Lack of association between angiotensin blockade and severity of influenza: a nationwide case-control study

Yaa-Hui Dong (yaahuidong@gmail.com)
National Yang-Ming University https://orcid.org/0000-0003-0748-7993
Jo-Hsuan Wu
University of California San Diego
Jiun-Ling Wang
National Cheng Kung University Medical Center: National Cheng Kung University Hospital
Ho-Min Chen
National Taiwan University
James L. Caffrey
University of North Texas Health Science Center
Chia-Hsuin Chang
National Taiwan University Hospital
Jou-Wei Lin
National Taiwan University Hospital Yun Lin Branch

Research Article

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Abstract

Purpose

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may modulate ACE2 level and the risk of viral infections. However, studies of the risk of the severity of influenza associated with ACEIs or ARBs in the real-world settings were limited and the findings are conflicting.

Methods

This case-control study evaluated the risk of developing severe influenza disease associated with ACEIs and ARBs in hypertension patients hospitalized for influenza from a population-based Taiwanese database. Logistic regression models were conducted to estimate ORs and 95% CIs associated with ACEIs or ARBs within 30 days before hospitalization.

Results

We included 1,369 cases (severe influenza patients) and 4,107 matched controls (non-severe influenza patients). ORs for any use of ACEIs and ARBs were 1.15 (95% CI, 0.93–1.42) and 0.97 (0.84–1.12) versus nonuse. Similarly, no significant association was observed for monotherapy with ACEIs (1.47; 0.95–2.29) or ARBs (0·76; 0.53–1.10) versus nonuse. Combination therapy between calcium channel blockers (CCBs) and either ACEIs (1.57; 0.91–2.70) or ARBs (1.23; 0·93-1.62) were not significantly different from CCBs alone.

Conclusions

Our findings did not suggest an association between ACEIs and/or ARBs and the severity of influenza. Stable patients should maintain their anti-hypertensive regimens in the influenza epidemic era.

Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used anti-hypertensive medications [1]. There are multiple interactions among these drugs, the rennin-angiotensin-aldosterone system (RAAS), and the central catalyst, angiotensin-converting enzyme 2 (ACE2) [2]. ACEIs and ARBs therapy may provoke an increase in ACE2 expression in animals and humans [3, 4]. Higher ACE2 activity may then raise concerns since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the current coronavirus disease 2019 (Covid-19) pandemic, enters host cells through binding to ACE2 [5, 6]. Thus, ACEIs and ARBs might pose an unforeseen Covid-19 risk for vulnerable patients contracting the virus or for those infected developing more severe forms of the illness [7–11]. The lung damage observed in influenza infections was also reported in animal models as being mediated in part by ACE2 in particular [12–14]. Due to the shared mechanisms with coronaviruses, investigators have speculated that ACEIs and ARBs may modulate the occurrence or severity of influenza.

Observational studies have since argued that, after carefully adjusted for age, hypertension and other comorbidities, ACEIs or ARBs were not associated with increased risk of Covid-19 infection, disease severity, or subsequent death [15, 16]. Despite these assertions, limited studies have attempted to examine associations between either of these

medications and influenza in the real-world pandemic. A recent cohort study reported a 34% and 48% reduction in influenza associated with ACEIs and ARBs, respectively, in adult patients [17]. Of note, this study defined treatment status based on number of prescriptions after cohort entry. This design tends to favor the treatment group and may lead to methodological flaws due to immortal time bias [18, 19]. On the contrary, one nested case-control study and one cohort study found no benefit or risk for developing influenza [20] or increasing the severity of the illness [21] that was associated with these medication classes. Given scarce data, conflict findings, and potential methodological concerns, we sought to conduct a nationwide case-control study in exploring the risk of developing severe influenza disease associated with use of ACEIs and ARBs in patients with hypertension who were hospitalized for influenza.

Materials And Methods

Data source

A single-payer, compulsory National Health Insurance (NHI) program began in Taiwan in 1995. By 2019, the NHI program has enrolled more than 99% of total Taiwanese population (approximately 23 million) [22]. The Taiwan National Health Insurance Research Database (NHIRD) comprises complete demographic and enrollment records, diagnosis and procedure data from outpatient visits and hospital admissions, and pharmacy dispensing claims from outpatient visits and hospital admissions for individuals enrolled in the NHI program [23]. All the data are de-identified to ensure privacy protection for person-level and institutional-level information. Informed consent was waived by the National Taiwan University Hospital Research Ethics Committee because of the retrospective nature of the study and the analysis of anonymous clinical data.

