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CME Outcomes Following Possible Undiagnosed Aneurysmal Subarachnoid Hemorrhage: A Contemporary Analysis

Dustin G. Mark, MD, Mamata V. Kene, MD, MPH, David R. Vinson, MD, and Dustin W. Ballard, MD, MBE

A related article appears on page 1514.

ABSTRACT

Objectives: Existing literature suggests that patients with aneurysmal subarachnoid hemorrhage (aSAH) and "sentinel" aSAH symptoms prompting healthcare evaluations prior to aSAH diagnosis are at increased risk of unfavorable neurologic outcomes and death. Accordingly, these encounters have been presumed to be unrecognized opportunities to diagnose aSAH and the worse outcomes representative of the added risks of delayed diagnoses. We sought to reinvestigate this paradigm among a contemporary cohort of patients with aSAH.

Methods: A case-control cohort was retrospectively assembled among patients diagnosed with aSAH between January 1, 2007 and June 30, 2013 within an integrated healthcare delivery system. Patients with a discrete clinical evaluation for headache or neck pain within 14 days prior to formal aSAH diagnosis were identified as cases, and the remaining patients served as controls. Modified Rankin Scale scores at 90 days and 1 year were determined by structured chart review. Multivariable logistic regression controlling for age, sex, ethnicity, presence of intracerebral or intraventricular hemorrhage at diagnosis, and aneurysm size was used to compare adjusted outcomes. Sensitivity analyses were performed using varying definitions of favorable neurologic outcomes, a restricted control subgroup of patients with normal mental status at hospital admission, inclusion of additional cases that were diagnosed outside of the integrated health system, and exclusion of patients without evidence of subarachnoid blood on initial noncontrast cranial computed tomography (CT) at the diagnostic encounter (i.e. "CT-negative" SAH).

Results: A total of 450 patients with aSAH were identified, 46 (10%) of whom had clinical evaluations for possible aSAH-related symptoms in the 14 days preceding formal diagnosis (cases). In contrast to prior reports, no differences were observed among cases compared to control patients in adjusted odds of death or unfavorable neurologic status at 90 days (0.35, 95% confidence interval [CI] = 0.11–1.15; 0.59, 95% CI = 0.22–1.60, respectively) or at 1 year (0.58, 95% CI = 0.19–1.73; 0.52, 95% CI = 0.18–1.51, respectively). Likewise, neither restricting the analysis to a control subgroup of patients with normal mental status at hospital admission, varying the dichotomous definition of unfavorable neurologic outcome, inclusion of cases diagnosed outside the integrated health system, or exclusion of patients with CT-negative SAH resulted in significant adjusted outcome differences.

Conclusion: In a contemporary cohort of patients with aSAH, we observed no statistically significant increase in the adjusted odds of death or unfavorable neurologic outcomes among patients with clinical evaluations for possible aSAH-related symptoms in the 14 days preceding formal diagnosis of aSAH. While these findings cannot exclude a smaller risk difference than previously reported, they can help refine decision analyses and testing threshold determinations for patients with possible aSAH.

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Etiologies of nontraumatic subarachnoid hemorrhage (SAH) are broadly grouped into two major categories based on the absence or presence of central nervous system vascular anomalies, the latter of which portend a much higher risk for morbidity and mortality than the former.[1] The highest-risk cases are due to ruptured cerebral aneurysms, otherwise known as aneurysmal subarachnoid hemorrhage (aSAH), which cause roughly 80% of all SAH, occur with a known annual incidence of approximately 10 per 100,000 among North American populations (and likely higher due to undiagnosed aSAH causing out-of-hospital deaths), and result in serious morbidity or death in 50% to 70% of cases.[2] Rates of preceding encounters for possible aSAH-related symptoms (i.e., "sentinel" headaches) have historically ranged from 12% to 51% and have been associated with increased unadjusted downstream odds of death or severe disability compared to patients without such encounters, resulting in a recommended "no-miss" approach to aSAH diagnosis.[3–7] However, several factors arguably warrant repeat examination of this paradigm. First, the most recent study examining outcomes following possible unrecognized aSAH in the emergency department (ED) reported a considerably lower absolute rate of associated 1-year mortality (6.2%), compared to prior studies.[8] Second, there has been an apparent decrease over time in the number of closed claims concerning the diagnosis of SAH.[9,10] Third, there has been a steady increase in cranial computed tomography (CT) use among ED patients presenting with headache over the past 20 years, which is notable given that the predominant diagnostic error in a prior case series of possible undiagnosed aSAH was a failure to perform CT.[3,11] Finally, there have been progressive improvements in observed outcomes among patients with poor-grade aSAH over the past two decades, in part attributable to improvements in endovascular therapies.[12,13] Given these observations, it is conceivable that the contemporary rate of possible unrecognized diagnosis and/or the risk of adverse outcomes among misdiagnosed patients is lower than previously thought. To test the underlying hypothesis that presumed undiagnosed aSAH may now be a lower risk and/or less common scenario than previously appreciated, this study examined a contemporary case-control cohort of patients with aSAH diagnosed within in an integrated health delivery system.

