Neurological Injury and Outcomes in Fentanyl-related Cardiac Arrest

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Objectives: Fentanyl has become the primary drug responsible for fatal overdoses in most urban US regions. Information about the impact of fentanyl-related overdose in neurological outcomes after cardiac arrest (CA) compared with other etiologies of CA is limited.

Methods: Retrospective review of medical records from adult patients with out-of-hospital CA who had admission drug testing for fentanyl and opioids from August 2019 to June 2021. Good outcome was defined as a Cerebral Performance Category score of 1–2 at discharge. χ^2 was used for group comparison.

Results: Neurological prognosis evaluation was pursued for 233 patients, and 61 (26.2%) met criteria for good outcome. Thirty-six (15.45%) patients tested positive for fentanyl and 13 for other opioids (5.58%). The proportion of good outcomes was similar between groups (fentanyl 22.2%, other opioids 38.5%, nonopioid 26.1%, $P = 0.52$). Fewer fentanyl-related CA had bystander cardiopulmonary resuscitation (19.4% vs other opioids 38.5% vs nonopioid 43.8%, $P = 0.02$) shockable rhythms (2.9%, 16.7%, 25%, $P = 0.01$) or corneal reflexes 72 hours after CA (25.8%, 66.7%, 39.8%, $P = 0.046$), but no difference was seen for pupillary response at 72 hours ($P = 0.17$). More fentanyl-related CA cases had signs of severe brain dysfunction on EEG with burst suppression (54.8%, 0%, 39.4%, $P = 0.01$).

Conclusions: Cardiac arrest associated with fentanyl use was linked to decreased rates of bystander cardiopulmonary resuscitation, increased incidence of nonshockable Rhythms, and greater neurological injury as indicated by electroencephalography (EEG) suppression measures. However, the proportion of good neurological outcomes (CPC: 1–2) was similar across groups.

Key Words: EEG, hypoxic-ischemic encephalopathy, heart arrest, overdose, opioid crisis, fentanyl

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Overdose deaths in the United States have increased substantially, largely driven by fentanyl, an extremely potent synthetic opioid. From 2001 to 2023, the number of opioid-related overdose deaths increased significantly.[1,2] Fentanyl has been a major contributor to the surge in opioid-related deaths, both as a standalone substance and as an additive to other drugs to increase their potency.[3]

Cardiac arrest (CA) is a leading cause of morbidity and mortality associated with opioid-related overdoses, even though these patients are younger and have fewer comorbidities.[4] While there is a window of 30–90 minutes between heroin overdose and CA, the lipophilicity and high potency of fentanyl result in a more rapid respiratory arrest and more rapid progression to CA.[5] This limits the utility of bystander reversal medications, as medications cannot reach targeted tissues without blood flow. In San Francisco, the prevalence of drug-related CA has increased by 30% annually since fentanyl entered the street opioid market in 2015.[6] Information about fentanyl-related CA's clinical course, associated neurological injuries,

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and neurological prognosis is scarce.[7,8]

We aimed to describe the clinical characteristics, multimodal prognostication evaluation, and outcomes of patients with fentanyl-related CA in comparison to other opioid-related and nonopioid-related CA. Given the etiology of rapid respiratory depression leading to CA, we hypothesized that fentanyl-related CA is associated with worse functional outcomes and neurological injuries based on multimodal prognostic testing, independent of CA resuscitation characteristics.

METHODS

Patients

We conducted a retrospective chart review study of patients with out-of-hospital CA directly admitted to the Zuckerberg San Francisco General Hospital from August 2019 to June 2021. Patients were included if they had return of spontaneous circulation (ROSC) for at least 20 minutes, were comatose on arrival [Glasgow Coma Score (GCS) ≤ 8] and survived for > 6 hours after ROSC. Five patients were excluded because a toxicology screen was not completed. Among those who met the inclusion criteria, 56 individuals tested positive for fentanyl or other opioids. They were assigned to either the fentanyl-related or other opioid-related group if their arrest was judged to be primarily due to opioid overdose; 7 patients whose clinical data suggested an alternative cause of arrest, despite a positive opioid test, were included in the nonopioid-related group. Consequently, our final study cohort comprised 36 patients in the fentanyl-related group, 13 in the other opioid-related group, and 184 in the nonopioid-related group (Fig. 1). Our institution's protocol uses a temperature control goal of 32–34 °C, and a goal of 36 °C is used if there are contraindication to the lower temperature goal. The temperature is maintained at goal for 24 hours, followed by controlled rewarming using a closed-loop device. Sedation and analgesia are used as needed by the treating clinicians, and the most commonly used agents in our institution are propofol (dose range: 10–80 mcg/kg/h), midazolam (0.1–0.7 mg/kg/h), or fentanyl (25–200 mcg/h). This study was approved by the University of California, San Francisco Institutional Review Board (#20-31165).

