Journal of the American Heart Association

ORIGINAL RESEARCH

Cardiac Arrest Following Drug Overdose in the United States: An Analysis of the Cardiac Arrest Registry to Enhance Survival

Aditya C. Shekhar, MBE; Brian H. Nathanson, PhD; Timothy J. Mader, MD; Ryan A. Coute, DO

BACKGROUND: Given increases in drug overdose-associated mortality, there is interest in better understanding of drug overdose out-of-hospital cardiac arrest (OHCA). A comparison between overdose-attributable OHCA and nonoverdose-attributable OHCA will inform public health measures.

METHODS AND RESULTS: We analyzed data from 2017 to 2021 in the Cardiac Arrest Registry to Enhance Survival (CARES), comparing overdose-attributable OHCA (OD-OHCA) with OHCA from other nontraumatic causes (non-OD-OHCA). Arrests involving patients <18 years, health care facility residents, patients with cancer diagnoses, and patients with select missing data were excluded. Our main outcome of interest was survival with good neurological outcome, defined as Cerebral Performance Category score 1 or 2. From a data set with 537 100 entries, 29 500 OD-OHCA cases and 338 073 non-OD-OHCA cases met inclusion criteria. OD-OHCA cases involved younger patients with fewer comorbidities, were less likely to be witnessed, and less likely to present with a shockable rhythm. Unadjusted survival to hospital discharge with Cerebral Performance Category score =1 or 2 was significantly higher in the OD-OHCA cohort (OD: 15.2% versus non-OD: 6.9%). Adjusted results showed comparable survival with Cerebral Performance Category score =1 or 2 when the first monitored arrest rhythm was shockable (OD: 28.9% versus non-OD: 23.5%, P=0.087) but significantly higher survival rates with Cerebral Performance Category score =1 or 2 for OD-OHCA when the first monitored arrest rhythm was nonshockable (OD: 9.6% versus non-OD: 3.1%, P<0.001).

CONCLUSIONS: Among patients presenting with nonshockable rhythms, OD-OHCA is associated with significantly better outcomes. Further research should explore cardiac arrest causes, and public health efforts should attempt to reduce the burden from drug overdoses.

Key Words: cardiac arrest ■ drug overdose ■ out-of-hospital cardiac arrest ■ prehospital care ■ public health

In the United States, the incidence of drug overdose has dramatically increased over the past few decades.[1,2] Various types of overdoses can lead to hospitalization, long-term consequences, and death. For example, opioids diminish respiratory drive and subsequently can cause hypoxia and cardiac arrest.[3,4] Given the current high burden from overdoses, there is significant epidemiologic interest in the topic, and research in this area can inform efforts to reduce the associated disease burden.[5] In the past, out-of-hospital cardiac arrest (OHCA) was largely treated as epidemiologically homogenous. However, there is recent interest in investigating specific cardiac arrest causes with the goal of identifying potential differences.[6] The majority of cardiac arrests are attributable to presumed cardiac pathology (eg, myocardial infarction or electrophysiological aberrancies), whereas recent data suggest just under 5% of OHCA in the United States are overdose attributable.[7] Comparisons of the circumstances and outcomes surrounding overdose-attributable cardiac

Correspondence to: Aditya C. Shekhar, MBE, The Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029. Email: shekhar.aditya.c@gmail.com and Ryan A. Coute, DO, Department of Emergency Medicine, University of Alabama at Birmingham, 521 19th St S, General Services Bldg, RM 240, Birmingham, AL 35233. Email: rcoute@uabmc.edu

This article was sent to Kori S. Zachrison, MD, MSc, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 6.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Given the current morbidity and mortality due to drug overdose, there is immense public health interest in the topic of drug overdose cardiac arrest; therefore, we examined the Cardiac Arrest Registry to Enhance Survival (CARES), a nationwide registry of cardiac arrest, to compare overdose cardiac arrests with nonoverdose cardiac arrests.

What Are the Clinical Implications?

- Across 29 500 overdose cardiac arrests and 338 073 nonoverdose cardiac arrests, we found that overdose arrests involved younger patients with fewer comorbidities, were less likely to be witnessed, and less likely to present with a shockable rhythm; outcomes were comparable when the first monitored rhythm was shockable, but overdose arrests were associated with better outcomes when the first monitored rhythm was nonshockable.

