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Agitation after subarachnoid hemorrhage: a frequent omen of hospital complications associated with worse outcomes

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Abstract

Purpose—Agitated delirium is frequent following acute brain injury, but data are limited in patients with subarachnoid hemorrhage (SAH). We examined incidence, risk factors, and consequences of agitation in these patients in a single-center retrospective study.

Methods—We identified all patients treated with antipsychotics or dexmedetomidine from a prospective observational cohort of patients with spontaneous SAH. Agitation was confirmed by chart review. Outcomes were assessed at 12 months using the modified Rankin Scale (mRS), Telephone Interview for Cognitive Status (TICS), and Lawton-IADL (Instrumental Activities of Daily Living) score. Independent predictors were identified using logistic regression.

Results—From 309 SAH patients admitted between 1/2011 and 12/2015, 52 (17%) developed agitation, frequently in the first 72 hours (50%) and in patients with Hunt-Hess grades 3–4 (12% of grades 1–2, 28% of grades 3–4, 8% of grade 5). There was also a significant association between agitation and a history of cocaine use or prior psychiatric diagnosis. Agitated patients were more likely to develop multiple hospital complications, and in half of these patients complications were diagnosed within 24 hours of agitation onset. Agitation was associated with IADL impairment at 12 months (Lawton >8; $p = 0.03$, OR 2.7, 95% CI 1.1–6.8) in non-comatose patients (Hunt-Hess 1–4), but not with functional outcome (mRS >3), cognitive impairment (TICS 30), or ICU/hospital length of stay after controlling for other predictors.

Conclusion—Agitation occurs frequently after SAH, especially in non-comatose patients with higher clinical grades. It is associated with the development of multiple hospital complications, and may have an independent impact on long-term outcomes.

Keywords

Agitation; delirium; subarachnoid hemorrhage; stroke; brain injury

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Introduction

Agitation is frequently encountered after acquired brain injury, more commonly described during the recovery phase (i.e. while in a rehabilitation unit), but also noted in the acute setting. Characteristic features include excesses of behavior such as aggression, restlessness, disinhibition, and/or lability, all of which place agitation on the spectrum of hyperactive delirium.[1] Several validated scales such as the Confusion Assessment Method (CAM and CAM-ICU), Richmond Agitation-Sedation Scale (RASS), and Riker Sedation-Agitation Scale (SAS), have been developed with the aim of more objectively identifying and quantifying agitation. However, persistent challenges have remained, with possible confounders including medication administration, interrater validity, and differentiating hypoactive delirium from decreased arousal secondary to brain injury. Here we study the more severe end of hyperactive behavior following brain injury by focusing on patients that required medical intervention for agitation.

Most studies of patients with acquired brain injury have described the development of agitation after traumatic brain injury (TBI) or ischemic stroke, with sparse data available for patients with subarachnoid hemorrhage (SAH). Agitation may be a particular burden to patients with SAH, as it confounds their clinical examination and makes the detection of secondary complications such as delayed cerebral ischemia (DCI) more difficult. These complications are of particular interest in patients with SAH as they are major determinants of outcome and potentially treatable if detected early,[2, 3] but identification relies heavily on the clinical examination. In this single-center retrospective study, we therefore sought to further characterize the incidence, predictors, and impact on outcome of agitation in a large, prospectively collected observational cohort of patients suffering from aneurysmal SAH. In particular, we aimed to explore the hypothesis that agitation precedes the development of complications and could therefore serve as an early warning sign.

Methods

Study population

The cohort of patients studied includes patients enrolled in the Columbia University Subarachnoid Hemorrhage Outcomes Project (SHOP) between January 2011 and December 2015. SHOP is a single-center prospective observational cohort study that collects demographic, clinical, radiographic, and outcome data on all adult patients admitted to our hospital with spontaneous SAH, all of which is collectively adjudicated by attending physicians and research staff. The study was approved by the hospital's Institutional Review Board, and written informed consent was obtained from the patient or a surrogate in all cases.

