CLINICAL RESEARCH STUDY

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Increased Hospital Mortality in Patients with Bedside Hippus

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ABSTRACT

BACKGROUND: Hippus is a prominent, repetitive oscillation of the pupils. Although regarded by some as a normal variant of pupillary unrest, the clinical importance of hippus has not been investigated systematically in hospitalized patients.

METHODS: We conducted a retrospective cohort study of 117 hospitalized patients demonstrating hippus. To mitigate observer bias, 486 control patients were selected using 2 adjacent admissions by the same attending physician before and after each index case. The primary outcomes were mortality during the admission and within 30 days of discharge.

RESULTS: Patients with bedside hippus were more likely to die within 30 days of observation ($P < .00005$). Independent risk factors for death by 30 days were altered mental status (odds ratio [OR] 4.11; 95% confidence interval [CI], 2.05-8.25, $P < .001$), hippus (OR 2.99; 95% CI, 1.46-6.11, $P = .003$), cirrhosis ($P = .029$), and renal disease ($P = .054$); angiotensin-system inhibitors were protective ($P = .012$). Patients with hippus were more likely to have altered mental status (OR 11.23; 95% CI, 6.27-20.09, $P < .001$), a history of trauma (OR 3.76; 95% CI, 1.65-8.59, $P = .002$), cirrhosis ($P = .038$), renal disease ($P = .051$), and a history of using iron supplements ($P = .016$).

CONCLUSION: The recognition of hippus in hospitalized patients is a clinically important predictor of early mortality.

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KEYWORDS: Altered mental status; Cirrhosis; Hippus; Hospital mortality; Renal disease; Trauma

Hippus is an ancient word, probably derived from the Greek word *Hippos*, meaning horse.[1] Clinicians today note the presence of hippus when observing rhythmic pupillary oscillations during an examination of the eyes. Typically, most physicians recognize this oscillating constriction and dilation while checking for light reflexes or accommodative function.[2,3] This is particularly true if the degree of amplitude or frequency is prominent enough to be recognized by unaided clinical observation,[4] that is, without the use of pupillographic recordings.[5]

The recognition of hippus has inspired the publication of only a few small case series. Thompson et al[1] conducted a classic review 36 years ago and found an inconsistent association of hippus with disease, suggesting the finding might be a variant of normal. They argued the distinction between normal pupillary unrest and hippus might depend on observer perspective or perspicacity. Loewenfeld,[4] in recounting the various meanings of hippus over the centuries, suggests that "pathologic" hippus describes a more energetic variant of normal pupillary unrest of uncertain clinical significance. No systematic studies validate or refute the clinical importance of easily detectable hippus in the setting of hospital illness.

So persuasive was the early opinion of Thompson et al[1] that no major clinical studies of hippus have been reported since their requiem. Several small series during the intervening decades purported associations of hippus with diabetic neuropathy,[6] night blindness,[7] Cheyne-Stokes respiration,[8] seizures,[4] or prolonged exposure to visual display units.[3] However, many of these small group investiga-

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tions were performed in outpatient settings, and none were designed to test clinical significance. Current ophthalmologic opinion still suggests hippus is a variant of normal, seen more readily with fatigue or decreased vigilance,[9] where nonpathologic alterations in the opposing effects of sympathetic and parasympathetic stimulation disturb rhythmic balance.

We challenge the modern view that all hippus has no clinical import. Our study is the first to report that hospitalized patients with obvious hippus have increased mortality and are more likely to have cirrhosis, trauma, renal failure or altered mental status.

CLINICAL SIGNIFICANCE

- Our study is the first to suggest that pupillary hippus is an independent predictor of early mortality when recognized in the inpatient setting.
- Patients with hippus had an OR of 2.99 of dying within 30 days of discharge compared with controls admitted at a similar time by the same physician.
- Hippus is associated with altered mental status, cirrhosis, renal disease, and a history of trauma.

MATERIALS AND METHODS

Design

We performed a retrospective, single-center, cohort study using a robust electronic medical record. With institutional review board approval, we searched the entire record, representing more than 60 million electronic documents of 223,160 hospital admissions of adults and children from June of 1995 to June of 2005 for any mention of hippus.

