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ORIGINAL RESEARCH

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 co-morbid 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 heterogenous 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,

Correspondence to: Tiberiu Alexandru Pana, Room 1.130, Polwarth Building, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, Scotland, UK. E-mail: tiberiupana12@gmail.com

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CLINICAL PERSPECTIVE

What Is New?

- The association and underlying sex differences between comorbid pulmonary hypertension (PH) and acute ischemic stroke (AIS) in-hospital outcomes are described for the first time in this study, using a sample representative of 1.1 million AIS admissions between 2015 and 2017 from the US National Inpatient Sample.
- There was no association between PH and mortality, but PH was associated with a 15% increase in the odds of prolonged hospitalization and a 31% decrease in the odds of routine home discharge.
- Male patients with PH were at 31% increased odds of dying in the hospital after AIS compared with their female counterparts.

What Are the Clinical Implications?

- Clinicians should be aware of both the excess odds of adverse AIS in-hospital outcomes in patients with PH and the sex differences in mortality recorded in this population.
- Patients with AIS and PH, especially men, may benefit from therapeutic strategies personalized to their comorbidity profile, which may mitigate the PH-associated excess odds of adverse outcomes, such as early cardiovascular and chest physician assessment in the early stages after AIS.
- The associations between PH and AIS may be at least partly mediated by atrial fibrillation, and thus systematic atrial fibrillation screening may be advocated, since appropriate atrial fibrillation management may improve AIS-related outcomes.

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
NIS	National Inpatient Sample
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension

given their involvement in the pathogenesis of both stroke[11,12] and PH.[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[14] and decreased cardiac functional reserve[15] and may thus render patients more susceptible to the hemodynamic instability and cardiac complications associated with acute stroke,[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,[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.[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 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,[21] using the provided discharge weights as probability weights and survey data analysis techniques stratifying by NIS stratum and year of admission[22] 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=2187; 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.

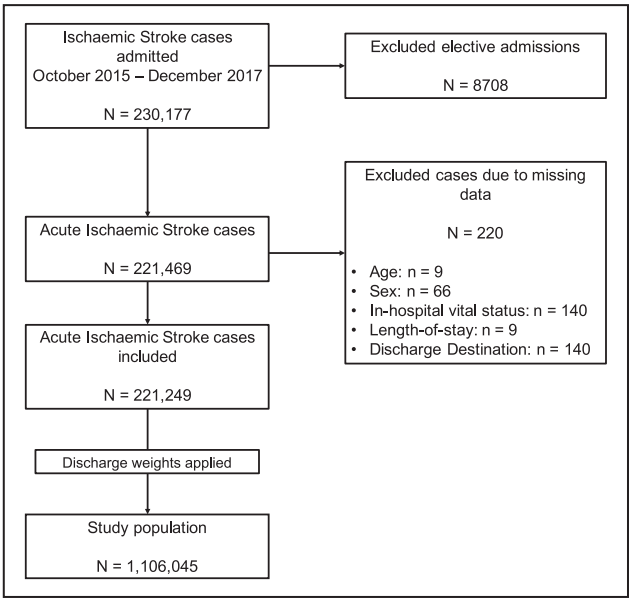

Figure 1. Patient population flowchart.

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.[33,34] 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[2] (Table S2).

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.[35,36] 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 coexisting 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.

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)	5535 (17.39)	
Hispanic	84 950 (7.68)	83 225 (7.75)	1725 (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)	3515 (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	8460 (0.76)	6525 (0.61)	1935 (6.08)	<0.001†
Peripheral vascular disease	112 065 (10.13)	107 395 (10.00)	4670 (14.67)	<0.001†
Paralysis	112 895 (10.21)	108 455 (10.10)	4440 (13.95)	<0.001†
Other neurological disorders	6620 (0.60)	6250 (0.58)	370 (1.16)	<0.001†
Chronic pulmonary disease	174 180 (15.75)	165 835 (15.44)	8345 (26.22)	<0.001†
Diabetes mellitus (without chronic complications)	210 220 (19.01)	204 970 (19.08)	5250 (16.49)	<0.001†
Diabetes mellitus (with chronic complications)	214 400 (19.38)	207 960 (19.36)	6440 (20.23)	0.091
Hypothyroidism	159 160 (14.39)	153 230 (14.26)	5930 (18.63)	<0.001†
Renal failure	181 950 (16.45)	172 590 (16.07)	9360 (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)	7370 (0.69)	325 (1.02)	0.001†
AIDS	2395 (0.22)	2335 (0.22)	60 (0.19)	0.647
Lymphoma	5315 (0.48)	5095 (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 (2.21)	0.006†
Rheumatoid arthritis/collagen vascular disease	30 150 (2.73)	28 755 (2.68)	1395 (4.38)	<0.001†
Coagulopathy	41 405 (3.74)	39 300 (3.66)	2105 (6.61)	<0.001†
Obesity	145 465 (13.15)	140 800 (13.11)	4665 (14.66)	<0.001†
Weight loss	44 030 (3.98)	41 720 (3.88)	2310 (7.26)	<0.001†
Fluid and electrolyte disorders	246 680 (22.30)	236 775 (22.04)	9905 (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)	7125 (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)	3755 (11.80)	0.179
Hypertension	946 140 (85.54)	917 875 (85.45)	28 265 (88.80)	<0.001†