Clinical management

Clinical management of patients with SAH conformed to American Heart Association guidelines.[4, 5] In our institution, patients that survive SAH typically remain admitted in the ICU for 10–14 days or more in order to identify and treat signs of DCI during its peak time of onset; however some patients with good clinical grades and an uncomplicated

hospital course may have this time reduced to 7 days. According to our protocol, agitation is initially treated with non-pharmacologic interventions. These include identifying and addressing possible causes of agitation such as pain, impaired sleep-wake cycles, urinary retention, and constipation, while making attempts at redirection and using restraints if necessary. Agitation refractory to these measures is typically treated pharmacologically, in which case dexmedetomidine and quetiapine have been the first-line drugs of choice, followed by adjunct antipsychotics such as haloperidol, olanzapine, or aripiprazole for breakthrough agitation.

Data collection

The calendar day of the index bleeding event was designated SAH day 0. We prospectively recorded baseline demographic data (age, sex, race) and prior medical history including history of psychiatric diagnoses (e.g., anxiety, depression, bipolar disorder, or schizophrenia), drug, and alcohol use. Location and size of the aneurysm, angiographic and TCD findings, and mode of aneurysm treatment (clipping versus coiling) were recorded. Neurological status on admission was assessed with the Hunt–Hess scale;[6] in addition, we also assessed the Acute Physiology and Chronic Health Evaluation-2 (APACHE-2) scale. Admission and follow-up CT scans were independently evaluated by a study neurointensivist for the amount and location of subarachnoid blood (with thick SAH considered >1mm in diameter in any cistern or fissure), intraventricular blood, the presence of hydrocephalus, the presence of cerebral edema, and cerebral infarction. DCI from cerebral vasospasm was defined as clinical deterioration (i.e. a new focal deficit, decrease in level of consciousness, or both), and/or a new infarct on CT that was not visible on the admission or immediate postoperative scan, when the cause was thought by the research team to be vasospasm.[2] Other treatments and medical and neurological complications are recorded as described previously.[7]

Definition and identification of agitation

Patients with agitation were identified retrospectively, first by querying the medication administration record for patients who received dexmedetomidine and/or antipsychotic medications (e.g., quetiapine, olanzapine, haloperidol, and aripiprazole), and then confirming the presence of agitation via chart review for evidence of relevant symptoms as defined previously.[1]

Agitation onset was defined as documented presence of hyperactive delirium, restlessness, combativeness, or aggression necessitating physical restraints or the administration of one or more of the medications listed above. The day of agitation onset was logged, and the medical record was also reviewed for possible causes of agitation as identified by the clinical team during patient care. When medical complications were identified, we also determined whether or not they resolved with treatment. Finally, the medical record was reviewed to determine if the agitation itself ultimately resolved, confirmed by the discontinuation of antipsychotic medications prior to discharge.

Outcome variables

Hospital outcomes included ICU and hospital lengths of stay (LOS) and hospital mortality. Global outcome at 12 months was assessed with a 7-point version of the modified Rankin Scale (mRS) rated from death (6) to symptom-free full recovery (0).[8] Poor outcome was defined as death or moderate-to-severe disability (unable to walk or tend to bodily needs, mRS score 4 to 6). Disability in instrumental activities of daily living (IADL) was assessed with the Lawton IADL Scale (scored 8 best, 30 worst) at 12 months, with a Lawton score of 8 indicating no impairment.[9] As an additional outcome measure, global cognitive status at 12 months was evaluated with the Telephone Interview of Cognitive Status (TICS, scored out of 51 points), with a cut point of TICS score ≥ 30 previously used to define cognitive impairment.[10] These outcome measures were chosen due to their popularity in stroke-related studies, and because they capture clinically relevant outcome domains.

Statistical analysis

Statistical analyses were performed using R version 3.2.4. The primary analysis was performed on non-comatose patients (Hunt and Hess grades 1–4). Patients who were initially comatose (Hunt and Hess grade 5) were analyzed separately because the development of agitation entails recovery of consciousness, and is therefore suggestive of a potential for clinical improvement when compared to others in this sub-population. Differences between categorical variables were analyzed using the Fisher exact test or χ^2 , as appropriate. Demographic variables and admission predictors found to have $p < 0.25$ on univariate analysis were entered into a backward elimination multiple logistic regression model to determine factors associated with developing agitation. Identical procedures, with the addition of hospital complications, were used to determine if agitation was significantly associated with the outcome measures of interest. Statistical significance was set at $p < 0.05$, and odds ratios (OR) and 95% confidence intervals (CI) were included with all analyses. Missing data were replaced via multiple imputation (50 chains, 30 iterations) using the ‘mi’ imputation package.[11] This included 33 patients (11%) who did not have a follow-up mRS score, 58 patients (19%) who did not have a follow-up Lawton score, and 131 patients (42%) who did not have a follow-up TICS score.