Our search identified 117 hospitalized patients with hippus; medical records were inspected manually to verify its presence. Recognizing that only prominent or energetic hippus is likely to be noted at the bedside, we chose this level of recognition as a definition.[5] To control for observer bias, patient acuity, and disease covariants based on patients from different clinical services, we selected 4 control patients seen by the same attending physician for each case: 2 admitted just before and 2 admitted just after each case. Each medical record for control patients was manually inspected to ensure hippus was not present.

Data Collection

We reviewed the medical record for each patient to ascertain demographics, comorbid diagnoses present on admission, and all admitting medications and discharge diagnoses. Hospital and 30-day mortality were defined as death or discharge to hospice during the hospitalization or within 30 days of discharge, respectively. Social security numbers were checked for subsequent 30-day mortality in all discharged patients lost to follow-up. We categorized all medications and diagnoses by class. Specific diseases and medications occurring in more than 10 of the cases were categorized individually. Alcohol and tobacco use were considered positive if the patient ever consumed either on a regular basis. Initial mental status was determined using the admission history and physical examination. A patient was considered to have an altered state of consciousness if "altered mental status" or a synonym for cognitive impairment was recorded on admission.

Statistical Analysis

We used the Fisher exact test for differences in proportions of demographics and the Student *t* test to compare continuous variables after verifying normal distributions. Our primary outcomes were hospital mortality and 30-day mortality after discharge. Univariate, unadjusted associations were calculated as odds ratios (ORs) and tested via Pearson's chi-square statistic. An unconditional multivariable logistic regression model was used to assess mortality adjusted for the variables given in Table 3, as well as age, gender, and race.[10] We confirmed these analyses with a conditional logistic model, using attending physician as the matching variable. To determine the potential causes of hippus, we used an unconditional multivariable logistic regression model adjusted for the variables given in Table 4. Goodness of fit was assessed by Hosmer-Lemeshow analysis. Survival time was calculated from the time of hospital admission and limited to 30 days after admission. Cumulative mortality was estimated with Kaplan-Meier curves and tested for significance with the log-rank test.

Provider Survey

We sent a 4-question survey to all physicians who had admitted hippus cases. This survey included 3 multiple-choice questions asking how the provider defined hippus, under what conditions it was recognized, and about its clinical implications. A fourth free-response question asked the provider to list any conditions believed associated with hippus. We compared their responses with the mortal outcomes of the patients by using the Fisher exact test.

RESULTS

A total of 585 patients (117 cases of hippus and 468 physician and time-matched controls) were included in our analyses. Eighty-six different physicians observed hippus (1-7 patients per physician; only 19 physicians admitted more than 1 case); 92% were documented by housestaff and 8% were documented by attending physicians in the admission note. Seventy-five percent of patients were admitted to a medicine service (39% of cases on the adult hepatology service and 12% on the adult general medicine service), followed by neurologic (13.7%), surgical (5.1%), pediatric (4.3%), and ophthalmologic (1.7%) services; both ophthalmology admissions had head and eye trauma from motor vehicle accidents. The incidence of reported hippus during

the study interval was 52 per 100,000 admissions. No patients had hippus documented in more than 1 admission. In Table 1, there were no significant differences in demographics, alcohol use, or tobacco use between the cases and controls. Sixty-two patients (10.6%, 48 controls and 14 cases, $P = .62$) were children aged less than 18 years. The overall age range was newborn to 97 years for controls and 3 months to 93 years for cases.

Of the 117 patients with hippus, 34 (29%) died during the hospitalization and 39 (33%) died within 30 days of hospital discharge. Of the 468 control patients, 42 (9%) died in the hospital and 54 (12%) died within 30 days of discharge. All hippus deaths were in adults; there were 2 child deaths in the control group. The average institutional mortality rate during the same interval was 2.67% (3.06% excluding the normal newborn nursery). Patients with hippus had significantly increased 30-day mortality (Figure; $P < .00005$). Fifty-two percent of controls and 67% of the hippus cases died within 10 days of observation ($P = .71$).