Nonstandard Abbreviations and Acronyms

CARES	Cardiac Arrest Registry to Enhance Survival
CPC	Cerebral Performance Category
non-OD-OHCA	nonoverdose-attributable out-of-hospital cardiac arrest
OD-OHCA	overdose-attributable out-of-hospital cardiac arrest
OHCA	out-of-hospital cardiac arrest

arrests with other arrest causes may help inform targeted public health efforts. For instance, it has been previously reported that overdose-attributable arrests may have lower rates of shockable first monitored arrest rhythms yet higher rates of return of spontaneous circulation achievement and neurologically intact survival.[8,9]

National-level databases provide an ideal resource to interrogate specific cardiac arrests causes. The Cardiac Arrest Registry to Enhance Survival (CARES) database is a well-established, national registry of OHCA in the United States.[10] CARES was created by the United States' Centers for Disease Control and Prevention in 2004 in order to provide effective surveillance of OHCA in the United States.[10] In this study, we used the CARES registry to compare overdose-attributable out-of-hospital cardiac arrests (OD-OHCA) with arrests attributable to other causes (non-OD-OHCA). Our overall goal was to identify any noteworthy differences between OD-OHCA and other causes, and our main outcome of interest was survival with a good neurologic outcome.

METHODS

Study Design and Patient Population

We performed a retrospective analysis of adult nontraumatic emergency medical services (EMS)-treated OHCA from the national CARES data set for 2017 to 2021. All adult (age >18 years) OHCA from January 2017 to December 2021 were analyzed. Arrests that were documented as overdose attributable (OD-OHCA) were compared with arrests that were documented as attributable to other causes (non-OD-OHCA). The following were specifically excluded: patients under age 18, arrests involving residents of nursing homes or other health care facilities; arrests after the arrival of 911-dispatched first responders, patients with cancer diagnoses, and patients where key arrest data (eg, age, sex, first rhythm, and outcomes) were missing (Table 1). National CARES deidentified data are available to researchers upon submission and subsequent approval of a project proposal by the registry.

Determining Cardiac Arrest Causes

For every cardiac arrest contained within the CARES database, EMS providers document a suspected arrest cause based on indicators identified on-scene (eg, drug paraphernalia) and information reported by bystanders/family members (eg, witness stating a patient may have overdosed). All arrests without cause-related on-scene indicators are presumed to have cardiac causes. Centers submitting to CARES have an opportunity to revise documented cause based on later evidence, such as reports produced by medical examiners or treating hospitals. The drug overdose cause is specifically defined as "all intentional and accidental arrests caused by a presumed or known overdose of medication or drugs (legal/illegal), to include alcohol."[11]

Data Source: Cardiac Arrest Registry to Enhance Survival

The CARES database was developed in 2004 as a collaborative effort between Emory University and the Centers for Disease Control and Prevention to serve as a central repository for cardiac arrest data from EMS systems throughout the United States.[10] The registry uses the Utstein style of OHCA reporting and includes variables from prehospital care through hospital discharge.[12] The program currently includes 27

