Sex Differences in Ischemic Stroke Outcomes in Patients With Pulmonary Hypertension

Tiberiu A. Pana, MRes; Dana K. Dawson, DPhil; Mohamed O. Mohamed, MRCP (UK); Fiona Murray, PhD; David L. Fischman, MD; Michael P. Savage, MD; Mamas A. Mamas, DPhil; Phyo K. Myint, MD

BACKGROUND: The association between systemic hypertension and cerebrovascular disease is well documented. However, the impact of pulmonary hypertension (PH) on acute ischemic stroke outcomes is unknown despite PH being recognized as a risk factor for acute ischemic stroke. We aimed to determine the association between PH and adverse in-hospital outcomes after acute ischemic stroke, as well as whether there are sex differences in this association.

METHODS AND RESULTS: Acute ischemic stroke admissions from the US National Inpatient Sample between October 2015 and December 2017 were included. The relationship between PH and outcomes (mortality, prolonged hospitalization >4 days, and routine home discharge) was analyzed using logistic regressions adjusting for demographics, comorbidities, and revascularization therapies. Interaction terms between PH and sex and age groups were also included. A total of 221,249 records representative of 1,106,045 admissions were included; 2.9% of patients had comorbid PH, and 35.34% of those were male. PH was not associated with in-hospital mortality (odds ratio [OR], 0.96; 95% CI, 0.86–1.09) but was associated with increased odds of prolonged hospitalization (OR, 1.15; 95% CI, 1.09–1.22) and decreased odds of routine discharge (OR, 0.87; 95% CI, 0.81–0.94) for both sexes. Older patients with PH were significantly less likely to be discharged routinely (P=0.028) than their younger counterparts. Compared with female patients with PH, men were 31% more likely to die in hospital (P=0.024).

CONCLUSIONS: PH was not significantly associated with in-hospital mortality but was associated with prolonged hospitalization and adverse discharge status. Male patients with PH were more likely to die in hospital than female patients.

Key Words: hospitalization ■ outcomes ■ pulmonary hypertension ■ stroke

Pulmonary hypertension (PH) is a disorder affecting the pulmonary vascular bed and is characterized by increased mean pulmonary arterial pressure (>20 mm Hg), as confirmed by right heart catheterization.1 PH is a heterogenous clinical entity and may be classified into 5 categories based on pathophysiology, clinical features, hemodynamic features, and management.1 The epidemiology of PH is similarly heterogeneous and varies among different clinical PH classes.2 While pulmonary arterial hypertension (PAH – group 1 PH) is a relatively uncommon disease, with an estimated prevalence between 5 and 52 per million,2,3 PH secondary to pulmonary disease or left heart disease (groups 2 and 3) is much more common.4–7 Furthermore, there are important sex differences in the epidemiology of PH: While female patients are more likely to develop the disease, male patients are more likely to have poorer outcomes.8,9

PH is associated with incident acute ischemic stroke (AIS),10 with comorbidities such as atrial fibrillation (AF) and cerebral venous congestion acting as likely mediators.10 In addition, endothelial dysfunction and decreased nitric oxide synthesis may also act as contributing pathophysiological processes,
given their involvement in the pathogenesis of both stroke\textsuperscript{11,12} and PH.\textsuperscript{13} This suggests an increased stroke burden among patients with PH than in the general population. Furthermore, given that PH may cause right ventricular failure\textsuperscript{14} and decreased cardiac functional reserve\textsuperscript{15} and may thus render patients more susceptible to the hemodynamic instability and cardiac complications associated with acute stroke,\textsuperscript{16,17} it may be associated with worse AIS outcomes. Nevertheless, there are no studies evaluating the impact of PH on AIS outcomes. This relationship is important, given that patients with PH not only have a higher stroke incidence than the general population but may also be more vulnerable to acute stroke complications. The identification of such relationships would not only alert clinicians treating patients with AIS with coexisting PH but also lead to further research efforts aiming to reduce the burden of stroke and stroke-related mortality among patients with PH. Furthermore, it also remains unknown whether any sex differences exist in the acute ischemic stroke outcomes of patients with PH.

In this study, we aimed to determine the association between PH and AIS in-hospital outcomes (mortality, length of hospitalization and routine home discharge) as well as to determine whether any sex differences exist. Furthermore, given that the etiology and prognosis of pulmonary hypertension also varies with age,\textsuperscript{8,18} we also aimed to determine whether any differences in the association between PH and AIS outcomes exist between different age groups.

METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki (1975) and later amendments. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source and Inclusion Criteria

The National Inpatient Sample (NIS) is a large publicly available database containing >7 million annual hospital admission records in the United States. The NIS contains admission records representing a 20% stratified sample of all community hospital admissions in the United States in a given time frame. Using the provided sampling weights, the NIS data can be used to provide national estimates for the sampling population, representative of ~95% of the US population.\textsuperscript{19,20} Before undertaking this project, all authors completed the online Healthcare Cost and Utilization Project Data Use Agreement Training Tool. All authors also read and signed the Data Use Agreement for Nationwide Databases. As the NIS is a publicly available database with no patient identifiable information, no ethical approval was needed. Using data files containing annual admissions between 2015 and 2017, all records with a primary diagnosis of ischemic stroke (International Classification of Diseases, Tenth Revision [ICD-10] codes I63.0-I63.9) were extracted. Only cases admitted between October 2015 and December 2017 were included because of a change in the sampling method of the NIS.
in comorbidity coding (International Classification of Diseases, Ninth Revision [ICD-9] to ICD-10) occurring after September 2015.20

Figure 1 details the study population. Of 230,177 records extracted from the NIS with a primary diagnosis of ischemic stroke admitted between October 2015 and December 2017, a total of 8708 elective admission records as well as 220 records with missing data were excluded, yielding a total of 221,249 included records. Elective admissions were excluded to ensure that only admissions that were triggered by the acute stroke event were included. After the application of sampling weights and the exclusion of strata with single sampling units, the included records were used to provide estimates for the population from which they were sampled: 1,106,045 patients admitted with a primary diagnosis of AIS.

Statistical Analysis
All analyses were performed using Stata 15.1SE (StataCorp, College Station, TX). A 5% threshold of statistical significance was used for all analyses (P<0.05). All analyses were performed according to Healthcare Cost and Utilization Project guidelines, using the provided discharge weights as probability weights and survey data analysis techniques stratifying by NIS stratum and year of admission to account for patient clustering within hospitals and produce US-wide estimates.23

Outcomes
The following outcomes were analyzed: (1) in-hospital mortality, (2) prolonged hospital stay in excess of 4 days, and (3) routine discharge from the hospital. Vital status upon hospital discharge (dead/alive) and the length of stay (LOS) in the hospital are provided as standard variables in the NIS.24,25 Prolonged hospitalization was defined as LOS >4 days, according to expert clinical opinion and previous studies assessing ischemic stroke outcomes among patients admitted to the hospital in the United States.26 A dichotomous variable indicating patients hospitalized for >4 days was subsequently used as an outcome for LOS analyses. Discharge status was coded using the provided discharge destination.27 All records of patients who were discharged against medical advice and those discharged to an unknown destination were excluded from the analyses before weighting (n=2,187; 0.99%), allowing estimates for this particular outcome to be provided for 1,095,110 (99.01%) of patients with AIS. Discharge destination was then dichotomized into routine discharges and other discharges (“home health care,” “short-term hospital,” “other facilities including intermediate care and skilled nursing home,” and “died in hospital”). The “other discharges” category was subsequently used as a reference category in all analyses evaluating discharge destination.

Exposure and Confounders
Comorbid PH was the exposure of interest. All models were adjusted for the following confounders: age, sex, ethnicity, Elixhauser comorbidities (congestive heart failure, valvular disease, peripheral vascular disease, paralysis, other neurological disorders, chronic pulmonary disease, diabetes mellitus, hypothyroidism, renal failure, liver disease, peptic ulcer disease, acquired immune deficiency syndrome, lymphoma, metastatic cancer, solid tumour without metastasis, rheumatoid arthritis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, anemia, alcohol abuse, drug abuse, psychosis, depression, and hypertension), other comorbidities (dyslipidemia, smoking, coronary heart disease, all-cause bleeding, deep venous thrombosis/pulmonary embolism, pericarditis, infectious endocarditis, atrial fibrillation, pneumonia [including aspiration], chronic lung disease, shock, family history of cerebrovascular disease, family history of heart disease, previous cerebrovascular disease), hospital location and teaching status, and revascularization therapy (thrombolysis, thrombectomy). Adjusting covariates were selected on the basis of clinical judgment and previous literature assessing the relationship between cardiovascular comorbidities and acute AIS outcomes.28–32

Diagnoses of PH and comorbid conditions were identified using ICD-10 codes (Table S1) and represent
diagnoses assigned before or during the index acute ischemic stroke hospitalization. Elixhauser comorbidities were determined using the Healthcare Cost and Utilization Project Elixhauser comorbidity software. To gain insight into the distribution of likely etiologies of PH in the included samples, combinations of ICD-10 codes were employed to approximate the World Health Organization classification of PH.

Descriptive Statistics
Patient characteristics were compared between patients with and without PH as well as between male and female patients with PH. Independent-sample t-test and Pearson’s chi-squared test were employed to compare patient characteristics for continuous and categorical variables, respectively.

Association Between Pulmonary Hypertension and In-Hospital Outcomes
Logistic regressions were employed to model the relationship between prevalent PH and all in-hospital outcomes and were adjusted for the confounders listed above. Interaction terms with sex and age were assessed to determine sex or age differences. Multivariable logistic regressions modeling the relationship between PH and in-hospital post-AIS outcomes were also performed separately for the different sex and age strata (<40 years, 40–50 years, 50–60 years, 60–70 years, 70–80 years, > 80 years).

Further stratified analyses were performed to determine the potential interactions between the relationship between PH and AIS outcomes and potential/likely prestroke treatment with lipid-lowering and anticoagulant agents. Despite the fact that the NIS does not record patient medication data, preexisting dyslipidemia/atherosclerotic vascular disease and AF were used as surrogates for likely pretreatment with lipid-lowering and anticoagulant agents, respectively, assuming compliance with contemporary primary and secondary cardiovascular prevention guidelines. Atherosclerotic vascular disease was defined as a composite of coronary heart disease, peripheral vascular disease, and previous stroke/transient ischemic attack.

Sensitivity LOS Analyses
Sensitivity analyses were also undertaken for this outcome only including patients surviving to hospital discharge to ascertain potential biases introduced in the main analyses by censoring due to deaths occurring before hospital discharge. The same analytic strategies were employed as in the main analysis.

RESULTS

Descriptive Statistics
Table 1 details the patient characteristics on admission, stratified by the presence or absence of PH. In a total sample of 1,106,045 included patients, the median (interquartile range) age was 72 (61–82) years, and there were 557,595 (50.41%) women. The recorded median (interquartile range) LOS was 3 (2–6) days. There were 31,830 (2.88%) patients with PH. Compared with patients without PH, those with PH were significantly older (median age, 71 and 80 years, respectively), and there was a higher proportion of women (49.99% versus 64.66%, respectively). Patients with PH also spent a significantly longer time in the hospital and were significantly more likely to suffer from cardiovascular, pulmonary, and other comorbidities compared with those without PH. Compared with patients without PH, those with PH were more likely to have coexisting AF (24.58% versus 56.83%, respectively). A total of 103,600 (9.37%) and 34,420 (3.11%) patients underwent intravenous thrombolysis and endovascular thrombectomy, respectively. Patients with PH were also more likely to receive revascularization therapies compared with those without: intravenous thrombolysis (11.26% versus 9.31%) and endovascular thrombectomy (5.17% versus 3.05%). Compared with patients without PH, those with PH had a significantly higher proportion of in-hospital mortality (3.86% versus 6.52%), prolonged hospitalization in excess of 4 days (33.99% versus 48.71%), and a significantly lower proportion of routine home discharges (37.54% versus 21.83%).

