Original Article

Hemorrhagic stroke outcomes of KApSR patients with co-morbid diabetes and Alzheimer's disease

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Background: Vascular risk factors, such as diabetes mellitus (DM), are associated with poorer outcomes following many neurodegenerative diseases, including hemorrhagic stroke and Alzheimer's disease (AD). Combined AD and DM co-morbidities are associated with an increased risk of hemorrhagic stroke and increased Medicare costs. Therefore, we hypothesized that patients with DM in combination with AD, termed DM/AD, would have increased hemorrhagic stroke severity.

Methods: Kentucky Appalachian Stroke Registry (KApSR) is a database of demographic and clinical data from patients that live in Appalachia, a distinct region with increased health disparities and stroke severity. Inpatients with a primary indication of hemorrhagic stroke were selected from KApSR for retrospective analysis and were separated into four groups: DM only, AD only, neither, or both.

Results: Hemorrhagic stroke patients (2,071 total) presented with either intracerebral hemorrhage (ICH), n=1,448, or subarachnoid hemorrhage (SAH), n=623. When examining all four groups, subjects with AD were significantly older (AD+, 80.9±6.6 yrs) (DM+/AD+, 77.4±10.0 yrs) than non AD subjects (DM-/AD-, 61.3±16.5 yrs) and (DM+, 66.0±12.5 yrs). A higher percentage of females were among the AD+ group and a higher percentage of males among the DM+/AD+ group. Interestingly, after adjusting for multiple comparison, DM+/AD+ subjects were ten times as likely to suffer a moderate to severe stroke based on a National Institute of Health Stroke (NIHSS) upon admission [odds ratio (95% CI)] compared to DM-/AD- [0.1 (0.02–0.55)], DM+ [0.11 (0.02–0.59)], and AD+ [0.09(0.01–0.63)]. The odds of DM+/AD+ subjects having an unfavorable discharge destination (death, hospice, long-term care) was significant (P<0.05) from DM-/AD- [0.26 (0.07–0.96)] when adjusting for sex, age, and comorbidities.

Conclusions: In our retrospective analysis utilizing KApSR, regardless of adjusting for age, sex, and comorbidities, DM+/AD+ patients were significantly more likely to have had a moderate or severe stroke leading to an unfavorable outcome following hemorrhagic stroke.

Keywords: Appalachia; Kentucky Appalachian Stroke Registry (KApSR); dementia

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Introduction

Kentucky and West Virginia lie within a portion of rural Appalachia, a population with an increased burden of negative health disparities (1-3). According to the United Heath Foundation, as of 2019, Kentucky and West Virginia ranked 43rd and 45th out of 50, respectively, for overall health in the US. Contributing to this overall negative heath disparity are their rankings of 44th and 46th for stroke and 44th and 50th for diabetes, respectively. Using Medicare costs as a measure of overall health (i.e., high Medicare cost indicates poor health), diabetes mellitus (DM; i.e., type 2 diabetes), has been shown to increase cost by a factor of 2.3 (4). DM is associated with an increased risk of Alzheimer's disease (AD) (5-7) and poorer outcomes following stroke (8). AD is also an additive comorbidity that doubles Medicare cost when associated with stroke and diabetes (9) and has an increased risk of hemorrhagic stroke (10). Stroke, AD, and DM are among the top 7 leading causes of death, not only in Kentucky and West Virginia (11), but globally (12). Many retrospective studies have examined how a single comorbidity influences a neurological disease, such as hemorrhagic stroke, but few have looked at the effect of dual comorbidities or specifically how AD influences hemorrhagic stroke outcomes.

The Kentucky Appalachian Stroke Registry (KApSR) is a database of demographic and clinical data from patients in the rural Kentucky and West Virgina regions with stroke (13). In this study, we used KApSR to retrospectively analyze the contributions of diabetes and AD to outcomes following hemorrhagic stroke such as length of stay, discharge destination, change in National Institute of Health Stroke (NIHSS), and 30-day readmission rates. Our central aim was to examine the relationship between the combination of diabetes and AD and hemorrhagic stroke severity.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-1451).

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Kentucky Appalachian Stroke Registry (KApSR) (de-identified data provided under IRB# 13-08058) and individual consent for this retrospective analysis was waived.

Study sample

Kentucky Appalachian Stroke Registry (KApSR) is a database of demographic and clinical data from patients that live in Appalachia Kentucky (13), a distinct region with increased health disparities and stroke severity. A cross-sectional analysis of inpatients with cardiovascular disease (CVD) containing a principle diagnosis of hemorrhagic stroke were evaluated for DM and/or AD in the KApSR database from 2010–2018. Hemorrhagic stroke patients were identified in KApSR as presenting with intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), methods previously described (13). Briefly, demographics, comorbidities (defined by International Classification of Disease (ICD) codes), glycated hemoglobin A1 (hbA1c) values, previous diagnosis of AD, and outcome measures were collected from electronic health records (EHR) for inpatients, >18 years old, with an ICH or SAH, ICD9 codes: 431 and 430; ICD10 codes of 161 and 160, respectively. The accuracy of using EHR in KApSR was previously validated and reported by Kitzman *et al.* (13). We separated patients into four comorbidity categories: no previous diagnosis of DM or AD (DM-/AD-), DM only (DM+), AD only (AD+), or combined DM and AD (DM+/AD+).

