Neurocrit Care (2021) 35:693–706
https://doi.org/10.1007/s12028-021-01220-5

NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Toxic Metabolic Encephalopathy in Hospitalized Patients with COVID-19

Jennifer A. Frontera[1*], Kara Melmed[1], Taolin Fang[1], Andre Granger[1], Jessica Lin[1], Shadi Yaghi[2], Ting Zhou[1], Ariane Lewis[1], Sebastian Kurz[3], D. Ethan Kahn[1], Adam de Havenon[4], Joshua Huang[5], Barry M. Czeisler[1], Aaron Lord[1], Sharon B. Meropol[6], Andrea B. Troxel[6], Thomas Wisniewski[1], Laura Balcer[1] and Steven Galetta[1]

Abstract

Background: Toxic metabolic encephalopathy (TME) has been reported in 7–31% of hospitalized patients with coronavirus disease 2019 (COVID-19); however, some reports include sedation-related delirium and few data exist on the etiology of TME. We aimed to identify the prevalence, etiologies, and mortality rates associated with TME in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive patients.

Methods: We conducted a retrospective, multicenter, observational cohort study among patients with reverse transcriptase–polymerase chain reaction-confirmed SARS-CoV-2 infection hospitalized at four New York City hospitals in the same health network between March 1, 2020, and May 20, 2020. TME was diagnosed in patients with altered mental status off sedation or after an adequate sedation washout. Patients with structural brain disease, seizures, or primary neurological diagnoses were excluded. The coprimary outcomes were the prevalence of TME stratified by etiology and in-hospital mortality (excluding comfort care only patients) assessed by using a multivariable time-dependent Cox proportional hazards models with adjustment for age, race, sex, intubation, intensive care unit requirement, Sequential Organ Failure Assessment scores, hospital location, and date of admission.

Results: Among 4491 patients with COVID-19, 559 (12%) were diagnosed with TME, of whom 435 of 559 (78%) developed encephalopathy immediately prior to hospital admission. The most common etiologies were septic encephalopathy ($n = 247$ of 559 [62%]), hypoxic-ischemic encephalopathy (HIE) ($n = 331$ of 559 [59%]), and uremia ($n = 156$ of 559 [28%]). Multiple etiologies were present in 435 (78%) patients. Compared with those without TME ($n = 3932$), patients with TME were older (76 vs. 62 years), had dementia (27% vs. 3%) or psychiatric history (20% vs. 10%), were more often intubated (37% vs. 20%), had a longer hospital length of stay (7.9 vs. 6.0 days), and were less often discharged home (25% vs. 66% [all $P < 0.001$]). Excluding comfort care patients ($n = 267$ of 4491 [6%]) and after adjustment for confounders, TME remained associated with increased risk of in-hospital death ($n = 128$ of 425 [30%] patients with TME died, compared with $n = 600$ of 3799 [16%] patients without TME; adjusted hazard ratio [aHR] 1.24, 95% confidence interval [CI] 1.02–1.52, $P = 0.031$), and TME due to hypoxemia conferred the highest risk ($n = 97$ of 233 [42%] patients with HIE died, compared with $n = 631$ of 3991 [16%] patients without HIE; aHR 1.56, 95% CI 1.21–2.00, $P = 0.001$).

Conclusions: TME occurred in one in eight hospitalized patients with COVID-19, was typically multifactorial, and was most often due to hypoxemia, sepsis, and uremia. After we adjustment for confounding factors, TME was associated with a 24% increased risk of in-hospital mortality.

*Correspondence: jennifer.frontera@nyulangone.org
[1] Department of Neurology, New York University Grossman School of Medicine, New York, NY, USA
Full list of author information is available at the end of the article

Springer

Keywords: COVID-19, SARS-CoV-2, Encephalopathy, Delirium, Confusion, Mental status

Introduction

Multiple studies have identified neurological events in the context of recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1–8]. Many of these complications are sequelae of severe illness or represent secondary effects of multisystem organ failure. In a prospective study of neurological disorders among hospitalized patients with coronavirus disease 2019 (COVID-19), we identified toxic metabolic encephalopathy (TME) as the most common neurological complication, occurring in 7% of all COVID-19 admissions [4]. Others reports estimated the prevalence of encephalopathy among patients with COVID-19 to be as high as 31% [9]; however, this study included patients who may have been sedated or were coded as having a positive Confusion Assessment Method (CAM) result [9, 10]. Although sedation-related delirium has been associated with worse outcomes [11, 12], the implications for long-term neurological recovery differ on the basis of the underlying etiologies of TME, which can best be ascertained when eliminating the confounding effect of sedative medications. We sought to explore the prevalence of specific etiologies of TME in patients with COVID-19 off sedation, or after an adequate sedation washout, and the differential impact of the most common etiologies on in-hospital mortality. In a secondary analysis, we assessed the relationship of TME with rates of discharge to home, hospital length of stay (LOS), and ventilator days.

Methods

Study Design and Participants

We conducted a retrospective multicenter cohort study of consecutive hospitalized patients admitted between March 1, 2020, and May 20, 2020. We included patients prospectively identified with TME following screening by a board-certified neurologist according to previously published protocols [4] and enriched this cohort with a retrospectively identified group of patients with encephalopathy using our systemwide mandatory admission comorbidity checklist (which has greater than 95% use/compliance). We added this retrospectively identified group to account for the fact that a neurology consultation may not be requested for all patients with altered mental status. Charts were then manually reviewed, and inclusion and exclusion criteria were applied (Fig. 1). Control patients were identified via query of the electronic medical record (EMR) (Epic; Epic Systems Corporation, Verona, WI) and included adult patients (aged 18 years or older) with reverse transcriptase–polymerase chain reaction (RT-PCR) results positive for SARS-CoV-2

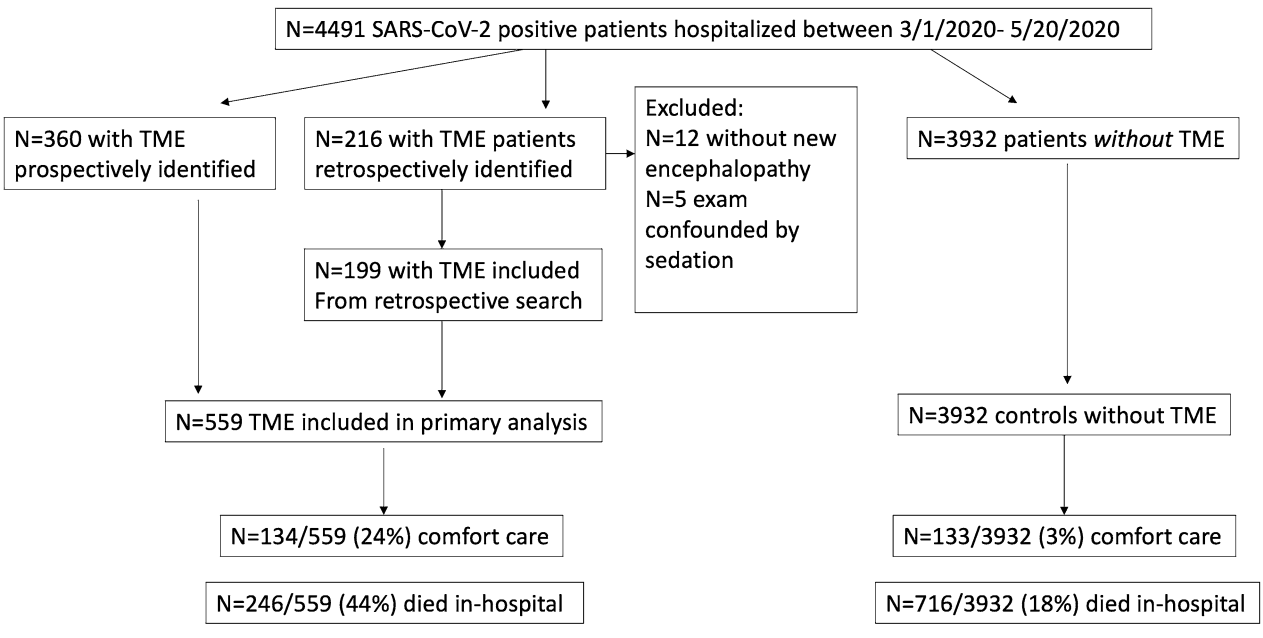

Fig. 1 Flow diagram of inclusion and exclusion criteria. SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, TME toxic metabolic encephalopathy

who were admitted to the same New York University (NYU) Langone hospitals during the same time frame as the case patients (March 1 to May 20, 2020). Control patients were neither diagnosed with TME by a neurology team nor coded as having encephalopathy at admission or during their hospital stay.