Exposure

Patients were stratified into 3 groups based on drug testing (urine or serum) at emergency room arrival: fentanyl-related CA, other opioids without fentanyl (opioid-related), and nonopioid-related (no fentanyl or opioid detected). Most patients presenting with cardiac arrest during the study period underwent drug testing, and the nonopioid group included a broad range of etiologies, including those with positive tests for other substances (eg, cocaine, amphetamines, and cannabinoids). Medication administration before testing was reviewed, and patients who received opioids, benzodiazepines, or other relevant medications before testing were classified as nonopioid-related. For all patients in the fentanyl-related and opioid-related groups, medical records and EMS reports were reviewed to confirm clinical evidence of opioid overdose.

Additional Measures

Demographic, clinical, and diagnostic test data were abstracted from electronic medical records and entered in the electronic research database (REDCap). The following clinical variables and resuscitation metrics were recorded from the time of admission: age, sex, race, ethnicity, initial cardiac rhythm [shockable (ventricular fibrillation or ventricular tachycardia), nonshockable (asystole, pulseless electrical activity, or unknown)], witnessed arrest, bystander cardiopulmonary resuscitation (CPR), minutes of CPR before ROSC, time to ROSC, and occurrence of rearrest in hospital, defibrillation, and temperature control. Time of CA was estimated as 1 hour before emergency room arrival if paramedic reports were not available. Housing status was determined through review of clinical documentation, including presence of provider notes indicating lack of stable housing or homelessness.

Neurological Prognostication

Neurological prognostication data were obtained through multimodal evaluation based on national guidelines,[10] including serial clinical examinations, electroencephalography (EEG), somatosensory evoked potentials (SSEP), and neuroimaging at the treating clinician's discretion. Following the 2021 European Resuscitation Council Guidelines,[9] severe neurological injury was defined in patients with a GCS motor score ≤ 3 by the presence of 2 or more of the following: absent pupillary reflexes, EEG background suppression or burst suppression, myoclonic status epilepticus within 48 hours of arrest, or diffuse hypoxic-ischemic injury on MRI or CT. Burst suppression, characterized by alternating high-voltage bursts and suppression periods on EEG, reflects profound cerebral dysfunction and is associated with poor neurological outcomes, particularly in coma, deep anesthesia, hypothermia, or severe brain injury.[11]

Specific elements of this assessment include the neurological examination, first conducted by a physician at the time of arrival to the emergency room, then again 72 hours after ROSC, with a good GCS motor score defined as a flexor response of 3 (withdraws from painful stimuli) or greater. EEG reports were based on continuous monitoring using 19 channels and the 10–20 international system. EEG reports were specifically reviewed for markers of serious brain injury that are predictors of poor outcome such as burst suppression, seizures, or status epilepticus. A study team neurologist reviewed neuroimaging tests (CT and MRI) for qualitative assessment of hypoxic-ischemic brain injury. Head CTs performed within 12 hours of admission were evaluated for the presence of diffuse reduced gray-white matter differentiation or effacement of cortical sulci throughout both hemispheres. Brain MRIs, performed 2–12 days after ROSC in patients who failed to regain consciousness, were evaluated for the presence of severe hypoxic-ischemic brain injury defined as extensive diffusion restriction in-