Table 1. Patient Variables Stratified by Non-OD-OHCA Versus OD-OHCA Status

Patient variables	Non-OD-OHCA N=338 073	OD-OHCA N=29 500
Year of OHCA		
2017	47 019 (13.9%)	4131 (14.0%)
2018	52 007 (15.4%)	4552 (15.4%)
2019	63 745 (18.9%)	5101 (17.3%)
2020	81 115 (24.0%)	7329 (24.8%)
2021	94 187 (27.9%)	8387 (28.4%)
Age, y, median [interquartile range]	64 [54, 75]	37 [29, 48]
Age, y, mean (SD)	63.6 (16.3)	39.0 (12.6)
Female sex, n (%)	120 668 (35.7%)	9569 (32.4%)
Race or ethnicity		
White	169 780 (50.2%)	17 251 (58.5%)
Black	72 778 (21.5%)	4693 (15.9%)
Hispanic	25 665 (7.6%)	2330 (7.9%)
Asian/others*	11 965 (3.5%)	391 (1.3%)
Unknown race and ethnicity	57 885 (17.1%)	4835 (16.4%)
Location		
Home	281 941 (83.4%)	22 876 (77.5%)
Public	56 132 (16.6%)	6624 (22.5%)
Arrest witnessed status		
Unwitnessed	182 248 (53.9%)	23 097 (78.3%)
Witnessed by bystander	155 825 (46.1%)	6403 (21.7%)
Bystander cardiopulmonary resuscitation (excluding 911 witnessed events and nursing home/health care facility events)		
Yes	135 741 (40.15%)	10 289 (34.88%)
No	202 332 (59.85%)	19 211 (35.12%)
Bystander automated external defibrillator was applied (public location only, excluding 911 witnessed events and nursing home/health care facility events)	6512 (11.60%)	259 (3.91%)
Sustained return of spontaneous circulation		
Yes	93 589 (27.7%)	10 435 (35.4%)
No	244 398 (72.3%)	19 060 (64.6%)
Missing/unknown	86 (0.0%)	5 (0.0%)
First monitored rhythm		
Asystole	178 145 (52.7%)	19 091 (64.7%)
Idioventricular/ pulseless electrical activity	62 201 (18.4%)	4365 (14.8%)
Unknown unshockable	27 164 (8.0%)	4550 (15.4%)
Ventricular fibrillation	51 658 (15.3%)	1021 (3.5%)
Ventricular tachycardia	3498 (1.0%)	93 (0.3%)
Unknown shockable	15 407 (4.6%)	380 (1.3%)
First monitored rhythm status		(0.0%)
Nonshockable	267 510 (79.1%)	28 006 (94.9%)
Shockable	70 563 (20.9%)	1494 (5.1%)
Comorbidities (missing values are assumed to be absent)		
Diabetes	56 679 (16.8%)	885 (3.0%)
Hypertension	91 471 (27.1%)	1841 (6.2%)
Renal disease	14 670 (4.3%)	150 (0.5%)
Heart disease	62 644 (18.5%)	611 (2.1%)
Respiratory disease	30 973 (9.2%)	766 (2.6%)
Hyperlipidemia	18 172 (5.4%)	178 (0.6%)
Stroke	11 162 (3.3%)	148 (0.5%)
Other disease	116 791 (34.5%)	14 429 (48.9%)
Types of drugs administered (missing values assumed to be absent)		
Epinephrine	272 319 (80.6%)	21 602 (73.2%)
Amiodarone	43 891 (13.0%)	1234 (4.2%)
Atropine	5939 (1.8%)	341 (1.2%)
Bicarbonate	72 327 (21.4%)	5817 (19.7%)
Calcium chloride	6656 (2.0%)	298 (1.0%)
Dextrose	14 811 (4.4%)	1760 (6.0%)
Lidocaine	9620 (2.8%)	234 (0.8%)
Magnesium sulfate	1157 (0.3%)	44 (0.1%)
Naloxone	33 277 (9.8%)	16 221 (55.0%)
Vasopressin	141 (0.0%)	15 (0.1%)
Other drugs	82 552 (24.4%)	7407 (25.1%)
Hypothermia care initiated or continued in the hospital	41 080 (12.2%)	4028 (13.7%)
Outcome		
Dead in field	142 727 (42.2%)	12 528 (42.5%)
Died in the emergency department	70 505 (20.9%)	3569 (12.1%)
Died in the hospital	95 447 (28.2%)	8468 (28.7%)
Survived; CPC 3 or 4	5957 (1.8%)	459 (1.6%)
Survived; CPC 1 or 2	23 437 (6.9%)	4476 (15.2%)

CPC indicates Cerebral Performance Category; OD-OHCA, overdose-attributable out-of-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.

*Asian, American-Indian/Alaska Native or Native Hawaiian/Pacific Islander

state-based registries and the District of Columbia with community sites in 14 additional states. CARES represents a catchment area of more than 162 million people or approximately 49% of the US population, with more than 2000 EMS agencies, and 2500 participating hospitals. Further details of CARES development, design, and data elements have been previously published.[10,13] Organizations participating in CARES, including EMS and receiving hospitals, document standardized information about cardiac arrests they encounter, and

data are aggregated for epidemiological research and monitoring purposes. Cardiac arrest cases submitted to CARES are reviewed to ensure data integrity. The CARES database has been used to answer a number of questions regarding broad trends in OHCA. Given all data are deidentified and publicly available, the use of CARES data has been determined to be exempt from institutional review board review. Furthermore, informed consent was not obtained, because the study involves a retrospective examination of patient data generated during normal care.