Outcomes

Admission and discharge NIHSS were collected, along with length of stay, and discharge destination (favorable or unfavorable). Favorable discharge destinations include: alive/routine, transfer to other institution, hospital swing bed, or home health services, rehabilitation facility/unit, against medical advice, police case, or billin. Unfavorable discharge destinations include: death (≤48 or >48 hrs), hospice, skilled nursing facility, or long-term care hospital. Change in NIHSS from admission to discharge was measured as an indicator of short-term inpatient outcome (14).

Statistical analysis

Demographic characteristics are presented without adjustment for covariates as mean ± standard deviation or sample number (percentages). A1Cs were categorized as normal (<5.7%) or as abnormal (≥5.7%) (15,16) that included diabetics (A1C ≥6.5%) and prediabetics (5.7≤ A1C <6.5) (17). Between-group differences in demographic

characteristics were investigated using a series of one-way ANOVAs for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Differences in non-normal continuous variables were assessed using a Kruskal-Wallis test. Significant between group differences were used as control variables in model 3 of the main outcome analysis (described below). To investigate between group differences in the main outcome variables, three models were employed. Model 1 was unadjusted, model 2 was adjusted for age and sex, and model 3 was adjusted for age, sex, type of hemorrhage, race, and all significant comorbidities (other than DM and AD). The DM/AD was the reference group for all analyses. Depending on the distribution of the outcome, these models were analyzed using linear regression, logistic regression, or ordinal logistic regression. Due to its non-normal distribution and inability to achieve normality under any data transformation, NIHSS was recoded into an ordinal variable defined as: 0–5= mild, 6–13= moderate, and >13= severe stroke (18-20). The change (Admission-Discharge) in NIHSS was transformed into an ordinal variable based on whether the patient was: declining, staying the same, or improving. This change was based on the continuous NIHSS value. Discharge destination, a binary variable, was classified as favorable or unfavorable using the rules outlined above. Length of stay positively skewed and was log transformed to approximate normality. For all models, odds ratios and 95% confidence intervals (CI) were calculated for all outcome measures. For each outcome, Dunnett's procedure was used to correct for multiple comparisons, since each category was being compared against the DM/AD condition (21). Graphical and statistical analysis was performed using Graphpad Prism and SAS version 9.4 (SAS Institute Inc.).

Missing data and statistical assumption

NIHSS, the main outcome, was missing for 40.2% (n=833) of the sample. Our hospital institution transitioned from the Primary Stroke Center to a Comprehensive Stroke Center in 2013, and our standards and mechanisms for documentation in the EMR changed. These evolutions could account for missing data points in our study, which, unfortunately, could not be recovered. A missing data analysis was performed using demographic and comorbidity variables as predictors of missingness in a multivariable logistic regression. Table S1 (see supplemental materials) contains the results of this analysis. The following characteristics and comorbidities were associated with lower odds of having missing NIHSS: older age, current hypertension, tobacco use, dyslipidemia and carotid stenosis. Females and those with SAH stroke type had higher levels of missing data. There were no significant differences between AD or DM conditions. These variables were included in the models where NIHSS were the outcome of interest. No covariates contained missing data.

As a result of missing NIHSS data and a small sample for the main comparison condition (DM+/AD+), a there is a concern for the violation of statistical assumptions due to the small expected cell sizes for the contingency tables of Model 1 (described above). To address this concern, Fisher's exact tests, a nonparametric version of a chi-square test of independence, was performed on NIHSS outcomes for all pairwise comparisons where DM+/AD+ was the reference group. The substantive results of these tests aligned with the parametric versions reported in the results. Despite certain statistical assumptions of our model not being met, the agreement between these two sets of analyses lends credence to our interpretations.