Identification of study patients

We identified patients aged ≥ 20 years who had hypertension (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes of 401–405) and who were hospitalized for influenza (ICD-9-CM code of 487) from the NHIRD. Because there was an outbreak of novel H1N1 influenza A virus worldwide in 2009 and Taiwan also had reported cases since the end of May [24], our study period was from May 1, 2009 to April 30, 2012. We classified patients as severe influenza disease (i.e., cases) if they were admitted to intensive care units (ICU) or accepted intubation and mechanical ventilation during hospitalization or died within 30 days after hospitalization. Patients who were hospitalized for influenza but did not experience above events were served as controls.

Exposure to anti-hypertensive medications

We used pharmacy dispensing claims from outpatient visits and hospital admission to determine exposure to anti-hypertensive medications within 30 days before hospitalization. Antihypertensive medications included ACEIs, ARBs, calcium channel blockers (CCBs), β-blockers, diuretics, or traditional anti-hypertensives (see **eTable 1** for codes). We defined patients as being exposed to any above anti-hypertensive medications if there were > 14 days' supply of the medications available within 30 days before hospitalization. We focused on ACEIs and ARBs, but CCBs were also included in the analysis because of their widespread use in Taiwan [25, 26].

Considering that patients may receive more than one anti-hypertensive medication class, we classified anti-hypertensive exposure into mutually exclusive groups of ACEIs monotherapy, ARBs monotherapy, CCBs monotherapy, other anti-hypertensive regimens (monotherapy of other medication classes or mixed use with more than one medication class), or no current anti-hypertensive treatment (no use of any anti-hypertensive medications or use of anti-hypertensive medications equal to or less than 14 days). In addition, we specified ACEIs and CCBs in

combination and ARBs and CCBs in combination from other anti-hypertensive regimens, which facilitated to examine potential increased risk of severe hospitalized influenza disease associated with both combination therapies. See the analysis below.

Baseline patient characteristics

We ascertained patient characteristics before hospitalization. Patient characteristics included demographics (age on admission, sex, and socioeconomic status based on monthly income), use of oseltamivir and glucocorticosteroids within 30 days before hospitalization, individual comorbidites and Charlson comorbidity score within 365 days before hospitalization, and medical cost within 365 days before hospitalization. We determined use of oseltamivir and glucocorticosteroids based on outpatient and inpatient pharmacy dispensing claims, assessed individual comorbidites and Charlson comorbidity score based on outpatient and inpatient diagnosis codes, and calculated medical cost due to outpatient visits and hospital admission. See **eTable 2** for codes.

Statistical analysis

We tabulated distribution of patient characteristics between severe hospitalized influenza patients and non-severe hospitalized influenza patients. We estimated standardized difference for each variable with a value of greater than 10% indicating substantial difference in that variable between groups [27]. For each severe hospitalized influenza patient, we randomly sampled three non-severe hospitalized influenza patients matched on age (± 5 years), sex, and year of the epidemic cycle (May 2009 to April 2010, May 2010 to April 2011, or May 2011 to April 2012). Three conditional logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval (CI) for the association between anti-hypertensive medications and severity of influenza in the matched population. The first model simultaneously included any use of ACEIs, ARBs, and CCBs as compared to nonuse of ACEIs, ARBs, and CCBs, respectively. The second model treated anti-hypertensive exposure as one variable and examined the association with monotherapy of each medication class (ACEIs, ARBs, or CCBs) or other anti-hypertensive regimens as compared to nonuse of any anti-hypertensive medications. Similar to the second model, the third model examined combination therapy of ACEIs and CCBs or ARBs and CCBs as compared to CCBs monotherapy. Each model additionally adjusted for aforementioned patient characteristics as potential confounders. Considering that patients with pre-existing cardiovascular disease are at a greater risk of developing severe complications from influenza [28], we also restricted the analysis to patients without cardiovascular comorbidities including ischemic heart disease, myocardial infarction, heart failure, and atrial fibrillation to mitigate potential confounding.

Results

Study patients

Among 11,090 hospitalized influenza patients; 1,369 were severe patients and 9,721 were non-severe patients (**Figure 1**). The severe patients tended to be older, male, and had more comorbidities and higher medical cost than the non-severe patients. After matching for age, sex, and year of the epidemic cycle, there were 1,369 severe patients and 4,107 non-severe patients included in the analysis. The distribution of patient characteristics between severe and non-severe patients was more similar, although the severe patients still had more disease burden than the non-severe patients (**Table 1**).

Association between the use of anti-hypertensive medications and the occurrence of severe influenza disease

Approximately 44% of patients with severe hospitalized influenza patients (i.e., cases) and matched non-severe hospitalized influenza patients (i.e., matched controls) ever used CCBs within 30 days before hospitalization; 30%

used ARBs, followed by diuretics (30% of the cases and 26% of the matched controls), β-blockers (28% of the cases and 24% of the controls), ACEIs (10% of the cases and 9% of the controls), and traditional anti-hypertensive medications (9% of the cases and 6% of the controls) (**eTable 3** and **Table 2**). Few patients received monotherapy with individual medication class, especially with ACEIs monotherapy (2.3% of the cases and 1.6% of the matched controls). There were even fewer patients with ACEIs and CCBs in combination (1.6% of the cases and 1.4% of the matched controls) (**Table 2**).