(*Continued*)

Table 1. Continued

	All	No Pulmonary Hypertension	Pulmonary Hypertension	*P* Value
Other comorbidities, n (%)				
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)	670 (2.10)	<0.001†
Dyslipidemia	640 010 (57.86)	621 995 (57.90)	18 015 (56.60)	0.038†
Dementia	131 650 (11.90)	126 515 (11.78)	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	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)	
Large	606 405 (54.83)	588 565 (54.79)	17 840 (56.05)	
Location/teaching status of hospital				
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)	
Urban teaching	757 070 (68.45)	735 075 (68.43)	21 995 (69.10)	
Region of hospital				
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)	
South	461 280 (41.71)	449 410 (41.84)	11 870 (37.29)	
West	207 380 (18.75)	200 740 (18.69)	6640 (20.86)	
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*)

Table 1. Continued

	All	No Pulmonary Hypertension	Pulmonary Hypertension	*P* Value
Disposition of the patient at discharge, n (%)				
Routine discharge	394 105 (35.63)	387 610 (36.08)	6495 (20.41)	…
Transfer to short-term hospital	31 995 (2.89)	31 305 (2.91)	690 (2.17)	
Transfer to other facility: Includes skilled nursing facility, intermediate care facility, another type of facility	468 640 (42.37)	451 480 (42.03)	17 160 (53.91)	
Home health care	156 825 (14.18)	151 585 (14.11)	5240 (16.46)	
Against medical advice	10 685 (0.97)	10 515 (0.98)	170 (0.53)	
Died	43 545 (3.94)	41 470 (3.86)	2075 (6.52)	
Discharged alive, destination unknown	250 (0.02)	250 (0.02)	<11*	

IQR indicates interquartile range.
*Cell sizes ≤10 were not reported to avoid patient re-identification, according to the Healthcare Cost and Utilization Project guidelines[21].
†Statistically significant differences ($P<0.05$).

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.

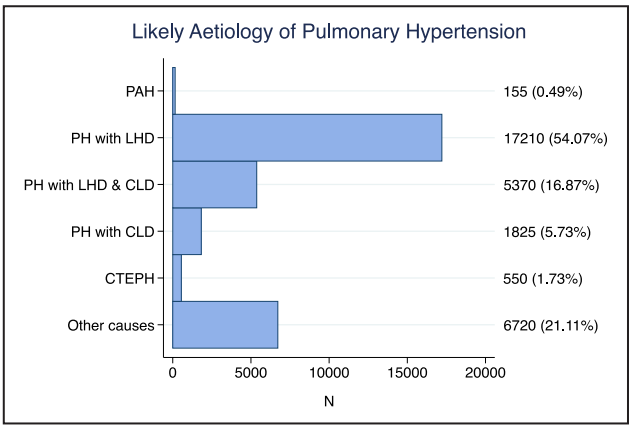

Figure 2. Bar chart detailing the distribution of the likely underlying etiologies of pulmonary hypertension in the included patient sample (total N with PH = 31 830).
CLD indicates chronic lung disease; CTEPH, chronic thromboembolic pulmonary hypertension; LHD, left heart disease; PAH, pulmonary arterial hypertension; and PH, pulmonary hypertension.

