Impact of Chronic Obstructive Pulmonary Disease on In-hospital Mortality in Patients with Aneurysmal Subarachnoid Hemorrhage: An Observational Cohort Study with Propensity Score Matching

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Research
Abstract

Objective: Chronic obstructive pulmonary disease (COPD) has been associated with several complications and mortality in acutely ill patients. For patients with aneurysmal subarachnoid hemorrhage (aSAH), the association between COPD and clinical outcomes remains unclear.

Methods: In this retrospective cohort study, we analyzed consecutive aSAH patients admitted to the West China Hospital between 2009 and 2019. Propensity score matching was performed to obtain the adjusted odds ratios (ORs) with 95% CI. The primary outcome was in hospital mortality.

Results: Using a ten-year clinical database from a large university medical center, 5643 patients with aSAH were identified, of whom 377 (7.9%) also had COPD. After matching, 289 patients were included in COPD group and 1156 in non-COPD groups. COPD was associated with increased in-hospital mortality (OR 1.63, 95% CI 1.02-2.62) and poor functional outcome at discharge (OR 1.37, 95% CI 1.04-1.80). Similarly, patients with COPD had significantly longer length of hospital stay, higher odds of seizure (OR 2.05, 95% CI 1.04-4.04), pneumonia (OR 3.10, 95% CI 2.38-4.04), intracranial infection (OR 1.62, 95% CI 1.14-2.29), urinary tract infection (OR 1.59, 95% CI 1.16-2.20) and bloodstream infection (OR 3.27, 95% CI 1.74-6.15).

Conclusions: Among aSAH patients, COPD is associated with increased mortality. COPD represents a significant risk factor for pneumonia and seizure.

Home Message

In this cohort study with propensity score matching of patients with aneurysmal subarachnoid hemorrhage, chronic obstructive pulmonary disease is associated with increased mortality. Chronic obstructive pulmonary disease represents a significant risk factor for infections and seizure.

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world[1] and is currently characterized by systemic involvement and multiple comorbidities[2]. Growing evidence indicated that COPD independently predicts mortality and morbidity in patients undergoing surgery and patients with critically ill.[3–6] However, the impact of COPD on outcomes in patients with aneurysmal subarachnoid hemorrhage (aSAH) remain unclear.[7] Only one observational study has addressed the association between COPD and mortality in patients with SAH.[8] That study demonstrated that COPD did not increased mortality. However, that study did not control for important confounders, such as severity of disease, smoking, or medical history. Moreover, there is no data identifying the impact of COPD on complications in patients with aSAH.

In the 2 largest phase III randomized clinical trials, use of prophylactic antibiotics for patients with stroke did not reduce the risk of pneumonia or death.[9, 10] A possible explanation for the lack of benefit of preventive antibiotics in randomized trials is that included patients have too low risk of infection, with 7% and 16% patients developing pneumonia, respectively. For patients with aSAH, about 20% of them develop a pneumonia.[11] COPD is also one of the most frequent comorbid conditions and a risk factor for developing pneumonia.[12] Patients with COPD and aSAH would have high risk of pneumonia and may benefit from prophylactic antibiotics.

With the increasing global incidence of COPD[13] and its high prevalence in patient with aSAH[8], we assessed the impact of COPD on outcomes of in patients with aSAH, using propensity score matching (PSM) to form groups for comparison with near-identical distributions of background and potential confounder variables.
Methods

Study Design

We performed a retrospective cohort study. We consecutively evaluated the electronic health record of patients with aSAH admitted to the West China Hospital, Sichuan University, from January 1, 2009 to June 31, 2019. This study was approved by the ethics committee of West China hospital (No. 20191133). The ethics committee has exempted written informed consent of patients included in the study because this study posed minimal-risk research and used only observational data.

Study Population

Patients were eligible if they had an intracranial aneurysm identified by imaging in the presence of SAH. Intracranial aneurysms were identified by cerebral angiography or by MRA or CTA > 3 mm. SAH was confirmed with neuroimaging (including CT, MRI, or angiography), cerebrospinal fluid analysis, or intraoperatively by a neurosurgeon. Aneurysms related to trauma, arteriovenous malformations, fusiform aneurysms, nondefinitive aneurysms, trauma SAH, nondefinitive SAH, or aneurysms that were treated before the presentation were excluded. Hospital length of stay less than 3 days were also excluded.