For any use of individual medication class, the adjusted ORs were 1.15 (95% CI, 0.93-1.42) for ACEIs, 0.97 (0.84-1.12) for ARBs, and 0.95 (0.84-1.09) for CCBs comparing with nonuse of that medication class. For monotherapy, the adjusted ORs were 1.47 (0.95-2.29) for ACEIs, 0.76 (0.53-1.10) for ARBs, and 0.70 (0.55-0.88) for CCBs versus no current anti-hypertensive treatment. In terms of combination therapy with CCBs, the adjusted ORs were 1.57 (0.91-2.70) for ACEIs and CCBs and 1.23 (0.93-1.62) for ARBs and CCBs versus CCBs monotherapy (**Table 2**). The results did not materially change when we restricted the analysis to patients without cardiovascular commorbidities (903 cases and 2,709 matched controls, see **Table 3**)

Discussion

This nationwide case-control study examined the risk of developing severe influenza disease associated with anti-hypertensive medications in patients with hypertension who were hospitalized for influenza. Treatment with ACEIs or ARBs, including any use, monotherapy, or combination therapy with CCBs, did not significantly decrease or increase risk of developing severe influenza disease. Although ACEIs alone or in combination with CCBs resulted in a numerically higher OR, the confidence interval tended to be wide. The findings should provide useful information for physicians in managing hypertension during the influenza epidemic season.

ACE2 and viral infections

The role of the RAAS in influenza remains somewhat clouded. ACE2 may play an integral part in the development of select viral infections [9–11]. Specifically, ACE2 has been implicated as a functional receptor for cell entry of SARS-CoV [29] and SARS-CoV-2 [5, 6]. On the other hand, ACE2 may have anti-inflammatory properties in reducing acute lung injury. Reports in animals suggest that SARS-CoV [30] and subtypes of influenza viruses [12–14] may down-regulate ACE2, which leads to aggravate pulmonary disease. Increases in ACE2 after recombinant ACE2 delivery or ARBs therapy may moderate lung damage [12–14]. However, whether therapy with ACEIs or ARBs represents harm or benefit during viral infections remains unclear and the potential clinical consequences warrant meticulous evaluation in the real-world settings.

Real-world data of treatment with angiotensin blockade and viral infections

Our findings need to be interpreted in the context of available epidemiological studies in real practice. Specially, designs details are important such that concomitant risk factors and treatment change over time can make results susceptible to confounding by indication or immortal time bias. The results are not all one sided. Chung *et al.* reported that any use of ACEIs (hazard ratio [HR], 0.66; 0.62–0.70) or ARBs (HR, 0.52; 0.47–0.57) was associated with a decreased risk of influenza versus nonuse in a cohort study of Canadian adult patients with a median follow-up of 8.7 years [17]. Lin *et al*. also observed that patients with hypertension who used either ACEIs (HR, 0.81; 0.74–0.88) or ARBs (HR, 0.53; 0.48–0.58) exhibited a decreased risk of non-respiratory viral infection than nonusers in a Taiwanese cohort study with a median follow-up greater than 7 years [31]. These apparent benefits of ACEIs or ARBs

were only slightly smaller than that of standard prophylaxis treatment for influenza observed in randomized placebo-controlled trials with a relative risk (RR) of 0.41(0.36–0.47) for influenza vaccine [32] and a RR of 0.45 (0.30–0.67) for oseltmivir [33]. We could not rule out the role of ACEIs or ARBs in lowering risk of influenza, but the large magnitude of the effect calls into question the biological plausibility and the methodological validity. Specifically, the studies by Chung and Lin et al. have characterized treatment status (use or nonuse of ACEIs or ARBs) based on number of prescription after cohort entry. Patients who received ACEIs or ARBs may therefore have a non-exposure follow-up time before treatment in which influenza could not occur, i.e., “immortal time”. The immortal time bias tends to occur in a cohort study with a long-term follow-up and with a nonuser comparison approach, leading to overestimation of the treatment effect [18, 19].