Table 2 shows the unadjusted risk factors contributing to 30-day mortality. Highly associated risks included hippus (OR 3.83; 95% confidence interval [CI], 2.30-6.33, $P < .0001$), altered mental status (OR 4.24; 95% CI, 2.60-6.95, $P < .0001$), and cirrhosis (OR 2.73; 95% CI, 1.70-4.41, $P < .0001$). Weaker associations were seen with alcohol use ($P = .042$) and renal disease ($P = .041$). Age also affected inpatient mortality (OR 1.022 per year of age; 95% CI, 1.009-1.036, $P = .001$) and 30-day mortality (OR 1.027 per year of age; 95% CI, 1.014-1.039, $P < .001$). Altered mental status was a predictor of hospital death in patients with cirrhosis (OR 3.83; 95% CI, 1.89-7.81, $P < .001$) and patients without cirrhosis (OR 6.00; 95% CI, 2.77-13.01, $P < .001$). Cirrhosis was not associated with neurologic disease (OR 0.82; 95% CI, 0.59-1.16, $P = .272$). Other unadjusted risk factors not shown in Table 2 were not significant (see Table 3 for a complete list).

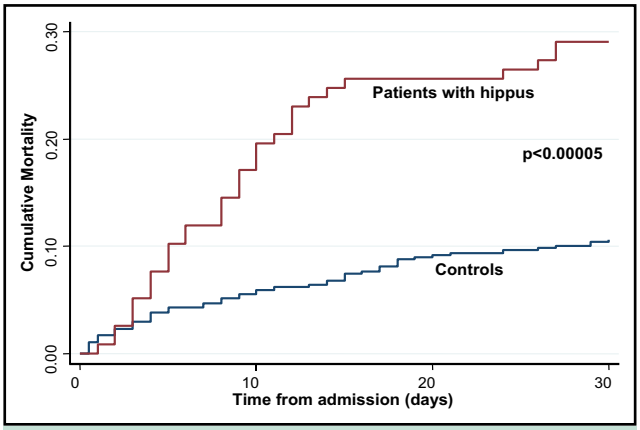

Figure Cumulative mortality of patients with hippus versus controls. Data are plotted as a Kaplan-Meier mortality curve.

Table 1 Demographics of Patients with Hippus and Controls

	Cases (n = 117)	Controls (n = 468)	*P*
No. female	50 (43%)	224 (48%)	.35
Age (y)	45.8 (1.8)	48.1 (1.0)	.27
Race			
White	103 (88%)	376 (80%)	.22
African-American	10 (9%)	65 (14%)	
Other	0 (0%)	8 (2%)	
Unknown	4 (3%)	19 (4%)	
Alcohol use	42 (40%)	162 (37%)	.66
Tobacco use	50 (47%)	192 (44%)	.67
Intensive care unit	19 (16%)	95 (16%)	1.00
Medical history			
Cirrhosis	61 (52%)	147 (31%)	.01
Diabetes	28 (24%)	98 (21%)	.48
Neurologic*	63 (54%)	192 (41%)	.01
Urologic†	12 (10%)	54 (12%)	.70
Trauma‡	24 (21%)	32 (7%)	.01
Cardiovascular§	24 (21%)	127 (27%)	.14
Renal‖	14 (12%)	79 (17%)	.19
Ophthalmologic¶	9 (8%)	44 (9%)	.57

*Composed primarily of current or history of delirium (32%), seizures (23%), and stroke (10%).

†Composed primarily of benign prostatic hypertrophy (18%), incontinence (14%), and prostate cancer (8%).

‡Composed primarily of closed head injuries (34%), motor vehicle crashes with no documentation of specific head trauma (28%), and gunshot wounds (13%). There were 2 cases (4%) of eye trauma.

§Composed primarily of coronary artery disease (36%), congestive heart failure (14%), and atrial fibrillation (11%).

‖Composed primarily of nondialysis chronic renal failure (40%), acute renal failure (16%), nephrolithiasis (18%), and dialysis (13%).

¶Composed primarily of cataracts (34%), glaucoma (23%), and blindness (11%).

Table 3 shows the adjusted risk factors contributing to hospital and 30-day mortality. Altered mental status, hippus, and age were the only markers for increased risk of both hospital and 30-day mortality in all models. The most pronounced effect for each was on hospital mortality. Cirrhosis was predictive of adjusted hospital mortality (OR 3.05; 95% CI, 1.12-8.31, $P = .029$; Table 3). Renal disease was weakly predictive of 30-day adjusted mortality ($P = .054$). Both models showed satisfactory fit by the Hosmer-Lemeshow test.