Results

Frequency, admission predictors, and treatment of agitation

Of the 309 SHOP patients eligible for analysis, 16.8% ($n = 52$) developed agitation during their ICU stay. Agitation was most common in the first several days of hospital admission and among patients with Hunt and Hess grades 3–4, while dexmedetomidine and quetiapine were the most commonly used medications of interest (Table 1). Haloperidol, olanzapine, and aripiprazole were the only other antipsychotic medications that were administered in the study population. Note that 48 patients received the medications listed for other reasons, including for general sedation, insomnia, or as a continued home medication, and were therefore excluded from consideration. Multivariable analysis revealed that patients experiencing agitation were more likely to have a history of psychiatric illness, cocaine use, and poor clinical grade; presence of IVH and APACHE-2 physiologic score were significant on univariate but not on multivariate analysis (Table 2).

Hospital complications

Multiple hospital complications occurred at significantly higher rates in patients with agitation, including hydrocephalus, DCI, fever, pneumonia, pulmonary edema, and myocardial infarction (Table 3). After retrospective chart review of clinical documentation, it was determined that 62% of patients with agitation ($n = 32$) had a clearly attributable cause that occurred within 24 hours of their agitation, the majority of whom ($n = 26$) had an attributable medical complication (Table 1).

When a potentially reversible medical complication was identified, it ultimately proved reversible in 21 of 26 cases (80.8%); the 5 patients in whom the complication did not resolve were all cases of DCI progressing to cerebral infarcts. Agitation ultimately resolved in 16 of 26 patients (61.5%) who had attributable medical complications, and 16 of 21 patients (76.2%) whose cause proved reversible. In comparison, agitation resolved in only 10 of 26 patients (38.5%) who did not have a clearly identifiable medical complication at the time of their agitation.

Outcomes

Non-comatose patients with agitation had increased ICU and hospital LOS when compared to those without agitation, but this was not significant in a multivariable model. Non-comatose agitated patients were more likely to have impairment in their IADLs (or death) at 12 months (OR: 2.5, 95% CI: 1.1–5.9, $p=0.03$), which remained significant even after controlling for age (OR: 1.0, 95% CI: 1.0–1.1) and APACHE-2 score (OR: 1.1; 95% CI: 1.0–1.1). Significant differences in cognitive function at 12 months were found on univariate but not on multivariate analysis, while no differences were seen in functional outcome at 12 months.

Amongst initially comatose patients, those with agitation ($n = 5$) all survived to hospital discharge while only 21% (12 of 57) of non-agitated comatose patients survived ($p = 0.001$). The median 3 month mRS of comatose patients who developed agitation was 3 compared to 6 for comatose patients without agitation ($p < 0.001$), and 5 among non-agitated comatose survivors ($p = 0.10$).

Discussion

Our findings indicate that agitation after subarachnoid hemorrhage is a common phenomenon, occurring in 1 out of 6 non-comatose patients, and up to 1 in 4 patients with Hunt and Hess grades 3 and 4. Agitation is most common in the first few days of hospitalization (Figure 1) and was frequently identified in the context of various neurological and other medical complications. Newly developing agitation may be an early warning for potentially treatable or reversible sequelae, or alternatively may itself represent a predisposing factor for these hospital complications—all of which taken together contributed to agitated non-comatose patients having worse outcomes than their non-agitated peers.

The incidence of agitation in our cohort is in line with previous reports of delirium in various types of acquired brain injury, with the caveat that our focus was on the hyperactive

end of the delirium spectrum. In patients with traumatic brain injury (TBI), studies have found that 11% exhibited signs of agitation during their hospitalization,[12] and 26–70% after discharge to acute rehabilitation settings;[13–17] in the latter, it was found that possible factors increasing the risk of developing agitation included lower cognitive function on hospital discharge as well as infection.