Results

Demographic characteristics

A total of 2,071 patients with hemorrhagic stroke were included: 1,459 (70.4%) were without DM and AD (DM-/AD-), 567 (27.4%) had DM alone (DM+), 29 (1.4%) had AD alone (AD+), and 16 had both DM and AD (DM+/AD+). *Table 1* presents descriptive statistics for the demographic and comorbidity variables with between group comparisons. There were significant (P<0.0001) differences in the age of the groups (*Figure 1A*): 61.3±16.5 yrs (DM-/AD-) to 66.01±12.5 yrs (DM+), 80.9±6.6 yrs (AD+), and 77.4±10.0 yrs (DM+/AD+). Patients with an AD diagnosis (AD+ or DM+/AD+) were significantly (P<0.0001, P<0.05, respectively) older than DM alone. Sex was significantly (P<0.05) different among the groups, with ~50% female for DM-/AD- and DM+ to ~76% female in AD+ and ~31% female in DM+/ AD+ (*Figure 1B*). A significantly higher percentage of DM+ (P<0.0001) and AD+ (P<0.01), compared to the DM-/AD- (*Figure 1C*), had a prior stroke. DM+/AD+ followed this trend but did not reach significance (P=0.08). No statistical difference among race in the four groups was observed (*Table 1*). Across the four groups, ICH was more common than SAH (*Figure 1D*), with DM+ and AD+ having significantly more ICH than SAH compared to DM-/AD-.

Table 1 Demographics of hemorrhagic stroke patients in KApSR

Variable	-DM/-AD	DM	AD	DM/AD	Test statistic	P value
Total N	1,459 (70.4%)	567 (27.4%)	29 (1.4%)	16 (0.8%)		
Age, yrs (mean ± SD)	61.3±16.5	66.0±12.5	80.9±6.6	77.4±10.0	31.1	<0.0001
Sex, female, N (%)	745 (51.1%)	290 (51.1%)	22 (75.9%)	5 (31.3%)	9.615	0.0221
Stroke type, ICH, n (%)	974 (66.8%)	436 (76.9%)	25 (86.2%)	13 (81.3%)	24.69	<0.0001
Race, n (%)						0.2954
White	1,317 (90.3%)	565 (99.8%)	29 (100%)	12 (75%)		
Black	107 (7.3%)	0	0	4 (25%)		
Asian	11 (0.8%)	0	0	0		
Hispanic	3 (0.2%)	0	0	0		
Other/non-Hispanic	8 (0.5%)	1 (0.2%)	0	0		
Refused/unreported	13 (0.9%)	1 (0.2%)	0	0		
Comorbidities, n (%)						
Prior stroke/transient ischemic attack	225 (15.4%)	130 (22.9%)	10 (34.5%)	5 (31.3%)	23.25	<0.0001
Atrial fibrillation	208 (14%)	131 (23%)	9 (31.0%)	6 (38.0%)	31.42	<0.0001
Coronary artery disease	258 (17.7%)	205 (36.2%)	11 (37.9%))	9 (56.3%)	91.32	<0.0001
Dyslipidemia	470 (32.2%)	324 (57.1%)	14 (48.3%)	10 (62.5%)	110.7	<0.0001
Hypertension	1,233 (84.6%)	544 (95.9%)	22 (75.9%)	14 (87.5%)	52.63	<0.0001
Obesity	177 (12.1%)	127 (22.4%)	2 (6.9%)	1 (6.25%)	36.52	<0.0001
Carotid stenosis	42 (2.9%)	36 (6.3%)	1 (3.4%)	0	14.06	0.0048
History of myocardial infarction	72 (4.9%)	45 (7.9%)	1 (3.4%)	2 (12.5%)	8.351	0.0301
Acute myocardial infarction	78 (5.3%)	41 (7.2%)	0 (0)	2 (12.5%)	5.729	0.1036
Tobacco	600 (41.2%)	188 (33.2%)	6 (20.7%)	6 (37.5%)	15.14	0.0014
hbAlc						
n	413	369	12	11		
Mean ± SD	5.6±0.7	7.5±1.9	5.4±0.4	6.6±0.6	119.2	<0.0001
≥5.7 AIC (%)	162 (39.0%)	326 (88%)	6 (50%)	10 (100)	207.8	<0.0001
Outcomes[†]						
Admission NIHSS value, median [IQR]	7 [1–19]	7 [2–18]	9 [2–23]	19 [15–26]		
Ordinal admission NIHSS, n (%)						
Mild: 0–5	389 (46.6%)	160 (43.4%)	9 (39.1%)	1 (9.1%)		
Moderate: 6–13	166 (19.9%)	78 (21.1%)	6 (26.1%)	1 (9.1%)		
Severe: >13	280 (33.5%)	131 (35.5%)	8 (34.8%)	9 (81.8%)		
Discharge NIHSS value, median [IQR]	6 [1–18]	6 [1–19]	12 [4–23]	19 [10–22]		