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 preexisting 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 (%)				
White	21 655 (68.03)	7645 (67.96)	14 010 (68.08)	0.640
Black	5535 (17.39)	1860 (16.53)	3675 (17.86)	
Hispanic	1725 (5.42)	660 (5.87)	1065 (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	1340 (4.21)	510 (4.53)	830 (4.03)	
Year of admission, n (%)				
2015	3515 (11.04)	1315 (11.69)	2200 (10.69)	0.016†
2016	15 895 (49.94)	5345 (47.51)	10 550 (51.26)	
2017	12 420 (39.02)	4590 (40.80)	7830 (38.05)	
Elixhauser comorbidities, n (%)				
Congestive heart failure	15 150 (47.60)	5670 (50.40)	9480 (46.06)	0.001†
Valvular disease	13 345 (41.93)	4585 (40.76)	8760 (42.57)	0.159
Pulmonary circulation disease	1935 (6.08)	695 (6.18)	1240 (6.03)	0.816
Peripheral vascular disease	4670 (14.67)	1870 (16.62)	2800 (13.61)	0.001†
Paralysis	4440 (13.95)	1505 (13.38)	2935 (14.26)	0.333
Other neurological disorders	370 (1.16)	135 (1.20)	235 (1.14)	0.836
Chronic pulmonary disease	8345 (26.22)	2870 (25.51)	5475 (26.60)	0.344
Diabetes mellitus (without chronic complications)	5250 (16.49)	1830 (16.27)	3420 (16.62)	0.721
Diabetes mellitus (with chronic complications)	6440 (20.23)	2485 (22.09)	3955 (19.22)	0.007†
Hypothyroidism	5930 (18.63)	1105 (9.82)	4825 (23.45)	<0.001†
Renal failure	9360 (29.41)	3595 (31.96)	5765 (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	1395 (4.38)	255 (2.27)	1140 (5.54)	<0.001†
Coagulopathy	2105 (6.61)	1020 (9.07)	1085 (5.27)	<0.001†
Obesity	4665 (14.66)	1645 (14.62)	3020 (14.67)	0.953
Weight loss	2310 (7.26)	735 (6.53)	1575 (7.65)	0.103
Fluid and electrolyte disorders	9905 (31.12)	3340 (29.69)	6565 (31.90)	0.069
Anemia (chronic blood loss)	250 (0.79)	80 (0.71)	170 (0.83)	0.620
Anemia (deficiency)	7125 (22.38)	2475 (22.00)	4650 (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	3755 (11.80)	1070 (9.51)	2685 (13.05)	<0.001†
Hypertension	28 265 (88.80)	9950 (88.44)	18 315 (88.99)	0.517

(*Continued*)

Table 2. Continued

	All (Pulmonary Hypertension)	Male	Female	*P* Value
Other comorbidities, n (%)				
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)	2295 (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)	0.368
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 (58.00)	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)	

(*Continued*)

Table 2. Continued

	All (Pulmonary Hypertension)	Male	Female	*P* Value
Disposition of the patient at discharge				
Routine discharge	6495 (20.41)	2875 (25.56)	3620 (17.59)	<0.001†
Transfer to short-term hospital	690 (2.17)	260 (2.31)	430 (2.09)	
Transfer to other facility: includes skilled nursing facility, intermediate care facility, another type of facility	17 160 (53.91)	5450 (48.44)	11 710 (56.90)	
Home health care	5240 (16.46)	1765 (15.69)	3475 (16.89)	
Against medical advice	170 (0.53)	90 (0.80)	80 (0.39)	
Died	2075 (6.52)	810 (7.20)	1265 (6.15)	
Discharged alive, destination unknown	<11*	<11*	<11*	

IQR indicates interquartile range.
*Cell sizes ≤10 were not reported to avoid patient reidentification, according to the Healthcare Cost and Utilization Project guidelines.[21]
†Statistically significant differences ($P<0.05$).

