Original Article

Prior metformin therapy and 30-day mortality in patients with acute respiratory distress syndrome: a nationwide cohort study

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Background: The pleiotropic effect of metformin prevents lung injury in animal models. However, metformin has a controversial effect on survival outcomes in patients with acute respiratory distress syndrome (ARDS). This study aimed to investigate the effect of metformin therapy before ARDS diagnosis on mortality in ARDS patients with diabetes mellitus (DM).

Methods: Medical records from the national database, stored and provided by the National Health Insurance Service (NHIS) in South Korea were used. All adult diabetic patients admitted to a hospital for ARDS treatment from January 1, 2013 to December 31, 2017 were included in this study. Metformin users were defined as those prescribed continuous oral metformin for ≥30 days before ARDS diagnosis. All other patients were included in the control group.

Results: Of the 6,500 patients selected for the study; 2,876 patients were prior metformin users. After propensity score matching (PSM), a total of 5,752 patients (2,876 patients in each group) were included in the analysis. The hazard of 30-day mortality in metformin users was not significantly different compared to the control group [hazard ratio (HR), 1.05; 95% confidence interval (CI), 0.97–1.14; P=0.154]. The survival time by the log-rank test was not significantly different between metformin users and controls (median time, 39.0 *vs.* 42.0 days, respectively; P=0.735).

Conclusions: This population-based cohort study showed no significant association between prior metformin therapy and 30-day mortality in ARDS patients with DM. Moreover, prior metformin therapy was not associated with increase in overall survival times in ARDS patients with DM.

Keywords: Critical care; diabetes mellitus (DM); metformin; respiratory distress syndrome, adult; intensive care units (ICUs)

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Introduction

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by acute onset of hypoxemia, bilateral pulmonary infiltrations and respiratory failure (1-3). In patients admitted to the intensive care unit (ICU), the incidence of ARDS is 10.4% (4), and its mortality ranges from 11% to 87% (5). The global burden of ARDS is an important global health issue and appears to be high in high- and upper-middle-income countries (6,7).

Metformin is a biguanide drug that is most commonly prescribed for the management of type 2 diabetes mellitus (DM) (8), due to its well-known hypoglycemic effect. Its

pleiotropic effects might ameliorate inflammatory injuries *in vivo* based on its inhibition of the expression of pro-inflammatory factors *in vitro* (9-12). In several experimental animal models of acute lung injury, pretreatment with metformin preserves the alveolar-capillary permeability and decreases the occurrence and severity of acute lung injury in high-pressure ventilation (13). In a recent study, metformin reduced lipopolysaccharide-induced lung injury in a rat model and increased the expression of inflammatory factors. These mechanisms might be related to alleviating ARDS (14). However, there is not enough information on prior metformin therapy and mortality in patients with ARDS. A retrospective single-center cohort study reported no significant association between prior metformin therapy and 30-day mortality in ARDS patients with DM (15). However, the study was performed in 2005 with a small sample (n=128) of ARDS patients with DM.

Therefore, this nationwide study of a large population aimed to investigate the association between metformin therapy before ARDS diagnosis and mortality in ARDS patients with DM. We hypothesized that prior metformin therapy would be associated with better survival outcomes in ARDS patients with DM compared to controls.

Methods

Ethics statement

This population-based cohort study was performed per the ethical standards of the institutional and national research committee at the Seoul National University Bundang Hospital (X-1903-531-902) and the Health Insurance Review and Assessment Service (NHIS-2019-1-274).

Data source

The medical records from the national database, which are stored and provided by the National Health Insurance Service (NHIS) in South Korea, were used. The NHIS is the country's key institution for protecting the health of the nation, and is responsible for the management of national health insurance which safeguards the nation from disease, provides long-term care, and enables comfortable aging. In South Korea, all disease diagnoses, drug prescription information, and procedures should be registered in the NHIS database. The extraction of data was performed by a medical record technician in the NHIS center, who had no conflict of interest associated with this study.