Table 1 *(continued)*

Table 1 *(continued)*

Variable	-DM/-AD	DM	AD	DM/AD	Test statistic	P value
Ordinal discharge NIHSS, n (%)						
Mild: 0–5	412 (49.3%)	179 (48.5%)	7 (30.4%)	0 (0%)		
Moderate: 6–13	149 (17.8%)	68 (18.4%)	5 (21.7%)	4 (36.4%)		
Severe: >13	274 (32.8%)	122 (33.1%)	11 (47.8%)	7 (63.6%)		
NIHSS change value, median [IQR]	0 [–1 to 1]	0 [–1 to 2]	0 [–4 to 1]	1 [0 to 7]		
Ordinal NIHSS change, n (%)						
Decline	228 (27.3%)	108 (29.3%)	9 (39.1%)	2 (18.2%)		
Stable	332 (39.8%)	122 (33.1%)	7 (30.4%)	3 (27.3%)		
Improve	275 (32.9%)	139 (37.7%)	7 (30.4%)	6 (54.6%)		
Unfavorable discharge, n (%)	571 (39.1%)	240 (42.3%)	18 (62.1%)	12 (75.0%)		
Length of stay (log), mean (SD)	1.63 (1.16)	1.71 (1.09)	1.28 (0.90)	1.83 (1.10)		

Data are mean ± SD and number with percent of population. †, statistical analysis for outcome presented in Model 1 of Table 2. AD, Alzheimer's disease; DM, diabetes mellitus; F, female; hbA1c, glycosylated hemoglobin A1c; ICH, intracerebral hemorrhage; IQR, interquartile range; KApSR, Kentucky Appalachian Stroke Registry; M, male; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; SAH, subarachnoid hemorrhage.

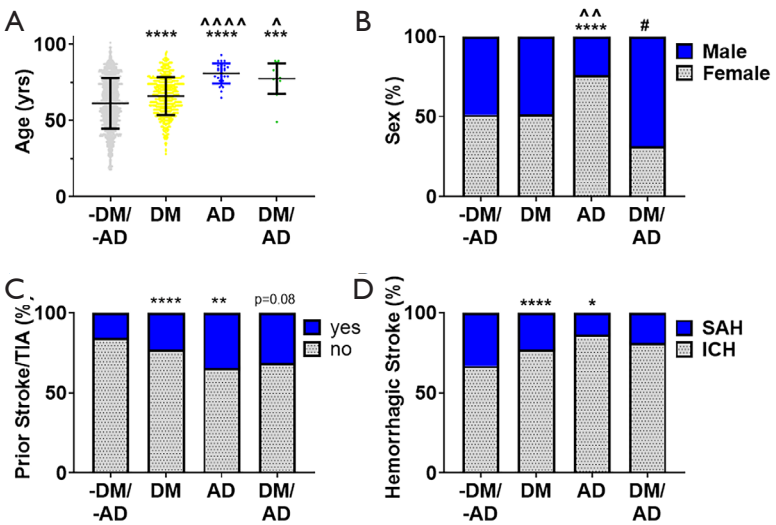

Figure 1 Hemorrhagic stroke demographic among KApSR. The average (A) age as well as percentage of (B) males to females, (C) patients with a prior stroke, and (D) type of hemorrhagic stroke among the four subgroups (-DM/-AD, DM, AD, and DM/AD). Data are mean ± SEM. P values were assessed by ANOVA or Chi-squared followed by followed by a Tukey's post-hoc test or a 2×2 Chi-squared. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001 indicates significance from -DM/-AD. ^, P<0.05; ^^, P<0.01; and ^^^^, P<0.0001 indicates significance from DM. #P<0.05 indicates significance from AD. AD, Alzheimer's disease; ANOVA, Analysis of Variance; DM, diabetes mellitus; ICH, intracerebral hemorrhage; KApSR, Kentucky Appalachian Stroke Registry; TIA, transient ischemic attack; SEM, standard error of mean; SAH, subarachnoid hemorrhage; yrs, years.

