Pioglitazone Use and Sepsis Mortality

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The pioglitazone use via the PPARγ agonist in sepsis patients is inconclusive. It was based on a great number of animal studies. However, except for information from animal studies, there are merely no data of human for reference. This study was conducted by a unique database including 1.6 million of diabetic patients. From 1999 to 2013, a total of 145,327 type 2 diabetic patients, first admitted for sepsis, were enrolled. Propensity score matching was conducted in a 1:5 ratio between pioglitazone users and nonusers. Multivariate logistic regression was conducted to evaluate the adjusted odds ratios (aORs) of hospital mortality in pioglitazone users. Further stratification analysis and Kaplan-Meier plot were utilized. A total of 9,310 sepsis pioglitazone users (defined as "ever" use pioglitazone in any dose within 3 months prior to the first admission for sepsis) and 46,550 matched nonusers were retrieved, respectively. In the multivariate logistic regression model, the cohort of pioglitazone users (9,310) had a decreased aOR = 0.95 (95% CI, 0.89-1.02) of sepsis mortality. Further stratification analysis demonstrated that "chronic pioglitazone users" (defined as "at least" 4 weeks drug use within 3 months) (3,399) was much associated with significant aOR = 0.80 (95% CI, 0.72-0.89) in reducing sepsis mortality. This first human cohort study demonstrated the potential protective effect of chronic pioglitazone use in type 2 diabetic sepsis patients.

Peroxisome proliferator-activated receptor-gamma (PPARγ) Pioglitazone Sepsis Thiazolinedione (TZD)

1. Introduction

Sepsis is a major cause of mortality worldwide, especially in the immunocompromised patients, such as those with multiple comorbidities. [1][2][3] Sepsis is a complex syndrome that is induced by severe infection with series of unregulated immune responses, caused majorly by the pro-inflammatory cytokines. Acute organ failure and subsequent high mortality rate will induce long-term morbidities, such as stroke and cardiovascular diseases.[3][4] Despite advances in treatment strategies, therapies to mitigate the severity of sepsis are currently unsatisfactory.[5]

Thiazolidinediones [TZD], a kind of oral anti-diabetic drugs (OADs), are used for the treatment of Type 2 diabetes via being the insulin sensitizers.[6] Currently, pioglitazone is the only TZD available in the market. It is proposed to have protection effect during the sepsis course by acting as the peroxisome proliferator-activated receptor-gamma (PPARγ) agonist.[7]

Accumulating evidence in animal studies demonstrated that PPARγ agonists improved the outcomes of sepsis via multiple mechanisms.[8] In the mouse model, pioglitazone administration decreased inflammation and improved survival of sepsis induced by cecal ligation and puncture (CLP).[9] Because of the growing amount of evidence, the randomized clinical trial of pioglitazone use in sepsis patients is underway.[10] However, currently, there are limited data on this topic in humans, especially in type 2 diabetic patients. Because the varied levels of diabetic complication burdens in each person were not easily compared.[11]

In the current study, we used a specially applied nationwide database of diabetic patients, from 1999 to 2013, with the first admission for sepsis to evaluate the impacts of pioglitazone use in sepsis with the main outcome of the total hospital mortality. This cohort study addressed the selection bias from diabetic severity by using the propensity score matching and simulated a real-world clinical trial to compare subjects in each group.

2. Methods

2.1. Data sources and study participants

We conducted this cohort study by using the National Health Insurance Research Database (NHIRD) of Taiwan. The National Health Insurance program in Taiwan currently provides coverage for more than 23.03 million residents (> 99% of the entire population). The National Health Insurance in Taiwan provides excellent health care service to the people.[12][13][14][15] The deidentified patient information and claims data were released to the National Health Research Institute to establish the NHIRD. The diagnosis codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) are used in the NHIRD. The confidentiality and credibility of these data are strictly maintained in accordance with the NHIRD regulations and have been documented to have high quality for research.

From the NHIRD, we conducted this study by using the specially applied database of "Longitudinal Cohort of Diabetes Patients (LHDB)" which enrolled a longitudinal cohort of 1.6 million of newly diagnosed diabetic patients from 1999 to 2013. We retrieved data from LHDB to constitute the study and comparison cohorts, composed by type 2 diabetic patients with a first admission for sepsis with and without pioglitazone use. In patients with repeated admissions, only the data of the first hospitalization for sepsis within LHDB were used.

