

Description of Opioid-involved Hospital Deaths that Do Not Have a Subsequent Autopsy

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Background: Surveillance systems rely on death records to monitor the most severe outcome of the opioid epidemic. However, few studies have linked data from hospital systems with death records to determine potential undercount of opioid-involved deaths occurring in hospitals. This study describes characteristics of decedents less likely to have an autopsy following an opioid-involved death in hospitals and estimates the resulting undercount.

Methods: A probabilistic data linkage of hospital and medical examiner data involving 4,936 opioid-involved deaths among residents of Cook County, Illinois, US from 2016 to 2019. We included only hospital deaths that met a national case definition and presented with clinical signs of opioid overdose.

Results: Decedents had higher odds of not having an autopsy if they were 50+ years, admitted to the hospital (aOR = 3.7: 2.1, 6.5), hospitalized for 4+ days (aOR = 2.2: 1.5, 3.1), and had a comorbid diagnosis of malignant cancer (aOR = 4.3: 1.8, 10.1). However, decedents exposed to heroin and synthetic opioids (aOR = 0.39: 0.28, 0.55), and concurrent exposure to stimulants (aOR = 0.44: 0.31, 0.64) were more likely to have an autopsy). Compared to estimates from the US Centers for Disease Control and Prevention (CDC), we observed undercounts of opioid overdose deaths ranging from 6% to 15%.

Conclusions: Surveillance systems may undercount decedents that do not meet the typical profile of those more likely to have an autopsy, particularly older patients with chronic health conditions. Our undercount estimate likely exists in addition to the estimated 20%–40% undercount reported elsewhere. See video abstract at, <http://links.lww.com/EDE/B990>.

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Medical examiner data are publicly available at <https://datacatalog.cookcountyl.gov/Public-Safety/Medical-Examiner-Case-Archive/cjeq-bs86>; CDC vital records data are publicly available at <https://wonder.cdc.gov/mcd.html>. A claim of exemption was approved for this project by the University of Illinois Chicago IRB (#2020-0753).

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INTRODUCTION

The ongoing opioid epidemic has caused immeasurable loss of human life and has adversely impacted families and communities in the United States.¹ Opioid-use disorders are associated with diminished health status, high economic and medical costs, increased disability, and early death.¹ In 2019, an estimated 0.8% of the US population met the criteria for opioid-use disorders,² with 2%–3% of the population meeting the criteria during their lifetime.³

Over the past two decades among persons 12 years or older in the United States, the percent misusing and meeting the criteria for opioid-use disorders relating to prescription opioids has slightly declined, while lifetime and recent use of heroin has slightly increased.² Despite these modest changes in misuse and prevalence of opioid-use disorders, the rate of opioid-involved deaths has increased sevenfold since 2000 from 2.8 to 21 per 100,000 persons in 2020.⁴ While there are multiple reasons for the increase in mortality, it has principally been attributed to the introduction of fentanyl, its analogs, and other adulterants in illegally obtained opioids. Furthermore, while only an estimated 8% of persons misusing opioids use heroin and fentanyl analogs,² studies show that fentanyl is found in 50%–70% of fatal opioid overdoses.^{5–7} The opioid overdose toxidrome is characterized by a constellation of cardiovascular, respiratory, immunologic, and gastrointestinal signs.^{8–11}

Comprehensive surveillance data of nonfatal and fatal opioid-involved overdoses is crucial for designing interventions, informing public health planning, and guiding research outcomes.^{12,13} In the United States, surveillance data primarily relies on death records to monitor the opioid epidemic despite research showing that death records are likely undercounting opioid-involved deaths by 20% to over 40%.^{14–19} However, past studies only provide an estimate of the overall undercount, and do not provide detailed information about who is more likely to be undercounted.