Statistical Analysis

We summarized continuous variables with means and SDs and categorical variables with counts and percentages. We compared continuous variables with the Student's *t* test and categorical variables with the chi-square test. Our primary outcome of interest was survival to hospital discharge with good neurological status (Cerebral Performance Category score [CPC]=1 or 2). Given known differences in outcomes by whether or not the patient has a shockable or nonshockable first rhythm, we stratified the patients into shockable and nonshockable groups for multivariable modeling. We created a multivariable logistic regression model to determine the association of cause on survival with CPC=1 or 2, using all predictors in Table 1 other than patient outcomes and first rhythm type (shockable versus nonshockable status) as the latter variable was used for stratification. Two separate models were subsequently created depending on whether the patient presented with a shockable or nonshockable rhythm. The multivariable regression models also included interactions with cause and age. All inference tests were 2-tailed, and *P* values <0.05 were considered statistically significant. All analyses were done using Stata/MP 17.0 for Windows, StataCorp, LLC College Station, TX.

RESULTS

From a data set with 537 100 entries, 29 500 OD-OHCA cases (8.0%) and 338 073 non-OD-OHCA (92.0%) cases met inclusion criteria (Figure 1). When comparing OD-OHCA with non-OD-OHCA, several noteworthy results become apparent (Table 1). First, OD-OHCA involved younger patients than non-OD-OHCA (OD: 39.0±12.6 years old versus non-OD: 63.6±16.3 years old, *P*<0.001). Second, OD-OHCA patients had significantly fewer comorbidities (eg, diabetes, hypertension,