A conditional logistic model (model not shown) controlling for physician confirmed these data. In this model, hippus was the strongest predictor of hospital mortality (OR 4.84; 95% CI, 1.88-12.51, $P = .001$) and remained a strong predictor of 30-day mortality (OR 2.89; 95% CI, 1.35-6.20, $P = .006$); however, the magnitude of this risk factor and its associated statistical significance are reduced because of the confounding effects of the attending physician and other covariates on mortal risk. Altered mental status predicted both hospital (OR 3.17; 95% CI, 1.25-8.01, $P = .015$) and 30-day mortality (OR 3.12; 95% CI, 1.45-6.69, $P = .003$). Age was also associated with hospital (OR 1.08 per year; 95% CI, 1.04-1.13, $P < .001$) and 30-day mortality (OR 1.05 per year; 95% CI, 1.02-1.08, $P < .001$).

Table 2 Unadjusted Risk of 30-day Mortality Among Study Subjects with Hippus and Other Risk Factors

Risk Factor	No. of Patients		No. of Deaths		OR (95% CI)	*P*
	With Risk Factor	Without Risk Factor	With Risk Factor	Without Risk Factor		
Prominent hippus	117	468	39	54	3.83 (2.30-6.33)	<.0001
Altered mental status	202	383	59	34	4.24 (2.60-6.95)	<.0001
Alcohol use	204	381	41	52	1.59 (0.99-2.55)	.0420
Tobacco use	242	343	40	53	1.08 (0.67-1.74)	.7257
Medical history						
Cirrhosis	208	377	52	41	2.73 (1.70-4.41)	<.0001
Diabetes	126	459	24	69	1.33 (0.76-2.27)	.2749
Neurologic	254	331	38	55	0.88 (0.55-1.42)	.5872
Urologic	49	536	10	83	1.40 (0.60-2.99)	.3670
Trauma	54	531	11	82	1.40 (0.62-2.90)	.3454
Cardiovascular	149	436	29	64	1.40 (0.83-2.33)	.1680
Renal	91	494	21	72	1.76 (0.96-3.11)	.0415
Ophthalmologic	53	532	2	91	0.19 (0.02-0.75)	.0114
Medications						
Antiarrhythmics	12	573	2	91	1.06 (0.11-5.09)	.9413
Beta-blockers	117	468	17	76	0.88 (0.46-1.58)	.6511
Angiotensin-system inhibitors	103	482	5	88	0.23 (0.07-0.58)	.0007
Aspirin	68	517	6	87	0.48 (0.16-1.15)	.0897
NSAIDs	44	541	5	88	0.66 (0.20-1.74)	.3924
Lactulose	104	481	28	65	2.36 (1.36-4.00)	.0007
Spironolactone	132	453	27	66	1.51 (0.88-2.53)	.1037
Opiates	107	478	24	69	1.71 (0.97-2.95)	.0409
Iron	33	552	4	89	0.72 (0.18-2.12)	.5414
Antiepileptics	72	513	3	90	0.20 (0.04-0.65)	.0036

OR = odds ratio; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug.

Ophthalmologic diseases, angiotensin-system inhibitors (including both angiotensin-converting enzyme inhibitors and receptor blockers), aspirin, iron use, and anti-epileptics were each weakly protective when cases and controls were pooled for unadjusted or adjusted risk. Patients with cirrhosis were less likely to be receiving angiotensin-system inhibitors (OR 0.4; 95% CI, 0.24-0.67, $P = .001$) than those without cirrhosis but also had a lower prevalence of cardiovascular disease. Lactulose, a prominent risk factor for death in the univariate analysis, was not significant when adjusted for other risk factors. A subgroup analysis of cases for mortality did not show any benefit for specific treatments (data not shown).

Table 4 demonstrates the unadjusted and adjusted risk factors contributing to hippus. In the adjusted analysis, altered mental status was the strongest association (OR 11.23, $P <.001$), but trauma (OR 3.76, $P = .002$), cirrhosis ($P = .038$), renal disease ($P = .051$), and use of iron ($P = .016$) were also associated. Altered mental status, trauma, and cirrhosis were also associated with hippus by unadjusted logistic regression ($P <.001$); neurologic disease and use of lactulose or spironolactone were associated by univariable analysis but not when adjusted for other factors. There was no association with ophthalmologic diseases by either univariate or multivariable analysis.

On the provider survey (n = 47, 67% response rate), 40% and 42% of the physicians defined hippus as any large amplitude oscillation and as any detectable pupillary oscillation, respectively. Sixty-four percent indicated they diagnosed hippus under any light condition in the hospital. Only 39% thought hippus suggested a poor prognosis, although none considered hippus a favorable finding. Physicians caring for patients with hippus who died were no more likely to suggest that hippus indicated a poor prognosis (33% in patients who died, 45% in patients who lived, $P = .32$). Forty-three percent of the respondents suggested various encephalopathies associated with hippus.