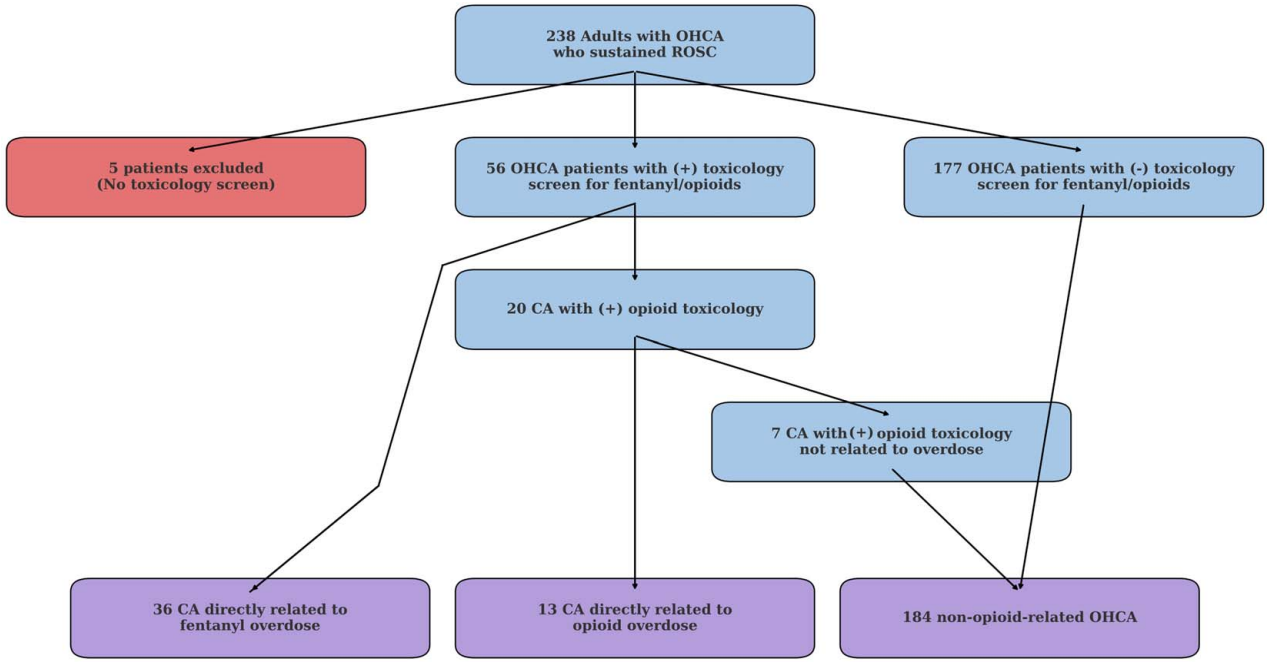

FIGURE 1. Flow diagram illustrating inclusion and exclusion of adult patients with out-of-hospital cardiac arrest (OHCA) who achieved return of spontaneous circulation (ROSC).

volving both cerebral hemispheres on diffusion-weighted imaging (DWI) with corresponding low apparent diffusion coefficient (ADC) values. Data points collected and used in this study from DWI only considered global imaging analysis; focal injury data points were not included.

Neurological Outcome

Neurological functional assessment was determined at the time of hospital discharge using the Cerebral Performance Category (CPC) scale. Neurological assessment was scored based on neurological examination documentation in clinical notes from the primary medical team, neurology, physical therapy, or occupational therapy. The CPC is an ordinal scale with 1-2 consistent with independence in activities of daily living, 3 with severe disability, 4 with a vegetative state (ie, unresponsive wakefulness syndrome), and 5 with death. The CPC is a widely used benchmarks denoting relative independence and functional recovery in cardiac arrest. In this study, we defined a "good outcome" as CPC 1–2 at hospital discharge. Mortality was defined as in-hospital death before discharge.

Withdrawal of Life-sustaining Therapies and Cause of Death

Information about withdrawal of life-sustaining therapies (WLST) and cause of death was derived from provider progress notes, palliative care consultation notes, and death records. Reasons for withdrawal of life-sustaining therapies were stratified as: poor neurological prognosis, multiorgan or hemodynamic failure, social, family, or ethical reasons, or other.