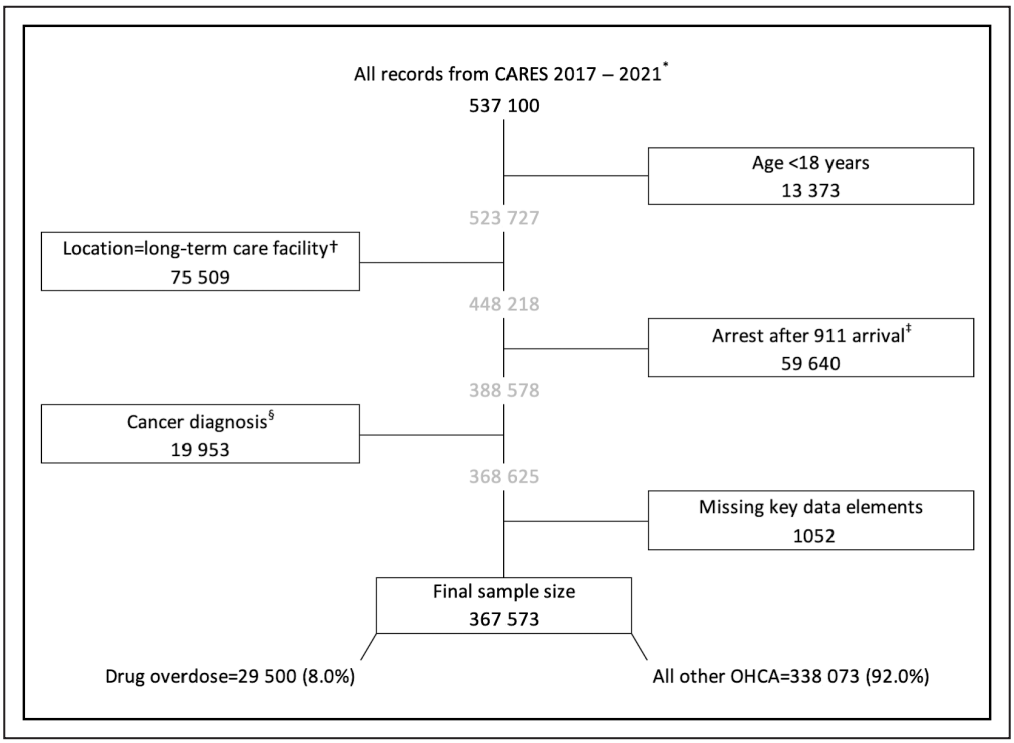

Figure 1. Derivation of the study population.
*Nontraumatic cardiac arrest with attempted resuscitation. †Surrogate for likely poor baseline function leading to early postresuscitation decision for early palliative care. ‡Surrogate for likely short arrest duration precluding need for aggressive postresuscitative care. §Assumed to be early palliative care and therefore not a candidate for aggressive postresuscitation critical care. CARES indicates Cardiac Arrest Registry to Enhance Survival; and OHCA, out-of-hospital cardiac arrest.

Table 2. Adjusted Marginal Probability of Survival to Hospital Discharge With Cerebral Performance Category Score=1 or 2 by Rhythm Status

First documented rhythm type	Non-OD-OHCA	OD-OHCA	*P* value
Nonshockable first documented rhythm	3.1% 95% CI (2.8%–3.4%)	9.6% 95% CI (8.6%–10.7%)	<0.001
Shockable first documented rhythm	23.5% 95% CI (22.5%–24.4%)	28.9% 95% CI (22.6%–35.1%)	0.087

OD-OHCA indicates overdose-attributable out-of-hospital cardiac arrest.

renal disease, heart disease, respiratory disease, hyperlipidemia, and stroke) than non-OD-OHCA patients. Third, OD-OHCA were less likely to be witnessed (OD: 21.7% versus non-OD: 46.1%, *P*<0.001). Fourth, OD-OHCA had significantly lower rates of shockable first monitored arrest rhythms (OD: 5.1% versus non-OD: 20.9%, *P*<0.001).

Overall outcomes were significantly better within the OD-OHCA cohort in the unadjusted analysis (Table 1). Namely, survival with favorable neurological outcomes (CPC=1 or 2) was higher in the OD-OHCA cohort (OD: 15.2% versus non-OD: 6.9%, *P*<0.001). However, multivariable adjusted results Table 2) showed comparable survival with CPC 1 or 2 between OD-OHCA and non-OD-OHCA when the first monitored arrest rhythm was shockable (OD: 28.9% versus non-OD: 23.5%, *P*=0.087) (Figure 2A), but significantly higher rates of survival with CPC 1 or 2 for OD-OHCA when the first monitored arrest rhythm was nonshockable (OD: 9.6% versus non-OD: 3.1%, *P*<0.001) (Figure 2B).

DISCUSSION

Our examination of a large, national registry of OHCA reveals key differences when comparing OD-OHCA with non-OD-OHCA. For example, OD-OHCA involved younger individuals with fewer comorbidities, were less likely to be witnessed, and less likely to present with a shockable first monitored arrest rhythm. These findings are consistent with what has been shown in smaller-scale studies.[8,14–16] Neurological outcomes were significantly better in the OD-OHCA cohort, even