Inclusion criteria were as follows: aged 18 years or older, hospital admission, RT-PCR-confirmed SARS-CoV-2 infection, and TME. TME was coded for patients with new changes in mental status in the absence of focal neurological deficits or primary structural brain disease. Patients with baseline abnormal mental status (due to dementia or psychiatric illness) could be included if there was significant worsening of mental status during hospitalization. Patients with hyperglycemia or hypoglycemia with focal neurological deficits that were transient and resolved with glucose correction were eligible for inclusion. For patients who had received sedating medications (including continuous infusions or intermittent doses of propofol, dexmedetomidine, benzodiazepines, barbiturates, or opiates), an adequate washout of four to five half-lives (accounting for active metabolites or renal or hepatic failure) was required for mental status assessment. Exclusion criteria were as follow: treatment in an emergency department or outpatient setting only, altered mental status due to another acute neurological diagnosis that could account for the observed examination findings (e.g., stroke, seizure, or traumatic brain injury) [13] or abnormal mental status due to sedative medications. Only index admissions were included.

Setting

This study included patients admitted to four NYU Langone hospitals located in Manhattan, Brooklyn, and Mineola, New York. All four hospitals use the same EMR and information technology center, and all have integrated clinical protocols for patient management. This study was approved with a waiver of authorization and informed consent by the NYU Grossman School of Medicine Institutional Review Board.

Encephalopathy Categories

Potential TME etiologies were identified a priori and included the following: electrolyte abnormalities (hyponatremia or hypernatremia, hypoglycemia or hyperglycemia, hypocalcemia or hypercalcemia, hypomagnesemia or hypermagnesemia, or hypophosphatemia or hyperphosphatemia; acidosis/acidemia; or alkalosis/alkalemia), organ failure (renal failure/uremia, liver failure, or pulmonary failure [including hypoxemia or hypercarbia]), hypertensive encephalopathy, sepsis or active infection (from either SARS-CoV-2 or another infection), fever, nutritional deficiency (Wernicke encephalopathy, vitamin B_{12} deficiency, or niacin deficiency), or environmental injury (hypothermia or exposure or poisoning) [7, 13]. Hypoxic-ischemic encephalopathy (HIE) (also known as anoxic or hypoxic brain injury) was defined as a global cerebral insult due to oxygen deprivation to the brain or lack of perfusion to the brain caused by systemic hypoxemia, hypotension, or cardiac arrest [14]. HIE was diagnosed among survivors of cardiac arrest with new central nervous system dysfunction and among patients with prolonged and/or severe hypoxemia (oxygen saturation less than 88%) or hypotension (mean arterial pressure less than65 mmHg) with new neurologic deficits and/or characteristic radiographic findings on head computed tomography or magnetic resonance imaging (MRI) scans [4]. Sepsis-associated encephalopathy was diagnosed among patients with altered mental status and sepsis defined by Sepsis-3 consensus criteria [15] and life-threatening organ dysfunction caused by a dysregulated immune response to infection. The maximum recorded Sequential Organ Failure Assessment (SOFA) score was used to assess severity of illness and has been shown to be predictive of organ failure and in-hospital mortality [16–18]. Upper and lower laboratory value limits were used to define electrolyte abnormalities. Drug intoxication or withdrawal was coded for illicit substances only, and encephalopathy related to supratherapeutic drug levels was coded for medications such as digoxin, antiseizure medications, or lithium.

Data Collection

Initial neurologic diagnosis coding was performed by attending neurologists and neurology resident physicians during data abstraction according to previously published methodology [4]. Past neurologic history was assessed via manual chart review and validated by EMR data query based on *International Classification of Diseases, Tenth Revision* diagnosis codes. Four neurologists (TF, AG, KM, and JL) reviewed charts to verify the diagnosis of encephalopathy and identify potential etiologies, which could be multifactorial. Demographics, past medical history, medication use, hospital complications, laboratory values, and in-hospital outcomes (in-hospital mortality, discharge disposition, intubation, ventilator days, and hospital LOS) were extracted from the EMR and via manual chart review. CAM [10] and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [19] scores, which were documented by trained nurses every 12 h, were recorded.

Study Outcomes

The coprimary outcomes were the prevalence of TME stratified by etiology and in-hospital death among patients with TME compared with those without TME.

Patients who transitioned to comfort care at any time during hospitalization were excluded from mortality analyses. To avoid time-to-event bias among patients who were discharged, a cutoff of 75 days was used as the event time for right-censored patients who were not dead or discharged to hospice. Seventy-five days was selected because it exceeded the maximum LOS observed in this cohort (71.4 days). Secondary outcomes included rates of discharge to home, acute respiratory failure requiring invasive mechanical ventilation, ventilator days, and hospital LOS.

Statistical Analyses

Demographic variables, past medical and neurological history, clinical features, hospital medications, hospital complications, and in-hospital outcomes (ventilator days, LOS, intubation status, and discharge to home) were compared between patients with COVID-19 with or without TME by using the Mann–Whitney *U* test for continuous variables and χ^2 test for categorical values, as appropriate.

A multivariable Cox proportional hazards model was fit for the time to in-hospital death by using a time-dependent TME covariate to account for "immortal time bias," which can occur when an event is observed more frequently in patients who survive long enough to be diagnosed with a condition [20]. This model was adjusted for confounders, including age, sex, race, week of admission, hospital location, maximum SOFA score recorded during hospitalization, intensive care unit (ICU) requirement, and intubation status. Subgroup analyses were conducted to evaluate in-hospital mortality, discharge disposition, ventilator days, and hospital LOS among patients with HIE, uremic encephalopathy, and sepsis-associated encephalopathy by using the same statistical modeling. Predictors of HIE were assessed by using multivariable logistic regression models. All analyses were conducted by using IBM SPSS Statistics for Mac version 25 (IBM Corporation, Armonk, NY).

Results

Of 4491 patients with COVID-19 hospitalized between March 1, 2020, and May 20, 2020, 559 (12%) had TME, and 3932 controls were identified. Of patients with TME, 360 of 559 (64%) were prospectively identified and 199 of 559 (36%) were retrospectively identified (Fig. 1). Among the 979 of 4491 (22%) patients who required ICU care, 196 of 979 (20%) had TME. The most common etiology was sepsis-associated encephalopathy, occurring in 347 of 559 (62%) patients, followed by HIE (331 of 559 [59%]) and uremic encephalopathy (156 of 559 [28%]) (Table 1 and Figs. 2 and 3). Multiple etiologies were identified in 435 of 559 (78%) patients (Figs. 2 and 3). The median time from admission to diagnosis of TME was −0.05 days (interquartile range [IQR] −2.0 to 0.36 days), indicating that most patients were encephalopathic at the time of hospital presentation. Indeed, 435 of 559 (78%) patients developed encephalopathy prior to or at the time of hospital admission.

