Hospitalized Prognosis of Ischemic Stroke with COPD: A Propensity Score Matching Study

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Abstract

Purpose: The relationship between chronic obstructive pulmonary disease (COPD) and hospitalized prognosis, in ischemic stroke patients, as well as complications is not well understood. This study aimed to investigate the influence of COPD on inpatient outcomes among ischemic stroke patients.

Methods: A retrospective investigation was conducted in 9260 patients with confirmed ischemic stroke, in the First Affiliated Hospital of Shantou University Medical College, from 2013 to 2020. After excluding patients with missing data or hospital discharge within 24 hours, we divided the eligible 9021 patients into two groups based on whether or not they had been diagnosed with COPD. After a 1:3 ratio propensity score matching (PSM) (n=290, COPD group vs n=856, non-COPD group), we compared hospitalized prognosis and complications between two groups.

Results: Stroke patients with COPD had a significantly higher rate of non-recovered and deceased patients at discharge (4.1% vs 2.1%, OR=1.972, P=0.023), and a higher risk of infection (66.2% vs 48.3%, OR=2.10, P<0.001), especially pulmonary infection (48.1% vs 32.3%, OR=1.944, P<0.001), compared to stroke patients without COPD. After propensity score matching analysis, the differences were still statistically significant concerning inpatient non-recovery and death (4.1% vs 1.9%; OR=2.266, P=0.031),

infection (66.2% vs 52.9%, OR=1.743, P<0.001) and pulmonary infection (48.3% vs 36.6%, OR=1.619, P<0.001).

Conclusion: Stroke patients with COPD have poorer hospitalized prognosis, with a higher rate of non-recovered and deceased patients, as well as higher incidence of infection, compared with those without COPD.

1. Background

Stroke is epidemic worldwide. In spite of stable incidence rate and declining mortality over the past 20 years, the number of incident strokes, generalized stroke survivors, stroke-induced disability, and stroke-related deaths is increasing[1]. The latest estimate from the Global Burden of Disease Study in 2015 shows that stroke is the major cause of disability and the second leading cause of death worldwide[2]. Moreover, ischemic stroke is the most common type of stroke. Due to the aggressive treatment of dyslipidemia and hypertension, which are common in the stroke population, the mortality in ischemic stroke has decreased in the past[3].Therefore, other comorbidities in ischemic stroke should receive more attention.

Chronic obstructive pulmonary disease (COPD) is one of a number of common diseases around the world that also cause a major health-care burden[4]. According to the Global Burden of Disease Study in 2015, there are approximately 174 million people suffered from COPD each year all over the world[5]. Comorbidities are a defining feature of COPD. A recent study, showed that 86.0% of patients with COPD had at least one comorbidity, and 22.3% had 5 or more comorbid conditions[6]. Stroke was one of the comorbidities of COPD. There has been ample clinical research demonstrating that COPD is correlated with increased stroke risk, especially upon acute exacerbations of COPD[7–10]. However, there is a paucity of evidence on the effect of COPD on the prognosis of admitted stroke patients. In this study, our aim was to explore the influence of COPD on the hospitalized outcomes in participants with ischemic stroke.

2. Methods

2.1 Study Object

The study was conducted retrospectively between 1 January 2013 and 29 November 2020 in the First Affiliated Hospital of Shantou University Medical College. In total, 9260 patients with a primary diagnosis of ischemic stroke were consecutively enrolled in our study. The diagnosis of ischemic stroke was documented via clinical manifestations and head computed

tomography and/or head magnetic resonance imaging. The diagnosis of COPD was made based on emphysema and/or chronic bronchitis, and the assessment of pulmonary function testing by a respiratory physician. Patients with missing information or hospital discharge within 24 hours were excluded, because their influence on the assessment of discharge prognosis. After that, we divided patients into two groups on the basis of whether or not they were diagnosed with COPD. Fig. 1 presents the flowchart of participant selection and the results of propensity score matching (PSM). This survey was fully approved by the ethics committee of the First Affiliated Hospital of Shantou University Medical College. All procedures conformed to the tenets the Declaration of Helsinki.