Study population

All adult (≥18 years old) diabetic patients who were admitted to a hospital for ARDS treatment [International Classification of Diseases; ICD-10 codes of J80* and E10–E14 (DM)] from January 1, 2013 to December 31, 2017 were included in this study. For patients with multiple admissions (≥2) for ARDS treatment, only the most recent admission was considered for analysis. Patients with incomplete or missing data were excluded.

The ARDS patients with DM were divided into metformin users, defined as those who had been prescribed continuous oral metformin for ≥30 days before ARDS diagnosis, and the control, group which included all other patients.

Study endpoint

The primary endpoint was any 30-day mortality after the initiation of ARDS treatment. The date of death of all ARDS patients was extracted until May 30, 2019, from the NHIS database. The secondary endpoint was overall survival time. The survival time was calculated from the date of initial ARDS treatment to date of death or May 30, 2019 for ARDS survivors.

Potential confounder

The potential confounders of the study results included demographic information (age and sex), place of residence (Seoul, metropolitan cities, and other), and income level in quartile ratio at ARDS diagnosis. The comorbidities by ICD-10 codes [hypertension (I10–I16), coronary artery disease (I20*–I25*), cerebrovascular disease (I60*–I69*), lung cancer (C30–C39), chronic kidney disease (N18*), dyslipidemia (E78.0), anemia (D64*), chronic obstructive pulmonary disease (COPD) (J44*), asthma (J45*), arrhythmia (I49*), and liver cirrhosis (K74*)] present before ARDS diagnosis were also included as confounders in this study.

Statistical analysis

The baseline characteristics of the patients were presented

as mean with standard deviation for continuous variables, and numbers with percentages for categorical variables. First, we performed propensity score matching (PSM), which is known to reduce confounders in observational studies (16). PSM was performed without replacement at 1:1 ratio with caliper 0.2 via nearest neighbor method. All covariates were included in the PSM, and logistic regression analysis was performed to calculate propensity scores (PSs) as a logistic model. The absolute value of standardized mean difference (ASD) was used to determine the balance before and after PSM, and all ASDs <0.1 were used to determine that all covariates were sufficiently balanced through PSM.

After PSM, Cox regression analysis was performed in PS-matched cohort to investigate the hazard function of prior metformin therapy in 30-day mortality after initiation of ARDS treatment in patients, as compared to the control group. The results of the Cox regression analysis were presented as hazard ratio (HR) with 95% confidence intervals (CIs). Next, we performed multivariable Cox regression analysis for 30-day mortality in the entire cohort of all ARDS and diabetic patients as a sensitivity analysis. From this sensitivity analysis, we investigated the results derived from PS-matched cohort to generalize to all diabetic ARDS patients in South Korea. The proportional hazards assumption of the Cox proportional hazards model was tested using the log-minus-log plots. C-statistics were used to identify the C-index of the multivariable Cox regression models. There was no collinearity between the variables in the model as the variance inflation factor was <2.0. Finally, the survival time before and after PSM was estimated using Kaplan-Meier estimator for up to 365 days, considering that all diabetic ARDS patients were followed up for at least 450 days in this study. The survival time in the two groups was presented as median time with 95% CI. The log-rank test was used to test statistical significance of difference in survival time between the two groups. All statistical analyses were performed using the R software (version 3.6.1 with R packages), and P<0.05 was considered statistically significant.

Results

From January 1, 2013 to December 31, 2017; 14,921 adult patients were admitted 17,022 times to the ICU for treatment of ARDS. Among the admissions, 2,101 were excluded due to multiple (≥2) admissions for ARDS treatment in a single patient. Only the last episode of hospital admission for ARDS treatment was included in the analysis. DM was diagnosed in 6,500 patients, and these patients divided into two groups; prior metformin users (n=2,876) and controls (n=3,624). After PSM, a total of 5,752 patients (2,876 patients in each group) were included in analysis (*Figure 1*). The results of comparison of characteristics between metformin users and control group before and after PSM were presented in *Table 1*. The ASDs of all covariates were below 0.1, indicating that the two groups were sufficiently balanced after PS matching. *Figure S1* shows the distribution of PSs before (A) and after (B) PSM. The distribution of PS between the two groups became similar after PSM.