Table 1 Etiologies of toxic metabolic encephalopathy among hospitalized patients with COVID-19

Etiology	Prevalence, *n* (%)
Total N	559
Electrolyte abnormalities	223/559 (40)
Hyponatremia	79 (14)
Hypernatremia	93 (17)
Hypoglycemia	6 (1)
Hyperglycemia	17 (3)
Hypercalcemia	3 (1)
Acidosis/acidemia	25 (4)
Organ failure	525/559 (94)
Uremia	156 (28)
Hepatic encephalopathy	16 (3)
Pulmonary	
Hypoxia	330 (59)
Hypercapnia	17 (3)
Hypertensive encephalopathy/crisis	7 (1)
Medication/drug related	32/559 (6)
Drug/alcohol withdrawal	5 (1)
Drug/alcohol intoxication	6 (1)
Supratherapeutic drug levels	21 (4)
Infection/inflammatory	421/559 (75)
Infection/sepsis encephalopathy	347 (62)
Fever	74 (13)
Nutritional	2/559 (0.4)
Vitamin deficiency (Wernicke encephalopathy, vitamin B_{12} deficiency, niacin deficiency)	2 (0.4)
Environmental	2/559 (0.4)
Hypothermia/exposure	1 (0.2)
Poisoning	1 (0.2)
Other	9/559 (2)

COVID-19 coronavirus disease 2019

Risk Factors for TME

Risk factors for TME included older age, male sex, past neurological history (dementia, ischemic stroke, seizure, or movement disorder), psychiatric history, chronic kidney or liver disease, hypertension, diabetes, and coronary artery disease (Table 2 and Supplementary Table 1). Patients with TME had higher severity of illness markers, including higher maximum SOFA scores, higher rates of intubation and ICU stay, and more acute renal failure. Similarly, these patients had significantly lower nadir

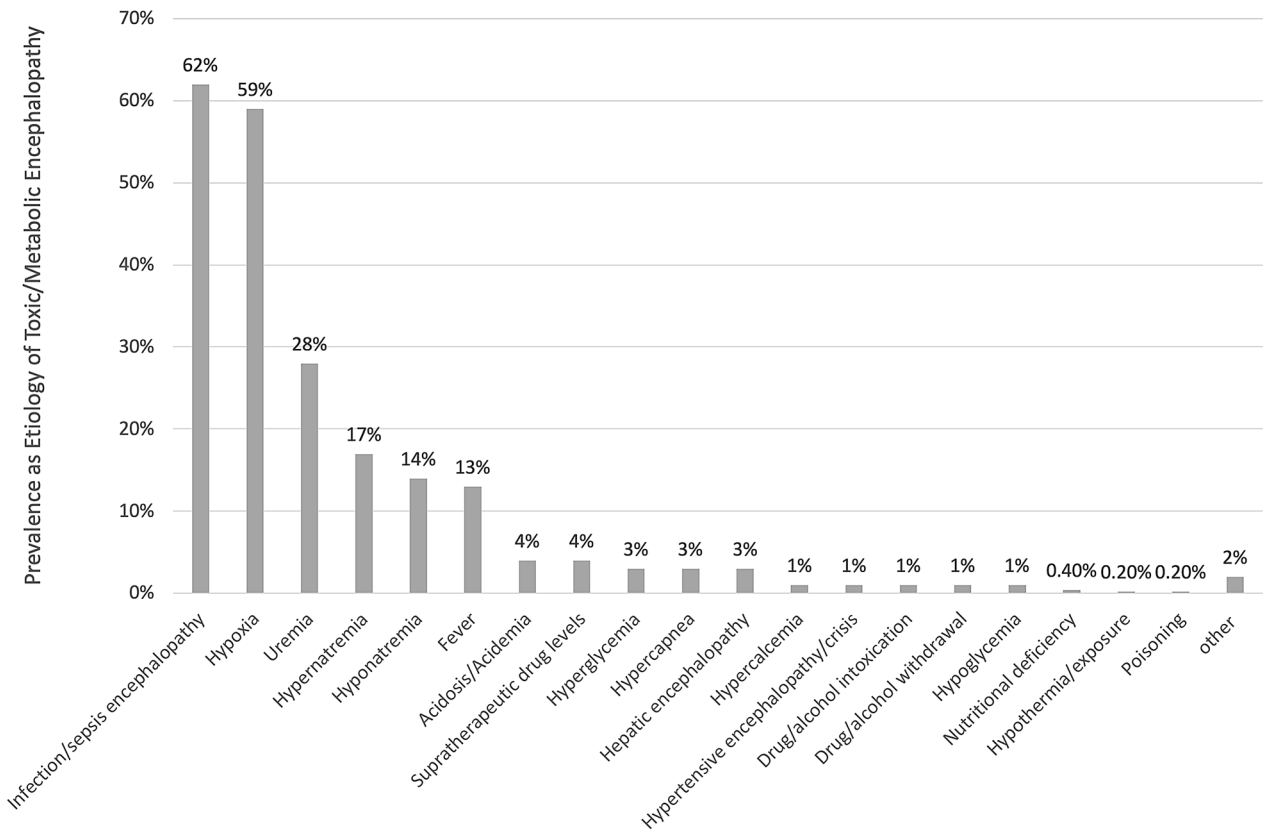

Fig. 2 The prevalence of different etiologies of toxic metabolic encephalopathy among hospitalized patients with coronavirus disease 2019 (COVID-19) ($N=559$)

oxygen saturation levels, higher blood urea nitrogen and creatinine levels, and higher levels of inflammatory markers, including interleukin 6 (IL-6) and D-dimer levels (Table 2). Of note, results of the CAM or CAM-ICU assessments were more often positive in patients with TME, but only 33% of patients with TME tested positive using either tool. Cerebrospinal fluid (CSF) analyses were performed in only 2% of patients with TME and 1% of controls. A total of 18 patients underwent CSF SARS-CoV-2 RT-PCR testing ($n=9$ in each group), and all RT-PCR results were negative (Supplementary Table 2).

Association of TME with Outcome

In the univariate analysis, patients with TME from any etiology had higher rates of intubation, longer hospital LOS, higher mortality rates, and reduced rates of discharge to home (all $P<0.001$; Table 3). These differences were noted in all three of the most common TME etiologies, including uremic encephalopathy, HIE, and sepsis-associated encephalopathy.

Overall, 246 of 559 (44%) patients with TME died in the hospital or were discharged to hospice, compared with 716 of 3832 (18%) patients without TME ($P<0.001$; Table 3). After we excluded patients receiving comfort care only ($n=267$ of 4491 [6%]) and adjusted for confounders in the multivariable analysis (including age, sex, race, worst SOFA score during hospitalization, ventilator status, week of study, hospital location, and ICU level of care), TME was associated with a 24% increased risk of in-hospital death ($n=128$ of 425 [30%] patients with TME died, compared with $n=600$ of 3799 [16%] patients without TME; adjusted hazard ratio [aHR] 1.24, 95% confidence interval [CI] 1.02–1.52, $P=0.031$; Table 4). A sensitivity analysis that included comfort care patients yielded similar results ($n=246$ of 559 [44%] patients with TME died, compared with $n=716$ of 3832 [18%] patients without TME; aHR 1.64, 95% CI 1.42–1.92, $P<0.001$).