2.2 Study Variables

Demographic data and cerebrovascular risk factors were collected, including sex, age, smoking, drinking, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, myocardial infarction, and chronic heart failure. Other factors affecting prognosis and treatment options were also included, such as hyperthyroidism, tumor, a history of hyperuricemia or gout, and a history of ischemic stroke or cerebral hemorrhage.

2.3 Patient outcomes

The primary outcomes were defined as unhealed or deceased, based on inpatient medical records home page information. All information on the home page of inpatient medical records was filled in accordance with the requirements of the Quality Specifications for Data Filling on the Home Page of Inpatient Medical Records published by the National Health and Family Planning Commission. The secondary outcomes were length of stay, hospitalization expenses and various common complications, inclusive of epilepsy, deep venous thrombosis, infection, hemorrhage, hydrocephalus, massive cerebral infarction and cerebral hernia.

2.4 Statistical analysis

We used counts (percentage) to describe discrete variables and means with standard deviation (SD) to perform continuous variables. Chi-squared or t test were used to assess the differences between groups.

In order to minimize the effect of 16 clinical factors, including sex, age, habits and other comorbidities, propensity score matching was applied to match patients on whether or not they suffered from COPD. Propensity score matching analysis methods are increasingly being used in observational studies as an alternative to control for potential confounding factors[11,12]. Our research opted for PSM based on the following considerations. First, compared with the multivariable regression model, the linearity assumption between propensity score and outcomes is eliminated in PSM[13]. Second, the method optimizes the balance of covariates between groups and, in this way, aims to achieve some of the characteristics of randomized controlled trials (RCTs). Moreover, it can discriminate against actual or suspected bias on the part of selection by the researcher[13]. This allows us to gain two comparable groups, even though there was a huge difference in the number of people between the two groups. Last but not least, the number of outcome indicators does not limit the number of confounding factors to be included in our study compared to the multivariable regression model[12].

In our survey, propensity scores were calculated by logistic regression. In addition, we created a 1:3 ratio PSM study group by using nearest neighbor matching. The caliper match tolerance was 0.05. All demographic data (sex, age, habits) and risk factors were incorporated to adjust for bias. After the matching, we divided the stroke patients into two subsets: 290 with COPD and 856 without. Then, the outcomes and complications between the two groups were compared in both the original samples and matched samples.

All statistical analyses were conducted using SPSS 25.0 and R statistics software (version 4.0.3). The MatchIt package in R software was used in the matching process. P-value < 0.05 was defined as significant. To assess our PSM adjustment, we checked by using standardized mean difference (SMD). An SMD value less than 0.1 was considered to indicated balanced[14].

3. Results

3.1 Baseline variables

As shown in Table 1, a total of 9021 eligible patients with a primary diagnosis of ischemic stroke were enrolled in the study, which included 293 patients with COPD and 8728 without. According to a 1:3 ratio PSM, 290 stroke patients with COPD and 856 stroke patients without COPD were matched.

In the original samples, the patients with COPD were older (74.53±8.99 vs 67.18±11.65, P<0.001), more likely to be male (88.1% vs 61.1%, P<0.001), used tobacco (49.8% vs 31.9%, P<0.001), had a history of ischemic stroke (24.2% vs 19.2%, P=0.032) and had more heart comorbidities, comprised of atrial fibrillation (14.0% vs 9.5%, P=0.010), coronary heart disease (7.8% vs 5%, P=0.030), and chronic heart failure (4.4% vs 2.4%, P=0.031). Interestingly, fewer patients with COPD had diabetes mellitus (19.1% vs 39.4%, P<0.001) and hypertension (70% vs 79.2%, P=0.008), and hyperlipidemia (12.6% vs 22.1%, P<0.001) compared with the patients without COPD. After matching, there were no significant differences in previously associated covariates between the two groups (Fig. 2). In addition, the standardized mean difference between the matching groups was less than 0.1 (Table 1, Fig. 3).

Table 1

Clinical characteristics of patients with ischemic stroke.