Statistical Analysis

Univariate analysis was performed using Pearson χ^2 test for categorical variables, one-way analysis of variance (ANOVA) for continuous variables with normal distribution, and the Kruskal-Wallis H test for non-normally distributed variables. CIs for sample proportions were calculated using the Clopper-Pearson exact method through one-sample nonparametric binomial tests. Statistical significance was defined as $P < 0.05$. Univariate statistics and visualizations were performed using IBM SPSS Statistics, version 27. Multivariable logistic regression was initially performed to estimate associations between candidate predictors and outcome; feature selection was subsequently refined using Lasso regression with L1 regularization, implemented in Python 3.10 through the statsmodels.api and scikit-learn (version 1.1.2) libraries. Missing data were addressed using multivariate imputation by chained equations (MICE), with initial mean replacement iteratively refined using regression-based predictions until convergence. The data set was randomly split into equal training and testing sets. To address class imbalance in the outcome variable, the Synthetic Minority Oversampling Technique (SMOTE) was applied to the training set. Stratified 10-fold cross-validation was repeated over 3 iterations to evaluate model performance for predicting poor outcome, using the area under the receiver operating characteristic curve (AUC) as the primary metric. Feature selection was conducted using recursive feature elimination (RFE), followed by Lasso regression to further refine variable selection. Hyperparameter tuning with GridSearchCV was

used to identify the optimal alpha value that minimized mean squared error through 5-fold cross-validation. Final model coefficients were used to calculate odds ratios (ORs) and 95% CIs, and *P* values were reported to assess statistical significance. Additional details on data imputation, model training procedures, performance metrics, and final model results are provided in the supplementary methods (Supplemental Digital Content 1, http://links.lww.com/JAM/A677).

RESULTS

Two hundred thirty-three patients with out-of-hospital CA survived intensive care unit admission and underwent neurological prognostication (Table 1). Seventy-eight (33.5%) patients were alive at hospital discharge and 61 (26.2%) had a good outcome. Thirty-six (15.45%) patients were included in the fentanyl-related CA group and 13 in the opioid-related group (5.58%). Seven patients who tested positive for opioids were not included in the opioid-related group, as the cause of the CA was not concerning for overdose at the time of admission after detailed chart review. These patients were included in the nonopioid-related group. Five patients who presented after an out-of-hospital cardiac arrest during the study period did not have a toxicology screen completed and were excluded. Patients in the fentanyl-related group were younger than opioid and nonopioid groups (42 ± 12.2 vs 55.1 ± 12.7 vs 63.54 ± 17.7 y, $P < 0.001$); they also had a lower rate of bystander CPR (19.4% vs 38.5% vs 43.8%, $P = 0.02$) and a lower rate of shockable rhythm (2.9% vs 16.7% vs 25%, $P = 0.01$). Witnessed CA was less common in fentanyl-related and opioid-related CA compared with nonopioid cases (50% vs 46.2% vs 71%. $P = 0.01$). Patients in the fentanyl-related and opioid-related groups were more often unhoused or marginally housed than the nonopioid group (23.5% vs 38.5% vs 9.8%, $P = 0.002$). To address the concern that age may confound our findings—given that the fentanyl-positive group was significantly younger than the nonopioid group—we performed an analysis of these 2 groups stratified by age. Participants were divided into 2 categories: young adults (<45 y) and middle-aged/older adults (≥45 y). In the younger cohort (<45 y), the proportion of patients with CPC 1–2 was 13.0% in the fentanyl group and 20.8% in the nonopioid group ($P = 0.747$). In the older cohort (≥45 y), CPC 1–2 was observed in 23.1% of fentanyl group and 15.0% of nonopioid group ($P = 0.708$). These findings suggest that the differences in neurological outcomes between fentanyl and nonopioid groups are not significantly influenced by age stratification.

In the fentanyl-related group, only 12 patients (33%) had a drug screen exclusively positive for fentanyl. Most cases were associated with polysubstance use, including cocaine (N = 13, 36.1%), methamphetamine (N = 12, 33%), benzodiazepines (N = 10, 27.8%), other opioids (N = 4, 11.1%), methadone (N = 2, 5.6%), or cannabis (N = 1, 2.8%).

In the opioids-related group, several individuals tested positive for other substances such as methamphetamine (N = 4, 30.8%), cocaine (N = 4, 30.8%,) and benzodiazepines (N = 2, 15.4%).

In the nonopioids-related group, the breakdown of positive substances was methamphetamine (N = 24, 13.0%), cocaine (N = 21, 11.4%), benzodiazepines (N = 9, 4.9%), and cannabis (N = 3, 1.6%). Notably, 135 individuals (73.4%) tested negative for all substances.