Autopsies are essential for determining and documenting detailed cause of death. However, US Centers for Disease Control and Prevention (CDC) data demonstrates that no state requires an autopsy following a death related to drug use,

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abuse, and overdose.²⁰ The majority of persons who die from an acute injury (All S and T ICD-10 codes) do not have an autopsy and national data indicates that autopsy rates have remained relatively steady since 2005.⁴ Furthermore, prior studies demonstrate that the completeness of documenting multiple causes of death on death certificates, particularly identifying the drugs involved in a death, is lower among coroners compared to medical examiners or pathologists and varies across jurisdictions.^{14,16,21,22} Given the large proportion of deaths that do not have an autopsy and the varying resources across jurisdictions responsible for completing death certificates, it is possible that a large number of opioid-involved deaths are missed entirely by death certificates.

Since the current US surveillance system relies on death records to monitor the most severe outcome of opioid-use disorders, we need to ensure that opioid-involved deaths are captured as fully as possible and provide detailed information about those that die and the specific drugs contributing to their deaths. However, there continues to be a lack of reported findings that have linked other data systems with death records to determine how many overdose deaths are missed entirely. The current study links hospital data with medical examiner data to (1) describe characteristics of decedents from opioid-involved overdoses in Cook County hospitals that do not have an autopsy, and (2) evaluate the proportion of opioid-involved deaths not captured by the county medical examiner that may contribute to a cumulative undercount reported by the CDC.

MATERIALS AND METHODS

Design and study participants

We conducted a data linkage of hospital and medical examiner data of all opioid-involved deaths occurring among residents of Cook County who died in Cook County (county location for the city of Chicago) from 2016 to 2019. A claim of exemption was approved for this project by the BLINDED IRB (#2020-0753).

Outpatient and Inpatient Hospital Data

The data covers the period of January 1, 2016, through December 31, 2019 (2020 data were not available at the time of initiating this analysis). The hospital data are based on billing records compiled by the Illinois Hospital Association. The outpatient database includes all patients treated in emergency departments (ED) for less than 24 hours who were not admitted as an inpatient to the hospital. The outpatient data only includes patients seeking emergent care in the ED or those with referrals to clinics that require registration in the ED (e.g., orthopedic ambulatory surgery and gastrointestinal ambulatory procedures). The inpatient database includes all patients treated for 24 hours or more in Illinois hospitals for any medical reason. Both datasets include information on patient demographics (age, race, gender), clinical outcomes (diagnoses, hospital procedures, and discharge status), and

economic outcomes (hospital charges and payer source). Based on the annual state audit of hospitals, 97% of all inpatient admissions statewide are captured by the participating hospitals included in the dataset.^{23,24}

Cook County Medical Examiner Data

We obtained Cook County Medical Examiner (CCME) data for the period January 1, 2016, through December 31, 2019 through a public online open data portal.²⁵ A forensic pathologist conducts each investigation of deaths occurring under the jurisdiction of Cook County that includes suspected drug overdoses. The CCME dataset includes information on the date and time of death, demographics of the decedent including race and ethnicity, decedent residence, cause, and manner of death, contributing causes, and incident location including geolocation. In suspected drug overdoses, a toxicologic analysis is conducted that typically uses peripheral blood; in a very small proportion of cases, tissue from the liver, kidney and muscle is analyzed.

Toxicologic analysis for biologically active agents involves initial screening followed by confirmatory and quantification analyses. Initial screening is conducted using enzyme-linked immunosorbent assay (ELISA) techniques, which provides an initial rapid screening for drugs. Positive ELISA toxicologic analyses are then verified through (1) gas chromatography– mass spectrometry (GC-MS) or (2) liquid chromatography– mass spectrometry (LC-MS). These secondary tests are used to identify the specific agents and respective concentrations. When multiple agents are identified in the bioassay, all the agents are individually identified. Limits of detection varies for each agent analyzed.