Baseline variables	Original samples			Matched samples			
	stroke with COPD	stroke without COPD	P	stroke with COPD	stroke without COPD	P	SMD
n	293	8728		290	856		
Demographics data							
Male, n (%)	258(88.1)	5329(61.1)	<0.001	255(87.9)	772(90.2)	0.276	0.072
Female, n (%)	35(11.9)	3399(38.9)	<0.001	35 (12.1)	84 (9.8)	0.276	0.072
Age, (mean (SD))	74.53(8.99)	67.18(11.65)	<0.001	74.44 (8.94)	73.97 (9.46)	0.461	0.051
Habits, n (%)							
Smoking	146(49.8)	2782(31.9)	<0.001	145 (50.0)	419 (48.9)	0.757	0.021
Drinking	30(10.2)	979(11.2)	0.601	30 (10.3)	68 (7.9)	0.206	0.083
Comorbidities, n (%)							
Diabetes mellitus	56(19.1)	3443(39.4)	<0.001	56 (19.3)	171 (20.0)	0.806	0.017
Hypertension	205(70.0)	6911(79.2)	0.008	205 (70.7)	616 (72.0)	0.678	0.028
Hyperlipidemia	37(12.6)	1925(22.1)	<0.001	37 (12.8)	103 (12.0)	0.744	0.022
Atrial fibrillation	41(14.0)	826(9.5)	0.010	40 (13.8)	101 (11.8)	0.372	0.060
Coronary heart disease	23(7.8)	437(5.0)	0.030	22 (7.6)	47 (5.5)	0.195	0.085
Myocardial infarction	1(0.3)	126(1.4)	0.186	1 (0.3)	2 (0.2)	1	0.021
Chronic heart failure	13(4.4)	213(2.4)	0.031	12 (4.1)	23 (2.7)	0.215	0.080
History of ischemic stroke	71(24.2)	1675(19.2)	0.032	68 (23.4)	202 (23.6)	0.959	0.004
History of cerebral hemorrhage	7(2.4)	158(1.8)	0.467	6 (2.1)	11 (1.3)	0.501	0.061
History of hyperuricemia or gout	35(11.9)	1207(13.8)	0.357	35 (12.1)	105 (12.3)	0.929	0.017
Hyperthyroidism	3(1.0)	110(1.3)	0.928	3 (1.0)	6 (0.7)	0.864	0.036
Tumor, n (%)			0.619			0.910	0.03
Non-tumor	283(96.6)	8474(97.1)		280 (96.6)	822 (96.0)		
Benign tumor	0(0.0)	5(0.1)		0 (0.0)	0 (0.0)		
Malignant tumor	9(3.1)	226(2.6)		9 (3.1)	30 (3.5)		
Undefined types of tumor	1(0.3)	23(0.3)		1 (0.3)	4 (0.5)		

Abbreviations: SD, standard deviation.

3.2 Primary outcomes

In all, 12 of 293 (4.1%) stroke patients with COPD were unhealed or deceased at discharge, compared with 185 of 8728 (2.1%) stroke patients without COPD (OR=1.972, [95% CI 1.087-3.578], P=0.023). Furthermore, after PSM analysis, the patients with COPD still had a significantly higher rate of in-hospital unhealing and death (4.1% vs 1.9%, OR=2.266, [95% CI 1.059-4.849], P=0.031) (Table 2).

3.3 Secondary outcomes

In our research, the stroke patients with COPD had a higher risk of infection (original, 66.2% vs 48.3%, OR=2.10, [95% CI 1.643-2.685], P<0.001; matched, 66.2% vs 52.9%, OR=1.743, [95% CI 1.320-2.301], P<0.001), especially pulmonary infection (original, 48.1% vs 32.3%, OR=1.944, [95% CI 1.539-2.456], P<0.001; matched, 48.3% vs 36.6%, OR=1.619, [95% CI 1.237-2.119], P<0.001), than patients without COPD, both in the original samples and matched samples. However, we found no significant differences in both groups for incidence of epilepsy, deep venous thrombosis, urinary system infection, intracranial hemorrhage, digestive tract hemorrhage, hydrocephalus, massive cerebral infarction and cerebral hernia, before or after matching. Additionally, the length of stay and hospitalization expenses of ischemic stroke patients with or without COPD did not differ either before or after matching. The results are summarized in Table 2.