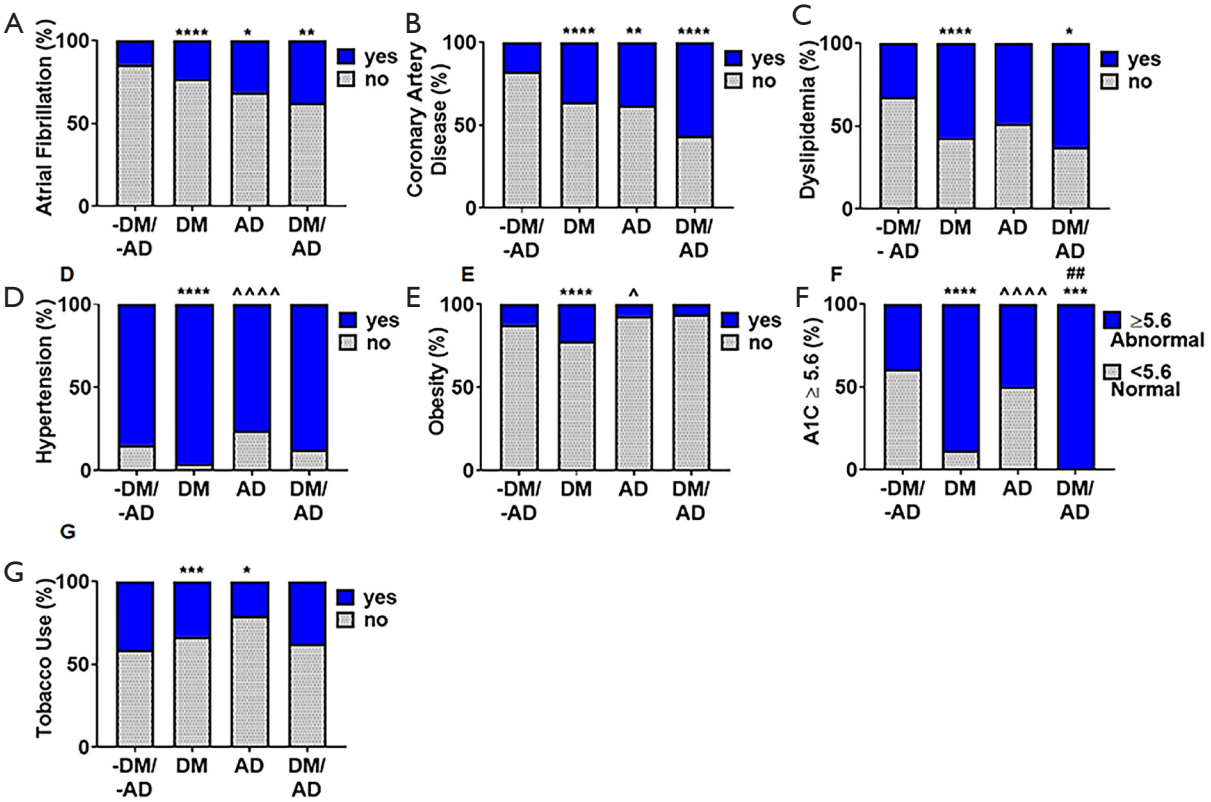

Figure 2 Comorbidities among KApSR patients with hemorrhagic stroke. The percentage of patients with (A) atrial fibrillation, (B) coronary artery disease, (C) dyslipidemia, (D) hypertension, (E) obesity, (F) hbA1c ≥5.6, and (G) tobacco use among the four subgroups (–DM/-AD, +DM, +AD, and DM/AD). Data are represented as percentage of yes/no. P values were assessed by Chi-squared, 4×2, followed by followed 2×2. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 indicates significance from -DM/-AD. ^P<0.05 and ^^^^P<0.0001 indicates significance from DM. ##P<0.01 indicates significance from AD. AD, Alzheimer's disease; DM, diabetes mellitus; hbA1c, glycosylated hemoglobin A1c.

When evaluating comorbidities, a significantly higher percentage of patients with atrial fibrillation (P<0.0001, *Figure 2A*) and coronary artery disease (P<0.0001, *Figure 2B*) were seen in DM+, AD+, and DM+/AD+ compared to DM-/AD-. Dyslipidemia was only significantly (P<0.0001) different among the subjects with DM (DM+ and DM+/AD+, *Figure 2C*) compared to DM-/AD-. Hypertension (P<0.0001, *Figure 2D*) and obesity (P<0.0001, *Figure 2E*) increased in subjects with only DM, compared to DM-/AD- and the AD groups. Differences in carotid stenosis (P<0.01) and a history of, but not acute, myocardial infarction (P<0.05) were observed with only the DM group compared to the DM-/AD- group (*Table 1*). A significantly (P<0.0001, *Figure 2F*) higher percentage of patients with A1C ≥5.6% were among subjects with DM (DM+ and DM+/AD+) compared to both DM-/AD- and AD. The percentage of prediabetics/diabetics, based on abnormal A1Cs, increase from 39% (DM-/AD-) to 88% (DM+), 50% (AD+), and 100% (DM+/AD+; *Figure 2F*). Tobacco use (P<0.01, *Figure 2G*) was significantly higher among DM and AD groups compared to DM-/AD-.

Outcomes

Differences in NIHSS was assessed using ordinal logistic regression. Results are presented in the first three sections of *Table 2*. Regardless of adjusting for age, sex, and comorbidities, DM+/AD+ patients were significantly more likely to have had a moderate or severe stroke compared to the other three groups. Using parameter estimates from Model 3 (*Table 2*), DM+/AD+ patients were 10 times (i.e., 1/0.10=10) more likely to have had a moderate or severe stroke based on the admission NIHSS (*Figure 3A*). At discharge, DM+/AD+ patients were approximately