2.2. Definition of sepsis and baseline comorbidities

The diagnosis of sepsis in the current study was retrieved using the ICD-9-CM code 038 plus a main infection diagnosis with antibiotics prescription. The accuracy of sepsis diagnosis in the NHIRD has been validated.[16] The patients were defined as having certain comorbidities if they had at least 2 outpatient service claims or if they had a single hospitalization in which the certain comorbidities was found in 1 of the 5 spaces used to report their diagnoses. The index date was defined as the first admission date for sepsis. The diagnosis of comorbidity was defined by tracing back for one year prior to the first admission date of sepsis but excluding the index hospitalization diagnosis.

2.3. Definition of drug use in pioglitazone

In this study, if a patient received the prescription of any dose of pioglitazone within 3 months prior to the index admission for sepsis, he or she would be defined as a pioglitazone user or "ever use" pioglitazone. Throughout the whole study, we used the above definition to describe any drug use.

To reduce the medical expenditure for the stable patients of type 2 diabetes or other chronic diseases, the physicians can use the refill card of consecutive prescription for 3 months rather than prescribing the drugs week by week or only 3 days. Based on the above medical regulation and culture in Taiwan, we therefore defined a person as a "chronic" pioglitazone user if he or she was prescribed pioglitazone for at least 4 weeks within 3 months prior to the first admission for sepsis".[17]

2.4. Propensity score matching

Propensity score matching was proposed by Austin PC et al. which could reduce the selection bias because it allowed the bundling of many potential confounding factors which were frequently presented in the observation studies. [18][19][20] In our study, multiple conditions had might affect the hospital outcome. For each patient, we calculated the propensity score using the multivariate logistic regression by entering the baseline covariates which included age, sex, comorbidities, insurance premium, medications, infection sites, and complication severity of type 2 DM.

Since type 2 diabetes related complications may be the most important factor to determine the hospital outcome. We matched 1 study cohort patient with 5 comparison cohort patients according to propensity score and obtained a dataset composed of matched patients who had a statistically identical likelihood of severity of diabetic complications.

In the database used in this study, individual income data could not be directly obtained; however, the individual insurance premium fee paid was a useful surrogate for the household income level, and this method was validated and widely adopted in the use of this administrative database.[21]

2.5. Selection process

The algorithm used for participant selection for the study and comparison cohorts is shown in **Figure 1**. Patients aged <18 or >100 years, patients with type 1 diabetes, and patients infected with human immunodeficiency virus were excluded from this study. Since the database contains deidentified data for research, our study was exempted from the requirement of informed consent from participants. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2020-01-012CC) and China Medical University (CMUH104-REC2-115).

2.6. Comparison between the study and matched cohorts

Differences in demographic characteristics, insurance premium, baseline comorbidities, medications (including nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, statins, biguanides, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), sulfonylureas, pioglitazone, insulin, immunosuppressants, and steroids), infection sites, adapted diabetes complications severity index (aDCSI) score which was a representation of diabetes complication severity, length of hospital stay, and the total hospital mortality were examined using the chi-squared test and two-sample t-test.

2.7. Logistic regression and Kaplan-Meier analysis

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for each variable in the logistic regression model. Adjusted ORs (aORs) for the total hospital mortality were obtained after adjusting for potential confounders, including age, sex, income, and comorbidities, in the multivariate logistic regression analysis. Kaplan-Meier analysis with log-rank test was conducted to compare the difference in the outcomes of total hospital mortality between the study and comparison cohorts (that is, pioglitazone users versus nonusers). The statistical analyses were performed using the SAS 9.4 statistical package (SAS Institute, Inc., Cary, NC, USA). A P value of 0.05 was set as significant.

3. Results

3.1. Demographic characteristics and baseline comorbidities between the enrolled sepsis patients of pioglitazone users and nonusers

From the LHDB, we initially retrieved a total of 145,327 type 2 diabetic patients with the first admission for sepsis from 1999 to 2013. After propensity score matching, a total of 9,310 pioglitazone users and 46,550 nonusers were included for further analysis.

Before PS matching, the mean age of pioglitazone users and nonusers were 67.08 ± 12.62 and 71.13 ± 13.90 years, respectively. After PS matching, the mean age of pioglitazone users and nonusers were 68.11 ± 12.50 and 68.96 ± 13.18 years, respectively. The detailed demographic and characteristics were shown in **Table 1.** Before matching, a greater proportion of pioglitazone users than nonusers received treatment with statins (30.85% versus 11.52%), biguanide (60.48% versus 28.80%), DPP-4 inhibitors (21.35% versus 3.52%), sulfonylurea (65.17% versus 31.84%), and insulin (68.11% versus 43.37%) (all $P < 0.001$). The pioglitazone users had fewer respiratory system infection site compared to nonusers (46.24% versus 51.76%) ($P < 0.001$). The pioglitazone users had more severe complication burdens (aDCSI score ≥ 5, 16.30% of pioglitazone users versus 8.95% of nonusers) ($P < 0.001$). However, the pioglitazone users had lower total hospital mortality rate (15.83% versus 18.6%) and shorter length of hospital stay (mean, 11 versus 12 days) than the nonusers.

