Toxic Metabolic Encephalopathy in Hospitalized Patients with COVID-19

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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 [44%]), 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.

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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.
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 B12 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 than 65 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 $\chi^2$ 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.

**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

| Etiology | Prevalence, n (%) |
|----------|------------------|
| Total N  | 559              |
| Electrolyte abnormalities | 223/559 (40) |
| Hyponatremia | 79 (14) |
| Hypermagnesemia | 93 (17) |
| Hypoglycemia | 6 (1) |
| Hyperglycemia | 17 (3) |
| Hypercalcemia | 3 (1) |
| Acidoysis/acidemia | 25 (4) |
| Organ failure | 525/559 (94) |
| Uremia | 156 (28) |
| Hepatic encephalopathy | 16 (3) |
| Pulmonary | 330 (59) |
| Hypoxia | 17 (3) |
| Hypertensive encephalopathy | 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 B12 deficiency, niacin deficiency) | 2 (0.4) |
| Environmental | 2/559 (0.4) |
| Hypothermia/exposure | 1 (0.2) |
| Poisoning | 1 (0.2) |
| Other | 9/559 (2) |
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.
with TME (aHR 3.82, 95% CI 2.47–5.92, \( P \leq 0.001 \); 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 \( P \leq 0.001 \); 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 (\( P \leq 0.001 \)). 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 (\( P \leq 0.001 \)). 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 (\( P \leq 0.001 \)). Of patients with HIE, 80% had at least one recorded MAP less than 65 mmHg, compared with 42% of those without HIE (\( P \leq 0.001 \)). 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 (\( P \leq 0.001 \)). 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, \( P \leq 0.001 \)) and an MAP less than 65 mmHg (adjusted odds ratio 4.41, 95% CI 2.74–7.10, \( P \leq 0.001 \)). 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)                                 | 1306/3932 (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 |
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, serotonergic, 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 (Pao2) levels (with mortality increasing for Pao2 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.
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 hypoxic 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 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 \( \sim 65\% \)) 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 Pao2 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 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
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 (Pao2 and fraction of inspired oxygen [FIO2]) may be less accurate than manual calculation [48, 49]. In our COVID-19 population, in whom Pao2 and FIO2 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 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 encephalopathya | 97/4224 (2)                             | 1.56 (1.21–2.00)     | 0.001|
| Uremic encephalopathyb           | 41/4224 (1)                             | 1.23 (0.88–1.74)     | 0.229|
| Septic encephalopacy             | 77/4224 (2)                             | 1.23 (0.94–1.61)     | 0.125|
| Any etiologyd                    | 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 encephalopathya | 97/425 (23)                             | 3.82 (2.47–5.92)     | <0.001|
| Uremic encephalopathyb           | 41/425 (10)                             | 1.48 (0.95–2.30)     | 0.081|
| Sepsis encephalopacy             | 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
| Characteristic                      | Uremic encephalopathy | No uremic encephalopathy | P    | Sepsis encephalopathy | No sepsis encephalopathy | P    | Hypoxic-ischemic encephalopathy | 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**|
| Characteristic | Uremic encephalopathy | No uremic encephalopathy | P | Sepsis encephalopathy | No sepsis encephalopathy | P | Hypoxic-ischemic encephalopathy | 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* |
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.

Table 5 (continued)

| Characteristic | Uremic encephalopathy | No uremic encephalopathy | P       | Sepsis encephalopathy | No sepsis encephalopathy | P       | Hypoxic-ischemic encephalopathy | 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 (4.82162) | 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

* Includes post-cardiac arrest hypoxic-ischemic encephalopathy (n = 41)

Conflicts of interest

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Ethical Approval/Informed Consent

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

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