Etiologies of TME and Impact on Outcome

HIE was significantly associated with increased in-hospital mortality in the multivariable analysis of the entire cohort, whereas uremic encephalopathy and sepsis-associated encephalopathy were not (Table 4). Compared with patients with other TME etiologies, and after we adjusted for the same confounders, patients with HIE had the highest risk of in-hospital death among all patients

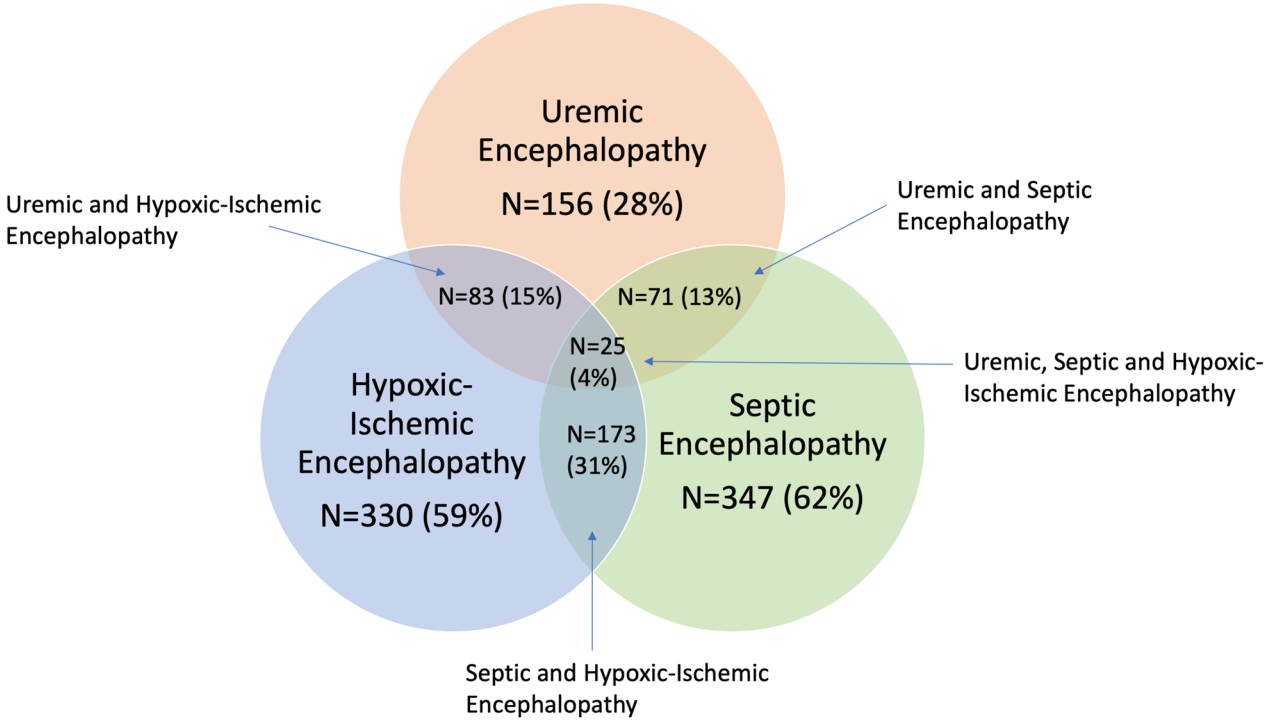

Fig. 3 Venn diagram demonstrating the frequency of concurrent etiologies of toxic metabolic encephalopathy

with TME (aHR 3.82, 95% CI 2.47–5.92, $P<0.001$; Table 4) and the lowest rates of discharge to home.

Risk Factors for HIE

Among patients with TME, patients with HIE had higher markers of severe illness (higher maximum SOFA scores, ICU admission, and intubation) than patients with other TME etiologies (all $P<0.001$; Table 5). Only 41 of 330 (12%) patients with HIE were survivors of cardiac arrest; the remainder had severe or protracted hypoxemia. Of patients with HIE who did not have cardiac arrest, the median minimum oxygen saturation was 80% (IQR 67–87%), compared with 88% (IQR 81–92%) among those without HIE ($P<0.001$). The median number of desaturations below 88% was 5 (IQR 1–14) for those with HIE, compared with 1 (IQR 0–4) for those without HIE ($P<0.001$). Hypotension was more common among patients with HIE, with a median minimum mean arterial pressure (MAP) of 55 mmHg (IQR 44–64) among those with HIE, compared with 67 mmHg (IQR 58–74) among those without HIE ($P<0.001$). Of patients with HIE, 80% had at least one recorded MAP less than 65 mmHg, compared with 42% of those without HIE ($P<0.001$). The median number of blood pressure readings with an MAP less than 65 mmHg was 1 (IQR 0–12) among patients with HIE, compared with 0 (IQR 0–1) among those without HIE ($P<0.001$). In multivariable logistic regression models, HIE was associated with both an oxygen saturation less than 88% (adjusted odds ratio 2.97, 95% CI 1.81–4.86, $P<0.001$) and an MAP less than 65 mmHg (adjusted odds ratio 4.41, 95% CI 2.74–7.10, $P<0.001$). However, there was not a significant interaction between these two variables ($P=0.336$ for interaction).

Discussion

In this study, we found that nearly one in eight patients hospitalized with COVID-19 had TME not attributable to the effects of sedative medications. TME was significantly

Table 2 Demographic, clinical, and laboratory findings among patients with or without toxic metabolic encephalopathy (*N* = 4491)

Characteristic	Toxic metabolic encephalopathy (*n* = 559)	No toxic metabolic encephalopathy (*n* = 3932)	*P*
Demographics			
Median age (IQR) (years)	76 (67–85)	62 (50–74)	< 0.001
Male sex, no./total no. (%)	351/559 (63)	2256/3932 (57)	0.015
Body mass index, median (IQR)	26 (23–30)	28 (25–33)	< 0.001
Race, no./total no. (%)			< 0.001
White	359/559 (64)	1757/3932 (45)	–
Black	95/559 (17)	609/3932 (16)	–
Asian	53/559 (10)	260/3932 (7)	–
Other	52/559 (9)	1306(33)	–
Past medical history, no./total no. (%)			
Dementia	152/559 (27)	120/3932 (3)	< 0.001
Psychiatric illness	113/559 (20)	408/3932 (10)	< 0.001
Ischemic stroke	82/559 (15)	308/3932 (8)	< 0.001
Seizure	52/559 (9)	161/3932 (4)	< 0.001
Movement disorder	36/559 (5)	53/559 (1)	< 0.001
Multiple sclerosis/demyelinating disease	4/559 (1)	16/3932 (0.4)	0.044
Chronic kidney disease	105/559 (19)	392/3932 (10)	< 0.001
Chronic liver disease	14/559 (3)	59/3932 (2)	0.016
Hypertension	277/559 (50)	1431/3932 (36)	< 0.001
Diabetes	187/559 (34)	987/3932 (25)	< 0.001
Coronary artery disease	127/559 (23)	477/3932 (12)	< 0.001
Clinical findings			
ICU vs. non-ICU, no./total no. (%)	196/559 (35)	783/3932 (20)	< 0.001
Intubation, no./total no. (%)	206 (37)	781 (20)	< 0.001
Maximum SOFA score, median (IQR)	4 (3–8)	3 (3–4)	< 0.001
CAM or CAM-ICU result positive, no./total no. (%)	183/559 (33)	533/3932 (14)	< 0.001
Medications, no./total no. (%)			
Corticosteroids	119/559 (21)	724/3932 (18)	0.103
Hydroxychloroquine	362/559 (65)	2653/3932 (68)	0.201
Azithromycin	320/559 (57)	2355/3932 (60)	0.233
Lopinavir/ritonavir	57/559 (10)	257/3932 (7)	0.001
Zinc	153/559 (27)	1410/3932 (36)	< 0.001
Ascorbic acid (vitamin C)	124/559 (22)	954/3932 (24)	0.281
Tocilizumab	65/559 (12)	474/3932 (12)	0.771
Remdesivir	3/559 (0.5)	11/3932 (0.3)	0.308
Therapeutic anticoagulation	228/559 (41)	917/3932 (23)	< 0.001
Acute renal failure, no./total no. (%)	147/559 (26)	499/3932 (13)	< 0.001
Comfort care status, no./total no. (%)	134/559 (24)	133/3932 (3)	< 0.001
Laboratory, imaging, and neurophysiology findings			
Admission oxygen saturation, median (IQR) (%)	94 (91–97)	94 (91–97)	0.926
Lowest oxygen saturation, median (IQR) (%)	84 (69–90)	88 (80–92)	< 0.001
Lowest mean arterial pressure, median (IQR) (mmHg)	58 (44–66)	67 (58–74)	< 0.001
Admission sodium, median (IQR) (mmol/dL)	138 (134–142)	137 (134–139)	< 0.001
Admission BUN, median (IQR) (mg/dL)	27 (18–47)	16 (11–25)	< 0.001
Admission creatinine, median (IQR) (mg/dL)	1.32 (0.92–2.04)	0.98 (0.80–1.30)	< 0.001
Admission glucose, median (IQR) (mg/dL)	130 (106–183)	117 (100–152)	< 0.001
Admission interleukin 6, median (IQR) (pg/mL)	33 (14–71)	21 (10–52)	0.002
Admission c-reactive protein, median (IQR) (mg/L)	107 (49–174)	104 (48–167)	0.600