Survival analysis after PS adjustment

Table 2 shows the results of survival analysis in the PS-matched cohort. The 30-day mortality in metformin users was 45.9% (1,320/2,876), and in the control group was 44.4% (1,278/2,876). In the Cox regression model of the PS-matched cohort, the hazard of 30-day mortality in metformin users was not significantly different compared to the control group (HR, 1.05; 95% CI, 0.97–1.14; P=0.154). *Figure 2* showed the Kaplan-Meir curve between metformin users and the control group before (A) and after (B) PSM. After PSM, the survival time was not significantly different (P=0.735) between metformin users (median time, 39.0 days; 95% CI, 35.0–45.0) and the control group (median time, 42.0 days; 95% CI, 38.0–49.0) by log-rank test.

Sensitivity analysis in entire cohort

Table 3 shows the results of uni- and multivariable Cox regression models for 30-day mortality in the entire cohort. The hazard of 30-day mortality in metformin users was not significantly different compared to the control group (HR, 1.07; 95% CI, 0.98–1.15; P=0.072). The C-index of the multivariable model was 0.79 (95% CI, 0.78–0.79).

Discussion

This population-based cohort study using nationwide data shows that prior metformin therapy is not associated with 30-day mortality in ARDS patients with DM. This association was similar in both the PS-matched cohort and multivariable adjustment of the entire cohort. Moreover, there was no significant difference in overall survival time after initiation of ARDS treatment for up to 450 days between prior metformin users and control group.

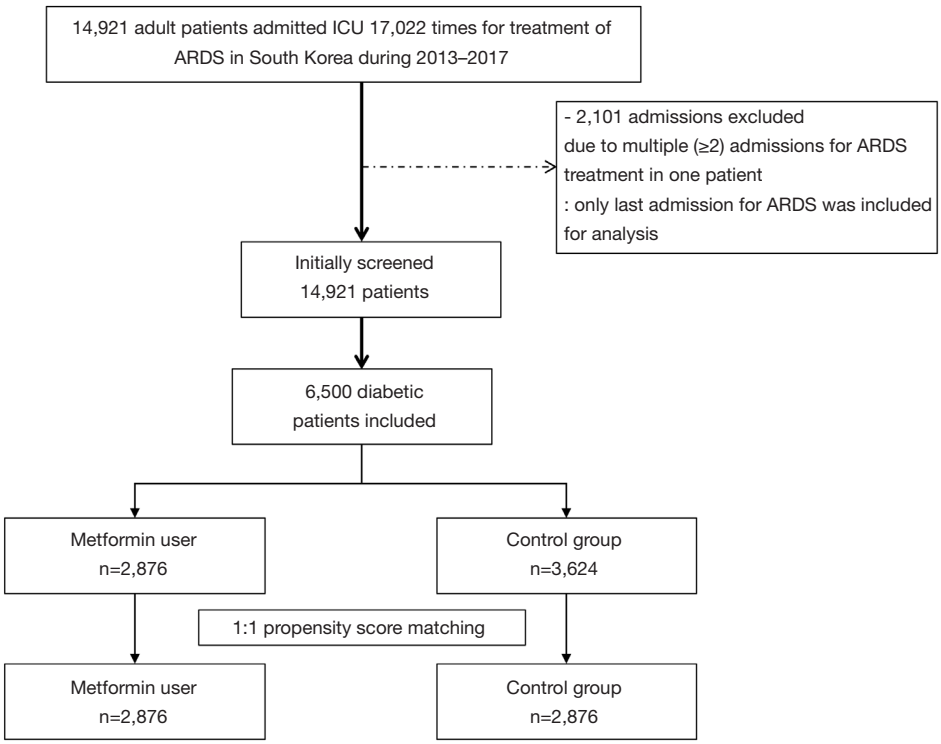

Figure 1 Patient selection flow chart. ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