Table 2

Outcomes and comorbidities in patients with ischemic stroke.

Variables	Original samples			Matched samples		
	stroke with COPD	stroke without COPD	P	stroke with COPD	stroke without COPD	P
n	293	8728	290	856		
Complications, n (%)						
Epilepsy	2(0.7)	72(0.8)	1	2(0.7)	2(0.2)	0.574
Deep venous thrombosis	57(19.5)	1804(20.7)	0.613	57(19.7)	186(21.7)	0.455
Infection	194(66.2)	4213(48.3)	<0.001	192(66.2)	453(52.9)	<0.001
Pneumonia	141(48.1)	2819(32.3)	<0.001	140(48.3)	313(36.6)	<0.001
Urinary system infection	74(25.3)	2061(23.6)	0.515	73(25.2)	199(23.2)	0.506
Intracranial hemorrhage	4(1.4)	122(1.4)	1	4(1.4)	16(1.9)	0.582
Digestive tract hemorrhage	127(43.3)	3474(39.8)	0.223	125(43.1)	368(43.0)	0.973
Hydrocephalus	1(0.3)	42(0.5)	1	1(0.3)	8(0.9)	0.550
Massive cerebral infarction, n (%)	10(3.4)	269(3.1)	0.748	10(3.4)	26(3.0)	0.729
Cerebral hernia, n (%)	1(0.3)	59(0.7)	0.743	1(0.3)	5(0.6)	0.986
Outcomes						
Rate of unhealing and death, n (%)	12(4.1)	185(2.1)	0.023	12(4.1)	16(1.9)	0.031
Length of stay (mean (SD))	12.97(9.71)	12.72(10.17)	0.681	12.93(9.73)	12.09(9.31)	0.188
Hospitalization expenses (mean (SD))	21934(19066.71)	20694(25227.86)	0.405	21945(19125.88)	20174(20601.84)	0.198

Abbreviations: SD, standard deviation.

4. Discussion

As far as we know, this is the first study to indicate the association between COPD and hospitalized outcomes in ischemic stroke patients with propensity score matching. In our case-control study, we show the important correlations between COPD and higher risk of in-hospital non-recovery and death in stroke patients, compared to those without COPD. Moreover, a higher incidence of infection, especially pulmonary infection was observed in patients with COPD after stroke. After adjusting for confounding factors with propensity score matching, COPD patients still tend to have a poorer prognosis and higher risk of infection.

In our study, the prevalence of COPD in patients with ischemic stroke was 3.25%, which is lower than reported in other studies (3.27%; 7.65% and 12.16%)[15-17]. One of the most well accepted explanations is the different regions and ethnicities, as previous research had been conducted in Sweden and the United States, while ours is in southern China[18]. According to previous studies, the Americas had the highest prevalence of COPD (about 15% in 2010) in the world, possibly owing to a high diagnostic rate[4].

Several factors might account for the co-morbidity of stroke and COPD. First, smoking and aging are shared risk factors for both brain and lung diseases, which makes stroke and COPD more likely to occur in the same individual. Second, it is reported that twice the risk of both a lipid core within carotid plaques and carotid artery wall thickening has been found in patients with COPD[19]. A lipid core in plaques signifies plaque vulnerability. Apparently, carotid artery wall thickening and vulnerable plaques are definite risk factors for ischemic stroke. However, the pathophysiological relationship between COPD and stroke is still under investigation and is likely to be interconnected[20]. Hypoxia, hypercapnia, systemic inflammation, and oxidative stress may be the critical factors that contribute to pathophysiological changes in COPD[21]. These factors then drive endothelial dysfunction, vascular reactivity, and even atherosclerotic plaque rupture, which may lead to stroke[22].