Table 2 (continued)

Characteristic	Toxic metabolic encephalopathy ($n=559$)	No toxic metabolic encephalopathy ($n=3932$)	*P*
Admission D-dimer, median (IQR) (ng/mL)	595 (335–1166)	420 (268–779)	< 0.001
Admission ferritin, median (IQR) (ng/mL)	689 (354–1460)	671 (314–1405)	0.197
Brain neuroimaging performed (any), no./total no. (%)	397/559 (71)	507/3932 (13)	< 0.001
Head CT scan performed, no./total no. (%)	396/559 (71)	492/3932 (13)	< 0.001
MRI performed, no./total no. (%)	51/559 (9)	79/3932 (2)	< 0.001
Lumbar puncture performed, no./total no. (%)	12/559 (2)	18/3932 (1)	0.258
EEG performed, no./total no. (%)	76/559 (14)	80/3932 (2)	< 0.001

BUN serum urea nitrogen, *CAM* Confusion Assessment Method, *CT* computed tomography, *ICU* intensive care unit, *IQR* interquartile range, *MRI* magnetic resonance imaging, *SOFA* Sequential Organ Failure Assessment

associated with a 24% increased risk of in-hospital mortality, even after we excluded patients receiving comfort care and adjusted for other confounders. TME was also associated with longer hospital LOS and a lower chance of discharge to home. Although TME is often thought of as a reversible condition, our data demonstrate that TME is associated with significantly worse hospital outcomes.

The most common etiologies of TME were sepsis-associated encephalopathy, uremic encephalopathy, and HIE. Sepsis-associated encephalopathy has been reported in up to 70% of patients with bacteremia or viremia and is mediated by inflammatory cytokines, alteration of neurotransmitters (particularly GABAergic, serotoninergic, and β-adrenergic release and receptor expression, along with glutamate excitotoxicity), blood–brain barrier breakdown, and microthrombosis [13, 21, 22]. Viral sepsis has been described in SARS-CoV-2 infection and is likely mediated by cytokines, including IL-6, tumor necrosis factor, and interleukin 1β (IL-1β) among others [23, 24]. Indeed, IL-6 levels were significantly elevated among patients with TME compared with those without TME in our cohort. Although others have demonstrated an association between sepsis-associated encephalopathy and increased mortality rates [25, 26], we did not observe this relationship among the entire hospitalized COVID-19 cohort, perhaps because of advances in sepsis resuscitation or because we included patients with a spectrum of sepsis severity.

Uremic encephalopathy is typically most severe in patients with acute renal failure and is due to neurotoxicity of nitrogenous waste products and other osmotically active toxins [13]. Secondary effects of acute renal failure, including acidosis, hyponatremia, hyperkalemia, hyperphosphatemia, and hypocalcemia, can compound uremic encephalopathy. Acute kidney injury (AKI) has been reported in 8–17% of patients with COVID-19 [27, 28] and 20–81% of patients with COVID-19 requiring ICU admission [27, 29], although only about 4–5% of patients with SARS-CoV-2-related AKI require renal replacement therapy [27, 28]. AKI in patients with COVID-19 is also likely related to proinflammatory cytokine storms, thrombotic events, and direct renal cellular injury due to viral entry [30]. Meta-analyses have demonstrated that AKI is significantly linked to mortality following SARS-CoV-2 infection [27, 28], and we have similarly observed higher mortality rates in patients with uremic encephalopathy.

Finally, we found that HIE was implicated in 60% of TME cases, even among patients who did not suffer cardiac arrest. Although a U-shaped curve has been described for the relationship between hospital mortality and partial pressure of oxygen, arterial (PaO_2) levels (with mortality increasing for PaO_2 less than 67 mmHg or greater than 225 mmHg) [31], there are few data describing optimal oxygenation thresholds to avoid hypoxic brain injury. Some data suggest that "permissive hypoxia" targeting oxygen saturations between 88 and 92% aimed at avoiding hyperoxia-related oxygen free radical damage, may be preferred to more liberal oxygenation strategies in terms of reducing hospital mortality [32], although recent randomized trials have found no benefit to conservative oxygen targets (55–70 mmHg) [33, 34]. Although hypoxemia is a hallmark of most hospitalized patients with COVID-19, the degree and duration of hypoxemia required to cause permanent brain injury remains unknown and may vary from patient to patient

Table 3 Univariate analysis of hospital complications and outcomes among patients with different encephalopathy etiologies

	Any toxic metabolic encephalopathy			Uremic encephalopathy			Hypoxic-ischemic encephalopathy			Sepsis-associated encephalopathy		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
N	559	3932	–	156	4335	–	330	4161	–	347	4144	–
Intubated, *n* (%)	206 (37)	781 (20)	< 0.001	58 (37)	929 (21)	< 0.001	160 (49)	827 (20)	< 0.001	108 (31)	879 (20)	< 0.001
Ventilator days, median (IQR)	6.3 (1.4–17.7)	6.2 (2.6–14.8)	0.940	5.5 (2.1–15.3)	6.3 (1.6–15.3)	0.697	6.2 (1.3–18.0)	6.2 (1.7–14.8)	0.758	5.5 (1.0–16.5)	6.3 (1.7–15.1)	0.350
Hospital LOS, median (IQR) (d)	7.9 (4.3–17.1)	6.0 (3.1–11.1)	< 0.001	8.4 (4.8–16.2)	6.1 (3.1–11.4)	< 0.001	8.2 (4.4–19.8)	6.0 (3.1–11.2)	< 0.001	7.8 (4.5–16.4)	6.0 (3.1–11.3)	< 0.001
In-hospital death, *n* (%)	246 (44)	716 (18)	< 0.001	83 (53)	879 (20)	< 0.001	188 (57)	774 (19)	< 0.001	144 (42)	818 (20)	< 0.001
Discharge home, *n* (%)	141 (25)	2608 (66)	< 0.001	33 (21)	2716 (63)	< 0.001	50 (15)	2699 (65)	< 0.001	93 (27)	2656 (64)	< 0.001

IQR interquartile range, *LOS* length of stay

depending on the presence of flow-limiting extra- or intracranial vessel stenosis, carbon dioxide levels, the integrity of cerebral autoregulation, prior ischemic damage, and the degree of brain metabolic activity and blood flow coupling. In our current study, it is likely that episodic hypotension, along with hypoxemia, contributed to the development of HIE, although hypoxemic events were more common. We found that 80% of patients with HIE had at least one blood pressure reading with a MAP less than 65 mmHg; however, the median number of hypotensive episodes was only 1 (IQR 0–12), whereas the median frequency of oxygen desaturations less than 88% was 5 (IQR 1–14).