Figure 2 details the distribution of the likely underlying etiology of pulmonary hypertension in the included sample. Of 31,830 patients with AIS with PH, there were 155 (0.49%) patients with PAH, 17,210 (54.07%) patients with PH and coexisting left heart disease, 5370 (16.87%) patients with PH and coexisting left heart disease and chronic lung disease, 1825 (5.73%) patients with PH and chronic lung disease, 550 (1.73%) patients with chronic thromboembolic PH, and 6720 (21.11%) patients with PH with likely other etiologies compared with those without PH. Compared with patients without PH, those with PH were more likely to have coexisting AF (24.58% versus 56.83%, respectively). A total of 103,600 (9.37%) and 34,420 (3.11%) patients underwent intravenous thrombolysis and endovascular thrombectomy, respectively. Patients with PH were also more likely to receive revascularization therapies compared with those without: intravenous thrombolysis (11.26% versus 9.31%) and endovascular thrombectomy (5.17% versus 3.05%). Compared with patients without PH, those with PH had a significantly higher proportion of in-hospital mortality (3.86% versus 6.52%), prolonged hospitalization in excess of 4 days (33.99% versus 48.71%), and a significantly lower proportion of routine home discharges (37.54% versus 21.83%).

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Table 2 details the characteristics on admission of patients with PH, stratified by sex. Of a total of 31,830 patients with PH with stroke, 11,250 (35.34%) were men. Compared with women, men were significantly younger (median age (interquartile range), 76 (66–85) years and 82 (72–88) years for men and women, respectively; P <0.001). Men were more likely to have comorbid congestive heart failure, peripheral vascular disease, diabetes mellitus, renal failure, and liver disease. Conversely, women were more likely to have comorbid AF, coronary heart disease, hypothyroidism,
### Table 1. Patient Characteristics on Admission, Stratified by Comorbid Pulmonary Hypertension

|                                | All                  | No Pulmonary Hypertension | Pulmonary Hypertension | P Value  |
|--------------------------------|----------------------|---------------------------|------------------------|----------|
| **N**                          | 1,106,045            | 1,074,215                 | 31,830                 |          |
| **Age, y, median (IQR)**       | 72.00 (61.00–82.00)  | 71.00 (60.00–82.00)       | 80.00 (69.00–87.00)    | <0.001†  |
| **Length of stay, d, median (IQR)** | 3.00 (2.00–6.00)   | 3.00 (2.00–6.00)          | 4.00 (3.00–7.00)       | <0.001†  |
| **Sex**                        |                      |                           |                        |          |
| Female, n (%)                  | 557,595 (50.41)      | 537,015 (49.99)           | 20,580 (64.66)         | <0.001†  |
| **Race/Ethnicity, n (%)**      |                      |                           |                        |          |
| White                          | 735,330 (66.48)      | 713,675 (66.44)           | 21,655 (68.03)         | <0.001†  |
| Black                          | 183,090 (16.55)      | 177,555 (16.53)           | 5,535 (17.39)          |          |
| Hispanic                       | 84,950 (7.68)        | 83,225 (7.75)             | 1,725 (5.42)           |          |
| Asian or Pacific Islander      | 31,635 (2.86)        | 30,825 (2.87)             | 810 (2.54)             |          |
| Native American                | 4700 (0.42)          | 4590 (0.43)               | 110 (0.35)             |          |
| Other                          | 27,460 (2.48)        | 26,805 (2.50)             | 655 (2.06)             |          |
| **Year of admission, n (%)**   |                      |                           |                        |          |
| 2015                           | 112,000 (10.13)      | 108,485 (10.10)           | 3,515 (11.04)          | <0.001†  |
| 2016                           | 488,005 (44.12)      | 472,110 (43.95)           | 15,895 (49.94)         |          |
| 2017                           | 506,040 (45.75)      | 493,620 (45.95)           | 12,420 (39.02)         |          |
| **Elixhauser comorbidities, n (%)** |                  |                           |                        |          |
| Congestive heart failure       | 172,170 (15.57)      | 157,020 (14.62)           | 15,150 (47.60)         | <0.001†  |
| Valvular disease               | 110,540 (9.99)       | 97,195 (9.05)             | 13,345 (41.93)         | <0.001†  |
| Pulmonary circulation disease  | 84,860 (0.76)        | 65,255 (0.61)             | 19,355 (6.08)          | <0.001†  |
| Peripheral vascular disease    | 112,065 (10.13)      | 107,395 (10.00)           | 4,670 (14.67)          | <0.001†  |
| Paralysis                      | 112,895 (10.21)      | 108,455 (10.10)           | 4,440 (13.95)          | <0.001†  |
| Other neurological disorders   | 6620 (0.60)          | 6,250 (0.58)              | 370 (1.16)             | <0.001†  |
| Chronic pulmonary disease      | 174,180 (15.75)      | 165,835 (15.44)           | 8,345 (26.22)          | <0.001†  |
| Diabetes mellitus (without chronic complications) | 210,220 (19.01) | 204,970 (19.08) | 5,250 (16.49) | <0.001† |
| Diabetes mellitus (with chronic complications) | 214,400 (19.38) | 207,960 (19.36) | 6,440 (20.23) | 0.091   |
| Hypothyroidism                 | 159,160 (14.39)      | 153,230 (14.26)           | 5,930 (18.63)          | <0.001†  |
| Renal failure                  | 181,950 (16.45)      | 172,590 (16.07)           | 9,360 (29.41)          | <0.001†  |
| Liver disease                  | 18,310 (1.66)        | 17,545 (1.63)             | 765 (2.40)             | <0.001†  |
| Peptic ulcer disease           | 7695 (0.70)          | 7,370 (0.69)              | 325 (1.02)             | 0.001†   |
| AIDS                           | 2395 (0.22)          | 2,335 (0.22)              | 60 (0.19)              | 0.647    |
| Lymphoma                       | 5315 (0.48)          | 5,095 (0.47)              | 220 (0.69)             | 0.013†   |
| Metastatic cancer              | 17,955 (1.62)        | 17,405 (1.62)             | 550 (1.73)             | 0.498    |
| Solid tumor without metastasis | 19,670 (1.78)        | 18,965 (1.77)             | 705 (2.1)              | 0.006†   |
| Rheumatoid arthritis/collagen vascular disease | 30,150 (2.73) | 28,755 (2.68) | 1,395 (4.38) | <0.001† |
| Coagulopathy                   | 41,405 (3.74)        | 39,300 (3.66)             | 2,105 (6.61)           | <0.001†  |
| Obesity                        | 145,465 (13.15)      | 140,800 (13.11)           | 4,665 (14.66)          | <0.001†  |
| Weight loss                    | 44,030 (3.98)        | 41,720 (3.88)             | 2,310 (7.26)           | <0.001†  |
| Fluid and electrolyte disorders | 246,680 (22.30)   | 236,775 (22.04)           | 9,905 (31.12)          | <0.001†  |
| Anemia (chronic blood loss)    | 4025 (0.36)          | 3775 (0.35)               | 250 (0.79)             | <0.001†  |
| Anemia (deficiency)            | 133,005 (12.03)      | 125,880 (11.72)           | 7,215 (22.38)          | <0.001†  |
| Alcohol abuse                  | 49,375 (4.46)        | 48,415 (4.51)             | 960 (3.02)             | <0.001†  |
| Drug abuse                     | 28,985 (2.62)        | 28,385 (2.64)             | 600 (1.89)             | <0.001†  |
| Psychoses                      | 26,255 (2.37)        | 25,745 (2.40)             | 510 (1.60)             | <0.001†  |
| Depression                     | 124,635 (11.27)      | 120,880 (11.25)           | 3,755 (11.80)          | 0.179    |
| Hypertension                   | 946,140 (85.54)      | 917,875 (85.45)           | 28,265 (88.80)         | <0.001†  |

(Continued)
Table 1. Continued

| Other comorbidities, n (%)          | All     | No Pulmonary Hypertension | Pulmonary Hypertension | P Value |
|-------------------------------------|---------|---------------------------|------------------------|---------|
| Atrial fibrillation                 | 282 175 (25.51) | 264 085 (24.58) | 18 090 (56.83) | <0.001† |
| Sepsis                              | 16 400 (1.48) | 15 730 (1.46) | 700 (2.10) | <0.001† |
| Dyslipidemia                        | 640 010 (57.86) | 621 995 (57.90) | 18 015 (56.60) | 0.038† |
| Dementia                            | 131 650 (1.19) | 126 515 (1.17) | 5135 (16.13) | <0.001† |
| Smoking                             | 203 440 (18.39) | 200 240 (18.64) | 3200 (10.05) | <0.001† |
| Parkinson disease                   | 15 795 (1.43) | 15 340 (1.43) | 455 (1.43) | 0.992 |
| Transient ischemic attack           | 8070 (0.73) | 7875 (0.73) | 195 (0.61) | 0.262 |
| Rheumatic heart disease             | 32 355 (2.93) | 25 415 (2.37) | 6940 (21.80) | <0.001† |
| Coronary heart disease              | 314 870 (28.47) | 301 100 (28.03) | 13 770 (43.26) | <0.001† |
| All-cause bleeding                  | 79 995 (7.23) | 76 540 (7.13) | 3455 (10.85) | <0.001† |
| Pulmonary embolism                  | 7000 (0.63) | 6435 (0.60) | 565 (1.78) | <0.001† |
| Congenital heart disease            | 33 495 (3.03) | 32 390 (3.02) | 1105 (3.47) | 0.040† |
| Pericarditis                        | 105 (0.01) | 90 (0.01) | 15 (0.05) | 0.002† |
| Infectious endocarditis             | 2310 (0.21) | 2175 (0.20) | 135 (0.42) | <0.001† |
| Deep venous thrombosis              | 14 845 (1.34) | 14 025 (1.31) | 820 (2.58) | <0.001† |
| Pneumonia                           | 29 905 (2.70) | 28 205 (2.63) | 1700 (5.34) | <0.001† |
| Chronic lung disease                | 136 505 (12.34) | 129 120 (12.02) | 7385 (23.20) | <0.001† |
| Chronic obstructive pulmonary disease| 126 505 (11.44) | 119 775 (11.15) | 6730 (21.14) | <0.001† |
| Shock                               | 5070 (0.46) | 4695 (0.44) | 375 (1.18) | <0.001† |
| Family history of cerebrovascular disease | 42 725 (3.86) | 41 760 (3.89) | 965 (3.03) | 0.001† |
| Family history of heart disease     | 640 00 (5.79) | 62 265 (5.80) | 1735 (5.45) | 0.249 |
| Previous cerebrovascular disease    | 172 600 (15.61) | 167 715 (15.61) | 4885 (15.35) | 0.569 |