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[37] and is also associated with incident cardiovascular disease.[10,38] 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.[10] 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.[9] While female patients are generally more likely to develop PH, male patients with PH tend to have worse right ventricular function[39] and generally worse outcomes than female patients with PH.[9] 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

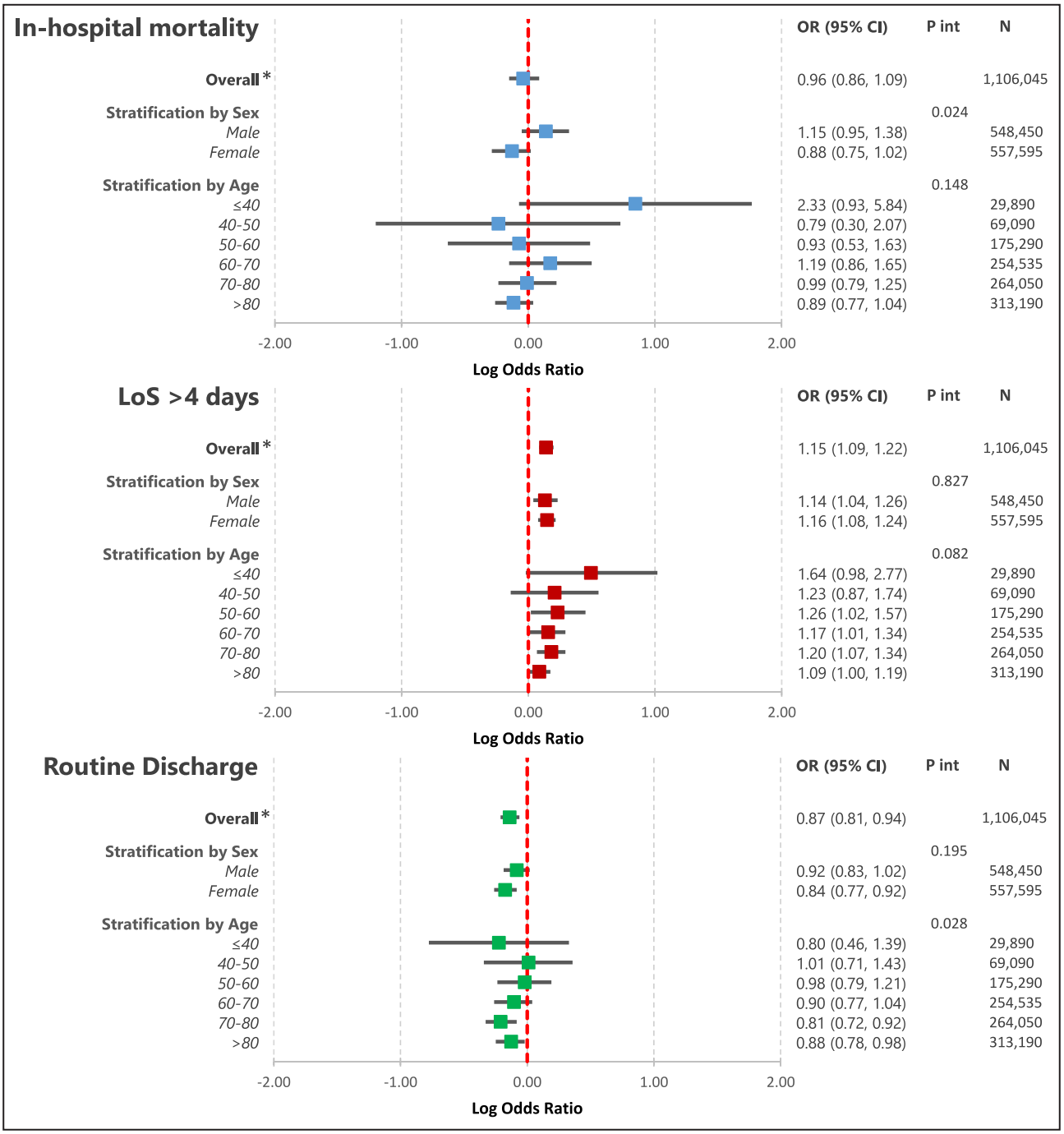

Figure 3. Results of multivariable logistic regressions assessing the association between pulmonary hypertension and in-hospital outcomes after acute ischemic stroke, including stratified analyses by sex and age groups.