Neurological Injury and Prognostication

Fentanyl-related CA was associated with less frequently present corneal reflexes at 72 hours post-CA than opioid-related or nonopioid-related CA (25.8% vs 66.7% vs 39.8%, $P = 0.04$). There was no difference between groups for bilateral pupillary response at 72 hours (71.9% vs 66.7% vs 83.2%, $P = 0.17$). Burst suppression on EEG was more common in the fentanyl-related group (54.8%) compared with opioid (0%) or nonopioid group (39.8%), $P = 0.01$. However, other EEG patterns (seizure, status epilepticus, myoclonic status epilepticus, generalized periodic discharges, lateralized periodic discharges, or sporadic epileptiform discharges) or neuroimaging findings on CT and MRI were not statistically significantly different (Table 2).

Neurological Outcome

There were no differences in the proportion of patients with good outcome at discharge (22.2% fentanyl, 38.5% other opioid, 26.1% nonopioid, $P = 0.52$), mortality (69.4% fentanyl, 53.8% other opioid, 66.8% nonopioid, $P = 0.58$), or WLST rate (50% fentanyl, 46.2% other opioid, 53.3% nonopioid, $P = 0.84$; Table 3). The median time from ROSC to WLST was 5 days. In the multivariable analysis using lasso regression for poor outcome prediction, fentanyl use, age, witnessed arrest, bystander CPR, and time to ROSC were not retained in the model, and were regularized out of the lasso model. A nonshockable rhythm was the only variable associated with poor outcome [OR: 2.38 (1.61–3.52 CI), $P < 0.001$] after Lasso regression.

DISCUSSION

Fentanyl-related CA was associated with worse resuscitation metrics, including less bystander CPR, more nonshockable rhythms, and more unwitnessed arrest; these patterns were particularly pronounced among individuals who lacked housing or were unstably housed. The findings regarding resuscitation were consistent with previous reports,[7,8] and there were some signs of potentially worse brain injury severity among fentanyl-related CA cases compared with other groups. Overall, these results confirm the urgent need for better out-of-hospital interventions strategically designed for people at risk for fentanyl overdose, with a focus on providing resources to people who are unhoused, and suggest a possible role of fentanyl in neurotoxicity related to CA.

Brain injury is the main driver of poor outcomes for patients who initially survive CA, and this study identified a higher incidence of brain injury severity markers in

TABLE 1. Characteristics of Study Population Stratified by Opioid Use

Variable	Fentanyl (n = 36)	Opioids (n = 13)	All Others (n = 184)	*P*
Age (mean ± SD)	42.06 ± 12.2	55.1 ± 12.7	63.54 ± 17.7	< 0.001
Sex (% male, CI)	80.6 (64–91.8)	53.8 (25.1–80.8)	69 (61.8–75.6)	0.16
Race				
American Indian/Alaska Native (%)	0.0 (0–9.7)	0.0 (0–24.7)	0.0 (0.0–2.0)	NA
Asian (%)	5.6 (0.7–18.7)	7.7 (0.2–36)	25.5 (19.4–32.5)	0.01
Black/African American (%)	30.6 (16.3–48.1)	53.8 (25.1–80.8)	19.6 (14.1–26.0)	0.009
Hawaiian/Pacific-Islander (%)	0.0 (0–9.7)	0.0 (0–24.7)	1.1 (0.1–3.9)	0.76
White (%)	22.2 (10.1–39.2)	30.8 (9.1–61.4)	23.9 (17.9–30.7)	0.82
Other (%)	5.6 (3.1–26.1)	0.0 (0–24.7)	2.1 (0.9–6.2)	0.53
Ethnicity				
Hispanic or Latino (%)	25 (12.1–42.2)	15.4 (1.9–45.4)	23.9 (17.9–30.7)	0.76
Homeless/marginal housing (%)	23.5 (10.7–41.2)	38.5 (13.9–68.4)	9.8 (5.9–15.0)	0.002
Witnessed (%)	50 (32.9–67.1)	46.2 (19.2–74.9)	71 (63.9–77.5)	0.01
Bystander CPR (%)	19.4 (8.2–36)	38.5 (13.9–68.4)	43.8 (36.4–51.4)	0.02
Minutes of CPR to ROSC; mean ± SD	18.42 ± 13.85	14.77 ± 8.68	20.85 ± 17.7	0.36
Time to ROSC (min); mean ± SD	26.88 ± 18.2	20.80 ± 10.7	26.08 ± 21.6	0.83
Shockable rhythm (%)	2.9 (0.1–14.9)	16.7 (2.1–48.4)	25 (18.9–32.0)	0.01
Received defibrillation (%)	22.9 (10.4–40.1)	23.1 (5–53.8)	37 (30.0–44.5)	0.18
Rearrest in hospital (%)	14.3 (4.8–30.3)	16.7 (2.1–48.4)	25.7 (19.4–32.9)	0.29
Underwent cardiac catheterization (%)	0.0 (0.0–9.7)	7.7 (0.2–36)	15.7 (18.6–55.9)	0.03
Received temperature control therapy (%)	91.7 (77.5–98.2)	84.6 (54.6–98.1)	73.9 (66.9–80.1)	0.05