Table 2 Regression analysis for outcome measures of hemorrhagic stroke patients

Variable	Model 1			Model 2			Model 3		
	Odds ratio (SE)	95% CI	P value	Odds ratio (SE)	95% CI	P value	Odds ratio (SE)	95% CI	P value
Admission NIHSS[†]									
-DM/-AD (n=835)	0.11 (0.78)	0.02–0.59	0.008	0.12 (0.78)	0.02–0.66	0.012	0.10 (0.80)	0.02–0.55	0.006
DM+ (n=369)	0.12 (0.78)	0.02–0.67	0.013	0.13 (0.78)	0.02–0.72	0.017	0.11 (0.80)	0.02–0.59	0.009
AD+ (n=23)	0.13 (0.87)	0.02–0.87	0.033	0.12 (0.87)	0.02–0.80	0.026	0.09 (0.88)	0.01–0.63	0.013
DM/AD (n=11)	1.0 (ref)			1.0 (ref)			1.0 (ref)		
Discharge NIHSS[†]									
-DM/-AD (n=835)	0.21 (0.65)	0.05–0.86	0.028	0.25 (0.65)	0.06–1.03	0.055	0.22 (0.65)	0.05–0.92	0.036
DM+ (n=369)	0.21 (0.65)	0.05–0.89	0.032	0.24 (0.65)	0.06–1.00	0.050	0.22 (0.66)	0.05–0.91	0.036
AD+ (n=23)	0.42 (0.76)	0.08–2.18	0.366	0.38 (0.76)	0.07–1.97	0.297	0.32 (0.76)	0.06–1.70	0.211
DM/AD (n=11)	1.0 (ref)			1.0 (ref)			1.0 (ref)		
Change NIHSS[†]									
-DM/-AD (n=835)	0.46 (0.58)	0.13–1.62	0.270	0.41 (0.58)	0.11–1.46	0.195	0.37 (0.59)	0.10–1.35	0.151
DM+ (n=369)	0.49 (0.59)	0.14–1.77	0.335	0.46 (0.59)	0.13–1.66	0.282	0.44 (0.59)	0.12–1.57	0.243
AD+ (n=23)	0.32 (0.69)	0.07–1.47	0.166	0.36 (0.70)	0.08–1.64	0.219	0.34 (0.70)	0.07–1.55	0.187
DM/AD (n=11)	1.0 (ref)			1.0 (ref)			1.0 (ref)		
Unfavorable discharge[‡]									
-DM/-AD (n=1,459)	0.21 (0.58)	0.06–0.76	0.014	0.33 (0.59)	0.09–1.19	0.097	0.26 (0.59)	0.07–0.96	0.040
DM+ (n=567)	0.25 (0.58)	0.07–0.87	0.028	0.33 (0.59)	0.09–1.20	0.099	0.31 (0.59)	0.08–1.29	0.078
AD+ (n=29)	0.55 (0.69)	0.12–2.46	0.532	0.46 (0.70)	0.10–2.10	0.383	0.36 (0.71)	0.08–1.70	0.234
DM/AD (n=16)	1.0 (ref)			1.0 (ref)			1.0 (ref)		
Average stay (log transformed)[§]	Mean (SE)			Mean (SE)			Mean (SE)		
-DM/-AD (n=1,459)	1.63 (0.03)		0.489	1.61 (0.03)		0.177	1.95 (0.06)		0.748
DM+ (n=567)	1.71 (0.05)		0.684	1.74 (0.05)		0.381	1.92 (0.07)		0.657
AD+ (n=29)	1.28 (0.21)		0.123	1.47 (0.21)		0.138	1.82 (0.21)		0.515
DM/AD (n=16)	1.83 (0.28)		REF	1.99 (0.28)		REF	2.04 (0.27)		REF

DM+, AD+ served as the reference group for analysis. Data are odds ratios and 95% CI or mean (SE). Both P values and confidence intervals were calculated using Dunnett's multiple comparison procedure. Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, type of hemorrhage, race, and all comorbidities (other than DM and AD). NIHSS was transformed into ordinal variables defined as: 0–5= mild, 6–13= moderate, and >13= severe stroke. The change (Admission-Discharge) in NIHSS was transformed into an ordinal variable based on whether the patient was: declining, staying the same, or improving. Discharge destination transformed into binary variable and classified as favorable or unfavorable. [†]Ordinal logistic regression. [‡]Logistic regression. [§]Linear Regression. CI, confidence interval; DM, diabetes mellitus; AD, Alzheimer's disease; NIHSS, National Institutes of Health Stroke Scale; SE, standard error.

