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https://doi.org/10.1016/j.jaad.2019.12.076

Association between bullous pemphigoid and ischemic heart diseases: A systematic review and meta-analysis

To the Editor: Bullous pemphigoid (BP), the most common autoimmune bullous disease affecting the elderly, is associated with several comorbidities and high mortality.[1,2] Previous meta-analyses have reported a significant association between BP and thrombotic complications such as stroke and venous thromboembolism.[3,4] In addition to stroke, ischemic heart diseases (IHDs) are a leading cause of death in older people. In this study, we performed a systematic review and meta-analysis to investigate the association between BP and IHDs.

We systematically searched the PubMed, Embase, Web of Science, and Cochrane Library databases for all relevant studies published before October 13, 2019, and included case-control studies investigating the IHDs prevalence in patients with BP and controls. Search keywords were "bullous pemphigoid" in combination with "ischemic heart diseases," "angina," "myocardial infarction," "acute coronary syndrome," or "coronary artery diseases." We excluded articles that (1) were conference abstracts, case series, or reviews; (2) enrolled patients based on diagnosis codes in databases without definite diagnostic items of BP or IHDs; and (3) lacked evaluable data. Study quality was evaluated using the Newcastle-Ottawa scale.

A random-effects model was used for the meta-analysis. Odds ratios and the corresponding 95% confidence intervals were used for pooled analysis. Heterogeneity across studies was assessed using χ^2 and I^2 statistics, and the risk of publication bias was evaluated using the Egger test. All analyses were performed using Comprehensive Meta-analysis version 3 software (Biostat, Englewood, NJ).

The systematic review initially identified 89 studies, of which 11 case-control studies that met the inclusion criteria were eligible for qualitative synthesis. After the exclusion of studies with indefinite diagnostic criteria for cases, 8 studies involving 814 patients with BP and 5147 controls were included in the final quantitative analysis. Table I presents the basic characteristics of these selected studies. The meta-analysis (Fig 1) revealed that the odds of IHDs was nonsignificantly higher in patients with BP than in controls (odds ratio, 1.153; 95% confidence interval, 0.938-1.418; $P = .176$). The heterogeneity across studies ($I^2 = 0.000\%$) and publication bias ($P = .38614$) were also nonsignificant. A leave-one-out sensitivity analysis confirmed the robustness of our findings.

In contrast to the well-established association of BP with stroke or thrombotic events, the possible correlation of BP with cardiovascular diseases was proposed on the basis of the hypercoagulable and inflammatory state noted in patients with BP.[2] Furthermore, only a few case series without matched controls have reported the possibility of an association between BP and cardiovascular diseases, particularly hypertension; however, other studies conducted in different populations have reported conflicting results.[1,2] Our results demonstrated only a nonsignificant trend for the association of BP with IHD.

The limitations of this study include the lack of information on the chronology of onset for both BP and IHDs and on the influence of medications or other comorbidities of BP on IHDs as well as the exclusion of studies that enrolled patients based on codes in databases.

In conclusion, our meta-analysis revealed no significant association between BP and IHDs.

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Table I. Basic characteristics of included studies for qualitative synthesis

Studies	Country	Group	No. (M/F)	Age, mean ± SD or (range), y	IHDs,* No.	Diagnostic criteria for BP	Diagnostic criteria for IHDs*	NOS†
Langan et al[5] 2009	UK	BP	868 (334/534)	80‡ (23-102)	12	Codes in databases	Codes in databases	7
		Control	3469 (1335/2134)	79‡ (20-103)	54			
Jedlickova et al[6] 2010	Czech	BP	89 (44/45)	76.01 ± 8.73	50	Clinical features, IIF	Clinical record review	8
		Control	89 (44/45)	Matched	44	Pathology with DIF		
Yang et al[7] 2011	Taiwan	BP	390 (224/166)	72.5 ± 12.5	37	Codes in databases	Codes in databases	7
		Control	1950 (1120/830)	72.5 ± 12.5	172			
Casas-de-la-Asunción et al[8] 2014	Spain	BP	56 (22/34)	79.04 ± 11.28	10	Clinical features	Clinical record review	8
		Control	112 (matched)	Matched	15	Pathology with DIF		
Kwan et al[9] 2015	Malaysia	BP	43 (24/19)	79.4‡	9	Clinical features	Clinical record review	8
		Control	43 (24/19)	79.6‡	12	Pathology with DIF		
Kibsgaard et al[10] 2017	Denmark	BP	3281 (1447/1834)	76.5 ± 12.6	857	Codes in databases	Codes in databases	7
		Control	32213 (14135/18078)	76.9 ± 12.8	6909			
Phuan et al[11] 2017	Singapore	BP	103 (53/50)	78.1	22	Clinical features	Clinical record review	8
		Control	103 (48/55)	78.2	18	Pathology with DIF		
Sim et al[12] 2017	Singapore	BP	105 (51/54)	78 ± 11	31	Clinical features, IIF	Clinical record review	8
		Control	315 (153/162)	76 ± 13	86	Pathology with DIF		
Su et al[13] 2017	China	BP	130 (60/70)	78.2	26	Clinical features, IIF	Clinical record review	8
		Control	130 (60/70)	78.9	25	Pathology with DIF		
Pankakoski et al[14] 2018	Finland	BP	70 (36/34)	77.1	18	Clinical features, IIF	Clinical record review	7
		Control	4187 (NA)	Matched	1289	Pathology with DIF		
Kalińska-Bienias et al[15] 2019	Poland	BP	218 (81/137)	76.23 ± 11.62	98	Clinical features, IIF	Clinical record review and consultation	8
		Control	168 (67/101)	75.03 ± 10.92	60	Pathology with DIF		