3.2. Regression model of the total hospital mortality

In the logistic regression model, after further adjusting for age, sex, income, and comorbidities, the pioglitazone users (ever use) showed to have a non-significant aOR slightly less than unity for total hospital mortality (aOR = 0.95 (95% CI, 0.89-1.03)) **(Table 2).**

In the further stratification analysis, the patients who were classified as "chronic pioglitazone users" demonstrated the significant aOR for total hospital mortality (aOR = 0.80 (95% CI, 0.72-0.89), P<0.05) **(Table 3).**

3.3. Kaplan-Meier analysis of the total hospital mortality

In the Kaplan-Meier analysis with log-rank test, the total hospital mortality did not differ significantly between the pioglitazone users ("ever use") and nonusers **(Figure 2)**. However, in the "chronic pioglitazone users", it was obvious that the cumulative survival rate was much better than that in the nonusers (P < 0.01) **(Figure 3).**

4. Discussion

In this real-world study, by using the nationwide database of diabetic patients with propensity score matching, we demonstrated that pioglitazone use can exert a significantly protective effect in "chronic pioglitazone users". This finding has been proved in multiple animal studies for a long term. However, it remained controversial in human beings. To the best of our knowledge, this is the first and largest cohort study of type 2 diabetic sepsis patients that simulated the human clinical trial via propensity score matching to examine the protective effect of pioglitazone. Our finding will surely attract more and more attention focusing on the potential of pioglitazone in sepsis.

PPARs which encoded by separate genes: PPARα, PPARβ⁄δ, and PPARγ, are expressed by a variety of cells of the immune system including macrophages, B and T, and monocytes, lymphocyte, natural killer cells, dendritic cells, mass cells, neutrophils and eosinophils[22] PPARs have received attention till now, since they play pivotal regulators in adipocyte differentiation, glucose homeostasis, and immune regulation. In the current study, we focus on the role of immune-modification of pioglitazone which is a kind of TZDs, activating as the PPARγ agonist.

PPARγs agonists can be simply classified into natural and artificial ones, respectively. Natural PPARγ agonists include saturated and unsaturated fatty acids, eicosanoid derivatives, such as 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 (15d-PGJ2), and oleic and nitrated linoleic acids. Synthetic PPARγ agonists are represented by TZDs, such as pioglitazone, rosiglitazone, troglitazone, and ciglitazone. TZDs (agonist) function via activating the PPARγ receptor.[23][24] In the absence of PPARγ agonists, these ligands remain inactive via binding to the corepressors.

Pioglitazone is currently the only available TZDs in the market since rosiglitazone has been suspended in Taiwan in 2011 due to its potentially increased risk of myocardial infarction and decompensated heart failure.[25] Pioglitazone targets to the transcription of PPARγ, and is involved in metabolic homeostasis, and most important of all, it much improves insulin sensitivity. This mechanism provides a choice to type 2 diabetic patients before being receiving insulin injection therapy. Following the suspension of rosiglitazone in 2011, pioglitazone later became another target of criticism, including that pioglitazone (1) increased the risk of osteoporosis and (2) increased the risk of

urinary bladder cancer. However, supporting data to pioglitazone passed these. [26][27] Moreover, many studies and specialist opinion support that pioglitazone should be kept used in T2D treatment.[28][29][30]

In addition to helping glucose control, the activation of PPARγ agonist of pioglitazone contributes to the modulation of inflammation.[31] Pioglitazone improves bacterial elimination in the peripheral blood, via inhibition of proinflammatory molecules such as IL-6, TNF, IL-1., and IL-12, has been well documented. It also enhanced bacterial elimination in the liver, by increasing the phagocytic and bactericidal activities. [8] Furthermore, accumulated evidence of animal models demonstrated that pioglitazone is effective in the prevention and treatment of sepsis in mice cecal ligation and puncture (CLP) model.[32][33][34] In the type 2 diabetic patients, who are prone to infection diseases, TZDs use with pioglitazone should be an adequate choice via the anti-inflammatory and enhancing bactericidal effects. Our study demonstrated the protective effect in sepsis patients which added a new important evidence in human body.