Although pure hypoxic brain injury, without hypotension or circulatory arrest, has historically been thought to be relatively benign [14, 35] and not associated with ischemic damage in animal and autopsy series [14, 36], some data suggest that isolated hypoxemia is deleterious. Transient cognitive deficits related to brief episodes of hypoxemia (oxygen saturation less than ~ 65%) without hypotension in healthy volunteers and hikers at altitude have been well documented [35, 37–40], and MRI scans of mountaineers with repeated exposure to altitude-related hypoxemia have shown abnormalities in primary and secondary motor cortex regions compared with controls [40]. Within the acute respiratory distress syndrome (ARDS) literature, long-term cognitive deficits have been described following severe hypoxemia, occurring in 30–55% of survivors of ARDS [41–43]. In one study, lower PaO_2 levels were significantly associated with worse long-term cognitive outcomes (after adjustment for demographics, severity of illness, and comorbid conditions), whereas systolic blood pressure, cardiac index, the presence of shock, and the use of vasopressors were not [43].

One strength of our study was that encephalopathy was assessed after we eliminated the confounding effects of sedation. This allowed us to more precisely identify underlying metabolic etiologies. Although some studies have found that sedation-related delirium is associated with worse outcomes [44], others have found that cognitive dysfunction correlates most strongly with the duration of delirium rather than the use or dose of sedative or analgesic medications [41]. Furthermore, much of the delirium literature has used a once daily CAM or CAM-ICU to identify patients with abnormal mental status. In our study, although significantly more patients with TME had a positive CAM [10] or CAM-ICU [19] result, overall only 33% of patients with TME were positive at any point during their hospital stay, suggesting limited sensitivity of these tools to identify encephalopathy [45]. Although it is suggested that the CAM or CAM-ICU be administered with a Richmond Agitation–Sedation

Table 4 Multivariable adjusted hazard ratios for in-hospital mortality among different etiologies of encephalopathy in the entire cohort and the subgroup of patients with toxic metabolic encephalopathy, excluding comfort care patients

Etiology	*n* (%) who died with each encephalopathy	Adjusted HR (95% CI)	*P*
Risk of in-hospital death among all patients, excluding comfort care patients ($n=4224$)			
Hypoxic-ischemic encephalopathy[a]	97/4224 (2)	1.56 (1.21–2.00)	0.001
Uremic encephalopathy[b]	41/4224 (1)	1.23 (0.88–1.74)	0.229
Septic encephalopathy[c]	77/4224 (2)	1.23 (0.94–1.61)	0.125
Any etiology[d]	128/4224 (3)	1.24 (1.02–1.52)	0.031
Risk of in-hospital death among patients with toxic metabolic encephalopathy, excluding comfort care patients ($n=425$)			
Hypoxic-ischemic encephalopathy[a]	97/425 (23)	3.82 (2.47–5.92)	< 0.001
Uremic encephalopathy[b]	41/425 (10)	1.48 (0.95–2.30)	0.081
Sepsis encephalopathy[c]	77/425 (18)	2.13 (1.44–3.16)	< 0.001

CI confidence interval, *HR* hazard ratio, *ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment

[a] Adjusted for age, sex, race, worst SOFA score during hospitalization, ventilator status, week of study, hospital location, ICU level of care, uremic encephalopathy, and sepsis encephalopathy

[b] Adjusted for age, sex, race, worst SOFA score during hospitalization, ventilator status, week of study, hospital location, ICU level of care, hypoxic-ischemic encephalopathy, sepsis encephalopathy, and acute renal failure

[c] Adjusted for age, sex, race, worst SOFA score during hospitalization, ventilator status, week of study, hospital location, ICU level of care, hypoxic-ischemic encephalopathy, and uremic encephalopathy

[d] Adjusted for age, sex, race, worst SOFA score during hospitalization, ventilator status, week of study, hospital location, and ICU level of care

Scale [46] score greater than or equal to − 3, it is not mandated that sedation be held for evaluation. Hence, encephalopathy detected with this tool may represent heterogeneous etiologies, including variable levels of sedation, acute structural neurological injury, seizure, or metabolic encephalopathy [47]. Despite this heterogeneity, studies using the CAM and CAM-ICU have found that sepsis- and hypoxia-related delirium are associated with worse 12-month outcomes [44]. Other strengths of our study include the large sample size and the fact that patients receiving comfort care only were excluded from the mortality analysis so that our results could be more reflective of the natural history of TME in patients with COVID-19. However, because comfort care was relatively common, we conducted a sensitivity analysis and confirmed the association of TME and mortality in the entire cohort, including comfort care patients.

Limitations of this study include a possible underestimation of the prevalence of TME in patients who were too severely ill to have their sedation held for assessment. Our previous study of neurological disorders in COVID-19 [4] included only prospectively enrolled patients and identified a 7% prevalence of TME. Although we retrospectively identified many additional patients with TME, we may underrepresent patients who developed encephalopathy during hospitalization but did not have a neurology consultation or have sedation held for an adequate evaluation. We did not have continuous data regarding the duration or severity of hypoxemia or hypotension to create predictive models for the risk of developing HIE. Further granular analysis with an adequate control group may help elucidate predictive thresholds. SOFA scores were calculated automatically in the medical record, and some studies have found that respiratory components (Pao_2 and fraction of inspired oxygen [FIO_2]) may be less accurate than manual calculation [48, 49]. In our COVID-19 population, in whom Pao_2 and FIO_2 values were rarely normal, it is possible that automatically generated SOFA scores underestimated severity of illness. Finally, although more than 70% of patients with TME had neuroimaging performed, it is possible that another primary neurological disorder could have contributed to encephalopathy and was undetected. Although patients with imaging findings suggestive of a primary neurological cause of altered mental status (e.g., stroke, intracranial hemorrhage, and infection) were excluded from this study, further detailed study of

Table 5 Risk factors and outcomes comparing patients with differing encephalopathy etiologies (*N* = 559)