Exposures

The primary exposure was COPD. Diagnosis of COPD was based on the judgment of two independent physicians on the basis of medical reports and previous COPD medication.

Demographics Characteristics

Demographic and clinical data included age, sex, hypertension, diabetes mellitus, coronary heart disease, smoking (current, ever, never), and alcohol use. Hunt & Hess grade and Fisher grade were also obtained on admission.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included neurological complications, infectious complications, acute kidney injury, length of hospital stay, and poor functional outcome at the time of discharge. Infectious outcomes were pneumonia, intracranial infection, urinary tract infection, and bloodstream infection. Neurological complications were hydrocephalus, delayed neurological ischemic deficits, re-bleeding, and seizures.

Poor functional outcome was defined as modified Rankin Scale (mRS) 4–6. Re-bleeding was defined as acute worsening in neurologic status along with an increase in hemorrhage volume which was confirmed in a repeat CT or MRI scan. Delayed ischemic neurological deficits (DIND) was defined as angiographic vasospasm associated with a decline in neurological status lasting > 2 hours and with other causes being ruled out. Infections were diagnosed by treating physicians.

Statistical Analysis

We used SPSS, version 24 (SPSS Inc) and R software version R3.3.2 (Matching and Frailty pack packages, R Foundation for Statistical Computing) for statistical analyses. Normally distributed continuous variables are summarized as means (SDs), and nonnormally distributed variables were reported as medians (interquartile ranges [IQRs]). All tests of significance were 2-sided, and P < .05 was considered statistically significant.

PSM[14] was used to minimize bias from confounding variables when comparing patients with COPD and patients without COPD in the cohort study. From our experience and from previous reports, age, sex, hypertension, diabetes mellitus, chronic renal failure, coronary heart disease, smoking, alcohol use, Hunt & Hess grade and Fisher grade were
considered important confounders. We calculated a propensity score for each patient through logistic regression modeling of a $10^{-5}$ unit difference, and then patients with COPD and patients without COPD were matched 1:4. We compared the characteristics of patients with COPD and patients without COPD using absolute standardized differences; a difference more than 0.1 is considered meaningful.

For proportional outcomes comparing between patients with COPD and patients without COPD after PSM, the paired t-test was used for continuous variables, and univariable logistic regression was used for binary variables.

We used the E-value to measure the robustness of the association between COPD and mortality for unmeasured or unadjusted confounding.[15] E-values were computed with an online E-value calculator (https://mmathur.shinyapps.io/evalue/).[16]

**Data availability**

The data and statistical analytical methods of this study are available from the corresponding author upon reasonable request.