In fact, one Danish nested case-control study did not find benefit in reducing risk of influenza associated with any use of ACEIs (OR,1.04; 95% CI; 0.99–1.10) or ARBs (OR, 1.06; 0.99–1.09) versus non-use within 3 years before developing influenza in adult patients [20]. Another Danish cohort study did not find a reduced risk of admission to ICUs (HR, 1.04; 0.80–1.37) or death (HR, 0.70; 0.47–1.05) associated with any use of ACEIs/ARBs (in a whole group) versus nonuse within 90 days before hospitalization due to influenza in adult patients [21]. Our case-control study focused on patients with hypertension and also did not observe a decreased risk of severe influenza disease associated with any use, monotherapy, or combination therapy of ACEIs or ARBs (versus non-use or CCBs) within 30 days before hospitalization due to influenza. All these study designs mitigated the concern of immortal time bias. As compared to both aforementioned Danish studies [20, 21], our study targeted a potential high-risk population and explored the effects of different regimens of ACEIs or ARBs. We considered ≥ 14 days’ day supply (rather than ≥ 1 day’s supply) of ACEIs or ARBs within a potential risk window as exposed, which may be more reasonable in terms of onset of action on influenza progression. We also examined the risk of severe influenza disease associated with CCBs which is considered independent of the RAAS; the null association provided by the CCB results adds internal consistency and supports for study validity.

Taken together, there are no compelling data to support changing anti-hypertensive therapies with ACEIs or ARBs due to perceived changes in the risk of influenza. Our current findings are in line with the recommendation from multiple specialty societies that ACEIs or ARBs should not be discontinued due to the concern of increased risk of Covid-19 [9–11, 34].

Limitations

Our study has limitations. First, previous studies usually explored the risk for any use of ACEIs or ARBs without considering concomitant use of other antihypertensive medication [17, 20]. To circumvent drug exposure misclassification, we explored the risk not only with any use of ACEIs or ARBs but also with monotherapy of either individual drugs. We also explored the risk with combination therapy with CCBs because patients may take multiple antihypertensive medications in clinical practice and CCBs are the most commonly used antihypertensive medication class in Taiwan. However, this approach yielded limited sample size in monousers and combination users, which may explain the numerically higher risk estimates for these treatment regimens. Second, we did not attempt to evaluate the history of ACEI/ARB beyond the stated 30 days given that severe influenza disease tends to be an acute event. Third, severe influenza disease by admission to ICU, acceptance of intubation or ventilation, or death might reflect the severity of companion diseases rather than specifically influenza. If so, we would expect this outcome misclassification to be non-differential between exposure groups, leading to a bias towards the null. Finally, the current study applied matching and regression adjustment to control for a number of potential covariates. Our sensitivity analysis also excluded patients with cardiovascular comorbidities to mitigate their confounding effects. However, we should recognize potential residual or unmeasured confounding factors which are inherent limitations

of observational studies. For example, the national influenza vaccination coverage rate was about 15% from 2009 to 2012 in Taiwan [35]. However, these vaccination records could not be well captured in our data source for confounding control.

Conclusion

This nationwide case-control study did not suggest decreased or increased risk of severity of influenza in patients with hypertension who were hospitalized for influenza and treated with ACEIs or ARBs. Until more evidence is available, patients in stable conditions should maintain their anti-hypertensive treatment in the influenza epidemic era.

Declarations

Author contributions: YHD, JHW, JLW, JLC, CHC, and JWL contributed to the study concept and design. JWL contributed to the data acquisition. HMC contributed to the data analysis. All the authors contributed to the data interpretation. YHD and JWL drafted the manuscript. JHW, JLW, HMC, JLC, and CHC provided critical revision of the manuscript for important intellectual content. JWL obtained the founding. CHC and JWL were the supervisors. All the authors have read, contributed to, and approved the final manuscript and agreed to transfer the copyright ownership in the event of acceptance.

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Data availability: The analysis of this study was based on data extracted from the Taiwan National Health Insurance Research Database, which cannot be publicly available according to the regulation of the Ministry of Health and Welfare in Taiwan. However, interested readers are encouraged to contact the corresponding authors for further discussion.

References

1. James PA, Oparil S, Carter BL, et al. 2014evidence-basedguideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
2. Varagic J, Ahmad S, Nagata S, Ferrario CM. ACE2: angiotensin II/angiotensin-(1-7) balance in cardiac and renal injury. Curr Hypertens Rep 2014;16:420.
3. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005;111:2605-10.
4. Soler MJ, Barrios C, Oliva R, Batlle D. Pharmacologic modulation of ACE2 expression. Curr Hypertens Rep 2008;10:410-4.
5. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.

6. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-280.e8.
7. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020;8:e21.
8. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? **J Hypertens**2020;38:781–2.
9. Jarcho JA, Ingelfinger JR, Hamel MB, D'Agostino RB Sr, Harrington DP. Inhibitors of the renin-angiotensin-aldosterone system and Covid-19. N Engl J Med 2020;382:2462-4.
10. Patel AB, Verma A. Covid-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? JAMA 2020;323:1769-70.
11. Vaduganathan M, Vardeny O, Michel T, McMurray JVC, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653-9.
12. Yang P, Gu H, Zhao Z, et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. Sci Rep 2014;4:7027.
13. Zou Z, Yan Y, Shu Y, et al. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun 2014;5:3594.
14. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112-6.
15. Mackey K, King VJ, Gurley S, et al. Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults: a living systematic review. Ann Intern Med 2020;173:195-203.
16. Chan CK, Huang YS, Liao HW, et al. Renin-angiotensin-aldosterone system inhibitors and risks of SARS-CoV-2 infection: a systematic review and meta-analysis. Hypertension 2020;76:1563-71.
17. Chung SC, Providencia R, Sofat R. Association between angiotensin blockade and incidence of influenza in the United Kingdom. N Engl J Med 2020;383:397-400.
18. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167:492-9.
19. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010;340:b5087.
20. Christensen DM, Gerds T, Gislason G, Torp-Pedersen C. Protective association of angiotensin blockade with influenza: a result of immortal time bias? Eur Heart J Cardiovasc Pharmacother 2020 Jun;pvaa068. doi: 10.1093/ehjcvp/pvaa068. (Online ahead of print).
21. Christiansen CF, Heide-Jørgensen U, Rasmussen TB, et al. Renin-angiotensin system blockers and adverse outcomes of influenza and pneumonia: a Danish cohort study. J Am Heart Assoc 2020;9:e017297.
22. National Health Insurance Administration. 2019-2020 National Health Insurance Annual Report. https://www.nhi.gov.tw/Content_List.aspx?n=9223A12B5B31CB37&topn=4864A82710DE35ED (accessed 26 August 2020).
23. Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). Epidemiol Health 2018;40:e2018062.
24. Gong YN, Kuo RL, Chen GW, Shih SR. Centennial review of influenza in Taiwan. Biomed J 2018;41:234-41.
25. Lin CS, Chu YH, Hung YJ, Lee DY, Chen CY. Outpatient hypertension control and prescribing habits for hypertension in Taiwan. Acta Cardiol Sin 2013;29:539-49.

26. Wu HY, Chien KL, Hung KY. Physician prescribing patterns of antihypertensives in diabetic patients before and after the implementation of Taiwan's guideline for the management of hypertension. J Formos Med Assoc 2018;117:650-1.
27. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med2009;28:3083-107.
28. Mohseni H, Kiran A, Khorshidi R, Rahimi K. Influenza vaccination and risk of hospitalization in patients with heart failure: a self-controlled case series study. Eur Heart J 2017;38:326-33.
29. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4.
30. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11:875-9.
31. Lin SY, Ju SW, Lin CL, et al. Risk of viral infection in patients using either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: a nationwide population-based propensity score matching study. Clin Infect Dis 2020 Jun;ciaa734. doi: 10.1093/cid/ciaa734. (Online ahead of print).
32. Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj C. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2018;2:CD001269.
33. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev2014;2014:CD008965.
34. Kario K, Morisawa Y, Sukonthasarn A, et al. COVID-19 and hypertension-evidence and practical management: Guidance from the HOPE Asia Network. J Clin Hypertens (Greenwich) 2020;;22:1109-19.
35. Meyer D, Shearer MP, Chih YC, Hsu YC, Lin YC, Nuzzo JB. Taiwan's annual seasonal influenza mass vaccination program-lessons for pandemic planning. Am J Public Health 2018;108:S188-93.

Tables

Table 1. Patient characteristics between severe and non-severe hospitalized influenza patients, before and after matching on age, sex, and year of the epidemic season

