may be attributed to the different brain regions involved: Alzheimer's disease affects the cortex and hippocampus, whereas Parkinson's disease affects the basal ganglia and substantia nigra.

In the present study, other comorbidities preceding BP diagnosis included psoriasis, dermatitis due to substances taken internally (drug eruption), and acute renal failure, with odds 3.15, 3.6, and 3.52 times higher, respectively, than those in the control group, consistent with previous studies. The mechanism linking psoriasis to BP may involve chronic disruption of the basement membrane, altering antigenicity and inducing autoantibodies. Both conditions also show elevated interleukin (IL)-23 and IL-17 levels is observed in patients with BP, suggesting psoriasis could trigger for BP.[34,35] Although BP is frequently associated with drugs, the pathogenesis of drug-induced BP is poorly understood, with various immunological hypotheses proposed.[36] Several classes of diuretics, including furosemide and aldosterone antagonists, as well as antidiabetic medications such as dipeptidyl peptidase-4 (DPP-4) inhibitors, have been identified in the literature as potential inducing agents of drug-associated BP.[37,38] In our study, the ORs for type 1 and type 2 diabetes before

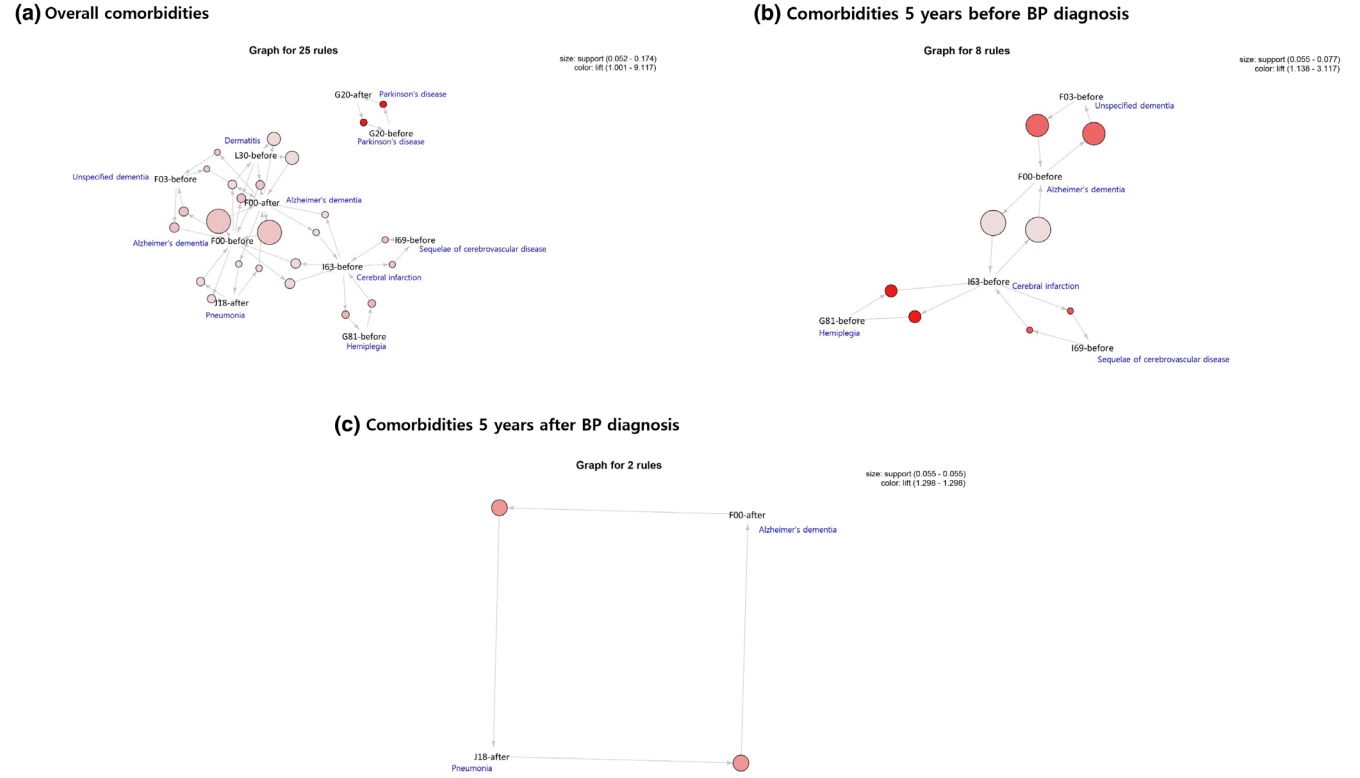

FIGURE 2 Network graph showing comorbidities with increased association with BP. The colors and sizes of the circles represent the support and lift values, respectively. Support indicates the probability of having two different comorbidities simultaneously. Lift indicates the strength and significance of the association rules discovered. (a) Overall comorbidities: 25 association rules were identified among eight comorbidities before and after the diagnosis of bullous pemphigoid (BP). (b) Comorbidities 5 years before BP diagnosis: prior to the BP diagnosis, correlations were observed between the following disease pairs: cerebral infarction and Alzheimer's dementia (rules 5, 6); Alzheimer's dementia and unspecified dementia (rules 7, 8); cerebral infarction and hemiplegia (rules 14, 15); and cerebral infarction and sequelae of cerebrovascular disease (rules 20, 21). (c) Comorbidities 5 years after BP diagnosis: following the BP diagnosis, a correlation was found between pneumonia and Alzheimer's dementia (rules 18, 19).

the BP diagnosis in patients with BP were 2.01 (95% CI 1.57–2.57) and 1.74 (95% CI 1.62–1.88), respectively, compared to the control group (data not shown). Since this result did not meet the predefined clinical significance in the automated mass screening analysis, diabetes could not be classified as a comorbidity with a significant association with BP. However, before the diagnosis of BP, patients with BP demonstrated a statistically significant association with diabetes, suggesting that antidiabetic medications, including DPP-4 inhibitors, may be related to the development of BP.