Characteristic	Uremic encephalopathy	No uremic encephalopathy	*P*	Sepsis encephalopathy	No sepsis encephalopathy	*P*	Hypoxic-ischemic encephalopathy[a]	No hypoxic-ischemic encephalopathy	*P*
Total *N*	156	403	–	347	212	–	330	229	–
Demographics									
Median age (IQR) (years)	77 (67–85)	76 (67–85)	0.606	77 (68–84)	74 (65–85)	0.132	77 (67–85)	76 (67–84)	0.224
Male sex, no./total no. (%)	113/156 (72)	238/403 (59)	**0.003**	212/347 (61)	139/212 (66)	0.289	215/330 (65)	136/229 (59)	0.166
Body mass index, median (IQR)	26 (22–29)	26 (23–30)	0.052	26 (23–30)	26 (23–29)	0.377	27 (24–30)	25 (22–29)	**0.003**
Race, no./total no. (%)			0.809			0.850			0.627
White	94/156 (60)	265/403 (66)	–	227/347 (65)	132/212 (62)	–	212/330 (64)	147/229 (64)	–
Black	32/156 (21)	63/403 (16)	–	54/347 (16)	41/212 (19)	–	50/330 (15)	45/229 (20)	–
Asian	16/156 (10)	37/403 (9)	–	33/347 (10)	20/212 (9)	–	37/330 (11)	16/229 (7)	–
Other	14/156 (9)	38/403 (9)	–	33/347 (10)	19/212 (9)	–	31/330 (9)	21/229 (9)	–
Past medical history, no./total no. (%)									
Dementia	36/156 (23)	116/403 (29)	0.319	105/347 (30)	47/212 (22)	0.080	92/330 (28)	60/229 (26)	0.635
Psychiatric illness	23/156 (15)	90/403 (22)	0.110	84/347 (24)	29/212 (14)	**0.010**	53/330 (16)	60/229 (26)	**0.013**
Ischemic stroke	26/156 (17)	56/403 (14)	0.489	50/347 (14)	32/212 (15)	0.531	52/330 (16)	30/229 (13)	0.332
Seizure	4/156 (3)	48/403 (12)	**0.002**	27/347 (8)	25/212 (12)	0.160	33/330 (10)	19/229 (8)	0.389
Movement disorder	7/156 (5)	19/403 (5)	0.673	14/347 (4)	12/212 (6)	0.371	18/330 (6)	8/229 (4)	0.273
Multiple sclerosis/demyelinating disease	0	4/403 (1)	0.309	3/347 (1)	1/212 (0.5)	0.468	3/330 (1)	1/229 (0.4)	0.401
Chronic kidney disease	51/156 (33)	54/403 (13)	**< 0.001**	65/347 (19)	40/212 (19)	0.542	63/330 (19)	42/229 (18)	0.482
Chronic liver disease	7/156 (5)	7/403 (2)	0.121	5/347 (1)	9/212 (4)	0.066	8/330 (2)	6/229 (3)	0.494
Hypertension	79/156 (51)	198/403 (49)	0.654	176/347 (51)	101/212 (48)	0.402	164/330 (50)	113/229 (49)	0.493
Diabetes	55/156 (35)	132/403 (33)	0.591	114/347 (33)	73/212 (34)	0.512	112/330 (34)	75/229 (33)	0.470
Coronary artery disease	41/156 (26)	86/403 (21)	0.321	79/347 (23)	48/212 (23)	0.540	79/330 (24)	48/229 (21)	0.343
Clinical findings									
ICU vs. non-ICU, no./total no. (%)	57/156 (37)	139/398 (35)	0.721	103/344 (30)	93/210 (44)	**0.001**	137/325 (42)	59/229 (26)	**< 0.001**

Table 5 (continued)

Characteristic	Uremic encephalopathy	No uremic encephalopathy	*P*	Sepsis encephalopathy	No sepsis encephalopathy	*P*	Hypoxic-ischemic encephalopathy[a]	No hypoxic-ischemic encephalopathy	*P*
Intubation, no./total no. (%)	58/156 (37)	148/402 (37)	0.952	108/347 (31)	98/212 (46)	**< 0.001**	160/330 (49)	46/229 (20)	**< 0.001**
Maximum SOFA score, median (IQR)	6 (4–9)	4 (3–8)	**< 0.001**	4 (3–7)	5 (4–11)	**0.002**	5 (4–11)	4 (3–6)	**< 0.001**
CAM or CAM-ICU result positive, no./total no. (%)	52/155 (34)	131/402 (33)	0.829	108/346 (31)	75/212 (36)	0.291	113/330 (34)	70/229 (31)	0.368
Medications, no./total no. (%)									
Corticosteroids	30/156 (19)	89/403 (22)	0.460	65/347 (19)	54/212 (26)	0.059	88/330 (27)	31/229 (14)	**< 0.001**
Hydroxychloroquine	97/156 (62)	265/403 (66)	0.427	226/347 (65)	136/212 (64)	0.814	228/330 (69)	134/229 (59)	**0.010**
Azithromycin	86/156 (55)	234/403 (58)	0.529	204/347 (59)	116/212 (55)	0.345	195/330 (59)	125/229 (55)	0.290
Lopinavir/ritonavir	20/156 (13)	37/403 (9)	0.202	35/347 (10)	22/212 (10)	0.912	38/330 (12)	19/229 (8)	0.216
Zinc	42/156 (27)	111/403 (28)	0.883	95/347 (27)	58/212 (27)	0.996	100/330 (30)	53/229 (23)	0.062
Ascorbic acid (vitamin C)	34/156 (22)	90/403 (22)	0.891	74/347 (21)	50/212 (40)	0.533	87/330 (26)	37/229 (16)	**0.004**
Tocilizumab	14/156 (9)	51/403 (13)	0.223	39/347 (11)	26/212 (12)	0.714	48/330 (15)	17/229 (7)	**0.010**
Remdesivir	0	3/403 (1)	0.280	2/347 (0.4)	1/212 (0.2)	0.869	1/330 (0.3)	2/229 (0.9)	0.364
Therapeutic anticoagulation	73/156 (47)	155/403 (39)	0.072	128/347 (37)	100/212 (47)	**0.012**	162/330 (49)	66/229 (29)	**< 0.001**
Acute renal failure, no./total no. (%)	126/156 (81)	152/403 (38)	**< 0.001**	156/347 (45)	122/212 (58)	**0.010**	177/330 (54)	101/229 (44)	**0.036**
Lowest oxygen saturation, median (IQR) (%)	84 (71–90)	85 (73–90)	0.158	85 (73–90)	83 (68–90)	0.114	80 (67–87)	89 (82–91)	**< 0.001**
Lowest mean arterial pressure, median (IQR) (mmHg)	55 (45–63)	59 (43–68)	**0.037**	60 (48–68)	53 (33–64)	**< 0.001**	52 (37–64)	63 (54–71)	**< 0.001**
Comfort care status, no./total no. (%)	48/156 (31)	86/403 (21)	**0.019**	78/347 (23)	56/212 (26)	0.290	97/330 (29)	37/229 (16)	**< 0.001**
Outcomes									
In-hospital death, no./total no. (%)	83/156 (53)	163/403 (40)	**0.006**	144/347 (42)	102/212 (48)	0.126	188/330 (57)	58/229 (25)	**< 0.001**

Table 5 (continued)

Characteristic	Uremic encephalopathy	No uremic encephalopathy	*P*	Sepsis encephalopathy	No sepsis encephalopathy	*P*	Hypoxic-ischemic encephalopathy[a]	No hypoxic-ischemic encephalopathy	*P*
Discharge home, no./total no. (%)	33/151 (22)	108/390 (28)	0.165	93/347 (28)	48/206 (23)	0.251	50/330 (16)	91/229 (41)	**< 0.001**
Ventilator days, median (IQR)	5.5 (2.1–15.3)	6.3 (1.3–18.3)	0.629	5.5 (1.0–16.5)	7.2 (2.1–18.7)	0.174	6.2 (1.3–18.0)	6.3 (1.7–17.2)	0.639
Hospital LOS, median (IQR) (d)	8.4 (4.8216.2)	7.8 (4.3–17.3)	0.429	7.8 (4.5–16.4)	8.2 (4.3–18.8)	0.507	8.2 (4.4–19.8)	7.7 (4.3–14.6)	0.124

Bold values indicate statistical significance at $P < 0.05$

CAM Confusion Assessment Method, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *SOFA* Sequential Organ Failure Assessment

[a] Includes post-cardiac arrest hypoxic-ischemic encephalopathy ($n = 41$)

imaging findings specific to HIE, uremic encephalopathy, or septic encephalopathy is merited.

Conclusions

TME occurred in 12% of all hospitalized patients with COVID-19 and 20% of ICU patients with COVID-19. TME was associated with a 24% increased risk of in-hospital mortality as well as significantly prolonged LOS and reduced chance of discharge to home. Although sepsis-associated encephalopathy and uremic encephalopathy were prevalent, HIE was associated with the highest risk of in-hospital death.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12028-021-01220-5.