METHODS

Study Design and Setting

We undertook a retrospective chart review of patients treated within Kaiser Permanente Northern California (KPNC) between January 2007 and June 2013 to establish a case-control cohort. KPNC is an integrated healthcare delivery system that provided comprehensive medical care for over 3.9 million health plan members during the study period, with over 1.2 million ED visits annually. The study was approved by the Kaiser Foundation Research Institute Institutional Review Board with a waiver of the requirement for informed consent.

Selection of Participants

Patient health records were screened for study inclusion if they had an ED or inpatient encounter within KPNC with an associated International Statistical Classification of Diseases and Related Health Problems, ninth edition (ICD-9), diagnosis code of subarachnoid hemorrhage (430). Since the ICD-9 code 430 encompasses both traumatic and nontraumatic SAH, patients were electronically excluded if they had an ICD-9 coded diagnosis within 24 hours of the index encounter that was consistent with head or neck trauma (ICD-9 codes 800–805, 850–854, 910, 918, 920, 921, 925, 941). Patients were also electronically excluded if they lacked continuous health plan membership within 14 days preceding aSAH diagnosis (the study time frame for possible undiagnosed aSAH), were under 18 years of age, or had a prior diagnosis of SAH between 2002 and 2006. Charts were then manually reviewed for evidence of SAH on noncontrast cranial CT or greater than five red blood cells per microliter on cerebrospinal fluid analysis, along with either 1) angiographic evidence of a cerebral aneurysm that was managed as a ruptured aneurysm by the treating clinicians, based on hemorrhage pattern and/or clinical presentation, or 2) failure to undergo angiography due to death or a moribund state (i.e., from a presumed aneurysm rupture).[14] Patients with suspected aSAH based on the above criteria were included in the study cohort. All cohort patients were then screened for possible undiagnosed aSAH, defined as a clinical encounter (including telephone calls) within 14 days prior to formal aSAH diagnosis in which a complaint of headache or neck pain was documented. A 14-day window was chosen since upwards of 90% of clinical encounters with possible aSAH-related

complaints prior to formal aSAH diagnoses occur within this time frame.[3,4] These patients with relevant prior encounters were designated as cases within the cohort, with the remainder being designated controls. The contemporary rate of possible undiagnosed aSAH diagnosis within the health system was thus established by dividing the number of cases by the total number of patients with aSAH.

Given the potential for selection bias in including only patients who were formally diagnosed with aSAH within the integrated health system, we sought to identify patients who had an initial clinical encounter with possible aSAH-related symptoms within the integrated health system, but who either were subsequently diagnosed with aSAH at an out-of-system facility or suffered an out-of-hospital death. To identify patients with aSAH diagnosed outside of KPNC, we queried an outside claims database for encounters with an ICD-9–coded diagnosis of SAH (430). These health records were then manually screened for possible undiagnosed aSAH, as detailed. To identify possible cases of possible undiagnosed aSAH resulting in an out-of-hospital death, we queried a composite KPNC death database (including both the California state and the Social Security Death Indices) for records with either an assigned cause of death of nontraumatic subarachnoid hemorrhage (ICD-10 code I60) or an unknown cause of death. In both cases, patients were excluded who met the electronic exclusion criteria specified above. We additionally excluded patients from the death database search who had been enrolled in palliative care or hospice within 30 days prior to death. Finally, for cases with an unknown cause of death, we reviewed only those patients with an outpatient or ED encounter within 14 days prior to death accompanied by one of the following ICD-9 diagnostic codes, all of which have been highly associated with SAH misdiagnosis in the literature: hypertension (401–405), sinusitis (461–473), stroke or transient ischemic attack (433–436), meningitis (013.0, 036.0, 047, 098.82, 320–322), syncope (780.2, 992.1), giant cell arteritis (446.5), migraine/headache (307.81, 339 [except 339.2], 346, 784.0), and neck pain (723.1).[8] A CONSORT diagram of the cohort selection is presented in Figure 1.

Methods and Measurements

Two emergency medicine physicians (DGM and MVK) conducted a structured explicit chart review and abstraction of records. Abstractors documented the Glasgow Coma Scale (GCS) score, Hunt-Hess grade both at the time of diagnosis and at hospital admission, presence or absence of SAH and intraventricular or intracerebral hemorrhage on cranial imaging at the time of diagnosis, aneurysm size and location (the largest documented if multiple), use of external ventricular drainage, treatment of delayed cerebral vasospasm during hospitalization, and the lowest modified Rankin Scale (mRS) score within 90 days and 1 year following the initial diagnosis, using previously described methodology.[15] A mRS score of 3 or greater was considered a priori to represent an unfavorable neurologic outcome (i.e., the inability to live independently). Both abstractors reviewed 13% of the sample to establish inter-rater reliability (reported as percent agreement), based on an expected minimal agreement of 66% and an estimated error margin of 20%.[16]

Outcomes

The primary outcomes of interest were the adjusted 90-day and 1-year odds of unfavorable neurologic outcomes and death among cases compared to controls.