CPR indicates cardiopulmonary resuscitation; NA, not applicable; ROSC, return of spontaneous circulation.

fentanyl-related CA, including absent corneal reflexes at 72 hours and burst suppression on EEG. However, cortical hyperexcitability reflecting hypoxic-ischemic brain injury, such as seizures or epileptiform activity, was not different among groups. These findings might indicate that the injury to the cortex in fentanyl-related CA may be so severe in some cases that hypersynchrony and organization into seizures are less common.[12–16] However, given the high variability and complexity of EEG changes in CA, systematic and prospective multicentric studies are needed to elucidate how mechanisms contributing to burst suppression and hyperexcitability may be exacerbated by neurotoxicity from fentanyl and other opioids.

Another important marker of brain injury that did not differ between groups was brain edema diagnosed on neuroimaging. Neuroimaging using CT within 12 hours from admission showed that more than half of patients across all groups had severe hypoxic-ischemic brain injury, which highlights that most brain injury seen in the setting of fentanyl use was not delayed or presenting as leukoencephalopathy as has been described in reports of fentanyl toxicity without CA.[12,17,18] The comparison between fentanyl-related CA and opioid-related CA is limited, as only 3 patients in the opioid-related group had MRIs completed. Furthermore, our analysis of MRIs utilized qualitative review focused on the identification of diffuse and extensive injury; future studies using quantitative ADC or advanced brain imaging techniques such as diffusion tensor MRI, perfusion imaging, and magnetic resonance spectroscopy imaging may contribute to elucidating mechanisms of injury in fentanyl-related CA as well as advance neurological prognostication.[19–22]

The fentanyl crisis has disproportionally affected minorities and black communities.[23–28] Our study involved a diverse population receiving care in a large university-affiliated safety-net hospital, with < 25% of non-Hispanic white patients. Non-hispanic black patients were overrepresented among fentanyl and opioid-related CA cases. In addition, a high proportion of patients with fentanyl-related CA were unhoused or marginally housed, a finding consistent with prior research.[25,26] It is imperative to prioritize health equity to address disparities in opioid overdose morbidity and mortality, and access to treatment services focused on preventing fentanyl and other opioid-related overdoses. In addition, it is critical to provide basic life support training for populations at risk, which may include more of a focus on chest compressions than has been provided in the past.[33] Of note, self-determination of race and ethnicity in this study was limited by the patient's comatose state and limited premorbid information. The differences observed are likely related to socioeconomic disparities and structural racism endured by these groups, as evidenced by other studies that focused on the influence of social determinants of health on CA outcomes.[29–33]

It is noteworthy that fentanyl use did not emerge as a significant predictor of poor neurological outcome in our multivariable analysis. This finding contrasts with established concerns regarding the neurological sequelae of opioid overdose[15] and may prompt further exploration into the pharmacological and physiological nuances of fentanyl-related cardiac events. One potential explanation for the absence of a difference between groups could be the rapid progression from respiratory to cardiac arrest in fentanyl overdose,[34] in contrast to heroin overdoses, which are thought to require 30–90 minutes to progress to CA.[35] This could result in sufficient variation in hypoxic time to obviate other differences between groups. Another possible explanation could be the younger age of patients experiencing fentanyl-related CA, which could protect some patients from the most severe consequences of CA. Future studies should delve deeper into the intricate interplay between fentanyl overdose, patient demo-