There is more available evidence in the non-SAH acute stroke literature, where delirium in general has been noted to occur in 11–48% of patients based on several reports that studied heterogeneous populations including both ischemic and hemorrhagic strokes[18–23], and another that only included patients with intracerebral hemorrhage (ICH).[24] Of those that further categorized delirium as hyperactive or hypoactive, one found an even split between both types among the patients studied,[18] while patients in the other study were described as almost exclusively experiencing hypoactive delirium only.[24] In most of these studies, including larger meta-analyses,[25, 26] lower pre-morbid cognitive baseline and overall severity of illness were commonly listed as risk factors, while another report of delirium in ICH patients suggested that hematoma location may also play a role, particularly in the right hemispheric subcortical white matter and parahippocampal gyrus.[27]

Data for subarachnoid hemorrhage (SAH) has been more limited, with only one study investigating delirium during hospitalization.[28] In this small cohort of SAH patients, 16% developed delirium, more than half of whom were categorized as having hyperactive delirium. Factors associated with the development of delirium in that study included higher clinical grade, older age, IVH, and hydrocephalus.

In our study, we found higher clinical grade, history of prior psychiatric diagnosis, and cocaine use to be associated with the development of agitation among non-comatose patients. The former likely reflects that patients with good-grade SAH have a relatively higher likelihood of an uncomplicated hospital course, along with a milder degree of brain injury and neurologic dysfunction. Meanwhile, since many comatose patients with high-grade SAH do not survive their hospitalization and therefore never have recovery of consciousness, the development of agitation in this sub-population may be considered a positive sign. This may either be because they have recovered to the point of being able to manifest signs of agitation (and therefore the recovery of consciousness itself improves their outcome), or because they may represent a subgroup within higher grade SAH patients with a better outcome to begin with. Indeed, in our cohort, all grade 5 SAH patients who developed agitation survived their hospitalization, with significantly better 3 month functional outcomes than grade 5 patients who did not develop agitation. Our findings also suggest that patients with a history of psychiatric disease or cocaine use may be more sensitive to the effects of acquired brain injuries, more likely to experience delirium with hyperactive manifestations, or more likely to develop withdrawal from psychoactive medications.

In keeping with literature from general critical care populations,[29–34] agitated patients were significantly more likely to have experienced multiple hospital complications during their clinical course, which in turn led to longer ICU and hospital lengths of stay. Further, half of agitated patients were found to have developed a hospital complication within 24

hours of the development of agitation, an association which suggests that in many cases agitation may be linked to an underlying issue and may represent a prodromal symptom. However, it is also possible that agitation itself may lead to complications (e.g. aspiration leading to pneumonia or tachycardia leading to coronary ischemia), and that there may be a bidirectional causal relationship. Meanwhile, for patients without a clear underlying cause, it is reasonable to suspect that ICU admission and frequent monitoring may have played a role in the development of agitation, along with other intrinsic factors such as the localization of their structural brain injury.

The most commonly identified culprit complications in our study were DCI, pneumocephalus, hydrocephalus, and ventriculitis, and the majority of hospital complications proved reversible. Indeed, the emergence of hyperactive delirium may make it easier to identify and treat patients experiencing hospital complications compared to patients with hypoactive delirium, who might not be able to manifest distress in as obvious a fashion. Further, in cases where the underlying cause was successfully treated, agitation was significantly more likely to resolve than in patients who did not have an identifiable cause.

Given these higher rates of hospital complications, it is not surprising that in our study agitated patients had worse outcomes in the long-term than their non-agitated cohorts—the question is whether agitation represents an epiphenomenon, or whether it has an independent effect on outcomes. Indeed, though several of the aforementioned retrospective studies in stroke patients did note that delirium was associated with longer hospitalizations and short-term functional impairments, only one found that delirium was independently associated with impairment in long-term cognitive outcomes.[35] In our study, meanwhile, patients with agitation had a persistent long-term impairment in IADLs even after controlling for the effects of hospital complications. Whether agitation itself is associated with long-term outcomes is a question worthy of further investigation in prospective studies; it is also unclear what effect the various approaches to treating agitation may have on outcomes.