The relationship between BP and renal impairment has been reported in previous studies. Recent nationwide population-based cohort studies in Taiwan indicated an increased risk of BP in patients with chronic kidney disease and those undergoing dialysis.[39,40] Several hypotheses have been proposed to explain the possible association between BP and renal impairment, including immune dysfunction related to renal failure and the Koebner or isomorphic phenomenon due to skin injuries from hemodialysis fistulas, peritoneal dialysis catheter placements, and acquired perforating dermatosis. Additionally, the use of diuretics in the development of BP may contribute to the association between BP and renal impairment.[37,38]

After BP diagnosis, the most frequent comorbidities were pneumonia (particularly from aspiration) and sepsis, with odds 8.72 and 7.41 times higher, respectively, than those in the control group. Disorders of pancreatic secretion, chronic kidney disease, and cardiac arrest also occurred frequently. These comorbidities may result from adverse effects of systemic steroids or immunosuppressants and the overall deterioration of health of the patient with BP. Although the risk of microorganism-induced pneumonia was higher in patients with BP than that in the control group, the risk of aspiration pneumonia was notably higher, likely due to the high rate of neurodegenerative disorders such as Alzheimer's disease, which are associated with oropharyngeal dysphagia and aspiration pneumonia.[41] Moreover, as mucosal involvements account for 20% of patients with BP and can cause dysphagia, monitoring for aspiration pneumonia in those with oral lesions is crucial.[42]

Our analysis revealed a decreased association between BP and viral warts, various eye and ear diseases, digestive system diseases, benign neoplasms of the thyroid gland, skin, and soft tissue, benign mammary dysplasia, musculoskeletal disorders, callus, corn, and neck injury. This may be attributed to patients with BP being less physically active and often bedridden due to underlying neuropsychiatric disorders and skin

lesions. Furthermore, the overall ORs for possible comorbidities were <1 (0.8 before BP diagnosis, 0.5 after BP diagnosis), suggesting that patients with BP have less healthcare utilization for mild diseases or regular checkups compared to the general population.