Outcomes, n (%)

| In-hospital mortality | 43 545 (3.94) | 41 470 (3.86) | 2075 (6.52) | <0.001† |
| Length of stay >4 days | 380 605 (34.41) | 365 100 (33.99) | 15 505 (48.71) | <0.001† |
| Routine discharge      | 394 105 (37.10) | 387 610 (37.54) | 6495 (21.83) | <0.001† |

Other characteristics, n (%)

| Hospital bed size          | Small    | Medium   | Large    | P Value |
|----------------------------|----------|----------|----------|---------|
| Small                      | 174 745 (15.80) | 169 930 (15.82) | 4815 (15.13) | 0.236 |
| Medium                     | 324 895 (29.37) | 315 720 (29.39) | 9175 (28.82) | 0.032† |
| Large                      | 606 405 (54.83) | 588 565 (54.79) | 17 840 (56.05) | 0.032† |

| Location/teaching status of hospital | Rural | Urban nonteaching | Urban teaching | P Value |
|-------------------------------------|-------|-------------------|----------------|---------|
| Rural                               | 82 535 (7.46) | 80 480 (7.49) | 2055 (6.46) | 0.032† |
| Urban nonteaching                   | 266 440 (24.09) | 258 660 (24.08) | 7780 (24.44) | 0.032† |
| Urban teaching                      | 757 070 (68.45) | 735 075 (68.43) | 21 995 (69.10) | 0.032† |

Region of hospital

| Region of hospital | Northeast | Midwest | South | West | P Value |
|--------------------|-----------|---------|-------|------|---------|
| Northeast          | 198 830 (17.98) | 193 045 (17.97) | 5785 (18.17) | <0.001† |
| Midwest            | 238 555 (21.57) | 231 020 (21.51) | 7535 (23.67) | <0.001† |
| South              | 481 280 (41.71) | 449 410 (41.84) | 11 870 (37.29) | <0.001† |
| West               | 207 380 (18.75) | 200 740 (18.69) | 6840 (20.86) | <0.001† |

All Patient Refined Diagnosis Related Group: Severity of illness subclass

| Minor loss of function | 89 400 (8.08) | 89 400 (8.32) | <11† |
| Moderate loss of function | 541 350 (48.94) | 533 440 (49.66) | 7910 (24.85) |
| Major loss of function | 365 580 (33.05) | 347 890 (32.39) | 17 690 (55.58) |
| Extreme loss of function | 109 715 (9.92) | 103 485 (9.63) | 6230 (19.57) |

(Continued)
rheumatoid arthritis, and depression. There were no statistically significant sex differences in rates of intravenous thrombolysis and endovascular thrombectomy among patients with PH. There were also no statistically significant sex differences in the proportion of patients with PH dying in the hospital (7.20% and 6.15% for men and women, respectively) or undergoing prolonged hospitalization (48.76% and 48.69% for men and women, respectively). Nevertheless, significantly fewer female patients with PH were discharged routinely than male patients with PH (17.66% and 25.76%, respectively).

Tables S3 and S4 detail the patient characteristics on admission, stratified by age group as well as PH. Regardless of age group, patients with coexisting PH had significantly longer LOS than those without PH. Nevertheless, the relative difference between patients with and without PH decreased with advancing age, as the LOS of patients with PH decreased while that of patients without PH increased. Patients with PH >50 years old, but not those <50 years old, were significantly more likely to be women. The female-to-male difference among patients with PH increased with increasing age.

### Association Between PH and In-Hospital Outcomes

Figure 3 and Table 3 detail the results of the logistic regressions assessing the association between PH and post-AIS in-hospital outcomes. Figure 4 provides a visual summary of the main study findings. The overall regression results of the association between PH and outcomes were derived from models not containing any interaction terms.

There was no association between PH and in-hospital mortality (odds ratio [OR], 1.02; 95% CI, 0.91–1.15). However, there was a significant sex interaction (OR, 0.76; 95% CI, 0.60–0.97; \(P=0.024\)). PH was associated with a nonsignificant 15% increase in the odds of in-hospital mortality among men (OR, 1.15; 95% CI, 0.95–1.38) but not among women (OR, 0.88; 95% CI, 0.75–1.02). There were no significant interactions with age.

PH was significantly associated with prolonged LOS >4 days (OR, 1.15; 95% CI, 1.09–1.22). There were no significant interactions with sex or age for this outcome.

PH was also significantly associated with decreased odds of routine home discharge (OR, 0.85; 95% CI, 0.79–0.91). There were no significant interactions with sex for this outcome. Nevertheless, there was a significant age interaction (\(P=0.028\)). Older patients were less likely to be discharged home, therefore requiring further rehabilitation or institutionalization after discharge: (OR for interaction term between PH and 10-year increase in age, 0.94; 95% CI, 0.89–0.993).

Table 3 also details the interaction terms with pre-existing dyslipidemia/atherosclerotic vascular disease
### Table 2. Patient Characteristics on Admission for Patients With Comorbid Pulmonary Hypertension, Stratified by Sex

|                                | All (Pulmonary Hypertension) | Male                  | Female                 | P Value   |
|--------------------------------|------------------------------|-----------------------|------------------------|-----------|
| N                              | 31,830                       | 11,250                | 20,580                 |           |
| Age, y, median (IQR)           | 80.00 (69.00–87.00)          | 76.00 (66.00–85.00)   | 82.00 (72.00–88.00)    | <0.001†  |
| Length of stay, d, median (IQR)| 4.00 (3.00–7.00)             | 4.00 (3.00–8.00)      | 4.00 (3.00–7.00)       | 0.547     |

Race/Ethnicity, n (%)

|                                          | All (Pulmonary Hypertension) | Male                  | Female                 | P Value   |
|------------------------------------------|------------------------------|-----------------------|------------------------|-----------|
| White                                    | 21,655 (68.03)               | 7645 (67.96)          | 14,010 (68.08)         | 0.640     |
| Black                                    | 5,535 (17.39)                | 1,860 (16.53)         | 3,675 (17.86)          |           |
| Hispanic                                 | 1,725 (5.42)                 | 660 (5.87)            | 1,065 (5.17)           |           |
| Asian or Pacific Islander                | 810 (2.54)                   | 305 (2.71)            | 505 (2.45)             |           |
| Native American                          | 110 (0.35)                   | 45 (0.40)             | 65 (0.32)              |           |
| Other                                    | 655 (2.06)                   | 225 (2.00)            | 430 (2.09)             |           |
| Missing                                  | 1,340 (4.21)                 | 510 (4.53)            | 830 (4.03)             |           |

Year of admission, n (%)

|                          | All (Pulmonary Hypertension) | Male                  | Female                 | P Value   |
|--------------------------|------------------------------|-----------------------|------------------------|-----------|
| 2015                     | 3,515 (11.04)                | 1,315 (11.69)         | 2,200 (10.69)          | 0.016†    |
| 2016                     | 15,895 (49.94)               | 5,345 (47.51)         | 10,550 (51.26)         |           |
| 2017                     | 12,420 (39.02)               | 4,590 (40.83)         | 7,830 (38.05)          |           |

Elixhauser comorbidities, n (%)

|                                                    | All (Pulmonary Hypertension) | Male                  | Female                 | P Value   |
|-----------------------------------------------------|------------------------------|-----------------------|------------------------|-----------|
| Congestive heart failure                            | 1,515 (47.60)                | 567 (50.40)           | 948 (46.06)            | 0.001†    |
| Valvular disease                                    | 13,345 (41.93)               | 4,585 (40.76)         | 8,760 (42.57)          | 0.159     |
| Pulmonary circulation disease                       | 1,935 (6.08)                 | 695 (6.18)            | 1,240 (6.03)           | 0.816     |
| Peripheral vascular disease                         | 4,670 (14.67)                | 1,870 (16.62)         | 2,800 (13.61)          | 0.001†    |
| Paralysis                                           | 4,440 (13.95)                | 1,505 (13.38)         | 2,935 (14.26)          | 0.333     |
| Other neurological disorders                        | 370 (1.16)                   | 135 (1.20)            | 235 (1.14)             | 0.836     |
| Chronic pulmonary disease                           | 8,345 (26.22)                | 2,870 (25.51)         | 5,475 (26.60)          | 0.344     |
| Diabetes mellitus (without chronic complications)   | 5,250 (16.49)                | 1,830 (16.27)         | 3,420 (16.62)          | 0.721     |
| Diabetes mellitus (with chronic complications)      | 6,440 (20.23)                | 2,485 (22.09)         | 3,955 (19.22)          | 0.007†    |
| Hypothyroidism                                      | 5,930 (18.63)                | 1,105 (9.82)          | 4,825 (23.45)          | <0.001†   |
| Renal failure                                       | 9,360 (29.41)                | 3,595 (31.96)         | 5,765 (28.01)          | 0.001†    |
| Liver disease                                       | 765 (2.40)                   | 365 (3.24)            | 400 (1.94)             | 0.001†    |
| Peptic ulcer disease                                | 325 (1.02)                   | 125 (1.11)            | 200 (0.97)             | 0.598     |
| Lymphoma                                            | 220 (0.69)                   | 100 (0.89)            | 120 (0.58)             | 0.160     |
| Metastatic cancer                                   | 550 (1.73)                   | 185 (1.64)            | 365 (1.77)             | 0.709     |
| Solid tumor without metastasis                      | 705 (2.21)                   | 300 (2.67)            | 405 (1.97)             | 0.072     |
| Rheumatoid arthritis/collagen vascular disease      | 1,395 (4.38)                 | 255 (2.27)            | 1,140 (5.54)           | <0.001†   |
| Coagulopathy                                        | 2,105 (6.61)                 | 1,020 (9.07)          | 1,085 (6.27)           | <0.001†   |
| Obesity                                              | 4,665 (14.66)                | 1,645 (14.62)         | 3,020 (14.67)          | 0.953     |
| Weight loss                                          | 2,310 (7.26)                 | 735 (6.53)            | 1,575 (7.65)           | 0.103     |
| Fluid and electrolyte disorders                     | 9,905 (31.12)                | 3,340 (29.69)         | 6,565 (31.90)          | 0.069     |
| Anemia (chronic blood loss)                         | 250 (0.79)                   | 80 (0.71)             | 170 (0.83)             | 0.620     |
| Anemia (deficiency)                                 | 7,125 (22.38)                | 2,475 (22.00)         | 4,650 (22.59)          | 0.593     |
| Alcohol abuse                                       | 960 (3.02)                   | 655 (5.82)            | 305 (1.48)             | <0.001†   |
| Drug abuse                                           | 600 (1.89)                   | 325 (2.89)            | 275 (1.34)             | <0.001†   |
| Psychoses                                           | 510 (1.60)                   | 175 (1.56)            | 335 (1.63)             | 0.827     |
| Depression                                          | 3,755 (11.80)                | 1,070 (9.51)          | 2,685 (13.05)          | <0.001†   |
| Hypertension                                        | 28,285 (88.80)               | 9,950 (88.44)         | 18,315 (88.99)         | 0.517     |