The repeated or accumulated doses of pioglitazone presented the dose-effect relationship compared with the single-dose use as observed in this study. Besides, PPARγ agonists are known to upregulate their receptors' expression, which render the greater anticipated effects of repeated or accumulating dosing.[35][36] However, currently, which is the optimal dose and which stage to start pioglitazone treatment in sepsis deserve further investigation. Combing with other studies, we inferred that the initial or chronic use of pioglitazone might inhibit the cytokine storm and therefore reduced the acute organ failure in the first fulminant stage. Continuous use during the sepsis course remains further study.

5. Limitations

This study has several limitations. First, this study lacked certain important laboratory data, that is, initial blood glucose level and hemoglobin A1C (HbA1c), which was an inevitable weak point in administrative database studies. However, we had demonstrated that there was no association between initial blood glucose, HbA1c and hospital outcomes of sepsis in our previous hospital-based study; the lack of initial blood glucose level and HbA1c may be not as important as previously thought.[11] Second, the impact of pioglitazone use to every sepsis stage remains further examined since systemic inflammatory response syndrome (SIRS) and subsequent compensatory anti-inflammatory response syndrome (CARS) might occur in sequence or concurrently , named as mixed antagonist response syndrome (MARS). Our study design mainly focused on the first stage, that is, SIRS. Because the information that if pioglitazone was kept in use could not be further available.

6. Conclusion

In this study, we demonstrated that currently regular preadmission pioglitazone use improved the total hospital mortality in type 2 diabetic sepsis patients after considering multiple variables, including comorbidities and household income.

References

1. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H et al: Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. The Lancet Respiratory medicine 2014, 2(5):380-386.
2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K: Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. American journal of respiratory and critical care medicine 2016, 193(3):259-272.
3. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama 2016, 315(8):801-810.
4. Ou SM, Chu H, Chao PW, Lee YJ, Kuo SC, Chen TJ, Tseng CM, Shih CJ, Chen YT: Long-Term Mortality and Major Adverse Cardiovascular Events in Sepsis Survivors. A Nationwide Population-based Study. American journal of respiratory and critical care medicine 2016, 194(2):209-217.
5. Wenzel RP, Edmond MB: Septic shock--evaluating another failed treatment. The New England journal of medicine 2012, 366(22):2122-2124.
6. Kubota N, Terauchi Y, Kubota T, Kumagai H, Itoh S, Satoh H, Yano W, Ogata H, Tokuyama K, Takamoto I et al: Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. The Journal of biological chemistry 2006, 281(13):8748-8755.
7. Carvalho MV, Gonçalves-de-Albuquerque CF, Silva AR: PPAR Gamma: From Definition to Molecular Targets and Therapy of Lung Diseases. Int J Mol Sci 2021, 22(2).
8. Nakashima M, Kinoshita M, Nakashima H, Kotani A, Ishikiriyama T, Kato S, Hiroi S, Seki S: Pioglitazone improves phagocytic activity of liver recruited macrophages in elderly mice possibly by promoting glucose catabolism. Innate immunity 2019, 25(6):356-368.
9. Haraguchi G, Kosuge H, Maejima Y, Suzuki J, Imai T, Yoshida M, Isobe M: Pioglitazone reduces systematic inflammation and improves mortality in apolipoprotein E knockout mice with sepsis. Intensive care medicine 2008, 34(7):1304-1312.
10. Kaplan JM, Zingarelli B, Krallman K, Tang Girdwood S, Lagory D, Mizuno T, Fei L, Wong HR, Vinks AA: Phase 1 safety and pharmacokinetic study on the use of pioglitazone in critically ill patients with sepsis: a randomized clinical trial. Intensive care medicine 2018, 44(11):2006-2008.
11. Hsieh MS, Hu SY, How CK, Seak CJ, Hsieh VC, Lin JW, Chen PC: Hospital outcomes and cumulative burden from complications in type 2 diabetic sepsis patients: a cohort study using

administrative and hospital-based databases. Therapeutic advances in endocrinology and metabolism 2019, 10:2042018819875406.