Author details

[1] Department of Neurology, New York University Grossman School of Medicine, New York, NY, USA. [2] Brown University School of Medicine, Providence, RI, USA. [3] Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [4] Department of Neurology, University of Utah School of Medicine, Salt Lake City, UT, USA. [5] New York University Langone Hospitals, New York, NY, USA. [6] Department of Population Health, New York University Grossman School of Medicine, New York, NY, USA.

Author contributions

JAF designed the study, analysed the data and wrote the original draft. KM, TF, AG, JL, TZ, AL, DEK, JH, BMC, AL collected data and revised the manuscript. SY, AL, SK, AdH, SBM, ABT, TW, LB and SG contributed to study design and revision of the final article.

Source of support

This study received no direct funding. TW, JAF, and LB were supported by National Institutes of Health (NIH)/National Institute on Aging (NIA) grant 3P30AG066512-01S1, and ABT, JAF, SBM, and SY were supported by National Institutes of Health/National Institute of Neurological Disorders and Stroke (NINDS) Grant 3U24NS11384401S1.

Conflicts of interest

LB reports grant support from NIH/NIA grant 3P30AG066512-01S1, outside the submitted work; JAF, ABT, SBM and SY report grant support from NIH/NIA grant 3P30AG066512-01S1 and NIH/NINDS grant 3U24NS11384401S1, outside the submitted work; TW reports grant support from NIH/NIA grant 3P30AG066512-01S1, outside the submitted work; the other authors have nothing to disclose.

Ethical Approval/Informed Consent

This study was approved with waiver of consent by the NYU Institutional Review Board.

Received: 27 November 2020 Accepted: 20 February 2021
Published online: 16 March 2021

References

1. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382(23):2268–70.
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan. China JAMA Neurol. 2020;77(6):683–90.
3. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19(9):767–83.
4. Frontera JA, Sabadia S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology. 2021;96(4):e575–86.
5. Agarwal S, Scher E, Rossan-Raghunath N, Marolia D, Butnar M, Torres J, et al. Acute stroke care in a New York City comprehensive stroke center during the COVID-19 pandemic. J Stroke Cerebrovasc Dis. 2020;29(9):105068.
6. Melmed KR, Cao M, Dogra S, Zhang R, Yaghi S, Lewis A, et al. Risk factors for intracerebral hemorrhage in patients with COVID-19. J Thromb Thrombolysis. 2020. https://doi.org/10.1007/s11239-020-02288-0.
7. Frontera JA, Valdes E, Huang J, Lewis A, Lord AS, Zhou T, et al. Prevalence and impact of hyponatremia in patients with coronavirus disease 2019 in New York City. Crit Care Med. 2020;48(12):e1211–7.
8. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. Stroke. 2020;51(7):e124–7.
9. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020;7(11):2221–30.

10. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941–8.
11. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. J Gen Intern Med. 1998;13(4):234–42.
12. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62.
13. Frontera JA. Metabolic encephalopathies in the critical care unit. Continuum (Minneap Minn). 2012;18(3):611–39.
14. Busl KM, Greer DM. Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms. NeuroRehabilitation. 2010;26(1):5–13.
15. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
16. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754–8.
17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al; on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707–710.
18. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al; Working Group on "Sepsis-Related Problems" of the European Society of Intensive Care Medicine. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med. 1998;26(11):1793–1800.
19. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703–10.
20. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087.
21. Young GB, Bolton CF, Austin TW, Archibald YM, Gonder J, Wells GA. The encephalopathy associated with septic illness. Clin Invest Med. 1990;13(6):297–304.
22. Iacobone E, Bailly-Salin J, Polito A, Friedman D, Stevens RD, Sharshar T. Sepsis-associated encephalopathy and its differential diagnosis. Crit Care Med. 2009;37(Suppl 10):S331–6.
23. Liu D, Wang Q, Zhang H, Cui L, Shen F, Chen Y, et al. Viral sepsis is a complication in patients with novel corona virus disease (COVID-19). Med Drug Discov. 2020;8:100057.
24. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020;395(10235):1517–20.
25. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA. 1996;275(6):470–3.
26. Sprung CL, Peduzzi PN, Shatney CH, Schein RM, Wilson MF, Sheagren JN, et al. The Veterans Administration Systemic Sepsis Cooperative Study Group. Impact of encephalopathy on mortality in the sepsis syndrome. Crit Care Med. 1990;18(8):801–6.
27. Hansrivijit P, Qian C, Boonpheng B, Thongprayoon C, Vallabhajosyula S, Cheungpasitporn W, et al. Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis. J Investig Med. 2020;68(7):1261–70.
28. Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, et al. Outcomes for patients with cOVID-19 and acute kidney injury: a systematic review and meta-analysis. Kidney Int Rep. 2020;5(8):1149–60.
29. Joseph A, Zafrani L, Mabrouki A, Azoulay E, Darmon M. Acute kidney injury in patients with SARS-CoV-2 infection. Ann Intensive Care. 2020;10(1):117.
30. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med. 2020;46(7):1339–48.
31. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PHJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12(6):R156.
32. Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood GM, Young PJ, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients. A pilot multicenter randomized controlled trial. Am J Respir Crit Care Med. 2016;193(1):43–51.
33. Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med. 2020;382(11):999–1008.
34. Schjorring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, et al. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. N Engl J Med. 2021. https://doi.org/10.1056/NEJMoa2032510.
35. Bickler PE, Feiner JR, Lipnick MS, Batchelder P, MacLeod DB, Severinghaus JW. Effects of acute, profound hypoxia on healthy humans: implications for safety of tests evaluating pulse oximetry or tissue oximetry performance. Anesth Analg. 2017;124(1):146–53.
36. Miyamoto O, Auer RN. Hypoxia, hyperoxia, ischemia, and brain necrosis. Neurology. 2000;54(2):362–71.
37. Bjursten H, Ederoth P, Sigurdsson E, Gottfredsson M, Syk I, Einarsson O, et al. S100B profiles and cognitive function at high altitude. High Alt Med Biol. 2010;11(1):31–8.
38. de Aquino LV, Antunes HKM, dos Santos RVT, Lira FS, Tufik S, de Mello MT. High altitude exposure impairs sleep patterns, mood, and cognitive functions. Psychophysiology. 2012;49(9):1298–306.
39. Virues-Ortega J, Buela-Casal G, Garrido E, Alcazar B. Neuropsychological functioning associated with high-altitude exposure. Neuropsychol Rev. 2004;14(4):197–224.
40. Di Paola M, Bozzali M, Fadda L, Musicco M, Sabatini U, Caltagirone C. Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas. Eur J Neurol. 2008;15(10):1050–7.
41. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–16.
42. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-Lohr V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160(1):50–6.
43. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012;185(12):1307–15.
44. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. Lancet Respir Med. 2018;6(3):213–22.
45. Reade MC, Eastwood GM, Peck L, Bellomo R, Baldwin I. Routine use of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by bedside nurses may underdiagnose delirium. Crit Care Resusc. 2011;13:217–24.
46. Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. Semin Respir Crit Care Med. 2001;22(2):211–26.
47. Frontera JA. Delirium and sedation in the ICU. Neurocrit Care. 2011;14(3):463–74.
48. Brundin-Mather R, Soo A, Zuege DJ, Niven DJ, Fiest K, Doig CJ, et al. Secondary EMR data for quality improvement and research: a comparison of manual and electronic data collection from an integrated critical care electronic medical record system. J Crit Care. 2018;47:295–301.
49. Huerta LE, Wanderer JP, Ehrenfeld JM, Freundlich RE, Rice TW, Semler MW; SMART Investigators and the Pragmatic Critical Care Research Group. Validation of a sequential organ failure assessment score using electronic health record data. J Med Syst. 2018;42:199.