	Before matching (n=11,090)			After matching (n=5,476)		
Variables	Cases: Severe hospitalized influenza patients (n=1,369)	Controls Non-severe hospitalized influenza patients (n=9,721)	Standardized difference[a], %	Cases: Severe hospitalized influenza cases (n=1,369)	Matched controls: Non-severe hospitalized influenza patients (n=4,107)	Standardized difference[a], %
Year of the epidemic cycle, n (%)						
May 2009 to April 2010	302 (22.1)	1,395 (14.4)	20.03	302 (22.1)	906 (22.1)	0.00
May 2010 to April 2011	595 (43.5)	4,140 (42.6)	1.82	595 (43.5)	1,785 (43.5)	0.00
May 2011 to April 2012	472 (34.5)	4,186 (43.1)	-17.72	472 (34.5)	1,416 (34.5)	0.00
Demographic, n (%)						
Age[b], years						
Mean (SD)	68.4 (14.3)	66.3 (14.9)	0.98	68.4 (14.3)	68.3 (14.4)	0.05
20-39	48 (3.5)	500 (5.1)	-7.89	48 (3.5)	144 (3.5)	0.00
40-59	326 (23.8)	2,677 (27.5)	-8.48	326 (23.8)	978 (23.8)	0.00
60-69	270 (19.7)	1,979 (20.4)	-1.75	270 (19.7)	810 (19.7)	0.00
70-79	378 (27.6)	2,533 (26.1)	3.39	378 (27.6)	1,134 (27.6)	0.00
>80	347 (25.3)	2,032 (20.9)	10.45	347 (25.3)	1,041 (25.3)	0.00
Male	798 (58.3)	5,056 (52.0)	12.69	798 (58.3)	2,394 (58.3)	0.00
Socioeconomic status, monthly income in NTD						
<=17,280	447 (32.7)	2,850 (29.3)	7.36	447 (32.7)	1,233 (30.0)	5.82
17,281-22,800	602 (44.0)	4,290 (44.1)	-0.20	602 (44.0)	1,856 (45.2)	-2.41
22,801-28,800	75 (5.5)	553 (5.7)	-0.87	75 (5.5)	223 (5.4)	0.44
28,801-36,300	81 (5.9)	643 (6.6)	-2.89	81 (5.9)	232 (5.6)	1.29
36,301-45,800	91 (6.6)	716 (7.4)	-3.14	91 (6.6)	286 (7.0)	-1.59
>45,800	73 (5.3)	669 (6.9)	-6.69	73 (5.3)	277 (6.7)	-5.90
Comedication[c], n (%)						

Oseltamivir	67 (4.9)	435 (4.5)	1.89	67 (4.9)	202 (4.9)	0.00
Glucocorticoids	146 (10.7)	780 (8)	9.28	146 (10.7)	324 (7.9)	9.65
Comorbidities[d], n (%)						
Cardiovascular disease	466 (34.0)	2764 (28.4)	12.11	466 (34.0)	1,239 (30.2)	8.15
Ischemic heart disease	316 (23.1)	2,050 (21.1)	4.82	316 (23.1)	918 (22.4)	1.67
Myocardial infarction	96 (7.0)	402 (4.1)	12.69	96 (7.0)	164 (4.0)	13.19
Heart failure	204 (14.9)	872 (9.0)	18.26	204 (14.9)	397 (9.7)	15.88
Atrial fibrillation	98 (7.2)	375 (3.9)	14.45	98 (7.2)	181 (4.4)	12.00
Diabetes mellitus	584 (42.7)	3,352 (34.5)	16.9	584 (42.7)	1,407 (34.3)	17.33
Neurological disease	398 (29.1)	2,100 (21.6)	17.31	398 (29.1)	1,010 (24.6)	10.17
Cerebrovascular disease	325 (23.7)	1,782 (18.3)	13.29	325 (23.7)	852 (20.7)	7.22
Stroke	47 (3.4)	174 (1.8)	10.07	47 (3.4)	79 (1.9)	9.35
Dementia	115 (8.4)	540 (5.6)	10.99	115 (8.4)	271 (6.6)	6.84
Pulmonary disease	523 (38.2)	2,712 (27.9)	22.03	523 (38.2)	1,227 (29.9)	17.58
Chronic lung disease	337 (24.6)	1,764 (18.1)	15.91	337 (24.6)	849 (20.7)	9.33
Asthma	180 (13.1)	1,181 (12.1)	3.01	180 (13.1)	505 (12.3)	2.40
Other lung disease	236 (17.2)	701 (7.2)	30.92	236 (17.2)	316 (7.7)	29.08
Chronic kidney disease	209 (15.3)	841 (8.7)	20.42	209 (15.3)	360 (8.8)	20.07
Rheumatoid arthritis/collagen vascular diseases	55 (4)	417 (4.3)	-1.50	55 (4.0)	157 (3.8)	1.03
Malignancy	109 (8)	703 (7.2)	3.02	109 (8.0)	295 (7.2)	3.02
Charlson comorbidity score, mean (SD)	2.5 (2.1)	2.0 (2.0)	11.89	2.5 (2.1)	2.0 (2.0)	11.89
Annual medical cost in NTD[d]						

<=24,999	275 (20.1)	2,827 (29.1)	-21.01	275 (20.1)	1,167 (28.4)	-19.52
25,000-50,000	222 (16.2)	2,121 (21.8)	-14.31	222 (16.2)	891 (21.7)	-14.01
50,001-100,000	295 (21.6)	2,006 (20.6)	2.45	295 (21.6)	845 (20.6)	2.39
>100,000	577 (42.1)	2,767 (28.5)	28.75	577 (42.1)	1,204 (29.3)	27.02

NTD, National Taiwan Dollar. One US dollar is approximately 30 New Taiwan Dollars.

[a]The values of greater than 10% indicated substantial differences in patient characteristics between severe and non-severe patients.