Our study finds that patients in COPD group have a higher inpatient unhealing and death rate, as well as a higher incidence of infection. Nevertheless, to date, we paid too little attention to the potential risk of COPD for ischemic stroke. Only a small number of studies have explored mortality in stroke patients with COPD[17,23]. Six considerations may account for the poor outcomes of stroke patients with COPD. First of all, patients with COPD have been in a state of ventilation dysfunction for a prolonged period, which results in chronically elevated levels of carbon monoxide in the blood, causing the oxyhemoglobin dissociation curve to shift to the left, and leaving the brain in a state of mild hypoxia. Moreover, hypoxemia may lead to increased turnover of neuronal membrane precursors, myelin damage and brain tissue breakdown, which is related to the increase of the level of brain choline[24,25]. Second, chronic low-grade systemic inflammation in patients with COPD may contribute to vascular wall changes, endothelial dysfunction, arteriosclerosis and impaired vascular reactivity[25-27]. Third, patients with COPD may lack of exercise because of poor lung function. Fourth, stroke patients often suffer from respiratory muscle weakness, caused by central diaphragm injury, which ultimately affects lung function[25,28-30]. Fifth, the risk of dysphagia is increased in stroke survivors, which likely results in aspiration pneumonia, leading to the exacerbation of COPD[31,32]. In fact, COPD patients are already more likely to develop pneumonia because of the use of corticosteroids and the compromised immune state[33]. Sixth, stroke patients with cognitive dysfunction have poor compliance with oxygen therapy and medication, and the risk of acute exacerbation of COPD will be increased because of this poor compliance. All in all, potential risk factors for ischemic stroke, such as lack of exercise, systemic inflammation, vascular disease, and oxygenation disturbance, may be exacerbated by COPD. Whereas stroke patients with dysphagia or weakness of breath or poor compliance will aggravate COPD. The interaction between COPD and stroke can thus result in a grave prognosis.

Interestingly, other prognostic indicators, such as epilepsy, hemorrhage and length of stay, were not significantly different between the COPD and non-COPD groups. This result is different from the findings of De et al., which represented COPD as an independent risk factor for epilepsy after stroke[34].

In response to the rising rate of uncured disease and mortality, early aggressive intervention in COPD is imperative. A number of studies have demonstrated that quitting smoking, lowering cholesterol, changing dietary habits, and exercising become integral parts of the treatment of COPD[35]. However, the impact of drug treatment of COPD on the risk and prognosis of ischemic stroke is complex, depending on the duration of treatment and medication regimen[36-39]. In addition, for COPD patients with stroke, oxygen therapy and antiplatelet therapy may be another positive intervention[40,41].

A few limitations should be acknowledged in this study. First, our study is a retrospective observational study. Thus, it can only establish associations instead of causality. Mechanistic studies are warranted to confirm this hypothesis. Second, because it was a single-center case-control study, more investigations are needed in different regions to explore the prevalence of COPD among stroke patients and the outcomes between COPD and non-COPD patients with stroke. Third, this study was unable to differentiate between stable and acute exacerbations of COPD because the severity of COPD was not known. Finally, there was a lack of data on whether patients received bronchodilator or hormone therapy, so we could not examine therapy-related effects in the study. Nonetheless, we performed propensity matching score analysis in an effort to minimize confounding factors, such as age and atrial fibrillation to confirm the validity of our results. To our knowledge, these confounding factors have a significant impact on the outcome of stroke patients.

5. Conclusions

This is the first propensity score matching study of ischemic stroke with or without COPD and demonstrate that suffering COPD contributed significantly to poor hospitalized outcomes, including a higher rate of unhealing and death, as well as a higher incidence of infection. More prospective studies are needed to verify this finding and explore more effective interventions to improve prognosis.

Declarations

Ethics approval and consent to participate

This survey was approved by the ethics committee of the First Affiliated Hospital of Shantou University Medical College. All procedures conformed to the tenets the Declaration of Helsinki. The need for informed consent was waived by the ethics committee of First Affiliated Hospital of Shantou University Medical College.

Consent for publication

Not applicable.

Availability of Data and Materials:

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations of interest:

The authors proclaim no conflicts of interest.