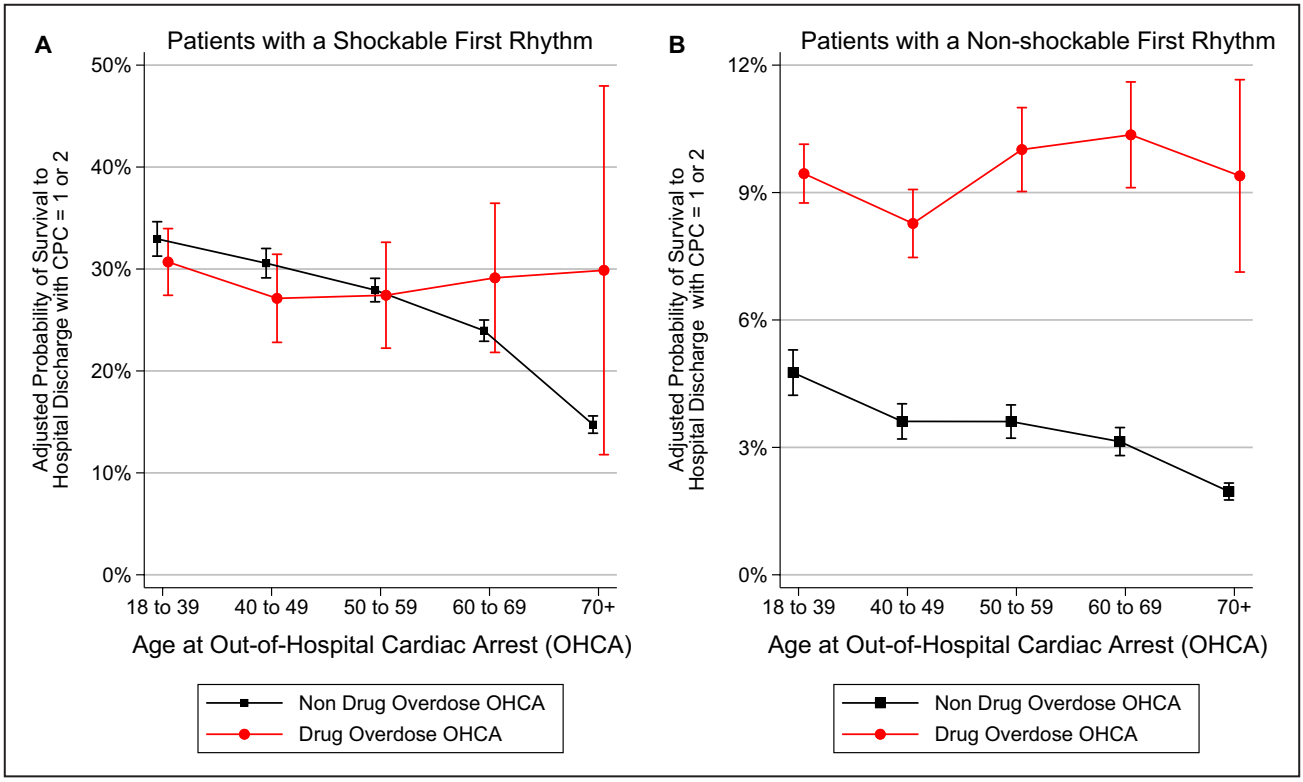

Figure 2. Adjusted marginal probabilities of survival to hospital discharge with Cerebral Performance Category score (CPC)=1 or 2.
A, Patients with a shockable first documented rhythm. **B**, Patients with a nonshockable first documented rhythm. CPC indicates Cerebral Performance Category.

after controlling for age and the presence of comorbidities. The finding that overdose-attributable cardiac arrests are paradoxically associated with lower rates of shockable rhythms but better outcomes than other cardiac arrest causes has been seen in other studies.[5,7–9,15] One speculation for this trend is that opioids, which may have been involved in many of the overdose-attributable cardiac arrests, may hold some neuroprotective properties. Emerging preclinical evidence supports this hypothesis.[17,18]

Currently, the topic of overdose-attributable cardiac arrest is especially timely. Data from multiple sources indicate the number of overdoses increased substantially during the COVID-19 pandemic.[19,20] This increase may have resulted from increased stress accompanying the pronounced societal changes that took place during the pandemic.[21–23] This is especially concerning given overdoses were already increasing well before the pandemic began.[1,2] Data also indicate our ability to manage overdose-attributable cardiac arrest has improved: 1 study from Australia found rates of survival to hospital discharge more than doubled between the years 2000 and 2017.[24] Our data further highlight this particularly vulnerable population and underscore the need for continued research specific to OD-OHCA resuscitation, which has the potential to significantly reduce the burden of OHCA in the US.

Our study is limited by the fact CARES only covers roughly half of the US population. It is possible that communities not submitting to CARES might experience markedly different patterns of cardiac arrest. Second, arrest cause was documented according to CARES definitions based on identifiers recognized on-scene. Other studies have hinted at a tendency to overclassify arrests as presumed cardiac in nature. Thus, it is possible that some arrests were misclassified.[6] Similarly, the categorization of arrests as being overdose attributable is also imperfect, and we do not have precise information as to what specific kinds of drugs (eg, percentage due to opioid overdoses) contributed to these arrests. Nevertheless, our study provides important national surveillance on a cardiac arrest cause of immense public health importance.