Analysis

The primary outcomes were examined using both unadjusted and adjusted odds ratios (ORs). While good clinical grade (Hunt-Hess grade 1 and 2 and/or GCS score of 15) had been shown to be nearly as accurate as most other predictive models for outcome in aSAH, research has suggested additional effects from age, sex, ethnicity, presence of intracerebral or intraventricular hemorrhage at diagnosis, and aneurysm size.[17–19] We thus adjusted for all these variables using logistic regression. Missing values for aneurysm size, which were missing at less than the commonly accepted threshold rate of 30% (21%), were estimated using multiple imputation via the MI function in STATA v13.0 (College Station, TX, USA) with five permutations for each missing datapoint.[20]

Since prior literature[3] used a restricted control cohort of patients with normal mental status (Hunt Hess grade 1 or 2) at the time of hospital admission, we performed a sensitivity analysis using this strategy. While this strategy is meant to more closely match control patients to their case counterparts in terms of mental status at the initial clinical contact (i.e., at the possible undiagnosed encounter for cases), this does assume that all cases truly had SAH at the time of their precedent encounter, an assumption that introduces bias toward a lower severity of illness in the

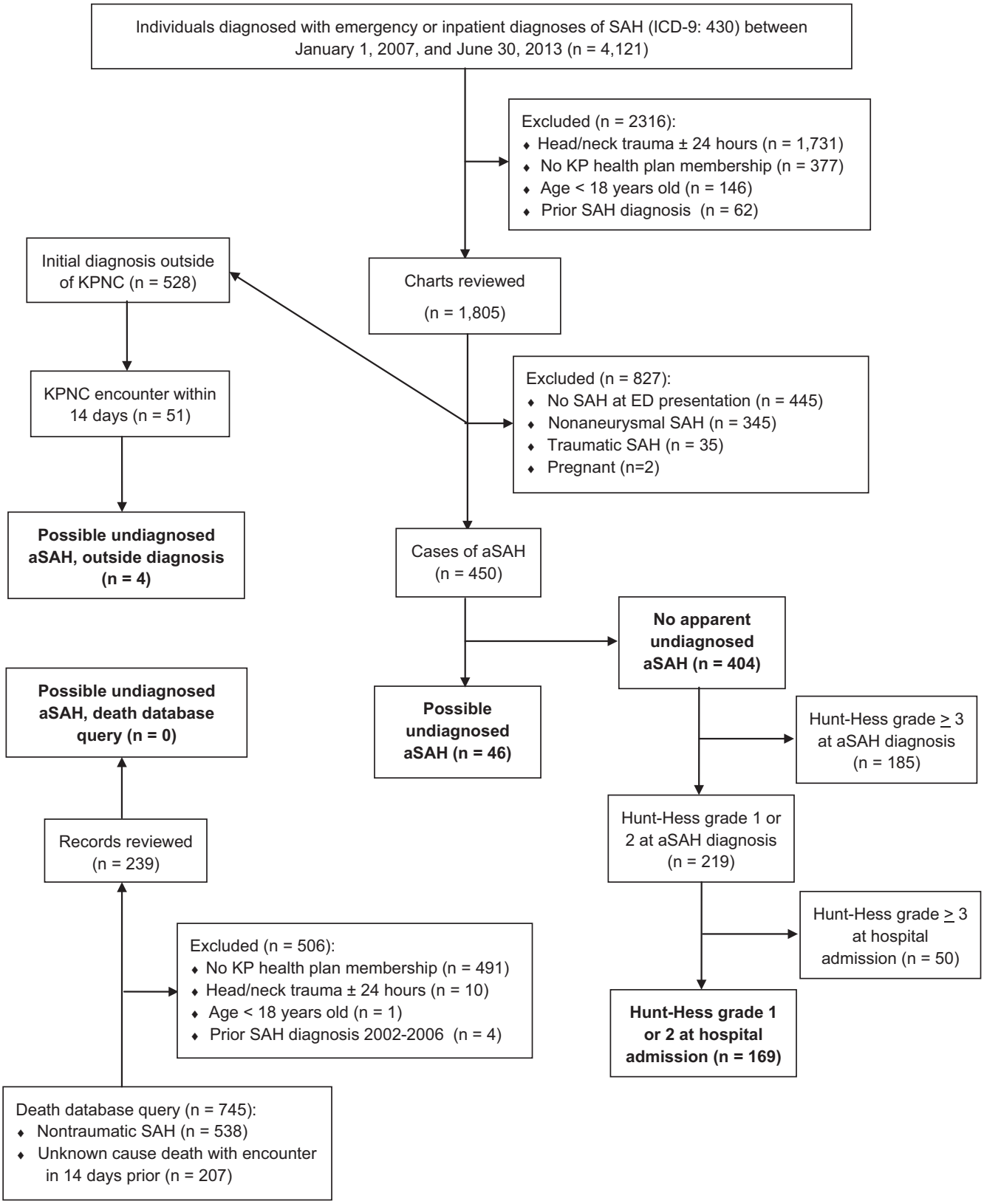

Figure 1. CONSORT diagram of study cohort selection. aSAH = aneurysmal subarachnoid hemorrhage; KPNC = Kaiser Permanente Northern California.