TABLE 2. Multimodal Neurological Prognostication Evaluation Stratified by Opioid Use

Variable	Fentanyl (n = 36)	Opioids (n = 13)	All Others (n = 184)	*P*
Admission neurological examination post-CA; %				
Pupillary reflex present	55.6 (38.1–72.1)	61.5 (31.6–86.1)	55.2 (47.7–62.5)	0.90
Corneal reflex present	14.7 (5.0–31.1)	7.7 (0.2–36)	25.3 (18.9–32.6)	0.16
Good Glasgow coma motor score	13.9 (4.7–29.5)	15.4 (1.9–45.4)	13.6 (9.0–19.4)	0.98
Myoclonus	22.9 (10.4–40.1)	23.1 (5–53.8)	13.8 (9.1–19.7)	0.30
Neurological examination 72 h post-CA; %	(n = 32)	(n = 12)	(n = 131)	
Pupillary reflex present	71.9 (53.3–86.3)	66.7 (34.9–90.1)	83.2 (75.7–89.2)	0.17
Corneal reflex present	25.8 (11.9–44.6)	66.7 (34.9–90.1)	39.8 (31.3–48.9)	0.04
Good Glasgow coma motor score	12.5 (3.5–29)	33.3 (9.9–65.1)	29.8 (22.1–38.4)	0.12
EEG data within 5 d post-CA; %	(n = 31)	(n = 9)	(n = 98)	
Background suppression at any time	70 (50.6–85.3)	42.9 (9.9–81.6)	50.6 (39.1–62.1)	0.15
Malignant present	77.4 (58.9–90.4)	33.3 (7.5–70.1)	64.3 (54–73.7)	0.04
Burst suppression	54.8 (36–72.7)	0.0 (0–33.6)	39.4 (29.7–49.7)	0.01
Seizure	22.6 (9.6–41.1)	0 (0–33.6)	20.1 (13.6–30.6)	0.29
Status epilepticus	16.1 (5.5–33.7)	0 (0–33.6)	12.1 (6.4–20.2)	0.42
Myoclonic status epilepticus	9.7 (2–25.8)	0 (0–33.6)	14.1 (8.0–22.6)	0.41
Generalized period discharges present	61.3 (42.2–78.2)	33.3 (7.5–70.1)	39.4 (29.7–49.7)	0.08
Lateralized period discharges present	3.2 (1–16.7)	0 (0–33.6)	2 (0.2–7.1)	0.82
Sporadic epileptiform discharges	35.5 (19.2–54.6)	44.4 (13.7–78.8)	37.4 (27.9–47.7)	0.88
Reactivity present	15.8 (3.4–39.6)	50 (1.3–98.7)	44 (30.0–58.7)	0.08
No brain activity	9.7 (2.0–25.8)	11.1 (0.3–48.2)	13.1 (7.2–21.4)	0.87
SSEP performed (%)	(n = 5)	(n = 2)	(n = 10)	
Bilateral absent SSEP	40 (5.3–85.3)	50 (1.3–98.7)	20 (2.5–55.6)	0.57
CT done within 12 h post-CA	(n = 12)	(n = 11)	(n = 94)	
Evidence of anoxic injury	58.3 (27.7–84.8)	54.5 (23.4–83.3)	40.4 (30.4–51.0)	0.37
MRI done within 7–12 d; %	(n = 16)	(n = 3)	(n = 60)	
Evidence of severe hypoxic ischemic injury	50 (24.7–75.3)	0.0 (0.0–70.8)	41.7 (29.1–55.1)	0.27

CA indicates cardiac arrest; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; SSEP, somatosensory evoked potentials.

graphics, and specific clinical indicators to elucidate the complex relationship between fentanyl use, cardiac arrest, and neurological injury and outcomes. The current analysis focuses on patients who survive CA for at least 6 hours so that measures of brain injury can be pursued; therefore, it underestimates the incidence and impact of fentanyl use in early CA outcomes.