CONCLUSIONS

Our analysis of a large registry of OHCA reveals stark differences when comparing OD-OHCA with non-OD-OHCA. Namely, OD-OHCA involved younger patients with fewer comorbidities, were less likely to be witnessed, and were less likely to present with a shockable rhythm. Multivariate analysis revealed neurologic outcomes were significantly better for OD-OHCA than non-OD-OHCA when patients presented with a nonshockable rhythm but were comparable when patients presented with a shockable rhythm. These insights may inform further research, as well as public health measures.

ARTICLE INFORMATION

Received June 1, 2023; accepted November 14, 2023.

Affiliations

The Icahn School of Medicine at Mount Sinai, New York, NY (A.C.S.); OptiStatim, LLC, Longmeadow, MA (B.H.N.); Department of Emergency Medicine (T.J.M.) and Department of Healthcare Delivery and Population Science (T.J.M.), UMass Chan Medical School—Baystate, Springfield, MA and Department of Emergency Medicine, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL (R.A.C.).

Acknowledgments

CARES participating sites can be located at https://mycares.net/sitepages/map.jsp. R.A.C., T.J.M., and A.C.S. designed the study, analyzed the data, and wrote the article. B.H.N. performed statistical analysis and participated in the writing. All authors have read and approved of the article.

Sources of Funding

This study was funded by a grant from the National Heart, Lung, and Blood Institute (R21HL156198).

Disclosures

Brian H. Nathanson's company, OptiStatim, LLC was paid a consulting fee for statistical services related to the article. CARES receives funding from the American Red Cross and the American Heart Association. The remaining authors have no disclosures to report.

REFERENCES

1. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000–2014. *Morb Mortal Wkly Rep*. 2016;64:1378–1382. doi: 10.15585/mmwr.mm6450a3
2. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The opioid crisis: a comprehensive overview. *Curr Pain Headache Rep*. 2018;22:1–6. doi: 10.1007/s11916-018-0670-z
3. Alqahtani S, Nehme Z, Williams B, Smith K. The incidence and outcomes of out-of-hospital cardiac arrest precipitated by drug overdose: a systematic review and meta-analysis. *Resuscitation*. 2019;134:10–18. doi: 10.1016/j.resuscitation.2018.12.020
4. Dezfulian C, Orkin AM, Maron BA, Elmer J, Girotra S, Gladwin MT, Merchant RM, Panchal AR, Perman SM, Starks MA, et al. Opioid-associated out-of-hospital cardiac arrest: distinctive clinical features and implications for health care and public responses: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e836–e870. doi: 10.1161/CIR.0000000000000958
5. Shekhar AC, Campbell T, Mann NC, Blumen I. Overdose-attributable out-of-hospital cardiac arrest in the United States (2017 to 2019). *Am J Cardiol*. 2022;162:200–201. doi: 10.1016/j.amjcard.2021.09.008
6. Chen N, Callaway CW, Guyette FX, Rittenberger JC, Doshi AA, Dezfulian C, Elmer J. Arrest etiology among patients resuscitated from cardiac arrest. *Resuscitation*. 2018;130:33–40. doi: 10.1016/j.resuscitation.2018.06.024
7. Shekhar AC, Campbell T, Mann NC, Blumen I. Etiology affects predictors of survival for out-of-hospital cardiac arrest. *Am J Emerg Med*. 2022;57:218–219. doi: 10.1016/j.ajem.2022.02.017
8. Katz AZ, Grossestreuer AV, Gaieski DF, Abella BS, Kumar V, Perrone J. Outcomes of patients resuscitated from cardiac arrest in the setting of drug overdose. *Resuscitation*. 2015;94:23–27. doi: 10.1016/j.resuscitation.2015.06.015
9. Shekhar AC, Adabag S. Characteristics and outcomes surrounding out-of-hospital cardiac arrests due to drug overdose in the United States. *Circulation*. 2021;144:A10430. doi: 10.1161/circ.144.suppl_1.10430
10. McNally B, Stokes A, Crouch A, Kellermann AL; CARES Surveillance Group. CARES: Cardiac Arrest Registry to Enhance Survival. *Ann Emerg Med*. 2009;54:674–683.e2. doi: 10.1016/j.annemergmed.2009.03.018