[b]Age on admission.

[c]Measured within 30 days before hospitalization.

[d]Measured within 365 days before hospitalization.

Table 2. Association between the use of anti-hypertensive medications[a] and the occurrence of severe influenza disease

	Cases: Severe hospitalized influenza patients (n=1,369)	Matched controls: Non-severe hospitalized influenza patients (n=4,107)	Adjusted OR (95% CI)[b]
Model 1[c]: any use of anti-hypertensive medication class, n (%)			
ACEIs	139 (10.2)	362 (8.8)	1.15 (0.93-1.42)
ARBs	410 (29.9)	1,217 (29.6)	0.97 (0.84-1.12)
CCBs	596 (43.5)	1,797 (43.8)	0.95 (0.84-1.09)
Model 2[d] monotherapy of anti-hypertensive medication class, n (%)			
ACEIs	32 (2.3)	67 (1.6)	1.47 (0.95-2.29)
ARBs	42 (3.1)	157 (3.8)	0.76 (0.53-1.10)
CCBs	121 (8.8)	498 (12.1)	0.70 (0.55-0.88)
No current anti-hypertensive treatment[e]	434 (31.7)	1,294 (31.5)	Ref
Model 3[f]: Combination therapy of anti-hypertensive regimen, n (%)			
ACEIs and CCBs in combination	22 (1.6)	57 (1.4)	1.57 (0.91-2.70)
ARBs and CCBs in combination	156 (11.4)	503 (12.3)	1.23 (0.93-1.62)
CCBs	121 (8.8)	498 (12.1)	Ref

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, Calcium channel blockers.

[a]Measured within 30 days before hospitalization.

[b]Matched on age, sex, and year of the epidemic cycle and adjusted for demographics, use of oseltamivir and glucocorticosteroids within 30 days before hospitalization, individual comorbitities and Charlson comorbidity score within 365 days before hospitalization, and medical cost within 365 days before hospitalization.

[c]Including any use of ACEIs, ARBs, and CCBs and patient characteristics which served as potential confounders.

[d]Data for other anti-hypertensive regimens (740 cases and 2,091 controls) were not presented in the table but were considered in the regression model for proper estimation of odds ratios of exposure of interest versus no current anti-hypertensive treatment.

[e]Patients may not use any anti-hypertensive medications or used anti-hypertensive medications equal to or less than 14 days within 30 days before hospitalization.

[f]Data for ACEIs monotherapy (32 cases and 67 controls), ARBs monotherapy (42 cases and 157 controls), other anti-hypertensive regimens (562 cases and 1,531 controls), and no current anti-hypertensive medications (434 cases and 1,294 controls) were not presented in the table but were considered in the regression model for proper estimation of odds ratios of exposure of interest versus no current anti-hypertensive treatment.

Table 3. Association between the use of anti-hypertensive medications[a] and the occurrence of severe influenza disease, restricting to patients without cardiovascular comorbidities

	Cases: Severe hospitalized influenza patients (n=903)	Matched controls: Non-severe hospitalized influenza patients (n=2,709)	Adjusted OR (95% CI)[b]
Model 1[c]: any use of anti-hypertensive medication class, n (%)			
ACEIs	84 (9.3)	217 (8.0)	1.14 (0.86-1.50)
ARBs	236 (26.1)	721 (26.6)	0.94 (0.78-1.12)
CCBs	372 (41.2)	1,166 (43.0)	0.88 (0.75-1.04)
Model 2[d] monotherapy of anti-hypertensive medication class, n (%)			
ACEIs	24 (2.7)	47 (1.7)	1.52 (0.91-2.54)
ARBs	31 (3.4)	110 (4.1)	0.78 (0.51-1.19)
CCBs	88 (9.7)	370 (13.7)	0.66 (0.50-0.87)
No current anti-hypertensive treatment[e]	328 (36.3)	959 (35.4)	Ref
Model 3[f]: Combination therapy of anti-hypertensive regimen, n (%)			
ACEIs and CCBs in combination	15 (1.7)	34 (1.3)	1.76 (0.90-3.44)
ARBs and CCBs in combination	83 (9.2)	315 (11.6)	1.06 (0.75-1.50)
CCBs	88 (9.7)	370 (13.7)	Ref

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, Calcium channel blockers.

[a]Measured within 30 days before hospitalization.

[b]Matched on age, sex, and year of the epidemic cycle and adjusted for demographics, use of oseltamivir and glucocorticosteroids within 30 days before hospitalization, individual comorbitities and Charlson comorbidity score

within 365 days before hospitalization, and medical cost within 365 days before hospitalization.

[c]Including any use of ACEs, ARBs, and CCBs and patient characteristics which served as potential confounders.