The results of this study coincide with the findings of a previous retrospective cohort study (15), suggesting that prior metformin therapy might not have potential benefits in ARDS patients with DM. However, previous animal studies report a reduction in lung injury by metformin therapy, possibly through various mechanisms (13,17). The current study findings could be explained by the following speculations. First, even though patients with prior metformin therapy before ARDS diagnosis were selected, metformin was not administered after ARDS diagnosis because most of the patients were intubated for ventilator care. Thus, blood glucose levels might have been controlled by other drugs such as insulin, in most ARDS patients with DM. In ICU practice, insulin is commonly used to control blood glucose levels in critically ill patients with DM (18). Another study reported the beneficial effects of metformin in decreasing inflammatory cytokines when added to intensive insulin therapy (19). The result might be different if metformin therapy were to be continued after ARDS diagnosis in DM patients instead of insulin therapy.

Second, ARDS is one of the fatal clinical syndromes with a mortality of up to 90% after diagnosis (5). In our study, the 30-day mortality was approximately 45%, and the median survival time in Kaplan-Meir curve was almost 40 days. Therefore, it is possible that the pleiotropic effect of prior metformin therapy might be limited in ARDS patients because there are other factors such as mechanical ventilation strategy (20) or prone positioning (21) that might be more closely related to prognosis in ARDS patients.

The differences between the current study and the previous retrospective cohort study must be carefully considered while interpreting the results (15). Both studies used PSM to adjust for confounders; however, the previous study included acute physiologic assessment, chronic health evaluation II scores, the simplified acute physiology score II scores, body mass index, heart rate, hemoglobin, lung injury score, and peak end-expiratory pressure. The current study did not include the above confounders due to limitation of data source. On the other hand, the current study included the income level, residence, and many other comorbidities before ARDS diagnosis, that were not included in the previous study. Despite the covariate differences in the PS model, it was notable that prior metformin therapy was not associated with 30-day mortality in both studies (15).

This study has several limitations. First, certain

Table 1 Comparison of characteristics between metformin users and control group before and after PSM