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| Other comorbidities, n (%) | All (Pulmonary Hypertension) | Male | Female | P Value |
|---------------------------|-----------------------------|------|--------|---------|
| Atrial fibrillation       | 18 090 (56.83)              | 6180 (54.93) | 11 910 (57.87) | 0.022† |
| Sepsis                    | 670 (2.10)                  | 265 (2.36)  | 405 (1.97)  | 0.287  |
| Dyslipidemia              | 18 015 (56.60)              | 6305 (56.04) | 11 710 (56.90) | 0.516  |
| Dementia                  | 5135 (16.13)                | 1320 (11.73) | 3815 (18.54)  | <0.001†|
| Smoking                   | 3200 (10.05)                | 1565 (13.91) | 1635 (7.94)   | <0.001†|
| Parkinson disease         | 455 (1.43)                  | 220 (1.96)   | 235 (1.14)   | 0.010† |
| Transient ischemic attack | 195 (0.61)                  | 75 (0.67)    | 120 (0.58)   | 0.684  |
| Rheumatic heart disease   | 6940 (21.80)                | 2395 (20.40) | 4645 (22.57)  | 0.046† |
| Coronary heart disease    | 13 770 (43.26)              | 5820 (51.73) | 7950 (38.63)  | <0.001†|
| All-cause bleeding        | 3455 (10.85)                | 1295 (11.51) | 2160 (10.50)  | 0.192  |
| Pulmonary embolism        | 565 (1.78)                  | 180 (1.60)   | 385 (1.87)   | 0.431  |
| Congenital heart disease  | 1105 (3.47)                 | 360 (3.20)   | 745 (3.62)   | 0.388  |
| Pericarditis              | 15 (0.05)                   | <11*        | <11*        | 0.942  |
| Infectious endocarditis   | 135 (0.42)                  | 60 (0.53)    | 75 (0.36)    | 0.321  |
| Deep venous thrombosis    | 820 (2.58)                  | 335 (2.98)   | 485 (2.36)   | 0.142  |
| Pneumonia                 | 1700 (5.34)                 | 745 (6.62)   | 955 (4.64)   | 0.001† |
| Chronic lung disease      | 7385 (23.20)                | 2650 (23.56) | 4735 (23.01)  | 0.627  |
| Chronic obstructive pulmonary disease | 6730 (21.14) | 2400 (21.33) | 4330 (21.04)  | 0.786  |
| Shock                     | 375 (1.18)                  | 215 (1.91)   | 160 (0.78)   | <0.001†|
| Family history of cerebrovascular disease | 965 (3.03) | 340 (3.02) | 625 (3.04) | 0.974 |
| Family history of heart disease | 1735 (5.45) | 600 (5.33) | 1135 (5.52) | 0.755 |
| Previous cerebrovascular disease | 4885 (15.35) | 1580 (14.04) | 3305 (16.06) | 0.030† |

**Outcomes, n (%)**

| In-hospital mortality       | 2075 (6.52) | 810 (7.20) | 1265 (6.15) | 0.097  |
| Length of stay >4 days      | 15 505 (48.71) | 5485 (48.76) | 10 020 (48.69) | 0.958  |
| Routine discharge           | 6495 (20.51) | 2875 (25.76) | 3620 (17.66) | <0.001†|

| Other characteristics, n (%) |      |      |       |       |
|-----------------------------|------|------|-------|-------|
| Hospital bed size, n (%)     |      |      |       |       |
| Small                       | 4815 (15.13) | 1590 (14.13) | 3225 (15.67) | 0.058  |
| Medium                      | 9175 (28.82) | 3135 (27.87) | 6040 (29.35) |       |
| Large                       | 17 840 (56.05) | 6525 (58.03) | 11 315 (54.98) |       |
| Location/teaching status of hospital |      |      |       |       |
| Rural                       | 2055 (6.46) | 775 (6.89) | 1280 (6.22) | 0.578  |
| Urban nonteaching           | 7780 (24.44) | 2730 (24.27) | 5050 (24.54) |       |
| Urban teaching              | 21 995 (69.10) | 7745 (68.84) | 14 250 (69.24) |       |

| Region of hospital          |      |      |       |       |
|-----------------------------|------|------|-------|-------|
| Northeast                   | 5785 (18.17) | 1915 (17.02) | 3870 (18.80) | 0.002† |
| Midwest                     | 7535 (23.67) | 2525 (22.44) | 5010 (24.34) |       |
| South                       | 11 870 (37.29) | 4195 (37.29) | 7675 (37.29) |       |
| West                        | 6640 (20.86) | 2615 (23.24) | 4025 (19.56) |       |

| All Patient Refined Diagnosis Related Group: severity of illness subclass |      |      |       |       |
|-----------------------------|------|------|-------|-------|
| Minor loss of function      | <11* | <11* | <11*  | 0.018†|
| Moderate loss of function   | 7910 (24.85) | 2675 (23.78) | 5235 (25.44) |       |
| Major loss of function      | 17 690 (55.58) | 6170 (54.84) | 11 520 (55.98) |       |
| Extreme loss of function    | 6230 (19.57) | 2405 (21.38) | 3825 (18.59) |       |
and AF. Upon full multivariable adjustment, preexisting dyslipidemia or atherosclerotic cardiovascular disease, as markers of likely prestroke lipid-lowering treatment, were not associated with changes in the association between PH and any outcomes. Nevertheless, preexisting AF, as a marker of likely prestroke anticoagulant treatment, was associated with a decrease in the association between PH and in-hospital mortality (OR, 0.77; 95% CI, 0.61–0.98) as well as prolonged hospitalization (OR, 0.88; 95% CI, 0.79–0.99).

Sensitivity LOS Analyses

Figure S1 details the results of the sensitivity analyses including only patients surviving to hospital discharge assessing the association between PH and prolonged hospitalization. Among patients surviving to hospital discharge, PH was also significantly associated with prolonged LOS (OR, 1.14; 95% CI, 1.07–1.21). There were also no significant interactions with either sex or age. These results are similar to those yielded by our main analyses, and it is thus unlikely that bias was introduced in the main analyses due to in-hospital deaths.

DISCUSSION

To the best of our knowledge, this is the first analysis of in-hospital outcomes of patients with PH who had AIS, as well as the first to describe sex differences in AIS outcomes among patients with PH. We have found that 76.7% of patients with AIS with comorbid PH had concomitant left heart disease, chronic lung disease, or both, patients in whom PH is likely secondary to their cardiologic or respiratory comorbidities. Only 155 (0.49%) patients with AIS were recorded to have PAH. Furthermore, we have found that upon multivariable adjustment for a wide range of confounders, including heart and lung diseases, there was no association between PH and in-hospital mortality. Our analysis also revealed a significant sex interaction: compared with female patients with PH, male patients were 31% more likely to die in hospital, while PH was associated with a nonsignificant 15% increase in the odds of in-hospital mortality among male patients. Patients with AIS and PH were at increased odds for prolonged hospitalization and less likely to be discharged routinely regardless of sex compared with patients with AIS without PH. Finally, our results suggest that patients with PH who were likely to have received prestroke treatment with anticoagulant agents had 23% decreased odds of in-hospital mortality and 12% decreased odds of prolonged hospitalization.

PH is a well-known risk factor for all-cause mortality and is also associated with incident cardiovascular disease. A meta-analysis including 32,523 patients, of whom 2976 (9.2%) had PH and a mean age of 52.2 years, found that patients with PH were at 46% increased odds of incident stroke compared with those without PH. The findings of our study thus offer further insight into this otherwise poorly studied area. While PH was not overall associated with in-hospital mortality, our analyses showed an important sex difference: among patients with PH and AIS, male patients were 31% more likely to die in the hospital than female patients. Sex differences are well documented among patients with PH, with most data originating from studies on PAH. While female patients are generally more likely to develop PH, male patients with PH tend to have worse right ventricular function and generally worse outcomes than female patients with PH. The shorter life expectancy of male patients with PH compared with their female counterparts is also reflected in our included sample, given the increase in the proportion of female patients with PH with increasing age. The complete lack of an association between PH and AIS mortality is surprising, given that even mild elevations...
in mean pulmonary artery pressure are associated with adverse mortality outcomes. Furthermore, patients with PH are more likely to develop right ventricular failure and decreased cardiac functional reserve and may thus be more susceptible to the hemodynamic instability and cardiac complications associated with pulmonary hypertension. and Ref, reference category.

**Figure 3.** Results of multivariable logistic regressions assessing the association between pulmonary hypertension and in-hospital outcomes after acute ischemic stroke, including stratified analyses by sex and age groups.

*Overall regression results were derived from regression models not containing any interaction terms. All models were adjusted for age, sex, ethnicity, Elixhauser comorbidities and other comorbidities (dyslipidemia, smoking, coronary heart disease, all-cause bleeding, deep venous thrombosis/pulmonary embolism, pericarditis, infectious endocarditis, atrial fibrillation, pneumonia [including aspiration], chronic lung disease, shock, family history of cerebrovascular disease, family history of heart disease, previous cerebrovascular disease), hospital characteristics (location and teaching status), and endovascular treatment (thrombolysis and thrombectomy). LOS indicates length of stay; OR, odds ratio; P int, statistical significance level of interaction between grouping variable and pulmonary hypertension; and Ref, reference category.

### In-hospital mortality

| Stratification by Sex | P int | N       |
|----------------------|-------|---------|
| Male                 | 0.024 | 548,450 |
| Female               | 0.148 | 557,595 |

### LoS >4 days

| Stratification by Sex | P int | N       |
|----------------------|-------|---------|
| Male                 | 0.827 | 548,450 |
| Female               | 0.082 | 557,595 |

### Routine Discharge

| Stratification by Sex | P int | N       |
|----------------------|-------|---------|
| Male                 | 0.195 | 548,450 |
| Female               | 0.028 | 557,595 |

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Our results showed that while more patients with PH died in the hospital compared with those without (6.52% versus 3.86%), there was no overall association upon comorbidity adjustment, including heart and lung disease. Given that 76.7% of patients with PH included in this study had coexisting cardiac and respiratory comorbidities and that these conditions are recognized independent risk factors for acute AIS mortality, it is likely that the increased in-hospital mortality rates recorded among patients with PH may be mainly driven by these underlying conditions and not by PH itself. Nevertheless, our results suggest that PH may be an independent risk factor for prolonged hospitalization and discharge disability regardless of sex, highlighting that both male and female patients may still have an overall worse prognosis after AIS. Our analyses also highlight that age is an important factor to consider in the relationship between PH and AIS, given that PH was associated with decreased odds of routine discharge among patients >70 years old but not among those <70 years old. These differences may be driven by differences in ischemic stroke etiology and severity between younger and older patients with PH. Nevertheless, this cannot be confirmed in the absence of stroke type and severity (National Institutes of Health Stroke Scale) information.

This study benefited from several strengths. Having included a large patient sample representative of over 1 million patients admitted between late 2015 and 2017 across the United States, our results reflect contemporary stroke clinical practice and are generalizable to patients with similar demographic characteristics, such as those in North America, Western Europe, and Australia. Furthermore, we were able to adjust for a wide range of important confounders, including cardiac and respiratory comorbidities as well as endovascular therapies for AIS.