**Results**

We screened 18824 consecutive individuals with aneurysms in West China hospital during the study period. A total of 5643 patients with aSAH were included in this study. In patients with aSAH, 377 (6.7%) patients also had COPD (Fig. 1). Patient demographics stratified by COPD are shown in Table 1. Before matching, there were more male and old patients in the COPD group than in the non-COPD group. Compared with patients without COPD, patients with COPD more frequently had other co-morbidities such as diabetes, chronic renal failure, coronary heart disease. More patients with COPD are smokers. Patients with COPD have higher Hunt & Hess grade. There was a total of 289:1156 matched pairs (1:4). After matching, the variables were balanced between patients with COPD and patients without COPD.
| Characteristics                      | Before matching | After matching | SMD   | Before matching | After matching | SMD   |
|--------------------------------------|-----------------|----------------|-------|-----------------|----------------|-------|
|                                      | COPD (n = 377)  | Non-COPD (n = 5266) |      | COPD (n = 289)  | Non-COPD (n = 1156) |      |
| Age, y, mean (SD)                    | 53.8(11.8)      | 66.9(9.3)      | 1.24  | 64.5(8.3)       | 64.5(8.3)      | 0.001 |
| Female                               | 212(56.2)       | 3440(65.3)     | 0.19  | 169(58.5)       | 688(59.5)      | 0.02  |
| Hypertension                         | 105(27.9)       | 1281(24.3)     | 0.08  | 77(26.6)        | 331(28.6)      | 0.04  |
| Diabetes                             | 34(9.0)         | 263(5.0)       | 0.16  | 24(8.3)         | 91(7.9)        | 0.02  |
| Coronary heart disease               | 19(5.0)         | 148(2.8)       | 0.12  | 11(3.8)         | 47(4.1)        | 0.01  |
| Chronic renal failure                | 4(1.1)          | 18(0.3)        | 0.09  | 3(1.0)          | 6(0.5)         | 0.06  |
| Smoking                              |                 |                |       |                 |                |       |
| Current Smoking                      | 87(23.1)        | 1009(19.2)     | 0.15  | 67(23.2)        | 244(21.1)      | 0.03  |
| Ever smoking                         | 24(6.4)         | 212(4.0)       | 15(5.2) | 82(7.1)       |                |       |
| Never smoking                        | 266(70.6)       | 4045(76.8)     | 207(71.6) | 830(71.8)      |                |       |
| Alcohol abuse                        | 81(21.5)        | 1023(19.4)     | 0.05  | 61(21.1)        | 250(21.6)      | 0.01  |
| Anterior circulation ruptured aneurysm| 302(80.1)       | 4350(82.6)     | 0.19  | 240(83.0)       | 965(83.5)      | 0.006 |
| Hunt & Hess grade                    |                 |                |       |                 |                |       |
| I                                    | 28(7.4)         | 500(9.5)       | 0.26  | 18(6.2)         | 72(6.2)        | < 0.01|
| II                                   | 166(44.0)       | 2738(52.0)     | 149(51.6) | 596(51.6)      |                |       |
| III                                  | 106(28.1)       | 1499(28.5)     | 85(29.4) | 340(29.4)      |                |       |
| IV                                   | 71(18.8)        | 474(9.0)       | 37(12.8) | 148(12.8)      |                |       |
| V                                    | 6(1.6)          | 55(1.0)        | 0(0)  | 0(0)            |                |       |
| Fisher grade                         |                 |                |       |                 |                |       |
| I                                    | 16(4.2)         | 203(3.9)       | 0.06  | 14(4.8)         | 25(2.2)        | 0.02  |
| II                                   | 63(16.7)        | 822(15.6)      | 54(18.7) | 159(13.8)      |                |       |
| III                                  | 35(9.3)         | 665(12.6)      | 32(11.1) | 99(8.6)        |                |       |
| IV                                   | 181(48.0)       | 2298(43.6)     | 126(43.6) | 571(49.4)      |                |       |
| Operation                            |                 |                |       |                 |                |       |
| Clipping                             | 240(63.7)       | 3769(71.6)     | 0.14  | 196(67.8)       | 808(69.9)      | 0.04  |
| Coil                                 | 51(13.5)        | 705(13.4)      | 40(13.8) | 136(11.8)      |                |       |
| No treatment                         | 86(22.8)        | 792(15.0)      | 53(18.3) | 212(18.3)      |                |       |

SMD: standardized mean difference; Chronic obstructive pulmonary disease
The univariable logistic regression and propensity-matched analysis for the association between COPD and outcomes were shown in Table 2. In univariate analysis, COPD was associated with increased odds of mortality (OR 2.05, 95% CI 1.44–2.93). Even after matching, our findings remained robust: COPD was associated with higher mortality (OR 1.63, 95% CI 1.02–2.62).