*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 mean pulmonary artery pressure are associated with adverse mortality outcomes.[37] Furthermore, patients with PH are more likely to develop right ventricular failure[14] and decreased cardiac functional reserve[15] and may thus be more susceptible to the hemodynamic instability and cardiac complications associated

Table 3. Results of Multivariable Logistic Regressions Assessing the Association Between Pulmonary Hypertension and In-Hospital Outcomes After Acute Ischemic Stroke, Including Interaction Terms With Sex and Age Groups as Well as Preexisting AF and ASVD

	In-Hospital Mortality	LOS >4 Days	Routine Discharge
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Overall*	0.96 (0.86–1.09)	1.15 (1.09–1.22)‡	0.87 (0.81–0.94)‡
Sex interaction term (Ref – females)	1.31 (1.04–1.65)‡	0.99 (0.88–1.11)	1.09 (0.96–1.25)
Age interaction term (10-y increase)	0.93 (0.83–1.03)	0.96 (0.92–1.01)	0.94 (0.89–0.993)‡
Preexisting AF interaction term	0.77 (0.61–0.98)‡	0.88 (0.79–0.99)‡	1.06 (0.93–1.22)
Dyslipidemia or Preexisting ASVD† interaction term	1.18 (0.91–1.53)	0.94 (0.82–1.09)	1.11 (0.94–1.32)

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). Statistically significant results ($P<0.05$) are displayed in bold.

AF indicates atrial fibrillation; ASVD, atherosclerotic vascular disease; LOS, length of stay; OR, odds ratio; and Ref, reference category.

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

†Preexisting ASVD was defined as a composite of coronary heart disease, peripheral vascular disease, or previous stroke/transient ischemic attack.

‡Statistically significant result (P <0.05).

with acute stroke.[16,17] 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,[37,40–42] 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

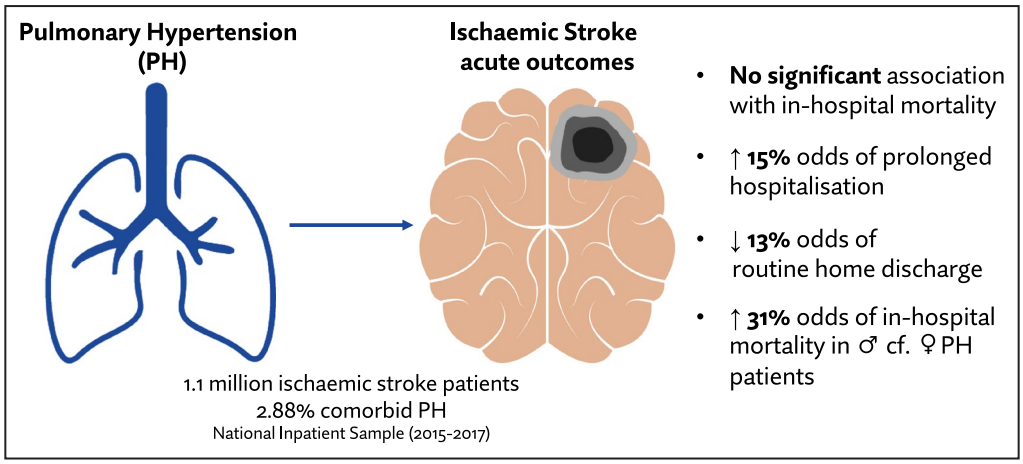

Figure 4. Visual summary of the main study findings.

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.[35,36] 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[10] 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,[10] 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,[43] 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.[2,44]

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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None.

Supplementary Material

Tables S1–S4
Figure S1

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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.

	≤ 40 years			41-50 years			51-60 years		
	No PH	PH	*P* value	No PH	PH	*P* value	No PH	PH	*P* value
N	29520	370		68230	860		172905	2385	
Age, median (IQR)	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 Female, N (%)	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 (%)									
Congestive Heart Failure	2000 (6.78)	130 (35.14)	<0.001	6570 (9.63)	440 (51.16)	<0.001	18850 (10.90)	1285 (53.88)	<0.001
Valvular Disease	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

