contrast, a larger coefficient of variation for percentage of N3-stage sleep is to be expected, given that the mean (SEM) percentage of N3 drops from 18.9% (1.3%) in early adulthood to 3.4% (1.0%) in midlife before stabilizing in later life. The N3 stage is also harder to score because slow-wave sleep is a continuum across N2 and N3 and decreases in amplitude with age. This is illustrated by lower levels of agreement for N3 (67.4%) vs REM (90.5%) across scoring technologists.

Because sleep stages are interdependent and slow-wave sleep has received more attention recently with respect to aging and dementia, one may wonder whether other stages, notably slow-wave sleep, could have driven our findings. This is unlikely, based on our analyses. All sleep stages were included in the 6-fold cross-validation process used to empirically identify covariates for the final models. We also created a random survival forest analysis and conditional inference trees to evaluate the importance of each sleep stage. In all these models, REM sleep was consistently found to be the most strongly associated with mortality, while N3 had the lowest importance based on the random forest classifier.

As mentioned in the article, lower levels of REM sleep may be a biomarker of aging or health rather than a direct mortality risk factor, given the relatively small effect size. The mortality risk of a 5% decrease in REM sleep is similar to about 1% of a risk factor, given the relatively small effect size. The mortality risk of a 5% decrease in REM sleep is similar to about 1% of a risk factor, given the relatively small effect size.

The authors report that in the entire cohort, 2 of 31 patients (7%) had a symptomatic hemorrhagic transformation. How-ever, it is unclear from the study how many patients receiving intravenous thrombolysis had a symptomatic or asymptomatic hemorrhagic transformation. Understanding the risk of intracranial hemorrhage in patients with COVID-19 is of paramount importance to inform the risk-benefit assessment of the use of both intravenous thrombolysis and anticoagulation in this patient population.

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Risk of Hemorrhagic Stroke in Patients With Coronavirus Disease 2019

To the Editor We read with interest the article by Merkler et al regarding the increased incidence of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) compared with those with influenza. The authors also reported that 13% of patients with COVID-19 were receiving anticoagulation at the time of the stroke. Could the authors comment on the rate of anticoagulant use in patients with COVID-19 who did not have an ischemic stroke? This would also be helpful to assess the possibility that anticoagulation may have been protective.

We would also like to know how many cases were excluded from the analysis because of hemorrhagic stroke in the COVID-19 and influenza populations. Recent data have suggested that hemorrhagic stroke may be common in patients with COVID-19, especially those receiving prophylactic anticoagulation. Varatharaj and colleagues, in a UK surveillance study of neurological complications associated with COVID-19, reported that 9 of 125 individuals (7.2%) had an intracerebral hemorrhage. Although individual case reports have suggested intracerebral hemorrhage as a complication of COVID-19, controlled data are still lacking to support an association.

We note that in the report by Merkler et al, 10% of patients with an acute ischemic stroke received intravenous thrombolysis. The authors report that in the entire cohort, 2 of 31 patients (7%) had a symptomatic hemorrhagic transformation. However, it is unclear from the study how many patients receiving intravenous thrombolysis had a symptomatic or asymptomatic hemorrhagic transformation. Understanding the risk of intracranial hemorrhage in patients with COVID-19 is of paramount importance to inform the risk-benefit assessment of the use of both intravenous thrombolysis and anticoagulation in this patient population.
In Reply We thank Dr Silverman and colleagues for their interest in our study and providing us the opportunity to expand on our results. Among the 1916 patients who visited the emergency department or were hospitalized with coronavirus disease 2019 (COVID-19) in our study, 8 patients (0.4% [95% CI, 0.2%-0.8%]) had hemorrhagic stroke, including 7 with intracerebral hemorrhage and 1 with subarachnoid hemorrhage. Among these 8 patients, 4 strokes were attributed to anticoagulant use.

Regarding the question about hemorrhagic transformation, 2 of 31 patients with COVID-19 and acute ischemic stroke in our study had symptomatic hemorrhagic transformation. One of these was attributed to intravenous thrombolysis, while the other was attributed to therapeutic-dose anticoagulant use. Overall, 1 of 3 patients (33.3% [95% CI, 8.4%-90.6%]) with COVID-19 who were treated with intravenous thrombolysis for acute ischemic stroke in our cohort developed symptomatic hemorrhagic transformation.

We agree that a better understanding of the risks of hemorrhagic stroke in patients with COVID-19 are necessary to inform the risk-benefit assessments of intravenous thrombolysis and anticoagulant therapy for this population. Since the publication of our study, several studies have reported on the risk of hemorrhagic stroke in patients hospitalized with COVID-19. We did not collect data on anticoagulant use among patients with COVID-19 who did not have ischemic or hemorrhagic stroke, and therefore we are unable to evaluate the association between anticoagulant use and incident stroke in our cohort. We acknowledge that both prophylactic-dose and therapeutic-dose anticoagulant therapy could affect the incidence of stroke and other thromboembolic events, including by potentially causing net harm through an increase in hemorrhagic stroke. We believe that randomized clinical trials are necessary to determine the safety and efficacy of these treatments. To our knowledge, there are multiple active trials evaluating this question, including the National Institutes of Health-funded Anti-thrombotics for Adults Hospitalized With COVID-19 (ACTIV-4) trial (NCT04505774). We eagerly await the results of ACTIV-4 and other, similar trials, which hopefully will answer the question of whether anticoagulant use in patients hospitalized with COVID-19 is beneficial.

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