control group. Thus we chose not to use this strategy for our primary analysis. However, this restricted control strategy does exclude patients who have a marked deterioration in mental status between diagnosis and hospital admission, a group that has worse observed outcomes than their presenting neurologic grade

would otherwise suggest.[21,22] As such, inclusion of these patients among the controls would likewise be a potential source of selection bias toward lower severity of disease in the case group. We removed regression adjustments for Hunt-Hess grade and presence of intraventricular or intracerebral hemorrhage on initial diagnostic imaging since these variables were not reliably available at the initial clinical contact among cases. We also removed adjustments for sex and ethnicity to maintain a minimum of 5 events per independent variable in all restricted cohort models, given nonsignificant associations with the outcomes of interest in the primary regression model.[23] In addition, given the differing cut points for binary neurologic outcome adjudication examined by prior authors,[3] we conducted sensitivity analyses using these alternate definitions of unfavorable neurologic outcome, defined as either an mRS score of 2 and higher or an mRS score of 4 and higher, in tandem with the restricted control cohort approach. We also reexamined all analyses after inclusion of additional patients with possible undiagnosed aSAH who were formally diagnosed with aSAH at an out-of-system facility or who suffered an out-of-hospital death, as described above. Finally, given the theoretical potential that false-positive cerebrospinal fluid analyses could be coupled with an incidental finding of a cerebral aneurysm, we performed a final sensitivity analysis excluding patients without evidence of subarachnoid blood on the initial noncontrast cranial CT performed at the diagnostic encounter (i.e., "CT-negative" SAH).

Statistical significance was defined as a p-value of 0.05 or less using the Student's t-test or Fisher's exact test for continuous and categorical variables, respectively, and a 95% confidence interval (CI) that did not include the null value (1.0) for ORs. All statistical analyses were performed using STATA v 13.0.

RESULTS

Of 4,121 potential patients identified by ICD-9 coding alone within KPNC, 450 patients were ultimately determined to have aSAH, of whom 46 (10%) were cases of possible undiagnosed aSAH, which is similar to previously reported rates.[3] Among the remaining 404 control patients, 219 (54%) had a normal mental status (Hunt-Hess grade 1 or 2) at the time of aSAH diagnosis; of these, 50 patients had worsening of their neurologic status prior to hospital admission; 30 to Hunt-Hess grade 3, 18 to grade 4, and two to grade 5, with 1-year mortality and poor neurologic outcome (mRS > 3) rates among these 50 patients of 32 and 38%, respectively. Subsequently, there were 169 (42%) patients with a normal mental status upon hospital admission comprising the restricted control cohort (Figure 1).

Compared with the control cohort, cases trended toward higher rates of normal mental status at the time of aSAH diagnosis (65% vs. 54%, p = 0.16), but otherwise had similar presenting characteristics including age, ethnicity, sex, aneurysm location, aneurysm size, and rates of intraventricular or intracerebral hemorrhage, as shown Table 1. Among cases, the most common venue for possible undiagnosed aSAH was equally split between the ED and outpatient clinics (46% vs. 43%, respectively), with 20% undergoing cranial CT imaging at the initial encounter, and the most common diagnostic impression being unspecified headache (67%, Table 2). Seven of the nine cases who had negative cranial CT examinations at the time of initial evaluation went on to manifest CT-positive aSAH at a median of 5 days later. Notably, cases were more likely to be treated for delayed cerebral vasospasm than control patients (39% vs. 22%, p = 0.02).

Compared to all control patients with aSAH, cases had lower unadjusted odds of certain primary outcomes (90-day mortality OR = 0.39, 95% CI = 0.16–0.94, p = 0.04; 1-year unfavorable neurologic outcome OR = 0.48, 95% CI = 0.23–0.99, p = 0.05). However, these differences became nonsignificant after adjustment for confounders (Table 3). Sensitivity analysis using the restricted control cohort conversely demonstrated an increase in the unadjusted odds of 1-year mortality (OR = 2.75, 95% CI = 1.05–7.22, p = 0.04) among cases, which likewise became nonsignificant after adjustment for confounding factors (Table 4). The nonsignificant findings of these adjusted analyses were robust with regard to varying dichotomous definitions of unfavorable neurologic outcomes (Table 5), the addition of four additional cases of possible undiagnosed aSAH identified through out-of-system claims and death record review (Table 6), and the exclusion of patients with CT-negative SAH (Table 7). Percent agreement between abstractors for absence of a clinical encounter for possible SAH-related symptoms in the 14 days prior to aSAH diagnosis, Hunt-Hess grade of < 2 at aSAH diagnosis, mRS > 3 within 90 days, and mRS > 3 at 1 year was 100, 95, 98, and 100%, respectively.