BP, Bullous pemphigoid; *DIF*, direct immunofluorescence; *F*, female; *IHDs*, ischemic heart diseases; *IIF*, indirect immunofluorescence; *M*, male; *NA*, not available; *No.*, number; *NOS*, Newcastle-Ottawa Scale; *SD*, standard deviation; *UK*, United Kingdom.

[5]*Br J Dermatol*. 2009;161:1149-1152; [6]*Eur J Dermatol*. 2010;20:96-101; [7]*Stroke*. 2011;42:319-323; [8]*Actas Dermosifiliogr*. 2014;105:860-865; [9]*Med J Malaysia*. 2015;70:81-85; [10]*Br J Dermatol*. 2017;176:1486-1491;[11]*Indian J Dermatol Venereol Leprol*. 2017;83:457-461; [12]*J Eur Acad Dermatol Venereol*. 2017;31:1709-1714; [13]*J Clin Dermatol*. 2017;46:617-619; [14]*Eur J Dermatol*. 2018;28:157-161;[15]*Adv Clin Exp Med*. 2019;28:637-642.

*IHDs including angina, myocardial infarction, and coronary artery diseases.

†NOS for case-control studies (total scores: 0 to 9).

‡Median.

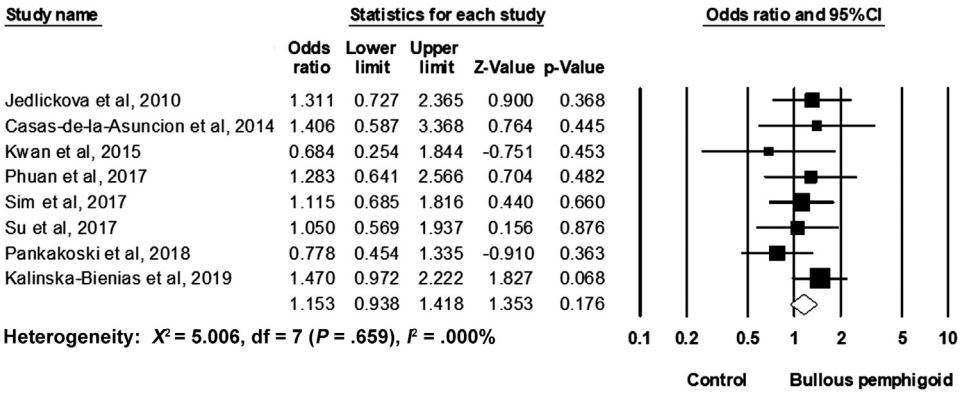

Fig 1. Meta-analysis of association of bullous pemphigoid with ischemic heart diseases. The size of the square corresponds to the relative weight assigned in the pooled analysis. The diamond denotes the pooled odds ratio, and the lateral tips of the diamond indicate the associated confidence interval (*CI*).

Dr Tsai and Dr Chang contributed equally as corresponding authors.

Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not required.

Supplemental material for this study is available at https://data.mendeley.com/datasets/xmrb5bp34f/1.

Reprints not available from the authors.

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https://doi.org/10.1016/j.jaad.2020.01.032

Green nail syndrome: Analysis of the association with onychomycosis

To the Editor: Green nail syndrome (GNS) is an infectious disorder caused by *Pseudomonas aeruginosa* that presents as greenish pigmented nails. Although an anecdotal association between GNS and onychomycosis has been reported,[1-4] data in the literature are limited. Therefore, we conducted this study to investigate the association of fungal coinfection with GNS.

We retrospectively evaluated patients with GNS from 2 hospitals from 2015 to 2018. Patients with clinical findings of greenish nails with bacterial culture results positive for *P aeruginosa* were included. During the study period, we cut or clipped the involved nail plate in all cases to detect fungal organisms. The samples were histopathologically stained with Grocott methenamine silver (GMS) and periodic acid—Schiff, which is the most sensitive method for diagnosing onychomycosis.[1] Detection of fungal hyphae or pseudohyphae and spores in the nail plates with clinical features of onychomycosis was regarded as a positive finding. This study was approved by the institutional review boards (Seoul National University Hospital 1809-106-974 and Seoul Metropolitan Government Seoul National University Boramae Medical Center 20181204/30-2018-97/123).

Twenty-three patients (6 men and 17 women) with a mean age of 53.8 years (standard deviation, 12.2; range, 32-81 years) were included, most of whom were referred by health care providers. The mean disease duration was 11.9 months (standard deviation, 13.5; range, 1-48 months). Five patients (21.7%) had immunosuppressive conditions such as internal malignancy, autoimmune disorders, or diabetes mellitus. A previous history of nail diseases was reported in 13 cases (56.5%), including 12