Variables	Entire cohort (n=6,500)		ASD	Propensity score-matched cohort (n=5,752)		ASD
	Metformin users (n=2,876), n (%)	Control group (n=3,624), n (%)		Metformin users (n=2,876), n (%)	Control group (n=2,876), n (%)	
Age, yr	70.5 (12.3)	71.4 (13.4)	0.072	70.5 (12.3)	71.0 (13.4)	0.041
Sex, male	1,829 (63.6)	2,230 (61.5)	0.043	1,829 (63.6)	1,803 (62.7)	0.019
Residence at diagnosis			0.053			0.011
Capital city, Seoul	440 (15.3)	626 (17.3)		440 (15.3)	460 (16.0)	
Other metropolitan city	696 (24.2)	795 (21.9)		696 (24.2)	682 (23.7)	
Others	1,740 (60.5)	2,203 (60.8)		1,740 (60.5)	1,734 (60.3)	
Income level in quartile			0.041			0.022
Q1	473 (16.4)	587 (16.2)		473 (16.4)	479 (16.7)	
Q2	518 (18.0)	634 (17.5)		518 (18.0)	532 (18.5)	
Q3	866 (30.1)	1,087 (30.0)		866 (30.1)	837 (29.1)	
Q4	1,019 (35.4)	1,316 (36.3)		1,019 (35.4)	1,028 (35.7)	
Comorbidities before diagnosis						
Hypertension	2,436 (84.7)	2,773 (76.5)	0.227	2,436 (84.7)	2.389 (83.1)	0.041
Coronary artery disease	1,149 (40.0)	1,365 (37.7)	0.047	1,149 (40.0)	1,159 (40.3)	0.045
Cerebrovascular disease	1,176 (40.9)	1,444 (39.8)	0.021	1,176 (40.9)	1,183 (41.1)	0.007
Lung cancer	233 (8.1)	252 (7.0)	0.042	233 (8.1)	225 (7.8)	0.010
Chronic kidney disease	391 (13.6)	627 (17.3)	0.108	391 (13.6)	455 (15.8)	0.065
Dyslipidemia	2,265 (78.8)	2,362 (65.2)	0.332	2,265 (78.8)	2,202 (76.6)	0.054
Anemia	627 (21.8)	804 (22.2)	0.009	627 (21.8)	658 (22.9)	0.026
COPD	731 (25.4)	1,048 (28.9)	0.080	731 (25.4)	799 (27.8)	0.054
Asthma	369 (12.8)	513 (14.2)	0.040	369 (12.8)	398 (13.8)	0.030
Arrhythmia	229 (8.0)	311 (8.6)	0.023	229 (8.0)	249 (8.7)	0.026
Liver cirrhosis	107 (3.7)	126 (3.5)	0.013	107 (3.7)	99 (3.4)	0.015
Diagnosis of year			0.059			0.020
2013	222 (7.7)	394 (10.9)		222 (7.7)	221 (7.7)	
2014	361 (12.6)	471 (13.0)		361 (12.6)	378 (13.1)	
2015	391 (13.6)	533 (14.7)		391 (13.6)	397 (13.8)	
2016	509 (17.7)	578 (15.9)		509 (17.7)	487 (16.9)	
2017	1,393 (48.4)	1,648 (45.5)		1,393 (48.4)	1,393 (48.4)	

PSM, propensity score matching; ASD, absolute value of standardized mean difference; COPD, chronic obstructive pulmonary disease.

physiologic variables, such as body mass index, were not included in the analysis because the NHIS database does not contain this information. Second, we used the ICD-10 codes registered in the NHIS database to define comorbidities of ARDS patients; however there is a possibility that the diseases specified in the ICD-10 codes might have differed from the actual comorbidities of all ARDS patients with DM. Third, certain factors (the P/

Table 2 Survival analysis in propensity score matched cohort

Variables	30-day mortality	Cox proportional hazard model	P value
	Number (%)	HR (95% CI)	
Unadjusted			
Control	1,653/1,971 (45.6)	1	
Metformin users	1,320/2,876 (45.9)	1.02 (0.95, 1.10)	0.613
After PSM			
Control	1,278/2,876 (44.4)	1	
Metformin users	1,320/2,876 (45.9)	1.05 (0.97, 1.14)	0.154

HR, hazard ratio; CI, confidence interval; PSM, propensity score matching.