Hypothyroidism	1465 (4.96)	15 (4.05)	0.721	4385 (6.43)	40 (4.65)	0.340	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	1275 (1.87)	25 (2.91)	0.316	4560 (2.64)	110 (4.61)	0.007
Peptic Ulcer Disease	95 (0.32)	<11	0.626	330 (0.48)	<11	0.207	950 (0.55)	15 (0.63)	0.816
Acquired Immune Deficiency Syndrome	190 (0.64)	<11	0.497	435 (0.64)	<11	0.926	970 (0.56)	15 (0.63)	0.878
Lymphoma	40 (0.14)	<11	0.008	130 (0.19)	<11	0.566	530 (0.31)	<11	0.658
Metastatic Cancer	145 (0.49)	<11	0.540	625 (0.92)	<11	0.735	2690 (1.56)	65 (2.73)	0.039
Solid tumour without metastasis	125 (0.42)	<11	0.566	425 (0.62)	<11	0.315	2010 (1.16)	25 (1.05)	0.816
Rheumatoid Arthritis / Collagen Vascular Disease	960 (3.25)	45 (12.16)	<0.001	1540 (2.26)	15 (1.74)	0.652	3530 (2.04)	120 (5.03)	<0.001
Coagulopathy	1165 (3.95)	20 (5.41)	0.520	1940 (2.84)	75 (8.72)	<0.001	5390 (3.12)	140 (5.87)	<0.001
Obesity	6490 (21.99)	110 (29.73)	0.123	16495 (24.18)	290 (33.72)	0.005	33500 (19.37)	645 (27.04)	<0.001
Weight loss	635 (2.15)	20 (5.41)	0.057	1365 (2.00)	45 (5.23)	0.003	4580 (2.65)	145 (6.08)	<0.001
Fluid and electrolyte disorders	5100 (17.28)	100 (27.03)	0.026	13280 (19.46)	285 (33.14)	<0.001	35050 (20.27)	740 (31.03)	<0.001
Anaemia (chronic blood loss)	130 (0.44)	<11	0.246	385 (0.56)	<11	0.329	370 (0.21)	20 (0.84)	.004
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	4920 (7.21)	60 (6.98)	0.905	15880 (9.18)	180 (7.55)	0.207
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

Hypertension	13965 (47.31)	215 (58.11)	0.063	51140 (74.95)	700 (81.40)	0.059	144910 (83.81)	2065 (86.58)	0.094
OTHER CO-MORBIDITIES, N (%)									
Sepsis	405 (1.37)	25 (6.76)	<0.001	850 (1.25)	20 (2.33)	0.208	2320 (1.34)	55 (2.31)	0.069
Dyslipidaemia	8555 (28.98)	80 (21.62)	0.176	33560 (49.19)	385 (44.77)	0.249	97590 (56.44)	1195 (50.10)	0.006
Dementia	75 (0.25)	<11	0.663	300 (0.44)	<11	0.392	2285 (1.32)	45 (1.89)	0.283
Smoking	9000 (30.49)	85 (22.97)	0.164	24790 (36.33)	250 (29.07)	0.045	63870 (36.94)	705 (29.56)	0.001
Parkinson Disease	15 (0.05)	<11	0.846	70 (0.10)	<11	.6950000000000001	390 (0.23)	<11	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)	<0.001	36565 (21.15)	1115 (46.75)	<0.001
All-cause Bleeding	1995 (6.76)	50 (13.51)	0.023	3910 (5.73)	105 (12.21)	<0.001	10225 (5.91)	285 (11.95)	<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)	0.089	6675 (3.86)	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)	0.006	430 (0.25)	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)	0.016
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	18575 (10.74)	655 (27.46)	<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)	0.955
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			0.351			0.112			<0.001
2015	2985 (10.11)	30 (8.11)		6780 (9.94)	85 (9.88)		17220 (9.96)	260 (10.90)	
2016	13050 (44.21)	140 (37.84)		30390 (44.54)	450 (52.33)		75905 (43.90)	1245 (52.20)	
2017	13485 (45.68)	200 (54.05)		31060 (45.52)	325 (37.79)		79780 (46.14)	880 (36.90)	
Ethnicity			0.016			0.081			<0.001

White	14495 (49.10)	105 (28.38)		34555 (50.64)	360 (41.86)		96575 (55.85)	1135 (47.59)	
Black	7490 (25.37)	150 (40.54)		18790 (27.54)	295 (34.30)		43790 (25.33)	790 (33.12)	
Hispanic	3820 (12.94)	65 (17.57)		7780 (11.40)	90 (10.47)		16035 (9.27)	210 (8.81)	
Asian or Pacific Islander	860 (2.91)	15 (4.05)		2155 (3.16)	55 (6.40)		4620 (2.67)	50 (2.10)	
Native American	190 (0.64)	<11		405 (0.59)	<11		1010 (0.58)	30 (1.26)	
Other	1175 (3.98)	<11		1965 (2.88)	25 (2.91)		4845 (2.80)	55 (2.31)	
Missing	1490 (5.05)	25 (6.76)		2580 (3.78)	35 (4.07)		6030 (3.49)	115 (4.82)	