12. Weng SJ, Lai LS, Gotcher D, Wu HH, Xu YY, Yang CW: Cloud Image Data Center for Healthcare Network in Taiwan. Journal of medical systems 2016, 40(4):89.
13. Schwartz J, King CC, Yen MY: Protecting Health Care Workers during the COVID-19 Coronavirus Outbreak -Lessons from Taiwan's SARS response. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2020.
14. Cheng HY, Li SY, Yang CH: Initial rapid and proactive response for the COVID-19 outbreak - Taiwan's experience. Journal of the Formosan Medical Association = Taiwan yi zhi 2020, 119(4):771-773.
15. Lin C, Braund WE, Auerbach J, Chou JH, Teng JH, Tu P, Mullen J: Policy Decisions and Use of Information Technology to Fight 2019 Novel Coronavirus Disease, Taiwan. Emerging infectious diseases 2020, 26(7).
16. Chao PW, Shih CJ, Lee YJ, Tseng CM, Kuo SC, Shih YN, Chou KT, Tarng DC, Li SY, Ou SM et al: Association of postdischarge rehabilitation with mortality in intensive care unit survivors of sepsis. American journal of respiratory and critical care medicine 2014, 190(9):1003-1011.
17. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, Lin JT: Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. Jama 2012, 308(18):1906-1914.
18. Austin PC: An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research 2011, 46(3):399-424.
19. Qin R, Titler MG, Shever LL, Kim T: Estimating effects of nursing intervention via propensity score analysis. Nursing research 2008, 57(6):444-452.
20. Austin PC: Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. Pharmacoepidemiology and drug safety 2008, 17(12):1218-1225.
21. Hsieh MS, How CK, Hsieh VC, Chen PC: Preadmission Antihypertensive Drug Use and Sepsis Outcome: Impact of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs). Shock (Augusta, Ga) 2019.
22. Kota BP, Huang TH, Roufogalis BD: An overview on biological mechanisms of PPARs. Pharmacol Res 2005, 51(2):85-94.
23. Picard F, Auwerx J: PPAR(gamma) and glucose homeostasis. Annu Rev Nutr 2002, 22:167-197.
24. Li Y, Zhang J, Schopfer FJ, Martynowski D, Garcia-Barrio MT, Kovach A, Suino-Powell K, Baker PR, Freeman BA, Chen YE et al: Molecular recognition of nitrated fatty acids by PPAR gamma.

Nat Struct Mol Biol 2008, 15(8):865-867.

25. Aspinall SE, Zhao X, Good CB, Stone RA, Smith KJ, Cunningham FE: FDA warning and removal of rosiglitazone from VA national formulary. The American journal of managed care 2013, 19(9):748-758.
26. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP, Jr., Vaughn DJ, Nessel L, Selby J, Strom BL: Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes care 2011, 34(4):916-922.
27. Tseng CH: Pioglitazone and bladder cancer: a population-based study of Taiwanese. Diabetes care 2012, 35(2):278-280.
28. DeFronzo RA, Inzucchi S, Abdul-Ghani M, Nissen SE: Pioglitazone: The forgotten, cost-effective cardioprotective drug for type 2 diabetes. Diab Vasc Dis Res 2019, 16(2):133-143.
29. Ryder RE: Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit. Diabetic medicine : a journal of the British Diabetic Association 2015, 32(3):305-313.
30. Korhonen P, Heintjes EM, Williams R, Hoti F, Christopher S, Majak M, Kool-Houweling L, Strongman H, Linder M, Dolin P et al: Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries. BMJ (Clinical research ed) 2016, 354:i3903.
31. Zingarelli B, Cook JA: Peroxisome proliferator-activated receptor-gamma is a new therapeutic target in sepsis and inflammation. Shock (Augusta, Ga) 2005, 23(5):393-399.
32. Kaplan J, Nowell M, Chima R, Zingarelli B: Pioglitazone reduces inflammation through inhibition of NF-κB in polymicrobial sepsis. Innate immunity 2014, 20(5):519-528.
33. Tsujimura Y, Matsutani T, Matsuda A, Kutsukake M, Uchida E, Sasajima K, Tamura K: Effects of pioglitazone on survival and omental adipocyte function in mice with sepsis induced by cecal ligation and puncture. The Journal of surgical research 2011, 171(2):e215-221.
34. Kaplan JM, Zingarelli B: Novel Therapeutic Agents in Pediatric Sepsis: Peroxisome Proliferator Receptor γ (PPAR γ) Agonists. The open inflammation journal 2011, 4(Suppl 1-M14):120-124.
35. Lakshmi SP, Reddy AT, Zhang Y, Sciurba FC, Mallampalli RK, Duncan SR, Reddy RC: Down-regulated peroxisome proliferator-activated receptor γ (PPARγ) in lung epithelial cells promotes a PPARγ agonist-reversible proinflammatory phenotype in chronic obstructive pulmonary disease (COPD). The Journal of biological chemistry 2014, 289(10):6383-6393.
36. Drosatos K, Khan RS, Trent CM, Jiang H, Son NH, Blaner WS, Homma S, Schulze PC and Goldberg IJ. Peroxisome proliferator-activated receptor-gamma activation prevents sepsis-related cardiac dysfunction and mortality in mice. Circulation Heart failure. 2013;6:550-62.