Table 1
Patient Characteristics and Outcomes Accordingly to Control, Restricted Control, and Case Cohorts

Variable	No Encounter in Past 14 Days (Control Cohort, n = 404)	No Encounter in Past 14 Days, Normal Mental Status at Hospital Admission (Restricted Control Cohort, n = 169)	Encounter in Past 14 Days (Case Cohort, n = 46)
Age (years)	59 (49–69)	53 (46–65)	61 (52–68)
Female (%)	75	72	76
Ethnicity (%)			
White	49	43	52
Asian	20	21	22
Black	14	18	9
Hispanic	1	2	2
Unknown/Other	15	15	15
Glasgow Coma Score	15 (13–15)	15 (15–15)	15 (14–15)
Hunt-Hess grade at aSAH diagnosis			
1	4	9	17
2	50	91	48
3	22	NA	20
4	12	NA	7
5	12	NA	9
Subarachnoid hemorrhage seen on initial cranial imaging (%)*	97	92	89
Intraventricular or intracerebral hemorrhage (%)*	39	11	35
Aneurysm location			
ACOM	16	20	24
PCOM	26	34	26
MCA	16	15	13
ICA	6	7	11
ACA	4	6	7
Basilar	5	4	4
PICA	3	2	2
Vertebral	2	3	2
Other	8	9	10
Unknown	14	0	4
Aneurysm size (mm)	5 (4–8)	5 (3–7)	6 (4–8)
Aneurysm side, right (%)	30	34	43
Vasospasm requiring intervention	22	22	39
Hydrocephalus requiring external ventricular drainage	35	16	35
Mortality (%)			
90-day	28	6	13
1-year	29	7	17
mRS score > 2			
90-day	58	33	48
1-year	51	24	33

(Continued)

Table 1 (continued)

Variable	No Encounter in Past 14 Days (Control Cohort, *n* = 404)	No Encounter in Past 14 Days, Normal Mental Status at Hospital Admission (Restricted Control Cohort, *n* = 169)	Encounter in Past 14 Days (Case Cohort, *n* = 46)
mRS score > 3			
90-day	41	14	26
1-year	37	12	22
mRS score > 4			
90-days	33	9	20
1-year	32	9	20

ACA = anterior cerebral artery; ACOM = anterior communicating artery; aSAH = aneurysmal subarachnoid hemorrhage; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; PCOM = posterior communicating artery; PICA = posterior inferior cerebellar artery.
*Does not include cranial imaging performed on encounters prior to correct diagnosis among patients with suspected misdiagnosis.

Table 2
Details Surrounding Cases of Possible Undiagnosed Aneurysmal Subarachnoid Hemorrhage

Days to formal diagnosis, median (IQR)	3 (1–5)
Location of care	
ED	21/46 (46%)
Outpatient clinic	20/46 (43%)
Telephone call	4/46 (9%)
Inpatient	1/46 (2%)
Testing prior to formal diagnosis	
None	36/46 (78%)
CT	9/46 (20%)
Magnetic resonance imaging	1/46 (2%)
Lumbar puncture	0/50 (0%)
Initial diagnostic impression	
Headache	31/46 (67%)
Neck pain	5/46 (11%)
Sinusitis	4/46 (9%)
Other*	5/46 (11%)

IQR = interquartile range.
*Included upper respiratory infection (2), hypertensive urgency (1), fatigue/stress (1), and unknown (1).

DISCUSSION

We observed that, among patients diagnosed with aSAH in the EDs of an integrated health system, approximately 10% of patients had contact with the health system in the 14 days prior to diagnosis with a possible aSAH-related complaint of headache or neck pain. However, in contrast to previous case-control reports,[3–5,7] when controlling for confounding factors, these patients did not demonstrate statistically significant increased odds of unfavorable neurologic outcomes, despite demonstrating a higher rate of delayed cerebral vasospasm. This was true whether compared to all other patients diagnosed with aSAH or compared to a restricted control cohort of patients with normal mental status at the time of hospital admission. These findings were robust to variations in dichotomous definitions of unfavorable neurologic outcome, as well as the addition of additional cases diagnosed out of system and the exclusion of cases with less evidence supporting the diagnosis of aSAH (i.e., CT-negative SAH).