Limitations of our study include the retrospective identification of agitation, as well as the method of screening for agitated patients via medication administration. However, given the thorough medical record review for each patient to confirm each case of agitation, it is more likely that some cases of agitation were missed—either from not being pharmacologically treated, or from receiving continuous sedative infusions other than dexmedetomidine that may have masked any signs of agitation—and that if these patients were instead classified correctly, our associations may have been even further strengthened. Dexmedetomidine was included because of its developing popularity in treating agitation among continuously infused sedatives, along with recent data that shows it may reduce the duration of agitated delirium in critically ill patients.[36] A further limitation is a lack of data that would allow for determining the duration of agitation. Future prospective studies would benefit from the use of clinical scoring systems to identify agitation and follow it over time, though the effectiveness of current grading scales developed for the general critical care population remains controversial in patients with neurologic critical illness.[37] Finally, the management of SAH patients may differ regionally, and our study may therefore have limited generalizability in practice settings where such patients are not routinely monitored in an ICU.

In conclusion, agitation is an important clinical manifestation to consider carefully in patients with acute brain injury, including subarachnoid hemorrhage, in whom it may be an omen for various hospital complications and other unintended consequences. It may also have an independent adverse impact on long-term outcomes, though further study is needed to determine whether other factors, such as the various options for treatment, may also play a role.

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Figure 1.

Comparison of post-bleed day agitation-free survival by Hunt and Hess grades.

Table 1

Selected characteristics of all agitated patients (n = 52).

Hunt and Hess grades	n (% of all same-grade patients)
1	3 (8.8%)
2	13 (13.1%)
3	16 (23.9%)
4	15 (34.9%)
5	5 (8.1%)
Day of agitation onset – mean 5.9 (SD 5.3)	n (% of all agitated patients)
1–3	26 (50%)
4–7	12 (23.1%)
8–14	11 (21.1%)
>14	3 (5.8%)
Attributable cause^a	32 (61.5%)
<i>Neurological or medical complication</i>	26 (50%)
Hydrocephalus	4 (7.7%)
Brain sagging or pneumocephalus	7 (13.5%)
Delayed cerebral ischemia	10 (19.2%)
Ventriculitis (infectious)	4 (7.7%)
Seizure or post-ictal state	1 (1.9%)
Severe hyponatremia	1 (1.9%)
Urinary tract infection	2 (3.8%)
EtOH withdrawal	1 (1.9%)
<i>Other</i>	6 (11.5%)
Underlying psychiatric disorder	5 (9.6%)
Underlying substance or alcohol abuse	3 (5.8%)
Drug or medication withdrawal	4 (7.7%)
Medication received for agitation treatment^b	
Dexmedetomidine	40 (76.9%)
Quetiapine	34 (65.4%)
Olanzapine	8 (15.4%)
Haloperidol	10 (19.2%)
Aripiprazole	2 (3.8%)

^aSome patients had multiple concurrent attributable causes for the development of agitation.

^bMany patients received multiple medications during their hospitalization, with the most common combination being dexmedetomidine and quetiapine.

Demographics and admission predictors in agitated vs. non-agitated patients (Hunt-Hess grades 1–4 only, n = 247). Univariate analysis (unadjusted) and multivariate analysis (adjusted) with a model for developing agitation including unique variables with $p < 0.25$ on univariate testing.