We acknowledge some limitations. Having conducted our analyses on administrative data on the basis of ICD-10 codes, we lacked information regarding the severity of PH as well as the World Health Organization classification of PH. While we used ICD-10 groups to establish the likely etiology of PH, the exact ascertainment of such PH causes was not possible without further clinical details. We were thus unable to perform stratified analyses by PH severity.
or cause. Furthermore, we also lacked information regarding stroke severity, such as the National Institutes of Health Stroke Scale as well as stroke etiological classification. Furthermore, we lacked medication data. Nevertheless, we used preexisting dyslipidemia/atherosclerotic vascular disease and AF as proxies for lipid-lowering therapy and anticoagulation, respectively. Given that we analyzed a contemporary patient cohort, admitted between 2015 and 2017, it is reasonable to assume that current cardiovascular prevention recommendations were followed. Finally, it is important to note that statistically significant results may be commonly encountered in analyses of large samples and thus may not be necessarily be clinically relevant. Nevertheless, our analyses were prespecified and hypothesis-driven, with the relationship between comorbid PH and adverse AIS outcomes also being plausibly supported by the pathophysiological considerations outlined above. It is thus likely that our results reflect these pathophysiological mechanisms in which the altered hemodynamic status associated with comorbid PH renders these patients more susceptible to adverse outcomes in the acute phase after AIS, rather than merely representing spurious statistically significant associations.

Despite these limitations, our study has several important implications for further research and clinical practice. The results of our study together with previous research suggest that PH is an important comorbidity to consider in the management of patients with AIS, given that patients with PH are not only at higher risk of AIS but also more likely to suffer worse acute outcomes after AIS. Patients with AIS and PH, especially male patients, may thus benefit from therapeutic strategies personalized to their comorbidity profile, which may mitigate the PH-associated excess odds of adverse outcomes. While the evidence-based disease-modifying therapies used in PAH may not be used for the same purposes in patients with secondary PH, which comprise the majority of patients with PH included in our study, certain other simpler interventions may be considered and evaluated in further studies. These may include early cardiovascular and chest physician assessment in the early stages after AIS. Furthermore, our results highlight for the first time that particular focus should be given to stroke prevention and management in older patients with PH, given that these patients are less likely to be discharged routinely compared with their younger counterparts. Our analyses also suggest that preventative therapies such as antithrombotic therapy may improve outcomes in patients with PH and AIS. However, these results need to be confirmed in other registries with available medication and stroke severity data as well as randomized clinical trials assessing optimal prevention strategies aiming to reduce the AIS burden in patients with PH. Our analyses also showed that patients with PH had a significantly higher prevalence of AF than those without PH: 56.83% versus 24.58%, respectively. Given our results and previous evidence of the association between comorbid PH and increased risk of incident AIS, it is likely that the associations between PH and AIS may be at least partly mediated by AF. Systematic AF screening may thus be advocated in patients with PH in line with current international guidelines, since the timely identification and appropriate management of AF in patients with PH may improve AIS-related outcomes.

The results of our study also have several implications for further studies. Further research is required to determine the relationship between PH and postdischarge AIS outcomes, such as medium- and long-term mortality and stroke recurrence. Further case-control studies are also required to determine the relationship between more rare PH etiologies such as PAH and chronic thromboembolic PH and AIS outcomes, given that we were unable to determine these relationships because of a low number of patients with PAH and chronic thromboembolic PH included in our study, consistent with the prevalence of these conditions in the general population.

In conclusion, we reported for the first time the relationship between PH and AIS in-hospital outcomes, in a large, unselected, and representative sample. While PH was not overall associated with in-hospital mortality, it was associated with increased odds of prolonged hospitalization and adverse discharge status after AIS. There were also significant sex differences among patients with PH and AIS, in which male patients were more likely to die in hospital than female patients. Further studies assessing postdischarge outcomes in the medium and long term after AIS are required to fully characterize the relationship between PH and AIS.

ARTICLE INFORMATION
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Affiliations
From the Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, Stoke-on-Trent, UK (T.A.P., M.O.M., M.A.M., P.K.M.); Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition (T.A.P., D.K.D., P.K.M.) and Institute of Medical Sciences, School of Medicine, Medical Sciences & Nutrition (T.A.P., F.M., P.K.M.), University of Aberdeen, Aberdeen, UK; and Department of Cardiology, Thomas Jefferson University, Philadelphia, PA (D.L.F., M.P.S.).

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SUPPLEMENTAL MATERIAL
Table S1. International Classification of Disease – tenth edition (ICD-10) codes used to extract admission diagnoses, co-morbidities and procedures.

| Exposures                                      | ICD-10 codes (Diagnosis) |
|-----------------------------------------------|--------------------------|
| Ischaemic Stroke                              | I63.x                    |
| Pulmonary Hypertension                        | I27.x                    |
| Patent Foramen Ovale/ Atrial Septal Defect    | Q21.1                    |

| Co-morbidities                                |                           |
|-----------------------------------------------|---------------------------|
| Chronic Lung Disease                          | J43.x – J47.x; J60.x – J67.x; J68.4; J68.8; J68.9; J84.0x; J84.111 – J84.113; J84.115 – J84.17; J84x |
| Coronary Heart Disease                        | I20.x – I25.x             |
| Deep Venous Thrombosis                        | I82.x                    |
| Pulmonary Embolism                            | I26.x                    |
| Pericarditis                                  | I30.x – I32              |
| Infectious Endocarditis                       | I33.0; I33.9             |
| Atrial Fibrillation/Flutter                   | I48.x                    |
| Pneumonia                                     | J12.x – J18.x            |
| All-cause bleeding                            | D69.8; D69.9; G97.x; H11.3x; H31.3x; H35.6x; H43.1x; H92.2x; I31.2; I60.x—I62.x; I85.01; I85.11; K25.x-K29.x; K31.811; K62.5; K92.0-K92.2 I97.418; I97.42; I97.618-I97.621; J60.x-J62.x; N93.8; N93.9; N95.0; R04.x; R31.0; R31.9; R58; S06.4x – S06.6x |
| Shock                                         | R57.x                    |
| Previous Cerebrovascular Disease              | Z86.73                   |
| Family History of Stroke                      | Z82.3                    |
| Family History of Coronary Heart Disease      | Z82.41; Z82.49           |
| Smoking                                       | F17.2x                   |
| Dyslipidaemia                                 | E78.0-E78.6              |

| Procedures                                    | ICD-10 codes (Procedural) |
|-----------------------------------------------|---------------------------|
| Thrombolysis                                  | 03CG3ZZ; 03CG4ZZ; 03CK3Z7; 03CK3ZZ; 03CK4ZZ; 03CL3Z7; 03CL3ZZ; 03CL4ZZ; 03CP3Z7; 03CP3ZZ; 03CP4ZZ; 03CQ3Z7; 03CQ3ZZ; 03CQ4ZZ |
| Thrombectomy                                  | 03CG3ZZ; 03CG4ZZ; 03CK3Z7 |
| Echocardiography                              | B24; B244YZZ; B244ZZ3; B244ZZ4; B244ZZZ; B245YZZ; B245ZZ3; B245ZZ4; B245ZZZ; B246YZZ; B246ZZ3; B246ZZ4; B246ZZZ; B24BYZZ; B24BZZ3; B24BZZ4; B24BZZZ; B24CYZZ; B24CZZ3; B24CZZ4; B24CZZZ; B24DYZZ; B24DZZ3; B24DZZ4; B24DZZZ |

ICD-10 - International Classification of Disease – tenth edition
Table S2. International Classification of Disease – tenth edition (ICD-10) codes used to determine the likely underlying aetiologies of pulmonary hypertension.

| Definition                        | Corresponding WHO classification (approximate) | ICD-10 codes (Diagnosis) |
|----------------------------------|-----------------------------------------------|--------------------------|
| Pulmonary Arterial Hypertension  | Group 1                                        | I27.0                    |
| PH due to LHD                    | Group 2                                        | I27.2; I27.89; I27.9     |
|                                  |                                               | AND Q20.x-Q25.x; Q26.2-Q26.4; I42.x; I43; I50.x; I11.0; I13.0; I13.2; I34.x; I35.x I36.x; I37.x; I38; I39 |
| PH due to LHD & CLD              | Groups 2 and 3                                 | I27.2; I27.89; I27.9     |
|                                  |                                               | AND Q20.x-Q25.x; Q26.2-Q26.4; I42.x; I43; I50.x; I11.0; I13.0; I13.2; I34.x; I35.x I36.x; I37.x; I38; I39; J43.x-J47.x; J60.x-J67.x; J68.4; J68.8; AND J68.9; J84.0x; J84.111- J84.113; J84.115-J84.17; J84x |
| PH due to CLD                    | Group 3                                        | I27.2; I27.89; I27.9     |
|                                  |                                               | AND J43.x-J47.x; J60.x-J67.x; J68.4; J68.8; J68.9; J84.0x; J84.111- J84.113; J84.115-J84.17; J84x |
| CTEPH                            | Group 4                                        | I27.82                   |
| Other causes                     | Group 5                                        | I27.2; I27.89; I27.9     |
|                                  |                                               | AND Not classified in any of the above categories |

PH – Pulmonary Hypertension; LHD – left heart disease; CLD – chronic lung disease; CTEPH – chronic thromboembolic pulmonary hypertension
Table S3. Patient characteristics on admission, stratified by co-morbid pulmonary hypertension and age group (≤40; 41-50; 51-60 years). Also see Supplementary Table 6 for age groups 61-70; 71-80 and >80 years.