A key difference in the current study design, compared to prior literature, is that we adjusted for confounding factors beyond simply selecting for control patients with normal mental status at hospital admission. It is notable that, in the primary analysis, cases had *improved* unadjusted outcomes and a trend toward improved adjusted outcomes, a finding that is

Table 3
Odds of Adverse Outcomes Among Cases of Possible Undiagnosed Aneurysmal Subarachnoid Hemorrhage Versus All Control Patients

	Unadjusted Odds (95% CI)	Adjusted Odds (95% CI)*
90-day mortality	0.39 (0.16–0.94), p = 0.04	0.35 (0.11–1.15), p = 0.09
90-day poor neurologic outcome (mRS > 3)	0.52 (0.26–1.03), p = 0.06	0.59 (0.22–1.60), p = 0.30
1-year mortality	0.52 (0.23–1.15), p = 0.10	0.58 (0.19–1.73), p = 0.33
1-year poor neurologic outcome (mRS > 3)	0.48 (0.23–0.99), p = 0.05	0.52 (0.18–1.51), p = 0.23

Whole control cohort *n* = 404, case cohort *n* = 46.
*Adjusted for age, sex, nonwhite ethnicity, aneurysm size, intracerebral or intraventricular hemorrhage on initial CT, and Hunt-Hess grade at diagnosis.
mRS = modified Rankin Scale

Table 4
Odds of Adverse Outcomes Among Cases of Possible Missed Diagnosis of Aneurysmal Subarachnoid Hemorrhage Versus Restricted Control Cohort With Normal Mental Status at the Time of Hospital Admission

	Unadjusted Odds (95% CI)	Adjusted Odds (95% CI)*
90-day mortality	2.39 (0.82–6.97), p = 0.11	1.84 (0.59–5.68), p = 0.29
90-day poor neurologic outcome (mRS > 3)	2.13 (0.97–4.69), p = 0.06	1.61 (0.67–3.85), p = 0.28
1-year mortality	2.75 (1.05–7.22), p = 0.04	2.07 (0.70–6.06), p = 0.19
1-year poor neurologic outcome (mRS > 3)	1.96 (0.85–4.53), p = 0.12	1.35 (0.52–3.49), p = 0.54

Restricted control cohort *n* = 169, case cohort *n* = 46.
*Adjusted for age and aneurysm size.
mRS = modified Rankin Scale

Table 5
Sensitivity Analysis Using Differing Definitions of Unfavorable Neurologic Outcome Among Cases of Possible Missed Diagnosis of Aneurysmal Subarachnoid Hemorrhage Versus Restricted Control Cohort With Normal Mental Status at the Time of Hospital Admission

	Unadjusted Odds (95% CI)	Adjusted Odds (95% CI)*
90-day poor neurologic outcome (mRS > 2)	1.85 (0.95–3.59), p = 0.07	1.62 (0.81–3.25), p = 0.18
90-day poor neurologic outcome (mRS > 4)	2.32 (0.95–5.69), p = 0.06	1.66 (0.63–4.39), p = 0.31
1-year poor neurologic outcome (mRS > 2)	1.56 (0.76–3.18), p = 0.22	1.24 (0.58–2.64), p = 0.59
1-year poor neurologic outcome (mRS > 4)	2.50 (1.01–6.16), p = 0.05	1.79 (0.66–4.83), p = 0.25

Restricted control cohort *n* = 169, case cohort *n* = 46.
*Adjusted for age and aneurysm size.
mRS = modified Rankin Scale.

Table 6
Odds of Adverse Outcomes Following Inclusion of Outside Diagnosis Cohort Patients Among Cases of Possible Missed Diagnosis of Aneurysmal Subarachnoid Hemorrhage

	Adjusted Odds (95% CI)v	
	Whole Cohort*	Restricted Cohort†
90-day mortality	0.29 (0.10–0.89), p = 0.03	1.70 (0.56–5.14), p = 0.35
90-day poor neurologic outcome (mRS > 3)	0.64 (0.25–1.63), p = 0.35	1.89 (0.81–4.43), p = 0.14
1-year mortality	0.47 (0.17–1.34), p = 0.16	1.91 (0.66–5.51), p = 0.23
1-year poor neurologic outcome (mRS > 3)	0.50 (0.18–1.35), p = 0.17	1.41 (0.56–3.54), p = 0.47

Whole control cohort *n* = 404, restricted control cohort *n* = 169, case cohort *n* = 50.
*Adjusted for age, sex, nonwhite ethnicity, aneurysm size, intracerebral or intraventricular hemorrhage on initial CT, and Hunt-Hess grade at diagnosis.
†Adjusted for age and aneurysm size.
mRS = modified Rankin Scale.