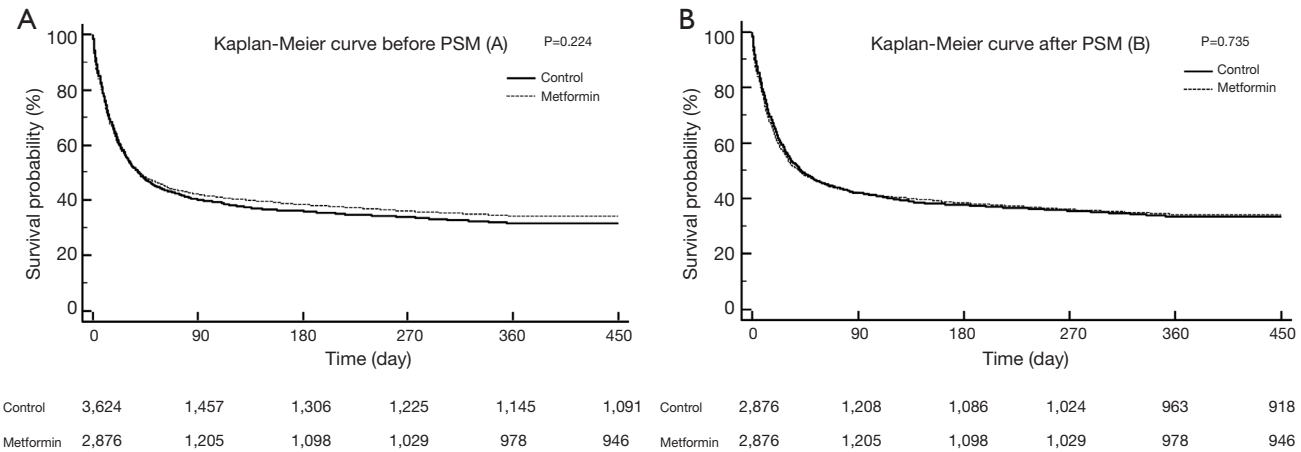

Figure 2 Kaplan-Meier curve of overall survival of metformin users and control group before (A) and after (B) PSM. PSM, propensity score matching.

F ratio, simplified acute physiology score-II score, the acute physiology and chronic health evaluation II score, and ventilator strategy) that are closely related to ARDS prognosis were not studied. The NHIS database contains data regarding prescription of drugs and procedures only. Lastly, PS adjustment and multivariable adjustment controlled only the known confounders. The possibility of unmeasured and unknown confounders cannot be excluded.

In conclusion, there is no significant association between prior metformin therapy and 30-day mortality in ARDS patients with DM. Moreover, prior metformin therapy was not associated with overall survival for up to 450 days in ARDS patients with DM. Thus, prior metformin therapy might have no benefit for survival improvement in ARDS

Table 3 Uni- and multivariable Cox regression analysis for 30-day mortality in entire cohort

Variables	Univariable model	P value	Multivariable model	P value
	HR (95% CI)		HR (95% CI)	
Age, yr	1.02 (1.01, 1.02)	<0.001	1.02 (1.01, 1.02)	<0.001
Sex, male	0.98 (0.91, 1.06)	0.580	1.02 (0.94, 1.10)	0.706
Residence at diagnosis				
Capital city, Seoul	1		1	
Other metropolitan city	1.08 (0.96, 1.22)	0.182	1.19 (1.06, 1.33)	0.004
Others	1.02 (0.92, 1.13)	0.728	1.05 (0.95, 1.17)	0.311
Income level in decile ratio				
Q1	1		1	
Q2	0.90 (0.79, 1.02)	0.085	0.97 (0.86, 1.10)	0.644
Q3	1.00 (0.89, 1.11)	0.942	1.02 (0.92, 1.15)	0.682
Q4	1.09 (0.98, 1.21)	0.106	1.00 (0.90, 1.11)	0.998
Comorbidities				
Hypertension	0.93 (0.85, 1.01)	0.100	0.97 (0.88, 1.06)	0.468
Coronary artery disease	0.86 (0.80, 0.93)	<0.001	0.96 (0.88, 1.04)	0.273
Cerebrovascular disease	0.86 (0.79, 0.92)	<0.001	0.84 (0.78, 0.90)	<0.001
Lung cancer	1.16 (1.02, 1.32)	0.023	1.07 (0.94, 1.21)	0.342
Chronic kidney disease	0.76 (0.68, 0.84)	<0.001	0.82 (0.73, 0.91)	<0.001
Dyslipidemia	0.67 (0.62, 0.72)	<0.001	0.99 (0.91, 1.08)	0.866
Anemia	0.83 (0.76, 0.91)	<0.001	0.96 (0.87, 1.05)	0.368
COPD	0.75 (0.69, 0.81)	<0.001	0.77 (0.71, 0.85)	<0.001
Asthma	0.75 (0.67, 0.85)	<0.001	0.96 (0.86, 1.08)	0.510
Arrhythmia	0.84 (0.73, 0.96)	0.013	0.98 (0.85, 1.12)	0.728
Liver cirrhosis	1.06 (0.88, 1.28)	0.553	1.11 (0.91, 1.34)	0.296
Diagnosis of year				
2013	1		1	
2014	0.88 (0.78, 1.00)	0.043	0.89 (0.78, 1.01)	0.073
2015	0.84 (0.75, 0.95)	0.006	0.88 (0.77, 0.99)	0.040
2016	0.73 (0.65. 0.83)	<0.001	0.77 (0.68, 0.88)	<0.001
2017	0.24 (0.21, 0.26)	<0.001	0.26 (0.23, 0.30)	<0.001
Prior metformin users	1.02 (0.95, 1.10)	0.613	1.07 (0.99, 1.15)	0.072