DISCUSSION

There is a strong association of hippus to mortality among patients admitted to the hospital. The adjusted OR for 30-day mortality is 2.99 ($P = .003$), indicating both statistical and clinical significance. A search of a comprehensive electronic medical record system allowed us to analyze a large number of hospitalized cases during a decade, despite the rarity of this finding. Hippus was second only to altered mental status as an independent predictor of mortality, greater than the risks associated with cardiovascular disease,

Table 3 Adjusted Mortal Risks Associated with Hippus and Other Risk Factors*

	Hospital Mortality		30-day Mortality	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Hippus	3.53 (1.61-7.75)	.002	2.99 (1.46-6.11)	.003
Altered mental status	4.68 (2.14-10.21)	<.001	4.11 (2.05-8.25)	<.001
Alcohol use	2.12 (1.03-4.40)	.043	1.61 (0.83-3.13)	.160
Tobacco use	0.66 (0.32-1.35)	.252	0.65 (0.34-1.24)	.190
Medical history				
Cirrhosis	3.05 (1.12-8.31)	.029	1.76 (0.72-4.31)	.214
Diabetes	0.72 (0.32-1.58)	.409	1.00 (0.50-1.99)	.998
Neurologic	0.70 (0.35-1.43)	.331	0.83 (0.44-1.56)	.568
Urologic	2.06 (0.65-6.48)	.218	1.55 (0.56-4.30)	.403
Trauma	2.01 (0.71-5.70)	.187	1.56 (0.58-4.18)	.377
Cardiovascular	1.28 (0.55-2.98)	.565	1.52 (0.72-3.20)	.268
Renal	2.27 (0.94-5.49)	.068	2.16 (0.99-4.70)	.054
Ophthalmologic	0.09 (0.01-0.82)	.033	0.13 (0.03-0.65)	.013
Medications				
Antiarrhythmics	11.00 (1.39-87.12)	.023	3.42 (0.45-25.82)	.234
Beta-blockers	0.67 (0.27-1.70)	.401	0.91 (0.41-2.02)	.820
Angiotensin-system inhibitors	0.09 (0.02-0.48)	.005	0.23 (0.07-0.73)	.012
Aspirin	0.14 (0.03-0.73)	.019	0.34 (0.11-1.09)	.070
NSAIDs	2.51 (0.71-8.82)	.151	1.43 (0.45-4.57)	.544
Lactulose	0.78 (0.31-1.94)	.596	1.31 (0.59-2.91)	.506
Spironolactone	0.53 (0.20-1.37)	.189	0.57 (0.25-1.31)	.187
Opiates	2.34 (1.08-5.07)	.031	1.80 (0.90-3.61)	.096
Iron	0.04 (0.00-0.50)	.012	0.26 (0.06-1.14)	.074
Antiepileptics	0.25 (0.05-1.11)	.068	0.16 (0.04-0.67)	.012

OR = odds ratio; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug.

*The ORs for the risk factors in this table are simultaneously adjusted for each other and age, gender, race, surgical history, pulmonary disease, noncirrhotic gastrointestinal disease, infectious disease, hematologic disease, oncologic history, and other current medications, including diuretics by class, antibiotics, ursodiol, antithrombotic agents, antipsychotics, antidepressants, and proton pump inhibitors.

diabetes, or renal disease. Obvious hippus, observed at the bedside, can no longer be viewed as a physiologic finding of little clinical relevance. Our conclusion is the first to be based on an analysis of hospitalized patients; most prior group studies were smaller outpatient investigations in healthier populations. In fact, there are only 26 abstracts matching a hippus query to MEDLINE.[11]

Others previously argued that recognition of hippus may depend on the observer.[1,4] Although our study does not suggest an exact operational definition of hippus, identification of bedside hippus prominent enough to have a physician enter this finding into the medical record provides a reasonable measure.[5] Physicians in this study defined hippus as large amplitude pupillary oscillations, typically under any light condition, that were more striking than what might be called a normal variant. Controlling for physician, time, and prior expected mortality by service lessens observer bias and increases the comparability of cases and controls with respect to other clinically relevant risk factors. This was particularly important in this study, because several of the physicians principally work in trauma or intensive care units.