Table 7
Odds of Adverse Outcomes Following Exclusion of Patients Diagnosed With Aneurysmal Subarachnoid Hemorrhage in the Absence of Subarachnoid Blood on Noncontrast Cranial CT (i.e., Diagnosis of Subarachnoid Hemorrhage Made by Cerebrospinal Fluid Analysis)

	Adjusted Odds (95% CI)	
	Whole Cohort*	Restricted Cohort†
90-day mortality	0.36 (0.11–1.16), p = 0.09	1.77 (0.55–5.72), p = 0.34
90-day poor neurologic outcome (mRS > 3)	0.51 (0.20–1.29), p = 0.16	1.47 (0.57–3.80), p = 0.42
1-year mortality	0.44 (0.14–1.37), p = 0.16	1.62 (0.49–5.31), p = 0.43
1-year poor neurologic outcome (mRS > 3)	0.43 (0.15–1.17), p = 0.10	1.16 (0.41–3.31), p = 0.78

Whole control cohort *n* = 390, restricted control cohort *n* = 155, case cohort *n* = 42.
*Adjusted for age, sex, nonwhite ethnicity, aneurysm size, intracerebral or intraventricular hemorrhage on initial CT, and Hunt-Hess grade at diagnosis.
†Adjusted for age and aneurysm size.
mRS = modified Rankin Scale.

particularly remarkable given that cases had significantly higher rates of delayed cerebral vasospasm, a complication of aSAH typically associated with significantly worse neurologic outcomes.[24] This observation might indicate the presence of protective factors among patients who initially present with "sentinel" or clinically unimpressive symptoms that are not reflected in the typical predictors of outcome following aSAH, perhaps because those aneurysms are more prone to manifest with minor and/or intermittent leakage as opposed to overt rupture.

If a state of minor and/or intermittent aneurysmal leakage truly exists among cases, it intuitively makes sense to select for control patients who maintain a stable normal mental status from the time of diagnosis through hospital admission. And indeed, when analyzed in an unadjusted manner, there do appear to be worse outcomes among cases compared to this restricted cohort of control patients, albeit not to the same degree as previously observed. However, this analytic paradigm is arguably flawed at its basis, since one cannot fully assume that all cases truly had undiagnosed aSAH prior to their formal diagnosis, meaning that the case cohort is undoubtedly contaminated with patients presenting for the first time with aSAH, as well as the corresponding full range of clinical severity and higher averaged rates of unfavorable outcomes. This assertion is supported by a study that found that CT and clinical characteristics were similar when comparing patients with and without sentinel headaches preceding aSAH diagnosis, while the features of patients with known rebleeding were drastically different at the time of rebleeding, arguing against the assertion that the diagnostic presentation in the patients with sentinel headaches always represents an episode of rebleeding, or at least not the high-risk hyperacute subtype that occurs after diagnosis but prior to definitive aneurysmal treatment.[21,25] As such, it is particularly relevant that we excluded patients with possible hyperacute rebleeding from the restricted control cohort. In the end, the finding that even minimal variable adjustment (i.e., for age and aneurysm size) in the restricted cohort analysis rendered any unadjusted suggestions of worsened outcomes among cases nonsignificant largely nullifies this debate in the context of the primary analysis findings.

Another important finding was the relatively stable rate of possible undiagnosed aSAH, compared to older studies.[3,7] We initially hypothesized that this rate would have decreased substantially owing to increased access to and availability of cranial CT over the past two decades. However, the proportion of patients undergoing cranial imaging at the time of misdiagnosis remained low (20%) and comparable to the rate observed by Kowalski et al.[3] (25%) nearly 15 years ago. Given that cranial CT is, on average, over 93% sensitive for SAH among patients with normal mental status, it is arguable that a failure to perform cranial CT imaging is the single most significant factor contributing to unrecognized diagnoses.[26–29]

A counterargument could be made that a predominance of cases had CT-negative SAH at the time of the initial clinical encounter. However, the clinical course observed among cases suggests otherwise. Most notable was that the rate of delayed cerebral vasospasm prompting treatment among the patients with possible undiagnosed aSAH were nearly double those observed in the overall cohort (39% vs. 22%), despite a lower average severity of neurologic grade at diagnosis and identical rates of intraventricular hemorrhage (35%), both of which are independent factors positively associated with the development of vasospasm.[30] This observation is in line with known associations between sentinel headaches and subsequent vasospasm, which have been recently bolstered by a reported independent association between delayed clinical vasospasm and evidence of antecedent minor SAH leaks on magnetic resonance imaging at a rate similar to that observed among cases in this study.[31,32] Considering that delays in aneurysm treatment following SAH raise the relative risk of vasospasm,[33] and that vasospasm is rarely seen in CT-negative SAH (only one of the 18 patients with CT-negative aSAH in this cohort had clinical vasospasm), the nearly doubled rate of vasospasm among patients in the case group supports the notion that SAH would have likely been present on CT in a majority of case patients at the time of initial presentation.

Considering other implications for clinical practice, these results can be used to better inform decision analyses, especially since the relative risk of mortality and unfavorable neurologic outcomes have been found to be among the most dominant factors driving the utility of post-CT testing for aSAH.[34,35] In the study by Ward et al.,[35] using an estimated threefold increased risk of severe disability following a delayed diagnosis of aSAH, the authors reported that performing a lumbar puncture (LP) following a nondiagnostic CT was a cost-effective diagnostic approach. However, in sensitivity analysis, when the odds were decreased to 1.5-fold, the CT/LP approach was no longer cost-effective.