### Table 2

Unadjusted and Propensity-Matched Analysis Results for in-hospital outcomes

| Characteristics                  | Entire Cohort | Propensity Score-Matched Cohort |
|-----------------------------------|---------------|---------------------------------|
|                                   | COPD (n = 377) | Non-COPD (n = 5266) | Unadjusted | COPD (n = 289) | Non-COPD (n = 1156) | Propensity-score matched |
| Mortality in hospital             |               |                               | OR (95% CI) | p Value | OR (95% CI) | p Value |  |
|                                   | 38(10.1)      | 273(5.2)                      | 2.05(1.44–2.93) | <0.001 | 1.63(1.02–2.62) | 0.04 |  |
| mRS 4–6 at discharge              |               |                               | 2.28(1.84–2.83) | <0.001 | 1.37(1.04–1.80) | 0.03 |  |
| Neurological complications        |               |                               |             |        |              |        |  |
| Hydrocephalus                     | 65(17.2)      | 520(9.9)                      | 1.90(1.43–2.52) | <0.001 | 1.30(0.91–1.86) | 0.15 |  |
| Re-bleeding                       | 23(6.1)       | 185(3.5)                      | 1.72(1.24–2.39) | 0.001 | 1.08(0.68–1.73) | 0.73 |  |
| DNIDs                             | 74(19.6)      | 989(18.8)                     | 1.06(0.81–1.37) | 0.68 | 0.91(0.65–1.26) | 0.56 |  |
| Seizures                          | 21(5.6)       | 169(3.2)                      | 1.78(1.12–2.84) | 0.02 | 1.05(1.04–4.04) | 0.04 |  |
| Infection complications           |               |                               |             |        |              |        |  |
| Pneumonia                         | 229(60.7)     | 1185(22.5)                    | 5.33(4.29–6.62) | <0.001 | 3.10(2.38–4.04) | <0.001 |  |
| Intracranial infection            | 69(18.3)      | 555(10.5)                     | 1.90(1.44–2.50) | <0.001 | 1.62(1.14–2.29) | 0.007 |  |
| Urinary tract infection           | 92(24.4)      | 744(14.1)                     | 1.96(1.53–2.51) | <0.001 | 1.59(1.16–2.20) | 0.004 |  |
| Bloodstream infection             | 24(6.4)       | 117(2.2)                      | 2.99(1.90–4.70) | <0.001 | 3.27(1.74–6.15) | <0.001 |  |
| Acute kidney injury               | 44(11.7)      | 241(4.6)                      | 2.76(1.96–3.87) | <0.001 | 1.05(0.64–1.74) | 0.84 |  |
| Length of hospital stay*          | 14(9–22)      | 19(9–16)                      | NA          | <0.001 | 13(9–21)      | 0.006 |  |

*day, median (IQR)

DNIDs: Delayed Neurological Ischemic Deficits

COPD: Chronic obstructive pulmonary disease
Before and after matching, COPD was associated with an increased risk in all infectious complications. Before matching, COPD was associated with several neurological complications (hydrocephalus [OR 1.90, 95% CI 1.43–2.52], re-bleeding [OR 1.72, 95% CI 1.24–2.39], and seizures [OR 1.78, 95% CI 1.12–2.84]). After matching, COPD was associated with an increased incidence of seizures, but not hydrocephalus and re-bleeding. After matching, the length of hospital stay was significantly longer in patients with COPD (p < 0.001).

The E-value obtained for the association between COPD and mortality after matching was 2.64 with a lower limit of 1.16, suggesting that unmeasured confounding was unlikely to explain the findings.

We further assessed interactions by other variables on COPD. There is no significant effect modification of the change in COPD and mortality on these variables (Fig. 2). Effect modification is present with Hunt & Hess grade (P for interaction = 0.002) in the analysis the association between COPD and pneumonia (Fig. 3).

**Discussion**

In this cohort study of patients with aSAH, we found that compared to patients without COPD, patients with COPD have increased odds of in-hospital death and poor functional outcome at discharge. Moreover, COPD is associated with an increased incidence of seizures and infectious complications, especially pneumonia, which may contribute to the increased mortality and poorer outcomes observed in aSAH patients with COPD.

**Mechanisms**

Several mechanisms may explain the association between COPD and poor outcomes. First, COPD causes spillover of multiple pro-inflammatory markers into the circulation, leading to chronic low-grade systemic inflammation, ultimately resulting in unstable plaque formation and prothrombotic events.[17] Second, COPD especially during exacerbation are hypoxemic and hypercapnic at baseline which may increase their susceptibility to brain injury. The intraneural hypoxemia can occur in approximately 40–50% of patients with mild COPD.[18] Third, COPD have associated comorbid conditions after stroke, such as seizure[19]. Fourth, COPD are commonly treated with corticosteroids, and hospitalized patients on corticosteroids have a heightened risk of nosocomial infection.