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Authors' contributions:

QZ contributed to designed the study protocol, revise manuscript and final approval of the content. LW conceived the protocol of the study and revised the manuscript. QZ and LW are co-correspondence authors. SZ performed the data

collection, statistical analysis, wrote and revised the manuscript. KL contributed to revise the manuscript. All authors have read and approved the final manuscript.

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Figures

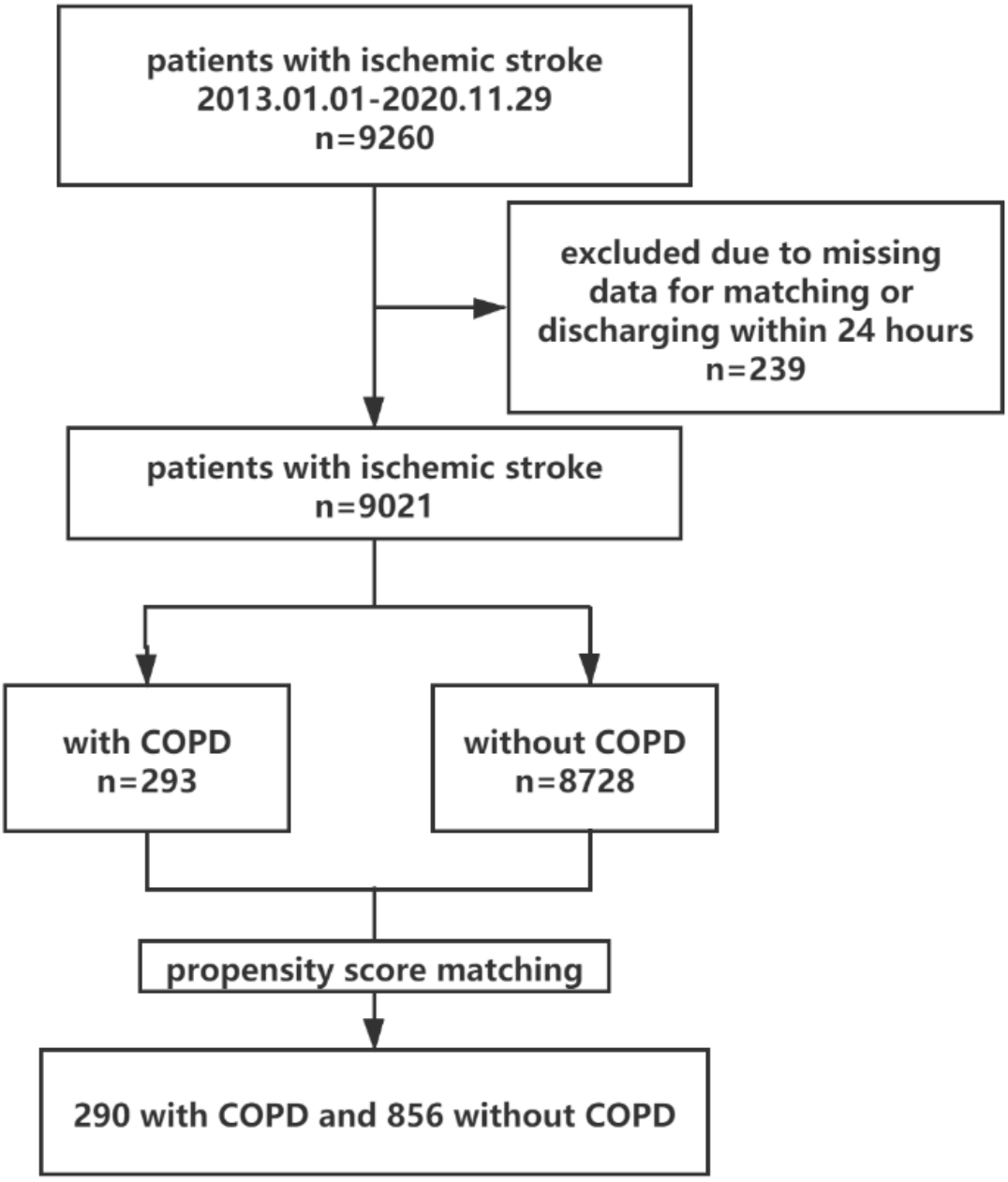

Figure 1