The average hospital mortality of our control patient population (9%) was higher than the institutional mortality rate (3.06%) during the same time period of this study. Thus, the patient populations cared for by physicians who recognize hippus have an increased risk of death at baseline because of relatively high severity or complexity of disease. Had the mortality of the control population been at our institutional baseline, the OR of mortality would be 13.28 for patients with hippus. Because hippus is an independent risk factor for increased mortality, even among patients with above-average risk, the recognition of hippus in the inpatient setting has ominous and confirmatory implications for prognosis.

Several limitations caution interpretation of our results. Because this was a retrospective cohort study, we were not able to prospectively define the criteria for hippus. Observers may be more likely to scan for hippus in sicker patients, and some physicians may be more conscientious about pupillary examinations when suspicious of advanced illness. Hippus was also reported infrequently in our hospitalized patients and may have been underreported because of prior assumptions in the literature about its relevance. Before this data collection, however, the clinical implications of hippus had not been studied in hospitalized patients and therefore should not have biased physicians to docu-

Table 4 Unadjusted and Adjusted Logistic Regression of Factors Associated with Hippus*

	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Altered mental status	10.60 (6.42-17.77)	<.001	11.23 (6.27-20.09)	<.001
Alcohol use	1.06 (0.67-1.64)	.795	0.71 (0.37-1.38)	.312
Tobacco use	1.07 (0.70-1.65)	.737	1.28 (0.70-2.35)	.428
Medical history				
Cirrhosis	2.38 (1.54-3.67)	<.001	2.52 (1.05-6.01)	.038
Diabetes	1.19 (0.71-1.96)	.481	1.19 (0.62-2.31)	.604
Neurologic disease	1.69 (1.10-2.60)	.011	0.91 (0.52-1.60)	.740
Genitourinary disease	0.53 (0.18-1.31)	.156	0.55 (0.17-1.75)	.309
Trauma	3.45 (1.83-6.41)	<.001	3.76 (1.65-8.59)	.002
Cardiovascular disease	0.66 (0.38-1.11)	.107	0.76 (0.36-1.61)	.478
Renal disease	0.63 (0.31-1.19)	.138	0.43 (0.18-1.00)	.051
Ophthalmologic	0.80 (0.33-1.73)	.565	1.60 (0.63-4.09)	.327
Medications				
Antiarrhythmics	0.36 (0.01-2.51)	.307	0.35 (0.03-4.47)	.422
Beta-blockers	0.85 (0.48-1.46)	.535	0.89 (0.41-1.91)	.758
Angiotensin-system inhibitors	0.58 (0.29-1.08)	.073	1.00 (0.42-2.38)	.997
Aspirin	0.84 (0.40-1.66)	.606	1.37 (0.52-3.63)	.521
NSAIDs	0.38 (0.10-1.08)	.060	0.31 (0.08-1.23)	.097
Lactulose	2.61 (1.58-4.27)	<.001	0.97 (0.43-2.21)	.946
Spironolactone	1.72 (1.06-2.76)	.018	0.73 (0.32-1.67)	.451
Opiates	1.46 (0.85-2.43)	.134	1.97 (1.00-3.90)	.050
Iron use	2.43 (1.05-5.36)	.016	3.66 (1.27-10.54)	.016
Antiepileptics	0.78 (0.37-1.53)	.450	0.76 (0.32-1.77)	.520

OR = odds ratio; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug.
*All factors from Table 3 analyzed in a multivariable logistic model.

ment hippus more frequently when they believed their patients were at increased risk of death. Our survey results support this conclusion; physicians caring for patients with hippus who died were no more likely to think hippus was a negative prognostic sign. Alternatively, physicians who are familiar with pupillary abnormalities in systemic conditions, such as the sluggish pupils in diabetes, may be biased to suspect pupillary abnormalities in certain diseases. However, we specifically controlled for observer bias and comorbid diseases.

Although prior knowledge of potential historical associations of hippus with selected diseases might confound its recognition, our findings suggest the presence of different comorbidities than that expected.[1-9] We also were not able to assess the severity of illness for cardiovascular disease, cirrhosis, or trauma in our study. By including medications by class, we have attempted to adjust for some of this variability, but more formal predictors of severity (eg, the Model for End-Stage Liver Disease scores[12]) would likely strengthen the associations with mortality.