| ELIXHAUSER CO-MORBIDITIES, N (%) | ≤ 40 years | 41-50 years | P value | 51-60 years | P value |
|-------------------------------|-------------|-------------|---------|-------------|---------|
| N                             | No PH | PH | P value | No PH | PH | P value | No PH | PH | P value |
| Age, median (IQR)             | 29520 | 370 | 68230 | 860 | 172905 | 2385 |
| No PH                         | 35.00 (30.00-38.00) | 34.00 (26.00-38.00) | 0.509 | 47.00 (44.00-49.00) | 47.00 (45.00-49.00) | 0.366 | 56.00 (54.00-58.00) | 57.00 (54.00-59.00) | 0.008 |
| Length-of-stay, median (IQR)  | 3.00 (2.00-6.00) | 6.00 (4.00-13.00) | <0.001 | 3.00 (2.00-5.00) | 5.00 (3.00-9.00) | <0.001 | 3.00 (2.00-6.00) | 5.00 (3.00-9.00) | <0.001 |
| Sex                           | 14715 (49.85) | 190 (51.35) | 0.798 | 30150 (44.19) | 430 (50.00) | 0.138 | 67065 (38.79) | 1195 (50.10) | <0.001 |
| ELIXHAUSER CO-MORBIDITIES, N (%) | 2000 (6.78) | 130 (35.14) | <0.001 | 6570 (9.63) | 440 (51.16) | <0.001 | 18850 (10.90) | 1285 (53.88) | <0.001 |
| Congestive Heart Failure      | 1840 (6.23) | 110 (29.73) | <0.001 | 3495 (5.12) | 295 (34.30) | <0.001 | 9085 (5.25) | 710 (29.77) | <0.001 |
| Pulmonary Circulation Disease | 220 (0.75) | 70 (18.92) | <0.001 | 460 (0.67) | 90 (10.47) | <0.001 | 1280 (0.74) | 195 (8.18) | <0.001 |
| Peripheral Vascular Disease   | 3340 (11.31) | 30 (8.11) | 0.380 | 5685 (8.33) | 75 (8.72) | 0.854 | 14665 (8.48) | 345 (14.47) | <0.001 |
| Paralysis                     | 4270 (14.46) | 95 (25.68) | 0.009 | 8920 (13.07) | 175 (20.35) | 0.005 | 19390 (11.21) | 355 (14.88) | 0.012 |
| Other Neurological Disorders  | 290 (0.98) | 20 (5.41) | <0.001 | 590 (0.86) | 25 (2.91) | 0.005 | 1210 (0.70) | 50 (2.10) | <0.001 |
| Chronic Pulmonary Disease     | 2825 (9.57) | 60 (16.22) | 0.054 | 7515 (11.01) | 215 (25.00) | <0.001 | 25325 (14.65) | 770 (32.29) | <0.001 |
| Diabetes (without chronic complications) | 2235 (7.57) | 15 (4.05) | 0.253 | 10345 (15.16) | 140 (16.28) | 0.681 | 31805 (18.39) | 400 (16.77) | 0.361 |
| Diabetes (with chronic complications) | 3405 (11.53) | 70 (18.92) | 0.062 | 14615 (21.42) | 215 (25.00) | 0.265 | 42065 (24.33) | 795 (33.33) | <0.001 |
| Condition                        | Rate (Percentage) | Rate (Percentage) | OR (95% CI) | p-Value | Rate (Percentage) | Rate (Percentage) | OR (95% CI) | p-Value | Rate (Percentage) | Rate (Percentage) | OR (95% CI) | p-Value | Rate (Percentage) | Rate (Percentage) | OR (95% CI) | p-Value |
|---------------------------------|-------------------|-------------------|-------------|---------|-------------------|-------------------|-------------|---------|-------------------|-------------------|-------------|---------|-------------------|-------------------|-------------|---------|
| Hypothyroidism                  | 1465 (4.96)       | 15 (4.05)         | 0.721       | <0.001 | 4385 (6.43)       | 40 (4.65)         | 0.340       | <0.001 | 12480 (7.22)      | 210 (8.81)        | 0.187       |
| Renal Failure                   | 1705 (5.78)       | 70 (18.92)        | <0.001      | 6325 (9.27) | 150 (17.44)      | <0.001 | 19630 (11.35) | 725 (30.40) | <0.001 |
| Liver Disease                   | 445 (1.51)        | 20 (5.41)         | 0.007       | <11     | 1275 (1.87)       | 25 (2.91)        | 0.316       | <11     | 4560 (2.64)       | 110 (4.61)        | 0.007       |
| Peptic Ulcer Disease            | 95 (0.32)         | <11               | 0.626       | <11     | 330 (0.48)        | <11               | 0.207       | <11     | 950 (0.55)        | 15 (0.63)         | 0.816       |
| Acquired Immune Deficiency      | 190 (0.64)        | <11               | 0.497       | <11     | 435 (0.64)        | <11               | 0.926       | <11     | 970 (0.56)        | 15 (0.63)         | 0.878       |
| Syndrome                        | 40 (0.14)         | <11               | 0.008       | <11     | 130 (0.19)        | <11               | 0.566       | <11     | 530 (0.31)        | <11               | 0.658       |
| Lymphoma                        | 145 (0.49)        | <11               | 0.540       | <11     | 625 (0.92)        | <11               | 0.735       | <11     | 2690 (1.56)       | 65 (2.73)         | 0.039       |
| Metastatic Cancer               | 125 (0.42)        | <11               | 0.566       | <11     | 425 (0.62)        | <11               | 0.315       | <11     | 2010 (1.16)       | 25 (1.05)         | 0.816       |
| Rheumatoid Arthritis / Collagen | 130 (0.44)        | <11               | 0.246       | <11     | 385 (0.56)        | <11               | 0.329       | <11     | 370 (0.21)        | 20 (0.84)         | .004        |
| Vascular Disease                | 1605 (5.44)       | 30 (8.11)         | 0.317       | <11     | 4920 (7.21)       | 60 (6.98)        | 0.905       | <11     | 15250 (8.82)      | 450 (18.87)       | <0.001 |
| Anaemia (chronic blood loss)    | 5100 (17.28)      | 100 (27.03)       | 0.026       | <11     | 13280 (19.46)     | 285 (33.14)      | <0.001      | <11     | 35050 (20.27)     | 740 (31.03)       | <0.001 |
| Anaemia (deficiency)            | 3020 (10.23)      | 95 (25.68)        | <0.001      | 7480 (10.96) | 190 (22.09)      | <0.001 | 15250 (8.82) | 450 (18.87) | <0.001 |
| Alcohol abuse                    | 1605 (5.44)       | 30 (8.11)         | 0.317       | <11     | 4920 (7.21)       | 60 (6.98)        | 0.905       | <11     | 15250 (8.82)      | 450 (18.87)       | <0.001 |
| Drug abuse                       | 2990 (10.13)      | 35 (9.46)         | 0.850       | 5480 (8.03) | 70 (8.14)        | 0.959 | 11580 (6.70) | 210 (8.81) | 0.062 |
| Psychoses                        | 1340 (4.54)       | <11               | 0.189       | 3185 (4.67) | 50 (5.81)        | 0.475 | 6950 (4.02) | 110 (4.61) | 0.510 |
| Depression                       | 3095 (10.48)      | 35 (9.46)         | 0.776       | 8495 (12.45) | 105 (12.21)      | 0.924 | 21280 (12.31) | 335 (14.05) | 0.252 |
| Condition                          | Hypertension   | OTHER CO-MORBIDITIES, N (%) |
|-----------------------------------|----------------|----------------------------|
|                                   | 13965 (47.31)  |                            |
|                                  | 215 (58.11)    | 0.063                      |
|                                  | 51140 (74.95)  | 700 (81.40)                |
|                                  | 144910 (83.81) | 2065 (86.58)               |
|                                  | 0.059          | 0.094                      |
| Sepsis                            | 405 (1.37)     | 25 (6.76)                  |
|                                  | <0.001         | 850 (1.25)                 |
|                                  | 20 (2.33)      | 2028 (1.40)                |
|                                  | 0.208          | 55 (2.31)                  |
|                                  | 0.069          |                            |
| Dyslipidaemia                     | 8555 (28.98)   | 80 (21.62)                 |
|                                  | 0.176          | 33560 (49.19)              |
|                                  | 385 (44.77)    | 2285 (1.32)                |
|                                  | 0.249          | 45 (1.89)                  |
|                                  | 0.006          |                            |
| Dementia                          | 75 (0.25)      | <11                        |
|                                  | 0.663          | 300 (0.44)                 |
|                                  | <11            | 69500000000000001          |
|                                  | <11            | 390 (0.23)                 |
|                                  | 0.069          |                            |
| Smoking                           | 9000 (30.49)   | 85 (22.97)                 |
|                                  | 0.164          | 24790 (36.33)              |
|                                  | 250 (29.07)    | 63870 (36.94)              |
|                                  | 0.045          | 705 (29.56)                |
|                                  | 0.001          |                            |
| Parkinson Disease                 | 15 (0.05)      | <11                        |
|                                  | 0.846          | 70 (0.10)                  |
|                                  | <11            | .69500000000000001         |
|                                  | <11            | 390 (0.23)                 |
|                                  | 0.379          |                            |
| Transient Ischaemic Attack        | 165 (0.56)     | <11                        |
|                                  | 0.355          | 410 (0.60)                 |
|                                  | <11            | 0.973                      |
|                                  | 1195 (0.69)    | <11                        |
|                                  | 0.473          |                            |
| Rheumatic Heart Disease           | 435 (1.47)     | 55 (14.86)                 |
|                                  | <0.001         | 875 (1.28)                 |
|                                  | 175 (20.35)    | <0.001                     |
|                                  | <2420 (1.40)   | 385 (16.14)                |
|                                  | <0.001         |                            |
| Coronary Heart Disease            | 2240 (7.59)    | 90 (24.32)                 |
|                                  | <0.001         | 10290 (15.08)              |
|                                  | 240 (27.91)    | 36565 (21.15)              |
|                                  | <0.001         | 1115 (46.75)               |
|                                  | <0.001         |                            |
| All-cause Bleeding                | 1995 (6.76)    | 50 (13.51)                 |
|                                  | 0.023          | 3910 (5.73)                |
|                                  | 105 (12.21)    | <0.001                     |
|                                  | 285 (11.95)    | <0.001                     |
|                                  | <0.001         |                            |
| Pulmonary Embolism                | 220 (0.75)     | 20 (5.41)                  |
|                                  | <0.001         | 455 (0.67)                 |
|                                  | 45 (5.23)      | <0.001                     |
|                                  | 1270 (0.73)    | 50 (2.10)                  |
|                                  | <0.001         |                            |
| Congenital Heart Disease          | 3625 (12.28)   | 80 (21.62)                 |
|                                  | 0.017          | 3880 (5.69)                |
|                                  | 75 (8.72)      | 6675 (3.86)                |
|                                  | 0.089          | 135 (5.66)                 |
|                                  | 0.043          |                            |
| Pericarditis                      | <11            | <11                        |
|                                  | 0.911          | <11                        |
|                                  | <11            | -                          |
|                                  | 25 (0.01)      | <11                        |
|                                  | 0.792          |                            |
| Infectious Endocarditis           | 245 (0.83)     | <11                        |
|                                  | 0.082          | 270 (0.40)                 |
|                                  | 15 (1.74)      | 430 (0.25)                 |
|                                  | 0.006          | 15 (0.63)                  |
|                                  | 0.103          |                            |
| Atrial Fibrillation               | 1115 (3.78)    | 55 (14.86)                 |
|                                  | <0.001         | 3940 (5.77)                |
|                                  | 185 (21.51)    | <0.001                     |
|                                  | 15685 (9.07)   | 615 (25.79)                |
|                                  | <0.001         |                            |
| Deep Venous Thrombosis            | 465 (1.58)     | 35 (9.46)                  |
|                                  | <0.001         | 1125 (1.65)                |
|                                  | 50 (5.81)      | <0.001                     |
|                                  | 2690 (1.56)    | 70 (2.94)                  |
|                                  | <0.001         |                            |
| Pneumonia                         | 580 (1.96)     | 25 (6.76)                  |
|                                  | 0.004          | 1375 (2.02)                |
|                                  | 50 (5.81)      | <0.001                     |
|                                  | 3850 (2.23)    | 155 (6.50)                 |
|                                  | <0.001         |                            |
| Chronic Lung Disease              | 500 (1.69)     | <11                        |
|                                  | 0.508          | 3510 (5.14)                |
|                                  | 130 (15.12)    | <0.001                     |
|                                  | 655 (27.46)    | <0.001                     |
|                                  | 0.001          |                            |
| Chronic Obstructive Pulmonary Disease | 415 (1.41) | <11 | 0.299 | 3260 (4.78) | 115 (13.37) | <0.001 | 17600 (10.18) | 615 (25.79) | <0.001 |
| Shock | 140 (0.47) | 20 (5.41) | <0.001 | 260 (0.38) | 25 (2.91) | <0.001 | 795 (0.46) | 55 (2.31) | <0.001 |
| Family history of cerebrovascular disease | 2140 (7.25) | 15 (4.05) | 0.292 | 4435 (6.50) | 25 (2.91) | 0.056 | 9040 (5.23) | 120 (5.03) | 0.848 |
| Family history of heart disease | 2280 (7.72) | 35 (9.46) | 0.579 | 5635 (8.26) | 65 (7.56) | 0.756 | 12930 (7.48) | 180 (7.55) | <0.001 |
| Previous cerebrovascular disease | 2985 (10.11) | 20 (5.41) | 0.180 | 8760 (12.84) | 70 (8.14) | 0.063 | 23295 (13.47) | 325 (13.63) | 0.921 |