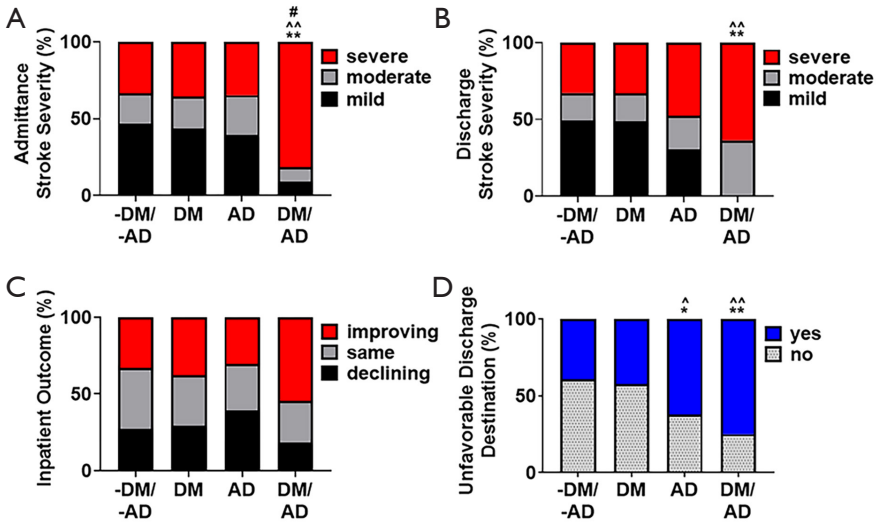

Figure 3 Hemorrhagic stroke outcomes among KApSR patients. NIHSS was transformed into ordinal variables defined as: 0–5= mild, 6–13= moderate, and >13= severe stroke for (A) admission and (B) discharge outcomes. (C) Inpatient outcomes defined as improving, same, or declining NIHSS (Admission-Discharge). (D) Discharge destination transformed into binary variable classified as favorable or unfavorable. Data are represented as percentage variables. P values were assessed by Chi-squared, 4×3, followed by followed 2×3. *P<0.05, **P<0.01 indicates significance from -DM/-AD. ^P<0.05 and ^^P<0.01 indicates significance from DM. #P<0.05 indicates significance from AD. AD, Alzheimer's disease; DM, diabetes mellitus; KApSR, Kentucky Appalachian Stroke Registry; NIHSS, National Institute of Heath Stroke Scale.

4.5 times more likely to be in the moderate or severe NIHSS categories compared to DM-/AD- and DM+, which translated into DM+/AD+ subjects having a higher percentage of strokes classified as severe at discharge (*Figure 3B*). However, even though DM+/AD+ patients had significantly worse admission and discharge NIHSS, their change in NIHSS (admission–discharge) indicating in patient outcome was not significantly different from the other three groups (*Figure 3C*, *Table 2*).

The relationship between comorbidity condition and experiencing an unfavorable discharge was examined using logistic regression. The DM+/AD+ subjects had a significantly higher percentage of unfavorable discharge destinations compared to DM-/AD- and DM+ (*Figure 3D*). Interestingly, when adjusting for age and sex (model 2), discharge destination was not significantly different among groups. However, in the unadjusted (model 1) and adjusted for age, sex, and comorbidities (model 3; *Table 2*), the odds of DM+/AD+ having an unfavorable discharge destination was significant (P<0.05) from DM-/AD- and DM+. The average number of days in the hospital (*Table 2*, regardless of modeling) was not significantly different from the DM+/AD+ group.

Several of the covariates included in Model 3 were significantly related to the outcomes. In particular, older individuals were more likely to have had a moderate to severe stroke based on their discharge NIHSS, they were less likely to remain stable or improve from admission to discharge, and were more likely to have an unfavorable outcome. Additionally, stroke type was a strong predictor of outcomes. Compared to those who experienced a SAH stroke, those who had an ICH stroke were more likely to have experienced a moderate to severe stroke based on both admission and discharge NIHSS, were less likely to remain stable or improve, and were more likely to experience an unfavorable discharge destination.

Discussion

Compared to ischemic stroke, hemorrhagic stroke leads to a higher mortality rate (22,23), increased need for palliative care (24), and higher hospitalization costs (25) associated with higher Medicare expenditures (26). This highlights the need to predict outcomes and manage comorbidities before hemorrhagic strokes occur. Studies have looked at the risk of AD and dementia after stroke (27,28), but few studies have looked at hemorrhagic stroke risk in patients with AD (29). Our study found DM+/AD+ patients had more

severe hemorrhagic strokes (higher NIHSS) at admission and discharge that contributed to a larger percentage with unfavorable discharge destinations. No differences between groups were observed for length of hospital stay and inpatient outcomes.

The presence of comorbidities is known to increase mortality following stroke (30,31). Specifically, high blood glucose, as occurs in diabetes, is associated with early mortality (32). An abnormal A1c may be an indicator that the patient is prediabetic or not managing their diabetes with their current regimen, possibly due to a lack of diagnosis, ability to treat, or patient compliance.

DM increases the risk of developing AD (33-36), and the metabolic changes associated with DM can initiate/accelerate AD pathologies through oxidative stress, inflammation, and vascular injury (37). AD is associated with amyloid and tau pathologies that damage neurons or weaken the vasculature. Changes in cognition associated with AD may be associated with the weakening of the cerebrovasculature that can present years before damage is apparent. Higher percentage of prior strokes among the AD population may be due to amyloid deposition (38), which repeatedly weakens the vasculature. Diabetes treatment has been shown to lower amyloid load (39,40). However, the effects of controlling A1c values are controversial in dementia (39-42) due to adverse effects of hypoglycemias on the brain. DM+/AD+ subjects in KApSR have lower A1c's, indicating controlled diabetes, but significantly worse NIHSS following hemorrhagic stroke. This suggests the importance of controlling diabetes, while preventing hypoglycemia, to prevent vascular injury and altered cognition. Patients with AD have higher relative risk and absolute rates of hemorrhagic stroke compared to non-AD controls (10,29,43-45). In our analysis, when controlling for age, the AD population had the worst outcomes.