C-index: 0.79 (95% CI: 0.78, 0.79). HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

patients with DM. Future prospective studies are required to confirm these findings.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm.2020.04.25). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This population-based cohort study was performed per the ethical standards of the institutional and national research committee at the Seoul National University Bundang Hospital (X-1903-531-902) and the Health Insurance Review and Assessment Service (NHIS-2019-1-274).

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Supplementary

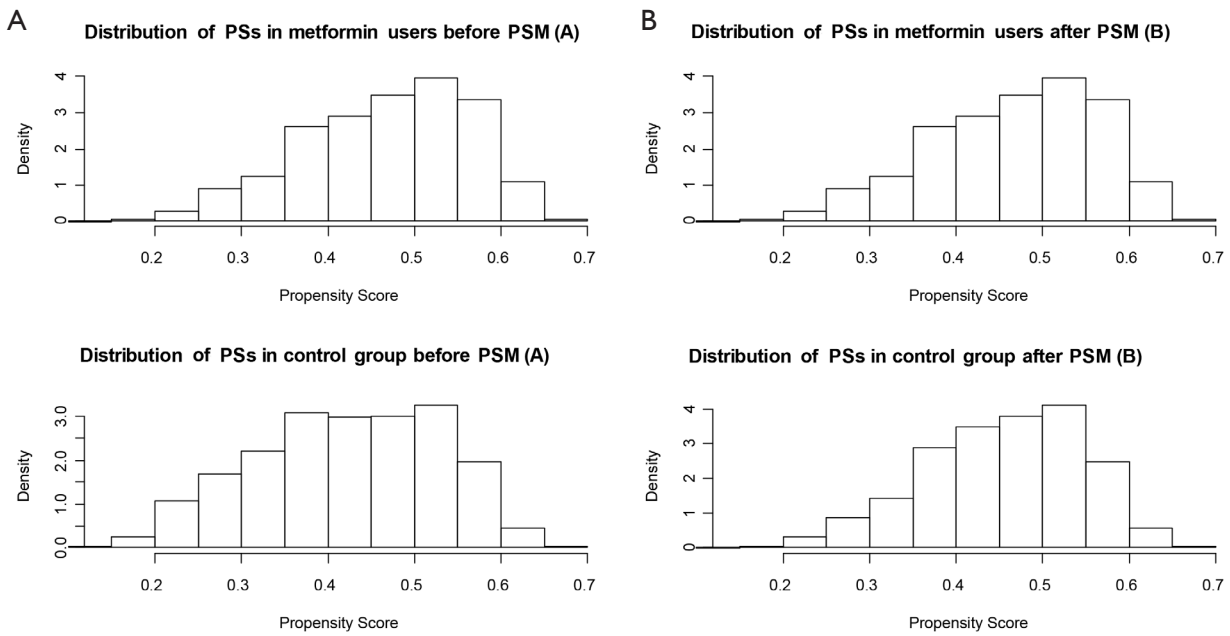

Figure S1 The distribution of PSs before (A) and after (B) PSM. PSs, propensity scores; PSM, propensity score matching.