**PROCEDURES, N (%)**

- Thrombectomy: 1500 (5.08), 50 (13.51), 0.001, 2410 (3.53), 50 (5.81), 0.109, 5270 (3.05), 140 (5.87), <0.001
- Thrombolysis: 3570 (12.09), 65 (17.57), 0.177, 8180 (11.99), 85 (9.88), 0.397, 17015 (9.84), 260 (10.90), 0.448
- Echocardiography: 5835 (19.77), 110 (29.73), 0.032, 10385 (15.22), 150 (17.44), 0.410, 20225 (11.70), 370 (15.51), 0.010

**OUTCOMES, N (%)**

- In-hospital mortality: 695 (2.35), 35 (9.46), <0.001, 1365 (2.00), 35 (4.07), 0.056, 3920 (2.27), 105 (4.40), 0.003
- Length-of-stay >4 days: 10235 (34.67), 230 (62.16), <0.001, 21855 (32.03), 450 (52.33), <0.001, 57040 (32.99), 1255 (52.62), <0.001
- Routine Discharge: 19040 (66.07), 170 (46.58), <0.001, 39500 (59.54), 395 (46.20), <0.001, 89545 (52.87), 930 (39.66), <0.001

**OTHER CHARACTERISTICS, N (%)**

- Year of admission:
  - 2015: 2985 (10.11), 30 (8.11), 0.351, 6780 (9.94), 85 (9.88), 0.112, 17220 (9.96), 260 (10.90), <0.001
  - 2016: 13050 (44.21), 140 (37.84), 0.016, 30390 (44.54), 450 (52.33), 0.081, 75905 (43.90), 1245 (52.20), <0.001
  - 2017: 13485 (45.68), 200 (54.05), 0.016, 31060 (45.52), 325 (37.79), 0.081, 79780 (46.14), 880 (36.90), <0.001
- Ethnicity: 0.016, 0.081, <0.001
| Category              | Count  | Percent |
|-----------------------|--------|---------|
| **White**             |        |         |
|                       | 14495  | (49.10) |
|                       | 7490   | (25.37) |
|                       | 3820   | (12.94) |
|                       | 860    | (2.91)  |
|                       | 190    | (0.64)  |
|                       | 1175   | (3.98)  |
|                       | 1490   | (5.05)  |
| **Black**             |        |         |
|                       | 105    | (28.38) |
|                       | 295    | (34.30) |
|                       | 65     | (17.57) |
|                       | 15     | (4.05)  |
|                       | <11    | <11     |
|                       | <11    | <11     |
|                       | 25     | (6.76)  |
| **Hispanic**          |        |         |
|                       | 34555  | (50.64) |
|                       | 7780   | (11.40) |
|                       | 2155   | (3.16)  |
|                       | 405    | (0.59)  |
|                       | 1965   | (2.88)  |
|                       | 2580   | (3.78)  |
| **Asian or Pacific Islander** | | |
|                       | 360    | (41.86) |
|                       | 90     | (10.47) |
|                       | 55     | (6.40)  |
|                       | <11    | <11     |
|                       | 25     | (2.91)  |
|                       | 35     | (4.07)  |
| **Native American**   |        |         |
|                       | 96575  | (55.85) |
|                       | 16035  | (9.27)  |
|                       | 1135   | (47.59) |
|                       | 43790  | (25.33) |
|                       | 16035  | (9.27)  |
|                       | 210    | (8.81)  |
| **Other**             |        |         |
|                       | 34555  | (50.64) |
|                       | 7780   | (11.40) |
|                       | 2155   | (3.16)  |
|                       | 405    | (0.59)  |
|                       | 1965   | (2.88)  |
|                       | 2580   | (3.78)  |
| **Missing**           |        |         |
|                       | 96575  | (55.85) |
|                       | 16035  | (9.27)  |
|                       | 1135   | (47.59) |
|                       | 43790  | (25.33) |
|                       | 16035  | (9.27)  |
|                       | 210    | (8.81)  |
Table S4. Patient characteristics on admission, stratified by co-morbid pulmonary hypertension and age group (61-70; 71-80; >80 years) (continued). Also see Supplementary Table 5 for age groups ≤40; 41-50; 51-60 years.