**Mortality**

Though COPD is known to be a risk for mortality in patients undergoing surgery and in the critically ill, there is a lack of scientific literature on COPD in patients with aSAH. The only study related to this topic assessed the association between mortality and COPD in stroke patients. In agreement with the current study, the previous study suggested that COPD was modestly associated with overall stroke mortality. In subgroup analysis of that study, the greater risks of mortality were seen in patients with intracerebral hemorrhage and patients with ischemic stroke, but not in patients with SAH (adjusted OR 0.98, 95% CI 0.85–1.13).[8] However, the previous study was limited by the epidemiologic study design that was unadjusted for important confounders (hemorrhage severity, smoking and any co-morbidity), which led to the uncertainty of their conclusions.

**Functional outcome**

This study found an association of COPD with poor functional outcome in patients with aSAH. While such an association has not been previously assessed in patients with aSAH, a study found that COPD increased the incidence of discharge to nursing homes and rehabilitation facilities after surgery[20], and another study found that the discharge
destination is a surrogate for mRS functional outcome in stroke survivors[21]. More research is needed to confirm the association of COPD with poor functional outcome in patients with aSAH.

Seizures

The association between seizures and COPD in patients were also found in patients with stroke from another study, where in a cohort of 237 patients with stroke, COPD was found to be a risk factor for seizures.[19] There are no reliable clinical guidelines for managing post-stroke seizures, and currently no evidence for prophylactic use in patients at risk of an epileptic episode as a complication from stroke[22]. The European Stroke Organization Guidelines do not support the prophylactic use of antiepileptic drugs (class IV, level C).[23] The American Heart Association/American Stroke Association Guidelines state that antiepileptic drugs may be considered in the immediate post-hemorrhagic period and for patients with known risk factors for delayed seizure disorder.[24] Our study provides evidence that COPD is a risk factor for seizures in patients with aSAH, suggesting that antiepileptic drugs may be considered in these patients.

Infection complications

In this study, COPD was associated with an increased frequency of a variety of infection complications. In a cohort study by Lee et al, COPD is an independent risk factor for pneumonia and septic shock after total shoulder arthroplasty.[25] Yakubek et al. published a study found that in patients undergoing total hip arthroplasty, patients with COPD are more likely to experience pneumonia and deep surgical site infection.[20]

Two large randomized clinical trials conducted in patients hospitalized for stroke found that prophylactic antibiotics did not reduce the incidence of pneumonia.[9, 10] A possible explanation for the lack of benefit is that the included patients have a general risk for pneumonia but not high risk, with 7–16% patients developing pneumonia in the control group. In the present study, half of the patients with COPD have pneumonia. The use of prophylactic antibiotics in patients with COPD may reduce the risk of progression to clinically overt pneumonia better than in general patients.

Strengths and limitations

One of the major strengths of our study is the high-quality, standardized, single-institution database, the large sample size, and the use of PSM to adjust for confounders. However, the limitations of this study must also be considered. First, pulmonary function testing was not recorded in our database, and long-term data were not available. This is a retrospective study, and thus data were not recorded for the aim of this study, limiting the strength of our conclusions. Moreover, recall bias may also be present because the medical history of a few cases with altered mental status were collected from their relatives.

Conclusions

In aSAH patients, COPD was associated with a significant increase in in-hospital mortality. COPD increased the risk of seizures and infectious complications, especially pneumonia. Since these complications can potentially be prevented by antibiotics and antiepileptic drugs, our findings are of clinical relevance and can open up new lines of inquiry.

Declarations

Author contributions:

Study concept and design: FF

Acquisition, analysis, or interpretation of data: XW, LP, YD, PW, HD, HF, YL, XC, YC
Statistical analysis: YZ and LL

Drafting of the manuscript: YZ and WC

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**Figures**

**Figure 1**

Flow diagram for selection of cohorts
Figure 1
Flow diagram for selection of cohorts
## Figure 2

Subgroup analysis of association between COPD and in-hospital mortality after propensity score matching.
## Figure 2