Several limitations should be considered when interpreting these results, including disparities in: diet (46,47), physical activity (48), socio-economic status (49), race (50), and drug use (51-54), all inherent to the rural Appalachian population (55,56). We used the diagnosis of AD rather than the broader umbrella term dementia. While AD is just one type of dementia (57) it accounts for ~60–70% of the cases (58). Diagnosis of AD and other dementias may be severely underreported or underdiagnosed, as occurs nationally (59-61), but may be heightened due to inherit health disparities in rural Appalachia. Additional cognitive and brain imaging diagnosis tools, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), were not available in this study. Any current medications for comorbidities, including diabetes, were also not available for our analysis. Comorbidities can also affect ischemic stroke, which can also lead to a secondary hemorrhagic stroke. As our analysis only included hemorrhagic strokes coded as primary diagnosis, the effect of diabetes and AD on a secondary hemorrhagic stroke was not analyzed and may be considered a limitation in our study. However, previous studies suggest alternate comorbidities may be associated with secondary hemorrhagic stroke following ischemic stroke. Arboix *et al.* found hemorrhagic lacunar stroke patients were more like to have hypertension, than diabetes (62) and patients with hemorrhagic stroke following cardioembolic stroke had a higher association with atrial fibrillation (63).

In conclusion, diabetes and AD should be considered as risk factors for an unfavorable outcome following hemorrhagic stroke. Diabetic screening and education for the AD population/caregivers is critical in addressing potential therapeutics to prevent hemorrhagic stroke.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Kentucky Appalachian Stroke Registry (KApSR) (de-identified data provided under IRB# 13-08058) and individual consent for the retrospective analysis was waived.

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Supplementary

Table S1 Predictors of missing NIHSS

Predictor	Not missing NIHSS (n=1238)	Missing NIHSS (n=833)	Odds ratio (95% CI)	P value
AD+/DM+ group				
DM+/AD+	11 (68.8%)	5 (31.2%)	Ref	0.613
DM+	369 (65.1%)	198 (34.9%)	0.96 (0.30–3.10)	
AD+	23 (79.3%)	6 (20.7%)	0.49 (0.11–2.21)	
DM-/AD-	835 (57.2%)	624 (42.8%)	0.96 (0.30–3.07)	
Age, mean (SD)	65.63 (15.21)	50.04 (15.61)	0.99 (0.98–0.99)	<0.001
Sex				0.021
Male	646 (64.0%)	363 (36.0%)	Ref	
Female	592 (55.7%)	470 (44.3%)	1.27 (1.04–1.54)	
Race				0.056
White	1,112 (59.6%)	754 (40.4%)	Ref	
Other	124 (61.7%)	77 (38.3%)	0.72 (0.52–1.01)	
Stroke type				<0.001
ICH	1,033 (71.3%)	415 (28.7%)	Ref	
SAH	205 (32.9%)	418 (67.1%)	4.38 (3.52–5.45)	
Comorbidities				
Hypertension	1,128 (62.2%)	685 (37.8%)	0.67 (0.49–0.90)	0.008
Atrial fibrillation	241 (68.1%)	113 (31.9%)	1.04 (0.79–1.38)	0.760
Coronary artery disease	316 (65.4%)	167 (34.6%)	1.14 (0.88–1.49)	0.326
Tobacco	471 (58.8%)	330 (41.2%)	0.78 (0.63–0.96)	0.019
Obesity	192 (62.5%)	115 (37.5%)	0.82 (0.62–1.09)	0.167
Dyslipidemia	566 (69.2%)	252 (30.8%)	0.64 (0.52–0.80)	<0.001
Carotid stenosis	65 (82.3%)	14 (17.7%)	0.41 (0.22–0.76)	0.005
Prior stroke/transient ischemic attack	259 (70.0%)	111 (30.0%)	0.91 (0.69–1.18)	0.468
Acute myocardial infarction	74 (61.1%)	47 (38.8%)	0.86 (0.57–1.31)	0.483
History myocardial infarction	71 (59.2%)	49 (40.8%)	1.51 (0.98–2.33)	0.065

Data are n (percent) and odds ratios with a 95% CI. Both P values and confidence intervals were calculated using Dunnett's multiple comparison procedure. AD, Alzheimer's disease; CI, confidence interval; DM, diabetes mellitus; ICH, intracerebral hemorrhage; SD, standard deviation; SAH, subarachnoid hemorrhage.

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