Study flowchart. Annotation: In total, 9260 patients with a primary diagnosis of ischemic stroke were enrolled in the study from 1 January 2013 to 29 November 2020. Of these patients, 239 were excluded due to missing data or hospital discharge within 24 hours. We divided eligible patients into two groups depending on whether or not they were diagnosed with COPD. According to a 1:3 ratio PSM, 290 stroke patients with COPD and 856 stroke patients without COPD entered our prognostic study. Acronyms: PSM, propensity score matching; COPD, chronic obstructive pulmonary disease.

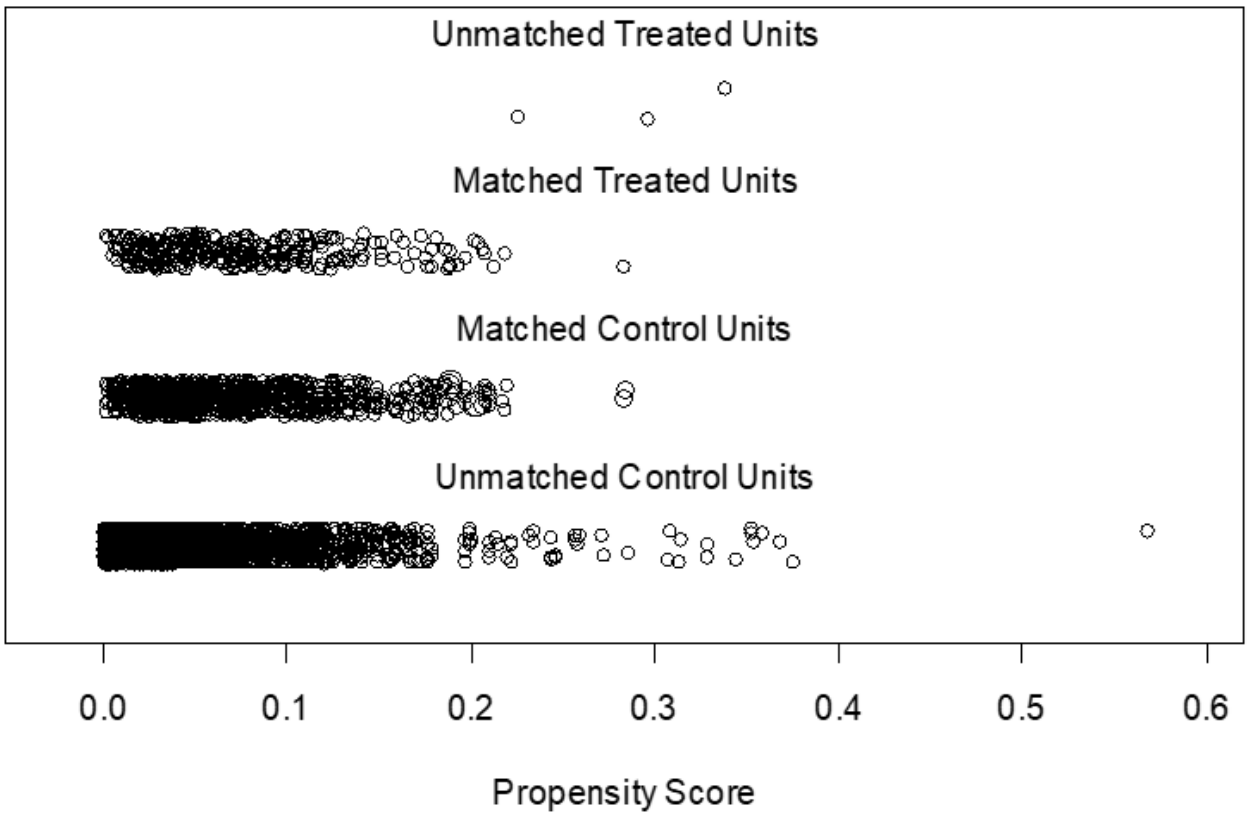

Figure 2

Distribution of propensity scores.