We found no evidence of neurologic or ophthalmologic diseases previously associated with hippus.[13] Several centuries ago physicians recognized the presence of hippus as a grave sign.[4] Pupillary signs reflect the general state of a patient and can sometimes herald endogenous intoxications from metabolic dysfunction, particularly in liver or renal disease. We found an association in patients with altered mental status and liver or kidney disease. In our search of the modern literature, we found case reports of hippus with altered mental status[14] and hepatic encephalopathy.[15] The association with iron use is unexpected, although iron deficiency can increase serum catecholamine levels,[16] possibly exaggerating normal pupillary oscillations. The weak association with opiate use may be a result of its effect on pupil size, aiding visualization or opposing sympathetic activity. Other medications did not associate with hippus.

Although our study was not designed to assess treatments, the use of angiotensin-system inhibitors and anti-epileptics reduced adjusted hospital and 30-day mortality. The effect of angiotensin-system inhibitors persisted even if those patients with any cardiovascular disease were excluded. The protective role of anti-epileptics may be exaggerated because of the use of these medications for neuropathic pain syndromes.

We collected these data to generate new hypotheses regarding the clinical utility of hippus at the bedside. Hippus is an independent risk factor for death. In an era of expensive testing, recording the presence of hippus costs nothing for the provider or patient, yet may focus clinical care on immediate prognosis more than a history of diabetes or cardiovascular disease. We suspect that hippus is underreported and largely ignored because of a lack of awareness or a belief that it is unimportant.[13]

Given our results, we suggest that hippus in hospitalized patients is clinically relevant and deserves more consideration.

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References

1. Thompson HS, Franceschetti AT, Thompson PM. Hippus. Semantic and historic considerations of the word. *Am J Ophthalmol*. 1971;71: 1116-1120.
2. Bouma H, Baghuis LC. Hippus of the pupil: periods of slow oscillations of unknown origin. *Vision Res*. 1971;11:1345-1351.
3. Ukai K, Tsuchiya K, Ishikawa S. Induced pupillary hippus following near vision: increased occurrence in visual display unit workers. Ergonomics. 1997;40:1201-1211.
4. Loewenfeld IE. *The Pupil: Anatomy, Physiology, and Clinical Applications*. Butterworth-Heinemann; 1999:1220-1243.
5. Yoss RE, Moyer NJ, Hollenhorst RW. Hippus and other spontaneous rhythmic pupillary waves. *Am J Ophthalmol*. 1970;70:935-941.
6. Smith SE, Smith SA, Brown PM, et al. Pupillary signs in diabetic autonomic neuropathy. *Br Med J*. 1978;2:924-927.
7. Myers GA, Barricks ME, Stark L. Paradoxic pupillary constriction in a patient with congenital stationary night blindness. *Invest Ophthalmol Vis Sci*. 1985;26:736-740.
8. Sullivan KN, Manfredi F, Behnke RH. Hippus in Cheyne-Stokes respiration. Observations in three patients with rhythmic respiratory and pupillary changes. *Arch Intern Med*. 1968;122:116-121.
9. Wilhelm B, Wilhelm H, Ludtke H, et al. Pupillographic assessment of sleepiness in sleep-deprived healthy subjects. *Sleep*. 1998;21: 258-265.
10. Breslow NE, Day NE. Statistical methods in cancer research. Volume I-The analysis of case-control studies. *IARC Sci Publ.* 1980:5-338.
11. PubMed. National Library of Medicine. Available at: http://www.ncbi.nlm.nih.gov/sites/entrez. Accessed August 15, 2006.
12. Cholongitas E, Marelli L, Shusang V, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. *Liver Transpl*. 2006;12:1049-1061.
13. Kardon RH. Anatomy and physiology of the pupil. In: Newman NJ, Miller NR, eds. *Walsh and Hoyt's Clinical Neuro-ophthalmology, 5th ed, vol 1*. Baltimore: Williams & Wilkins; 1998:885-887.
14. Teutsch C, Brennan RW. Amanita mushroom poisoning with recovery from coma: a case report. *Ann Neurol*. 1978;3:177-179.
15. Gill RQ, Sterling RK. Acute liver failure. *J Clin Gastroenterol*. 2001; 33:191-198.
16. Rosenzweig PH, Volpe SL. Iron, thermoregulation, and metabolic rate. *Crit Rev Food Sci Nutr*. 1999;39:131-148.