Accordingly, if the adjusted point estimates for odds of severe disability in this study (range = 0.43–1.68) were used in the authors' model, CT/LP would most likely have been deemed not cost-effective compared to a CT-only approach. Likewise in the study by Taylor et al.,[34] decreasing the odds of death following a delayed diagnosis of aSAH to 1.8-fold (point estimates of 0.43–2.07 at 1 year in our analyses) raised the LP testing threshold to an aSAH probability of 15.6%, well beyond reported prevalences of aSAH among ED patients presenting with headaches.[36]

In assessing the external validity of these findings, it is reassuring that the observed rates of mortality and severe disability among patients with possible undiagnosed aSAH in this study are comparable to other similar studies on the topic (mortality at up to 1 year of 17% vs. 15%–19% and severe disability [mRS > 4] rates of 20% vs. 15%–36%).[3–5] Similarly, the observed outcome rates in the whole and restricted control cohorts are consistent with the expected benchmark rates for similar cohorts as assessed in contemporary studies.[22,37–39]

LIMITATIONS

Given the retrospective nature of the study, our ability to precisely assess neurologic outcomes was limited by the quality of follow-up documentation. Although one previous study examining the determination of absolute mRS scores based on chart reviews demonstrated only moderate inter-rater reliability, other studies assessing the reliability of mRS scoring by retrospective chart review have found much more reliable consistency when using a dichotomous mRS score classification, as used in this study.[40,41] The stability of our findings with regard to variations in the dichotomous cut-point definition also mitigates the chance that our findings are significantly influenced by misclassification bias. Additionally, we had access to multiple visits from providers in separate specialties and disciplines, including occupational and physical therapists where key components of the mRS scores (i.e., functional limitations) are systematically and routinely addressed.

We were also unable to fully adjust for severity of illness based on imaging findings due to incomplete access to CT images, leaving us to rely primarily on written reports. However, prognosis in aSAH is much more closely tied to neurologic status at the time of hospitalization, which was well documented, with normal mental status and/or a GCS score of 15 being reliable predictors of low in-hospital mortality (observed rates of 3%–6%)[12,42,43] and low rates of unfavorable neurologic outcomes at both 3 months (13%–15%)[44,45] and 6 months (8%–16%).[46,47] Adjustment for other known outcome factors influencing outcomes (i.e., age, clinical vasospasm, aneurysm size) further strengthens our conclusions.

We considered patients to have aSAH based on the documented clinical impressions and management by the treating clinicians, as is standard methodology in research papers on this topic, without requiring ostensibly objective findings of aneurysm rupture such as perianeurysmal cerebral tissue staining noted at craniotomy or an irregular aneurysmal dome seen on digital subtraction angiography. This was necessary since assessing for such objective findings is not routinely possible (in the case of direct visualization at craniotomy, since the majority of cerebral aneurysms are treated endovascularly) or, in terms of aneurysm morphology noted at angiography, neither sensitive nor specific enough to define aneurysm rupture.[48,49] While we acknowledge that 2% to 3% of asymptomatic patients may harbor unruptured cerebral aneurysms in the general population,[50,51] it is unlikely that a significant number of patients had both nonaneurysmal SAH (or false-positive lumbar punctures) and incidental aneurysms, given that the observed clinical courses were comparable to a typical population of patients with aSAH, as discussed. The insensitivity of our findings to the exclusion of patients with CT-negative SAH reinforces this position.

Finally, given the retrospective nature of the study, we cannot be certain that there were undetected adverse outcomes among patients with delays in aSAH diagnosis. However, it is notable and reassuring that we were unable to identify any patients with out-of-hospital deaths due to aSAH or other unknown causes who had an encounter suggestive of undiagnosed aSAH in the 14 days prior to death. This is in keeping with the assumption that clinically mild presentations leading to unrecognized diagnoses may actually portend a more stable underlying pathophysiology, at least in the short term. This presumption is likewise supported by the markedly less severe CT findings among patients with presumed unrecognized aSAH at the time of diagnosis (presumed rebleeding) compared to patients with known aSAH and proven rebleeding, as previously discussed.[25] That being said, it should likewise be noted that, given that we included patients with any degree of headache and/or neck pain prior

to formal aSAH diagnosis, these findings may not apply to patients with highly suspicious, severe, rapidly peaking headaches.

CONCLUSION

In this contemporary cohort of patients with aneurysmal subarachnoid hemorrhage, we observed no significant increase in the 90-day or 1-year adjusted odds of death or unfavorable neurologic outcomes among patients with clinical evaluations for possible aneurysmal subarachnoid hemorrhage–related symptoms in the 14 days preceding formal diagnosis of aneurysmal subarachnoid hemorrhage. This was despite a similar prevalence of cases and similar rates of unfavorable outcomes among cases compared to older literature, which alternatively has held that cases have significantly increased relative risks of unfavorable outcomes. While these findings cannot exclude a smaller increased relative risk due to sample size limitations, these revised point estimates can help inform and further refine decision analysis design and testing threshold determinations for patients with possible aneurysmal subarachnoid hemorrhage.

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