[d]Data for other anti-hypertensive regimens (432 cases and 723 controls) were not presented in the table but were considered in the regression model for proper estimation of odds ratios of exposure of interest versus no current anti-hypertensive treatment.

[e]Patients may not use any anti-hypertensive medications or used anti-hypertensive medications equal to or less than 14 days within 30 days before hospitalization.

[f]Data for ACEIs monotherapy (24 cases and 47 controls), ARBs monotherapy (31 cases and 110 controls), other anti-hypertensive regimens (334 cases and 874 controls), and no current anti-hypertensive medications (328 cases and 959 controls) were not presented in the table but were considered in the regression model for proper estimation of odds ratios of exposure of interest versus no current anti-hypertensive treatment.

Figures

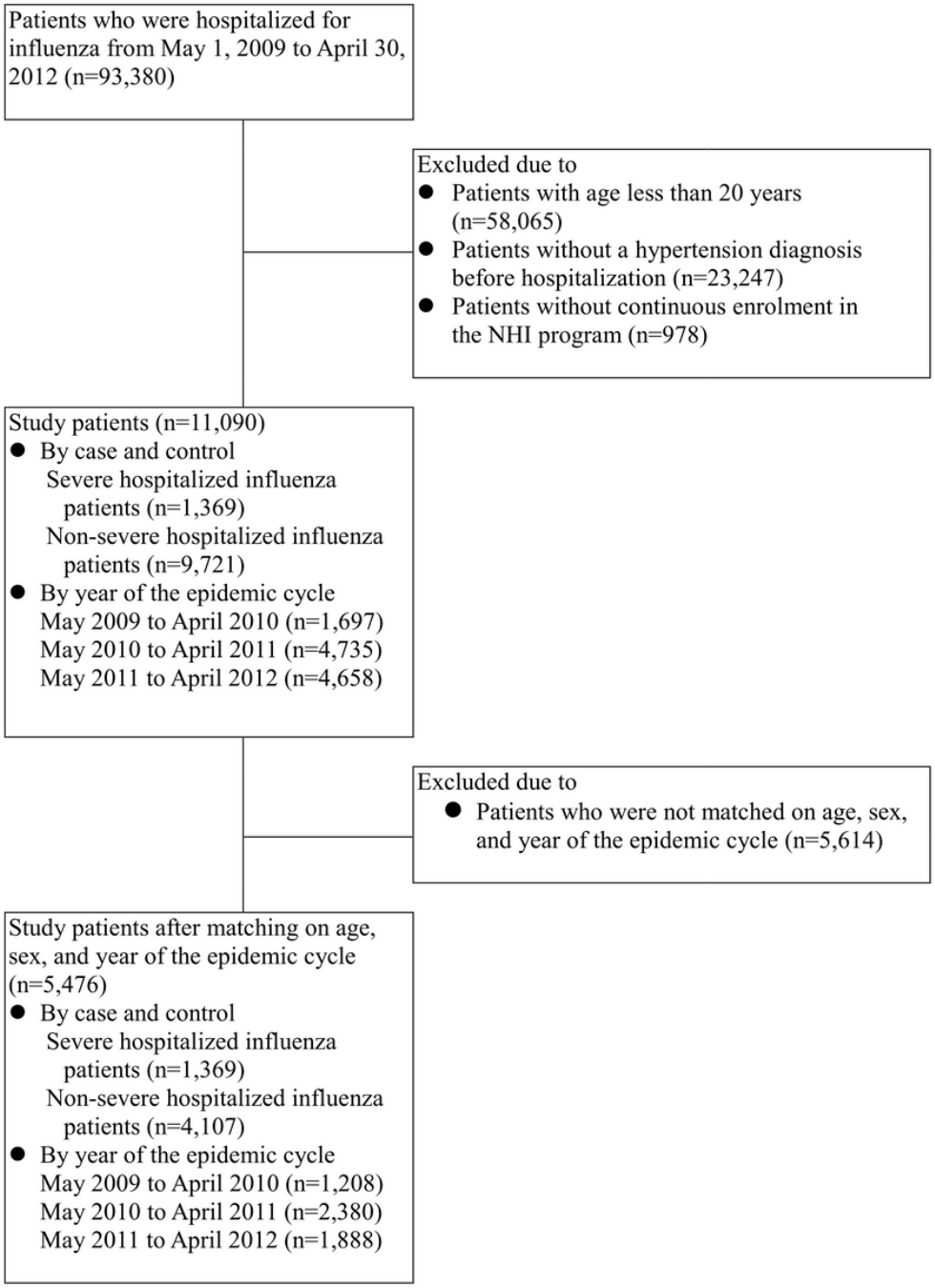

Figure 1

Study flowchart

Supplementary Files

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- 4.Supplementarymaterials20210209.doc