Subgroup analysis of association between COPD and in-hospital mortality after propensity score matching.
| Subgroup                  | COPD(N=289) | Non-COPD(n=1156) | Risk Ratio(95%CI) | P Value |
|--------------------------|-------------|------------------|-------------------|---------|
|                          | Event/Total | Event/Total      |                   |         |
| **Age**                  |             |                  |                   |         |
| >=65                     | 88/152(57.9)| 213/623(34.3)    | 1.69(1.42-2.01)   | 0.04    |
| <65                      | 76/137(55.5)| 131/535(24.5)    | 2.27(1.83-2.80)   |         |
| **Sex**                  |             |                  |                   | 0.63    |
| Male                     | 73/120(60.8)| 144/468(30.8)    | 1.85(1.54-2.22)   |         |
| Female                   | 91/169(53.8)| 200/688(29.1)    | 1.98(1.62-2.41)   |         |
| **Hypertension**         |             |                  |                   | 0.81    |
| Yes                      | 46/77(59.7)| 101/331(30.5)    | 1.96(1.53-2.50)   |         |
| No                       | 118/212(55.7)| 243/825(29.5)    | 1.89(1.61-2.22)   |         |
| **Diabetes**             |             |                  |                   | 0.73    |
| Yes                      | 14/24(58.3)| 30/91(33.0)      | 1.77(1.13-2.77)   |         |
| No                       | 150/265(56.6)| 314/1065(29.5)  | 1.92(1.67-2.21)   |         |
| **Coronary heart disease** |           |                  |                   | 0.84    |
| Yes                      | 8/11(72.7)| 17/47(36.2)      | 2.01(1.19-3.40)   |         |
| No                       | 156/278(56.1)| 327/1109(29.5)  | 1.90(1.66-2.19)   |         |
| **Chronic renal failure** |             |                  |                   | 0.33    |
| Yes                      | 3/3(100.0)| 4/6(66.7)        | 1.36(0.70-2.65)   |         |
| No                       | 161/280(55.3)| 340/1150(29.6)  | 1.90(1.66-2.18)   |         |
| **Smoking**              |             |                  |                   | 0.37    |
| Current                  | 38/67(56.7)| 77/244(31.6)     | 1.80(1.36-2.38)   |         |
| Ever                     | 11/15(73.3)| 23/82(28.0)      | 2.61(1.65-4.15)   |         |
| Never                    | 115/207(55.6)| 244/830(29.4)   | 1.89(1.61-2.22)   |         |
| **Alcohol abuse**        |             |                  |                   | 0.42    |
| Yes                      | 34/63(55.7)| 81/250(32.4)     | 1.72(1.29-2.99)   |         |
| No                       | 130/228(57.0)| 263/906(29.0)   | 1.96(1.69-2.29)   |         |
| **Aneurysmal location**  |             |                  |                   | 0.07    |
| Anterior circulation     | 132/240(55.0)| 265/965(27.5)   | 2.00(1.72-2.34)   |         |
| Posterior circulation    | 23/34(67.6)| 61/132(46.2)     | 1.46(1.09-1.97)   |         |
| **Hunt & Hess grade**    |             |                  |                   | 0.002   |
| I-III                    | 133/252(52.8)| 255/1008(25.3)  | 2.09(1.78-2.44)   |         |
| IV-V                     | 31/37(83.8)| 89/148(60.1)     | 1.39(1.15-1.69)   |         |
| **Fisher grade**         |             |                  |                   | 0.77    |
| I-II                     | 31/68(45.6)| 43/184(23.4)     | 1.95(1.35-2.82)   |         |
| III-IV                   | 101/158(63.9)| 233/670(34.8)   | 1.84(1.57-2.15)   |         |
| **Operation**            |             |                  |                   | 0.93    |
| Clipping                 | 117/196(59.7)| 248/808(30.7)   | 1.94(1.67-2.27)   |         |
| Coiling                  | 19/40(47.5)| 36/136(26.5)     | 1.79(1.17-2.76)   |         |
| No treatment             | 28/53(52.8)| 60/212(28.3)     | 1.87(1.34-2.60)   |         |

**Figure 3**

Subgroup analysis of association between COPD and Pneumonia after propensity score matching.
Figure 3

Subgroup analysis of association between COPD and Pneumonia after propensity score matching

Supplementary Files

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