Table 2

Characteristics	Unadjusted			Adjusted		
	Agitated (n = 47)	Non-agitated (n = 200)	OR (95% CI)	P-value	OR (95% CI)	P-value
Demographics						
Age	57.1 (12.9)	55.5 (14.9)	1.0 (1.0, 1.0)	0.50		
Female	32 (68.1%)	136 (68.7%)	1.0 (0.5, 2.0)	0.94		
Non-Caucasian ethnicity	34 (73.9%)	138 (70.1%)	1.2 (0.6, 2.6)	0.60		
History of anxiety	10 (21.3%)	22 (11.0%)	2.2 (0.9, 4.9)	0.06		
History of depression	12 (25.5%)	27 (13.5%)	2.2 (1, 4.7)	0.045		
History of schizophrenia	3 (6.4%)	3 (1.5%)	4.4 (0.8, 24.9)	0.07		
Any prior psychiatric diagnosis	17 (36.2%)	35 (17.5%)	2.7 (1.3, 5.3)	0.006	2.3 (1.1, 4.9)	0.026
History of cocaine use	8 (17.0%)	6 (3.0%)	6.6 (2.2, 21.2)	< 0.001	7.2 (2.3, 24.2)	< 0.001
History of significant alcohol use	4 (8.5%)	21 (10.5%)	0.8 (0.2, 2.2)	0.69		
Admission predictors						
Hunt and Hess grade	2.9 (0.9)	2.4 (0.9)	1.8 (1.3, 2.7)	< 0.001	1.9 (1.3, 2.8)	< 0.001
Thick SAH ^a	9 (22.5%)	27 (15.5%)	1.6 (0.6, 3.6)	0.29		
Intraventricular hemorrhage	23 (57.5%)	69 (39.7%)	2.1 (1.0, 4.2)	0.04		
APACHE-2 physiologic score	15.0 (5.1)	11.9 (6.6)	1.1 (1.0, 1.1)	0.004		
Aneurysm characteristics	14 (29.8%)	44 (22.0%)	1.5 (0.7, 3.0)	0.26		
ACA or A-comm	10 (21.3%)	52 (26.0%)	0.8 (0.3, 1.6)	0.50		
MCA or ICA	11 (23.4%)	34 (17.0%)	1.5 (0.7, 3.2)	0.31		
PCA or P-comm	5 (10.6%)	15 (7.5%)	1.5 (0.5, 4.0)	0.48		
Basilar, vertebral, or PICA	27 (60.0%)	104 (55.6%)	1.2 (0.6, 2.4)	0.60		
Repair via clipping	57.1 (12.9)	55.5 (14.9)	1.0 (1.0, 1.0)	0.50		

Values are N (%), mean (SD).

^aFisher Grade 3 or modified Fisher 3–4.

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Abbreviations: APACHE-2, Acute Physiology and Chronic Health Evaluation-2 score; A-comm, anterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; ICA, internal carotid artery; P-comm, posterior communicating artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery.

Table 3

Hospital complications in agitated vs. non-agitated patients (Hunt-Hess grades 1–4 only, n = 247).

Complications	Agitated (n = 47)	Non-agitated (n = 200)	OR (95% CI)	P-value
Neurological				
Rebleed	0 (0%)	8 (4.1%)	N/A	0.99
Hydrocephalus	28 (59.6%)	61 (31.1%)	3.3 (1.7, 6.4)	< 0.001
Brain sagging or pneumocephalus	4 (8.5%)	13 (6.6%)	1.3 (0.4, 3.9)	0.65
Delayed cerebral ischemia	16 (34.0%)	30 (15.4%)	2.8 (1.4, 5.8)	0.004
Seizure	4 (8.5%)	12 (6.2%)	1.4 (0.4, 4.3)	0.56
Cerebral edema	26 (56.5%)	85 (42.6%)	1.7 (0.9, 3.4)	0.09
Meningitis/ventriculitis	5 (10.6%)	7 (3.6%)	3.2 (0.9, 10.6)	0.056
Medical				
Fever > 101.5°F	25 (53.2%)	57 (29.1%)	2.8 (1.4, 5.3)	0.002
Pneumonia	13 (27.7%)	23 (11.7%)	2.9 (1.3, 6.2)	0.007
Sepsis	1 (2.1%)	9 (4.6%)	0.5 (0.02, 2.5)	0.46
Urinary tract infection	7 (14.9%)	29 (14.9%)	1.0 (0.4, 2.3)	1
Cardiopulmonary	8 (17.0%)	19 (9.8%)	1.9 (0.7, 4.5)	0.16
Arrhythmias	8 (17.0%)	10 (5.1%)	3.8 (1.4, 10.2)	0.008
Myocardial infarction	7 (14.9%)	14 (7.2%)	2.3 (0.8, 5.8)	0.10
Neurogenic stress cardiomyopathy	12 (25.5%)	18 (9.2%)	3.4 (1.5, 7.6)	0.003
Pulmonary edema	1 (2.1%)	0 (0%)	N/A	0.99
Pulmonary embolism				
ICU length of stay	15.7 (6.9)	11.2 (6.3)	1.1 (1.1, 1.2)	< 0.001
Hospital length of stay	22.3 (9.5)	16.0 (7.9)	1.1 (1.0, 1.1)	< 0.001
Hospital mortality	1 (2.1%)	11 (5.5%)	0.4 (0, 2.0)	0.35

Values are N (%), mean (SD).