|                  | 61-70 years | 71-80 years | >80 years |
|------------------|-------------|-------------|-----------|
|                  | No PH | PH | P value | No PH | PH | P value | No PH | PH | P value |
| N                | 249585 | 4950 |  | 256060 | 7990 |  | 297915 | 15275 |  |
| Age, median (IQR) | 66.00 (63.00-68.00) | 66.00 (63.00-68.00) | <0.001 | 75.00 (73.00-78.00) | 76.00 (73.00-78.00) | <0.001 | 87.00 (83.00-90.00) | 87.00 (84.00-90.00) | <0.001 |
| Length-of-stay, median (IQR) | 3.00 (2.00-6.00) | 5.00 (3.00-8.00) | <0.001 | 3.00 (2.00-6.00) | 4.00 (3.00-8.00) | <0.001 | 4.00 (2.00-6.00) | 4.00 (3.00-7.00) | <0.001 |
| Sex Female, N (%) | 106990 (42.87) | 2780 (56.16) | <0.001 | 128020 (50.00) | 4970 (62.20) | <0.001 | 190075 (63.80) | 11015 (72.11) | <0.001 |
| ELIXHAUSER COMORBIDITIES, N (%) |  |  |  |  |  |  |  |  |
| Congestive Heart Failure | 31110 | 2430 | <0.001 | 38245 | 3615 | <0.001 | 60245 | 7250 | <0.001 |
| Valvular Disease | 16790 | 1640 | <0.001 | 24655 | 3025 | <0.001 | 41330 | 7565 | <0.001 |
| Pulmonary Circulation Disease | 1730 (0.69) | 350 (7.07) | <0.001 | 1460 (0.57) | 560 (7.01) | <0.001 | 1375 (0.46) | 670 (4.39) | <0.001 |
| Peripheral Vascular Disease | 24355 | 525 (10.61) | 0.364 | 28410 | 1325 | <0.001 | 30940 | 2370 | <0.001 |
| Paralysis | 24795 | 695 (14.04) | <0.001 | 24665 | 1105 | <0.001 | 26415 | 2015 | <0.001 |
| Other Neurological Disorders | 1520 (0.61) | 70 (1.41) | 0.001 | 1535 (0.60) | 65 (0.81) | 0.276 | 1105 (0.37) | 140 (0.92) | <0.001 |
| Chronic Pulmonary Disease | 41890 | 1515 | <0.001 | 45300 | 2370 | <0.001 | 42980 | 3415 | <0.001 |
| Diabetes (without chronic complications) | 54190 | 980 (19.80) | 0.144 | 56365 | 1580 | 0.033 | 50030 | 2135 | <0.001 |
| Diabetes (with chronic complications) | 59155 | 1465 | <0.001 | 51830 | 1795 | 0.033 | 36890 | 2100 | 0.024 |
| Condition                              | Cases (Prevalence) | Age (Mean, SD) | Difference (t) | p-Value | Cases (Prevalence) | Age (Mean, SD) | Difference (t) | p-Value | Cases (Prevalence) | Age (Mean, SD) | Difference (t) | p-Value | Cases (Prevalence) | Age (Mean, SD) | Difference (t) | p-Value |
|---------------------------------------|--------------------|----------------|----------------|---------|--------------------|----------------|----------------|---------|--------------------|----------------|----------------|---------|--------------------|----------------|----------------|---------|
| Hypothyroidism                        | 26510 (10.62)      | 590 (11.92)    | 0.192          | <0.01   | 40495 (15.81)      | 1435 (17.96)   | 0.024          | <0.01   | 67895 (22.79)      | 3640 (23.83)   | 0.178          |
| Renal Failure                         | 35585 (14.26)      | 1485 (30.00)   | <0.001         | <0.001  | 46685 (18.23)      | 2365 (29.60)   | 0.001          | <0.001  | 62660 (21.03)      | 4565 (29.89)   | <0.001         |
| Liver Disease                         | 5770 (2.31)        | 200 (4.04)     | <0.001         | <0.001  | 3520 (1.37)        | 200 (2.50)     | <0.001         | <0.001  | 1975 (0.66)        | 210 (1.37)     | <0.001         |
| Peptic Ulcer Disease                  | 1705 (0.68)        | 65 (1.31)      | 0.018          | 0.244   | 1910 (0.75)        | 80 (1.00)      | 0.093          | 0.938   | 2380 (0.80)        | 155 (1.01)     | 0.196          |
| Acquired Immune Deficiency Syndrome   | 520 (0.21)         | 35 (0.71)      | <0.001         | 0.887   | 185 (0.07)         | <11            | 0.549          | 0.549   | 35 (0.01)          | <11            | 0.549          |
| Lymphoma                              | 1080 (0.43)        | 40 (0.81)      | 0.077          | 0.843   | 1660 (0.65)        | 55 (0.69)      | <0.001         | <0.001  | 1655 (0.56)        | 110 (0.72)     | 0.238          |
| Metastatic Cancer                     | 5370 (2.15)        | 115 (2.32)     | 0.723          | 0.311   | 5170 (2.02)        | 190 (2.38)     | <0.001         | <0.001  | 3405 (1.14)        | 170 (1.11)     | 0.881          |
| Solid tumour without metastasis       | 4410 (1.77)        | 150 (3.03)     | 0.003          | 0.502   | 5915 (2.31)        | 205 (2.57)     | <0.001         | <0.001  | 6080 (2.13)        | 325 (2.13)     | 0.735          |
| Rheumatoid Arthritis / Collagen Vascular Disease | 6185 (2.48)  | 210 (4.24)     | <0.001         | 0.850   | 8040 (3.14)        | 425 (5.32)     | <0.001         | <0.001  | 8500 (2.85)        | 580 (3.80)     | 0.002          |
| Coagulopathy                          | 8660 (3.47)        | 405 (8.18)     | <0.001         | 0.570   | 10215 (3.99)       | 575 (7.20)     | <0.001         | <0.001  | 11930 (4.00)       | 890 (5.83)     | <0.001         |
| Obesity                               | 40990 (16.42)      | 1235 (24.95)   | <0.001         | 0.139   | 29875 (11.67)      | 1395 (17.46)   | <0.001         | <0.001  | 13450 (4.51)       | 990 (6.48)     | <0.001         |
| Weight loss                           | 8555 (3.43)        | 375 (7.58)     | <0.001         | 0.480   | 10230 (4.00)       | 480 (6.01)     | <0.001         | <0.001  | 16355 (5.49)       | 1245 (8.15)    | <0.001         |
| Fluid and electrolyte disorders       | 53255 (21.34)      | 1625 (32.83)   | <0.001         | 0.229   | 57055 (22.28)      | 2290 (28.66)   | <0.001         | <0.001  | 73035 (24.52)      | 4865 (31.85)   | <0.001         |
| Anaemia (chronic blood loss)          | 710 (0.28)         | 35 (0.71)      | 0.013          | 0.031   | 915 (0.36)         | 55 (0.69)      | 0.031          | 0.031   | 1265 (0.42)        | 135 (0.88)     | <0.001         |
| Anaemia (deficiency)                  | 25295 (10.13)      | 1095 (22.12)   | <0.001         | 0.184   | 31795 (12.42)      | 1845 (23.09)   | <0.001         | <0.001  | 43040 (14.45)      | 3450 (22.59)   | <0.001         |
| Alcohol abuse                         | 15610 (6.25)       | 315 (6.36)     | 0.886          | 0.943   | 7610 (2.97)        | 235 (2.94)     | 0.943          | 0.943   | 2790 (0.94)        | 140 (0.92)     | 0.917          |
| Drug abuse                            | 6435 (2.58)        | 185 (3.74)     | 0.022          | 0.318   | 1440 (0.56)        | 60 (0.75)      | 0.318          | 0.318   | 460 (0.15)         | 40 (0.26)      | 0.126          |
| Psychoses                             | 6755 (2.71)        | 155 (3.13)     | 0.415          | 0.100   | 4420 (1.73)        | 95 (1.19)      | 0.100          | 0.100   | 3095 (1.04)        | 95 (0.62)      | 0.026          |
| Depression                            | 30335 (12.15)      | 750 (15.15)    | 0.005          | 0.938   | 28205 (11.01)      | 885 (11.08)    | 0.938          | 0.938   | 29470 (9.89)       | 1645 (10.77)   | 0.110          |
| Other Co-morbidities, N (%) | 216825 (86.87) | 4320 (87.27) | 0.718 | 226900 (89.61) | 7140 (89.36) | 0.351 | 264135 (88.66) | 13825 (90.51) | 0.002 |
|----------------------------|----------------|--------------|-------|----------------|-------------|-------|----------------|-------------|-------|
| Hypertension               |                |              |       |                |              |       |                |              |       |
| Sepsis                     | 3875 (1.55)    | 160 (3.23)   | <0.001 | 4145 (1.62)   | 165 (2.07)  | 0.176 | 4135 (1.39)    | 245 (1.60)  | 0.314 |
| Dyslipidaemia              | 153800 (61.62) | 2885 (58.28) | 0.033 | 160550 (62.70) | 4865 (60.89) | 0.146 | 167940 (56.37) | 8605 (56.33) | 0.967 |
| Dementia                   | 10320 (4.13)   | 245 (4.95)   | 0.205 | 31160 (12.17)  | 920 (11.51)  | 0.435 | 82375 (27.65)  | 3925 (25.70) | 0.020 |
| Smoking                    | 62265 (24.95)  | 895 (18.08)  | <0.001 | 30490 (11.91) | 815 (10.20)  | 0.038 | 9825 (3.30)    | 450 (2.95)  | 0.279 |
| Parkinson Disease         | 2065 (0.83)    | 20 (0.40)    | 0.144 | 5420 (2.12)    | 145 (1.81)   | 0.407 | 7380 (2.48)    | 280 (1.83)  | 0.023 |
| Transient Ischaemic Attack | 1830 (0.73)    | 40 (0.81)    | 0.785 | 2020 (0.79)    | 40 (0.50)    | 0.196 | 2255 (0.76)    | 95 (0.62)   | 0.399 |
| Rheumatic Heart Disease    | 4305 (1.72)    | 780 (15.76)  | <0.001 | 6225 (2.43)   | 1550 (19.40) | <0.001 | 11155 (3.74)  | 3995 (26.15) | <0.001 |
| Coronary Heart Disease     | 66465 (26.63)  | 2100 (42.42) | <0.001 | 84725 (33.09) | 3775 (47.25) | <0.001 | 100815 (33.84) | 6450 (42.23) | <0.001 |
| All-cause Bleeding         | 16655 (6.67)   | 585 (11.82)  | <0.001 | 19600 (7.65)  | 960 (12.02)  | <0.001 | 24155 (8.11)  | 1470 (9.62) | 0.002 |
| Pulmonary Embolism         | 1695 (0.68)    | 95 (1.92)    | <0.001 | 1435 (0.56)   | 155 (1.94)   | <0.001 | 1360 (0.46)    | 200 (1.31)  | <0.001 |
| Congenital Heart Disease   | 7615 (3.05)    | 185 (3.74)   | 0.210 | 6205 (2.42)    | 245 (3.07)   | 0.105 | 4390 (1.47)    | 385 (2.52)  | <0.001 |
| Pericarditis               | 25 (0.01)      | <11          | 0.009 | 25 (0.01)      | <11         | <0.001 | <11           | <11         | 0.749 |
| Infectious Endocarditis    | 510 (0.20)     | 35 (0.71)    | <0.001 | 430 (0.17)    | 45 (0.56)    | <0.001 | 290 (0.10)    | 15 (0.10)   | 0.988 |
| Atrial Fibrillation        | 41810 (16.75)  | 2070 (41.82) | <0.001 | 71885 (28.07) | 4460 (55.82) | <0.001 | 129650 (43.52) | 10705 (70.08) | <0.001 |
| Deep Venous Thrombosis     | 3590 (1.44)    | 180 (3.64)   | <0.001 | 3270 (1.28)   | 220 (2.75)   | <0.001 | 2885 (0.97)   | 265 (1.73)  | <0.001 |
| Pneumonia                  | 5875 (2.35)    | 325 (6.57)   | <0.001 | 6980 (2.73)   | 375 (4.69)   | <0.001 | 9545 (3.20)   | 770 (5.04)  | <0.001 |
| Chronic Lung Disease       | 32860 (13.17)  | 1340 (27.07) | <0.001 | 37705 (14.73) | 2195 (27.47) | <0.001 | 35970 (12.07) | 3055 (20.00) | <0.001 |
| Chronic Obstructive Pulmonary Disease | 30890 (12.38) | 1230 (4.85) | <0.001 | 34895 (13.63) | 2015 (25.22) | <0.001 | 32715 (10.98) | 2755 (18.04) | <0.001 |
| Shock | 1225 (0.49) | 90 (1.82) | <0.001 | 1200 (0.47) | 90 (1.13) | <0.001 | 1075 (0.36) | 95 (0.62) | 0.020 |
| Family history of cerebrovascular disease | 10385 (4.16) | 150 (3.03) | 0.074 | 8525 (3.33) | 265 (3.32) | 0.978 | 7235 (2.43) | 390 (2.55) | 0.666 |
| Family history of heart disease | 15810 (6.33) | 275 (5.56) | 0.034 | 13740 (5.37) | 495 (6.20) | 0.143 | 11870 (3.98) | 685 (4.48) | 0.160 |
| Previous cerebrovascular disease | 37995 (15.22) | 685 (13.84) | 0.223 | 42230 (16.49) | 1145 (14.33) | 0.019 | 52450 (17.61) | 2640 (17.28) | 0.650 |
| PROCEDURES, N (%) | | | | | | | | | |
| Thrombectomy | 7535 (3.02) | 280 (5.66) | <0.001 | 7865 (3.07) | 430 (5.38) | <0.001 | 8195 (2.75) | 695 (4.55) | <0.001 |
| Thrombolysis | 22670 (9.08) | 490 (9.90) | 0.371 | 23070 (9.01) | 860 (10.76) | 0.014 | 25510 (8.56) | 1825 (11.95) | <0.001 |
| Echocardiography | 25855 (10.36) | 490 (9.90) | 0.641 | 22940 (8.96) | 800 (10.01) | 0.150 | 17095 (5.74) | 1145 (7.50) | <0.001 |
| OUTCOMES, N (%) | | | | | | | | | |
| In-hospital mortality | 7110 (2.85) | 295 (5.96) | <0.001 | 9740 (3.80) | 465 (5.82) | <0.001 | 18640 (6.26) | 1140 (7.46) | 0.007 |
| Length-of-stay >4 days | 82395 (33.01) | 2500 (50.51) | <0.001 | 87735 (34.26) | 3925 (49.12) | <0.001 | 105840 (35.53) | 7145 (46.78) | <0.001 |
| Routine Discharge | 107790 (43.62) | 1470 (29.88) | <0.001 | 82315 (32.31) | 1720 (21.65) | <0.001 | 49420 (16.64) | 1810 (11.88) | <0.001 |
| OTHER CHARACTERISTICS, N (%) | | | | | | | | | |
| Year of admission | | | | | | | | | |
| 2015 | 24280 (9.73) | 535 (10.81) | 0.195 | 26350 (10.29) | 800 (10.01) | <0.001 | 30870 (10.36) | 1805 (11.82) | <0.001 |
| 2016 | 108870 (43.62) | 2245 (45.35) | | 112330 (43.87) | 4095 (51.25) | | 131565 (44.16) | 7720 (50.54) | |
| 2017 | 116435 (46.65) | 2170 (43.84) | | 117380 (45.84) | 3095 (38.74) | | 135480 (45.48) | 5750 (37.64) | |
| Ethnicity | | | | | | | | | <0.001 |
|                  |       |       |       |       |       |       |
|------------------|-------|-------|-------|-------|-------|-------|
|                  |       |       |       |       |       |       |
| White            | 157290| 2935  | 180130| 5460  | 230630| 11660 |
|                  | (63.02)| (59.29)| (70.35)| (68.34)| (77.41)| (76.33)|
| Black            | 48630 | 1265  | 34430 | 1475  | 24425 | 1560  |
|                  | (19.48)| (25.56)| (13.45)| (18.46)| (8.20) | (10.21)|
| Hispanic         | 19955 | 300   | 18090 | 440   | 17545 | 620   |
|                  | (8.00) | (6.06) | (7.06) | (5.51) | (5.89) | (4.06) |
| Asian or Pacific | 7250  | 125   | 7545  | 150   | 8395  | 415   |
| Islander         | (2.90) | (2.53) | (2.95) | (1.88) | (2.82) | (2.72) |
| Native American  | 1285  | 25    | 985   | 25    | 715   | 30    |
|                  | (0.51) | (0.51) | (0.38) | (0.31) | (0.24) | (0.20) |
| Other            | 6600  | 115   | 6200  | 140   | 6020  | 310   |
|                  | (2.64) | (2.32) | (2.42) | (1.75) | (2.02) | (2.03) |
| Missing          | 8575  | 185   | 8680  | 300   | 10185 | 680   |
|                  | (3.44) | (3.74) | (3.39) | (3.75) | (3.42) | (4.45) |
Figure S1. Results of sensitivity multivariable logistic regressions assessing the association between pulmonary hypertension and prolonged hospitalisation after acute ischaemic stroke only including patients surviving to hospital discharge.

*Overall regression results were derived from regression models not containing any interaction terms.

Models were adjusted for age, sex, ethnicity, Elixhauser co-morbidities and other co-morbidities (dyslipidaemia, smoking, coronary heart disease, all-cause bleeding, deep venous thrombosis/pulmonary embolism, pericarditis, infectious endocarditis, atrial fibrillation, pneumonia (incl. aspiration), chronic lung disease, shock, family history of cerebrovascular disease, family history of heart disease, previous cerebrovascular disease), hospital characteristics (location and teaching status) and endovascular treatment (thrombolysis and thrombectomy).

OR – odds ratio; CI – confidence interval; P int – Statistical significance level of interaction between grouping variable and pulmonary hypertension; Ref – Reference category; LoS – Length of stay.