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 CO-MORBIDITIES, N (%)									
Congestive Heart Failure	31110 (12.46)	2430 (49.09)	<0.001	38245 (14.94)	3615 (45.24)	<0.001	60245 (20.22)	7250 (47.46)	<0.001
Valvular Disease	16790 (6.73)	1640 (33.13)	<0.001	24655 (9.63)	3025 (37.86)	<0.001	41330 (13.87)	7565 (49.53)	<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 (9.76)	525 (10.61)	0.364	28410 (11.10)	1325 (16.58)	<0.001	30940 (10.39)	2370 (15.52)	<0.001
Paralysis	24795 (9.93)	695 (14.04)	<0.001	24665 (9.63)	1105 (13.83)	<0.001	26415 (8.87)	2015 (13.19)	<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 (16.78)	1515 (30.61)	<0.001	45300 (17.69)	2370 (29.66)	<0.001	42980 (14.43)	3415 (22.36)	<0.001
Diabetes (without chronic complications)	54190 (21.71)	980 (19.80)	0.144	56365 (22.01)	1580 (19.77)	0.033	50030 (16.79)	2135 (13.98)	<0.001
Diabetes (with chronic complications)	59155 (23.70)	1465 (29.60)	<0.001	51830 (20.24)	1795 (22.47)	0.033	36890 (12.38)	2100 (13.75)	0.024

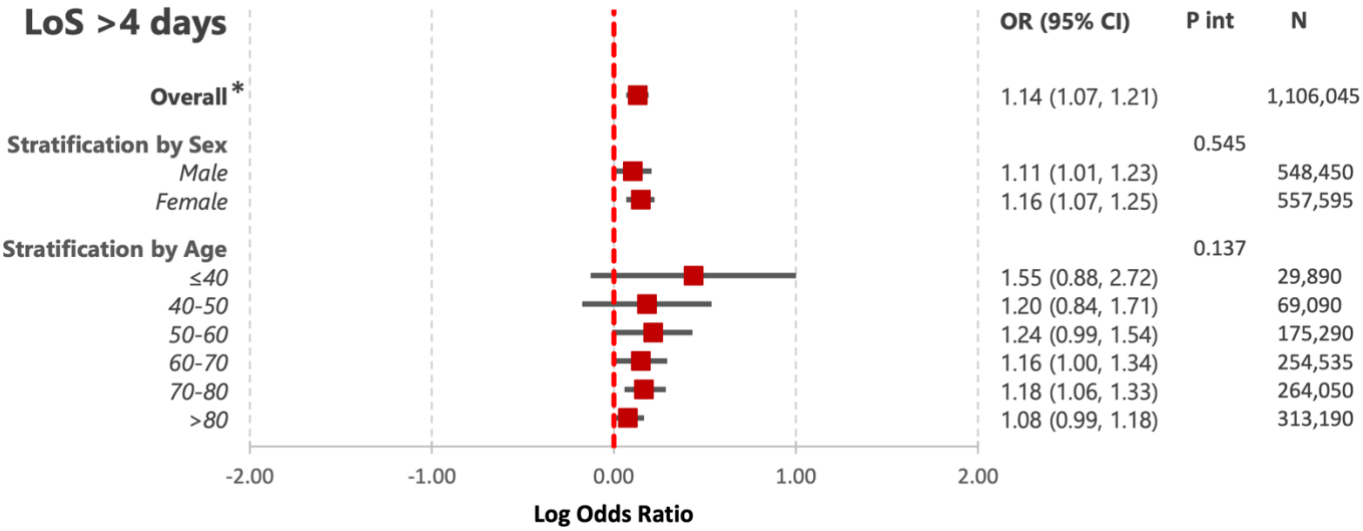
Hypothyroidism	26510 (10.62)	590 (11.92)	0.192	40495 (15.81)	1435 (17.96)	0.024	67895 (22.79)	3640 (23.83)	0.178
Renal Failure	35585 (14.26)	1485 (30.00)	<0.001	46685 (18.23)	2365 (29.60)	<0.001	62660 (21.03)	4565 (29.89)	<0.001
Liver Disease	5770 (2.31)	200 (4.04)	<0.001	3520 (1.37)	200 (2.50)	<0.001	1975 (0.66)	210 (1.37)	<0.001
Peptic Ulcer Disease	1705 (0.68)	65 (1.31)	0.018	1910 (0.75)	80 (1.00)	0.244	2380 (0.80)	155 (1.01)	0.196
Acquired Immune Deficiency Syndrome	520 (0.21)	35 (0.71)	<0.001	185 (0.07)	<11	0.887	35 (0.01)	<11	0.549
Lymphoma	1080 (0.43)	40 (0.81)	0.077	1660 (0.65)	55 (0.69)	0.843	1655 (0.56)	110 (0.72)	0.238
Metastatic Cancer	5370 (2.15)	115 (2.32)	0.723	5170 (2.02)	190 (2.38)	0.311	3405 (1.14)	170 (1.11)	0.881
Solid tumour without metastasis	4410 (1.77)	150 (3.03)	0.003	5915 (2.31)	205 (2.57)	0.502	6080 (2.04)	325 (2.13)	0.735
Rheumatoid Arthritis / Collagen Vascular Disease	6185 (2.48)	210 (4.24)	<0.001	8040 (3.14)	425 (5.32)	<0.001	8500 (2.85)	580 (3.80)	0.002
Coagulopathy	8660 (3.47)	405 (8.18)	<0.001	10215 (3.99)	575 (7.20)	<0.001	11930 (4.00)	890 (5.83)	<0.001
Obesity	40990 (16.42)	1235 (24.95)	<0.001	29875 (11.67)	1395 (17.46)	<0.001	13450 (4.51)	990 (6.48)	<0.001
Weight loss	8555 (3.43)	375 (7.58)	<0.001	10230 (4.00)	480 (6.01)	<0.001	16355 (5.49)	1245 (8.15)	<0.001
Fluid and electrolyte disorders	53255 (21.34)	1625 (32.83)	<0.001	57055 (22.28)	2290 (28.66)	<0.001	73035 (24.52)	4865 (31.85)	<0.001
Anaemia (chronic blood loss)	710 (0.28)	35 (0.71)	0.013	915 (0.36)	55 (0.69)	0.031	1265 (0.42)	135 (0.88)	<0.001
Anaemia (deficiency)	25295 (10.13)	1095 (22.12)	<0.001	31795 (12.42)	1845 (23.09)	<0.001	43040 (14.45)	3450 (22.59)	<0.001
Alcohol abuse	15610 (6.25)	315 (6.36)	0.886	7610 (2.97)	235 (2.94)	0.943	2790 (0.94)	140 (0.92)	0.917
Drug abuse	6435 (2.58)	185 (3.74)	0.022	1440 (0.56)	60 (0.75)	0.318	460 (0.15)	40 (0.26)	0.126
Psychoses	6755 (2.71)	155 (3.13)	0.415	4420 (1.73)	95 (1.19)	0.100	3095 (1.04)	95 (0.62)	0.026
Depression	30335 (12.15)	750 (15.15)	0.005	28205 (11.01)	885 (11.08)	0.938	29470 (9.89)	1645 (10.77)	0.110