The relationship between BP and malignancy has been debated for many years and remains controversial. Some studies have reported an increased frequency of certain types of cancer (e.g., stomach, colon, prostate, breast, lung and hematological malignancy),[10,43,44] whereas others found no association.[45,46] Our study found a reduced frequency of skin cancer and no correlation with other carcinomas. The higher risk of malignancy in patients with BP reported in previous studies may be attributed to BP predominantly affecting the older population. Additionally, the cancer risk in patients with BP was underestimated because of their lack of regular cancer screenings owing to immobility. Further studies are needed to confirm the association between BP and malignancy.

This study had several limitations. First, the diagnoses of comorbidities were based on diagnostic codes in the claims data without a review of medical records, thus the possibility of inherent inaccuracies cannot be excluded. For example, because diagnostic tests such as microscopic examinations were not necessarily required to assign the ICD-10 code for scabies, cases may include patients with true BP who were misdiagnosed or misclassified as having scabies prior to being correctly identified as having BP according to RID diagnostic criteria and registered in the RID program. This misclassification is possible because scabies can cause pruritic eruptions similar to the early stages of BP. Additionally, there remains a possibility that BP cases might include patients with conditions such as epidermolysis bullosa acquisita, p200 pemphigoid, and other rare pemphigoid diseases, as only one of the results from direct DIF, IIF, or ELISA needed to be met for registration as a BP case in the RID program. However, as our BP diagnosis combined ICD codes with an RID code, our results address the ambiguity observed in other studies that used only ICD codes for rare diseases. Moreover, the association found between Alzheimer's disease and unspecified dementia in the association rule analysis may indicate a general inaccuracy in the diagnostic codes, as the two conditions are not typically concurrent. Second, since we could not obtain matched data from a nonpatient control group through HIRA, patients with SK were selected as the control group. The rationale for choosing SK as a control is that it is a common benign skin tumor in the adult population, with an incidence that increases with age and peaks around 60 years, making it suitable for age-matching with patients with BP, a disease that predominantly affects the elderly, with an average age of 80 years. Although eruptive SK associated with malignant and non-malignant diseases could have been included in the control group, it is unlikely to significantly affect the results of this study, given the rarity of such cases reported to date.[47] However, there may be discrepancies between the actual general population and the group with SK. Third, the comorbidity frequencies calculated by the automated mass screening analysis represented the prevalence of cases rather than their incidence. In the case of the Korean HIRA database, confirming the incidence of various chronic diseases was challenging due to the limited data capacity, which extends to approximately 10 years. Lastly, since the study was conducted in Korea, our findings may not be generalizable to all populations.

Despite these limitations, this large case–control study of patients with BP thoroughly identified relevant comorbidities before and after BP diagnosis. We found that antecedent comorbidities of BP included neuropsychiatric disorders such as Alzheimer's dementia, Parkinson's disease, and stroke, pressure ulcers, scabies, psoriasis, drug eruption, and renal impairment, which may act as triggers for BP, suggesting the need for careful surveillance. The study also identified pneumonia, sepsis, pancreatic secretion abnormalities, chronic kidney disease, and cardiac arrest as important prognostic factors to manage and prevent after BP diagnosis. Further research on the direct and indirect etiologic associations between these comorbidities and BP will help elucidate the pathomechanisms and improve BP treatment.

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CONFLICT OF INTEREST STATEMENT

We declare no competing interests.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: This study was exempted from the review by the Institutional Review Board of Seoul National University Bundang Hospital (X-2209-780-903). Informed Consent: The requirement for informed consent was waived because we used only de-identified data. Registry and the Registration No. of the study/trial: N/A. Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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