11. 2023 Data Dictionary Cardiac Arrest Registry to Enhance Survival (CARES). Cardiac Arrest Registry to Enhance Survival. 2023. Accessed October 29, 2023. https://mycares.net/sitepages/uploads/2023/Data%20Dictionary%20(2023).pdf
12. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, Bossaert L, Delooz HH, Dick WF, Eisenberg MS. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation*. 1991;84:960–975. doi: 10.1161/01.CIR.84.2.960
13. McNally B, Robb R, Mehta M, Vellano K, Valderrama AL, Yoon PW, Sasson C, Crouch A, Perez AB, Merritt R, et al; Centers for Disease Control and Prevention. Out-of-hospital cardiac arrest surveillance—Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005–December 31, 2010. *Morb Mortal Wkly Rep Surveill Summ*. 2011;60:1–9.
14. Koller AC, Salcido DD, Callaway CW, Menegazzi JJ. Resuscitation characteristics and outcomes in suspected drug overdose-related out-of-hospital cardiac arrest. *Resuscitation*. 2014;85:1375–1379. doi: 10.1016/j.resuscitation.2014.05.036
15. Salcido DD, Torres C, Koller AC, Orkin AM, Schmicker RH, Morrison LJ, Nichol G, Stephens S, Menegazzi JJ; Resuscitation Outcomes Consortium Investigators. Regional incidence and outcome of out-of-hospital cardiac arrest associated with overdose. *Resuscitation*. 2016;99:13–19. doi: 10.1016/j.resuscitation.2015.11.010
16. Smith G, Beger S, Vadeboncoeur T, Chikani V, Walter F, Spaite DW, Bobrow B. Trends in overdose-related out-of-hospital cardiac arrest in Arizona. *Resuscitation*. 2019;134:122–126. doi: 10.1016/j.resuscitation.2018.10.019
17. Zhang J, Gibney GT, Zhao P, Xia Y. Neuroprotective role of δ-opioid receptors in cortical neurons. *Am J Phys Cell Phys*. 2002;282:C1225–C1234. doi: 10.1152/ajpcell.00226.2001
18. He X, Sandhu HK, Yang Y, Hua F, Belser N, Kim DH, Xia Y. Neuroprotection against hypoxia/ischemia: δ-opioid receptor-mediated cellular/molecular events. *Cell Mol Life Sci*. 2013;70:2291–2303. doi: 10.1007/s00018-012-1167-2
19. Friedman J, Mann NC, Hansen H, Bourgois P, Braslow J, Bui AA, Beletsky L, Schriger DL. Racial/ethnic, social, and geographic trends in overdose-associated cardiac arrests observed by US emergency medical services during the COVID-19 pandemic. *JAMA Psychiatry*. 2021;78:886–895. doi: 10.1001/jamapsychiatry.2021.0967
20. Cartus AR, Li Y, Macmadu A, Goedel WC, Allen B, Cerdá M, Marshall BD. Forecasted and observed drug overdose deaths in the US during the COVID-19 pandemic in 2020. *JAMA Netw Open*. 2022;5:e223418. doi: 10.1001/jamanetworkopen.2022.3418
21. Wakeman SE, Green TC, Rich J. An overdose surge will compound the COVID-19 pandemic if urgent action is not taken. *Nat Med*. 2020;26:819–820. doi: 10.1038/s41591-020-0898-0
22. Nguyen T, Buxton JA. Pathways between COVID-19 public health responses and increasing overdose risks: a rapid review and conceptual framework. *Int J Drug Policy*. 2021;93:103236. doi: 10.1016/j.drugpo.2021.103236
23. Shekhar AC, Boyd JW. Increases in overdoses during the COVID-19 pandemic. *Proc (Baylor Univ Med Cent)*. 2023;36:411–412. doi: 10.1080/08998280.2023.2180256
24. Alqahtani S, Nehme Z, Williams B, Bernard S, Smith K. Long-term trends in the epidemiology of out-of-hospital cardiac arrest precipitated by suspected drug overdose. *Resuscitation*. 2019;144:17–24. doi: 10.1016/j.resuscitation.2019.08.036