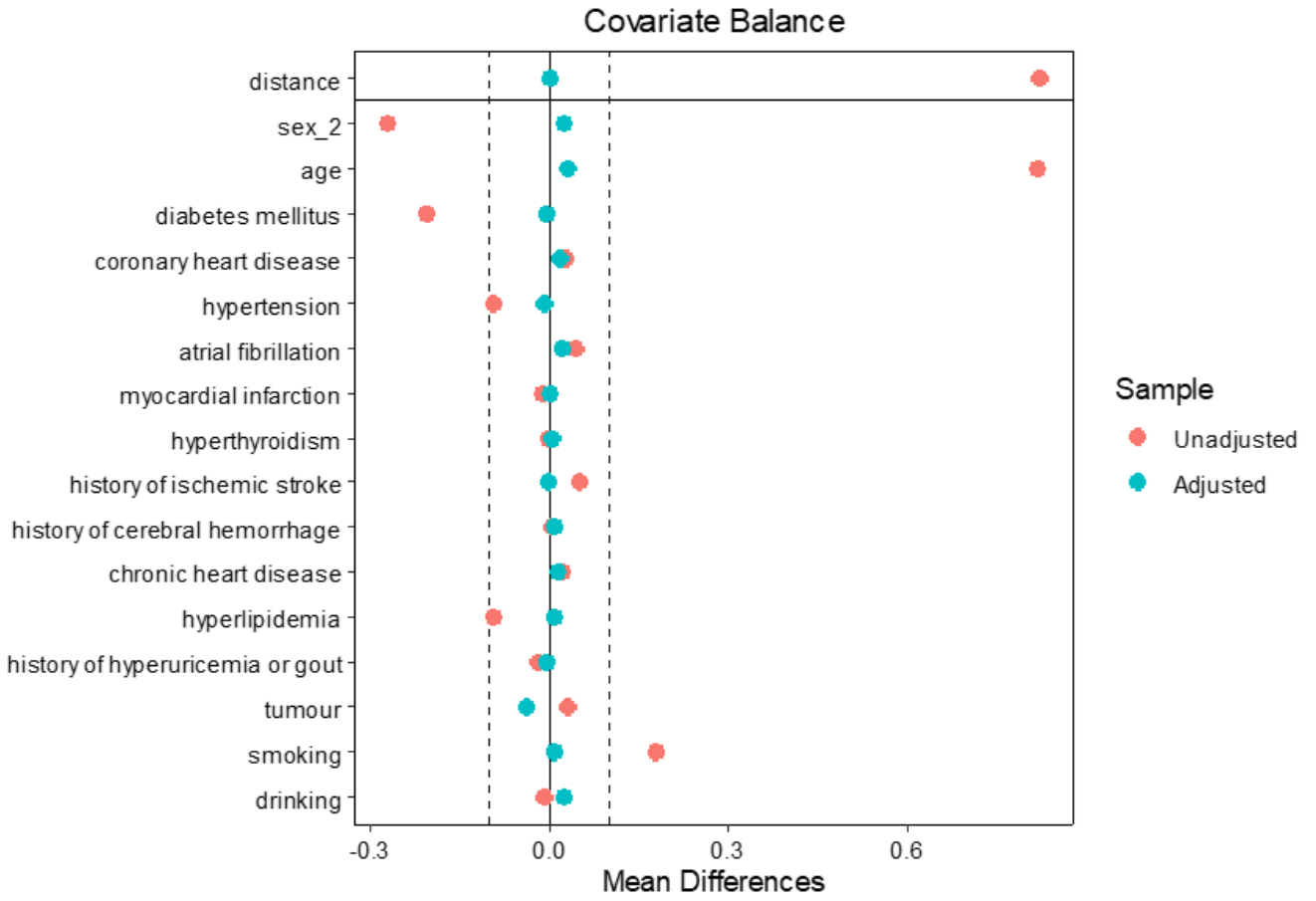

Figure 3

Standardized mean differences of covariates between stroke patients with and without COPD before and after PSM.