Hypertension	216825 (86.87)	4320 (87.27)	0.718	226900 (88.61)	7140 (89.36)	0.351	264135 (88.66)	13825 (90.51)	0.002
OTHER CO-MORBIDITIES, N (%)									
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 (24.85)	<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)	0.334	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			0.195			<0.001			<0.001
2015	24280 (9.73)	535 (10.81)		26350 (10.29)	800 (10.01)		30870 (10.36)	1805 (11.82)	
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			<0.001			<0.001

White	157290 (63.02)	2935 (59.29)		180130 (70.35)	5460 (68.34)		230630 (77.41)	11660 (76.33)	
Black	48630 (19.48)	1265 (25.56)		34430 (13.45)	1475 (18.46)		24425 (8.20)	1560 (10.21)	
Hispanic	19955 (8.00)	300 (6.06)		18090 (7.06)	440 (5.51)		17545 (5.89)	620 (4.06)	
Asian or Pacific Islander	7250 (2.90)	125 (2.53)		7545 (2.95)	150 (1.88)		8395 (2.82)	415 (2.72)	
Native American	1285 (0.51)	25 (0.51)		985 (0.38)	25 (0.31)		715 (0.24)	30 (0.20)	
Other	6600 (2.64)	115 (2.32)		6200 (2.42)	140 (1.75)		6020 (2.02)	310 (2.03)	
Missing	8575 (3.44)	185 (3.74)		8680 (3.39)	300 (3.75)		10185 (3.42)	680 (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