This study has several limitations. Our population was based in a large metropolitan area, limiting generalizability to rural communities. The number of fentanyl and opioid-related CA cases was relatively small compared with nonopioid-related CA, limiting power to detect differences. An age-stratified analysis found no significant differences between groups; however, the limited sample size weakens this conclusion. This study excluded individuals who died in the field or shortly after ED arrival, groups that represent a significant proportion of OHCA cases, introducing potential selection bias and limiting generalizability to the broader arrest population. In addition, fentanyl-related CA cases often tested positive for multiple substances, potentially confounding results. An in-depth EMR review was conducted only for patients testing positive for fentanyl or other opioids to confirm that overdose was the primary cause of cardiac arrest; for the nonopioid-related group, such comprehensive EMR review was not performed because toxicology data did not indicate opioid involvement. This discrepancy could introduce surveillance bias and lead to differential etiology detection. As a retrospective study, diagnostic testing for neurological prognostication depended on clinician discretion, limiting test comparisons. Data on comorbidities, particularly cardiovascular disease, would add context but were unavailable, requiring a substantial effort not feasible with our current resources. While we do not believe the inclusion of comorbidities would drastically change the main conclusions, we acknowledge that their absence limits our ability to fully assess potential differences in baseline health and their influence on outcomes. Furthermore, neuroimaging data were primarily qualitative, which are less sensitive and specific than quantitative analyses and may have limited the accuracy of our assessments of brain injury. The use of sedatives and other factors, such as temperature control, may have confounded clinical examination and EEG results. In addition, neither the treating clinicians nor those assessing exposure, outcomes, and conducting the analysis were blinded to the drug testing or other results, so clinician expectations could have influenced WLST decisions, possibly affecting results. However, multimodal prognostication following national and local guidelines in our center minimized this variability. WLST was not pursued solely based on a single test assessment and involved patient surrogate decision makers. The median time for WLST from ROSC in this study was 5 days, which might have partially minimized the potential impact of premature WLST, reflecting that clinical decisions were made after a better assessment of recovery potential with ancillary testing and serial examinations. Lastly, we defined a good neurological outcome as CPC 1–2 at discharge to align with a return to independence. However, we acknowledge this dichotomization is somewhat arbitrary and does not fully account for individual patient values. Recovery of

TABLE 3. Outcomes Stratified by Opioid Use

Variable	Fentanyl (n = 36)	Opioids (n = 13)	All Others (n = 184)	*P*
Good outcome (%)	22.2 (10.1–39.2)	38.5 (13.9–68.4)	26.1 (19.9–33.1)	0.52
Mortality (%)	69.4 (51.9–83.7)	53.8 (25.1–80.8)	66.8 (26.4–40.5)	0.58
WLST (%)	50 (32.9–67.1)	46.2 (19.2–74.9)	53.3 (45.8–60.6)	0.84
Reason for WLST	(n = 18)	(n = 7)	(n = 98)	
Poor neurological prognosis (%)	88.9 (65.3–98.6)	71.4 (29–96.3)	63.9 (53.5–73.4)	0.11
Multiorgan failure or hemodynamic instability (%)	11.1 (1.4–34.7)	14.3 (0.4–57.9)	20.6 (13.1–30)	0.60
Social, family, or ethical (%)	0.0 (0–18.5)	14.3 (0.4–57.9)	15.5 (8.9–24.2)	0.20

WLST indicates withdrawal of life-sustaining therapies.

consciousness with limited independence (CPC: 3) may be considered an acceptable outcome by some patients; 23 (10%) of our cohort had CPC 3.

CONCLUSIONS

Fentanyl overdose is a growing contributor to CA, and patients with fentanyl-related CA in our study demonstrated high rates of poor outcomes overall—often attributable to severe neurological injury. However, in our multivariable analysis, fentanyl use itself was not an independent predictor of poor neurological outcome. This underscores the complexity of fentanyl-related CA and highlights that factors beyond fentanyl exposure alone—such as comorbidities, prehospital interventions, and arrest characteristics—may influence the ultimate neurological trajectory. Fentanyl-related CA disproportionally affects people of color and vulnerable populations with limited resources, who often have worse resuscitation metrics and infrequent bystander CPR. Additional research is needed to clarify whether neurotoxicity from fentanyl overdose exacerbates hypoxic-ischemic brain injury in CA and how this and other resuscitation-related patient factors may affect neurological prognosis evaluation.

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