Inclusion Criteria

Based on the Council of State and Territorial Epidemiologists (CSTE) nonfatal opioid overdose standardized surveillance case definition,²⁶ we only included hospital deaths with an initial encounter ICD-10 diagnosis code indicating intoxication (F11.12, F11.22, F11.92) or poisonings (T40.0-T40.4, T40.6; excluding adverse effects and underdosing of prescription opioids, eAppendix A <http://links.lww.com/EDE/B964>). In addition, among the hospital cases that met the modified CSTE case definition, we only included cases that also had clinical signs associated with the constellation of opioid overdose prior to death^{8–11} and/or had an autopsy confirming that the death was opioid-related. Of the deaths that met the initial CSTE case definition, 51 did not have any clinical signs associated with opioid overdose and were excluded. To identify related deaths in the CCME data, we only included deaths in which opioids were identified as the primary cause of death by the pathologist (n = 34 deaths testing positive for opioids were excluded because opioids exposure was listed as a secondary cause).

Probabilistic Linkage

Unique identifiers were not available in either dataset. We used probabilistic data linkage to link suspected opioid-involved deaths from the hospital data to the ME data, which

was accomplished in multiple passes. The initial pass identified records that matched exactly on the following variables: residential ZIP code, race, Hispanic/Latino, birth year, gender, date of admission, date of death, and concurrent exposure to opioids and other agents (heroin/fentanyl, methadone, all other/unspecified opioids, ethanol, cocaine, amphetamine, and benzodiazepines). In subsequent passes, we used different combinations of the linkage variables (eAppendix B <http://links.lww.com/EDE/B964>).

Outcome

The main outcome evaluated was whether decedents dying from opioid-involved overdoses in a hospital setting were sent to the medical examiner for an autopsy, which were the hospital deaths that linked to the CCME data.

Statistical Analysis

For the descriptive analysis, we present data on diagnoses associated with the opioid toxidrome, and sociodemographic, clinical, and temporal factors of decedents related to occurrence of an autopsy. In addition, our analysis utilized the Elixhauser comorbidity index to assess comorbidities in hospital decedents.²⁷

We used multivariable logistic regression to assess selected predictors of not having an autopsy among those who died during hospital care. We used *a priori* knowledge informed by existing literature to determine inclusion of covariates in the multivariable analysis and present a model that includes the following predictors: age, race-ethnicity, year of death, whether decedent was admitted to the hospital, length of hospitalization, exposure to heroin and synthetic opioids, exposure to stimulants, and whether the hospital had a level I or II trauma center. We also evaluated individual comorbidities as measured by the Elixhauser comorbidity index and constructed a variable identifying patients with lymphoma, metastatic cancer, and solid tumor without metastasis. Odds ratios in the adjusted models are presented, including the 95% confidence intervals (95% CI). No evidence of multicollinearity was indicated among predictors based on evaluation of change in standard errors, variance of inflation (variance of inflation >10 suggests evidence of multicollinearity)³⁰ and tolerance tests (tolerance value <0.1 suggests evidence of multicollinearity).³¹ We used SAS software for all statistical analyses (SAS v.9.4; Cary, NC).

Estimate of Undercount

To estimate the potential undercount of opioid-involved deaths, we compared the number of opioid-involved deaths as reported by the CDC in the Multiple Cause of Death (MCO) data⁴ with total unique opioid-involved deaths captured in both the Cook County ME data and the hospital data for Cook County residents. Following the CDC case definition, we included deaths among Cook County residents with the following ICD-10 codes: T40.0-.4 and T40.6. However, we also included F11 ICD codes to be consistent with the CSTE case definition used in our analysis (*n* = 67 MCO cases had

F11 codes exclusively). We also present CDC data on autopsy rates, place of death, and age distribution.⁴

Sensitivity Analysis

As a sensitivity analysis, we excluded decedents dying within 3 days of receiving anesthesia to account for deaths associated with medical complications from surgical anesthesia.¹² Date of surgery identified through procedure codes was used to identify deaths occurring within 3 days of surgery. We assumed all surgical cases to have been exposed to anesthesia. In addition, even though the hospital deaths met the CSTE case definition, and all presented with clinical signs of the opioid toxidrome, it was plausible that not all cases in the medical records with a mention of opioids should be considered an opioid-involved death. Therefore, an additional sensitivity analysis was conducted, which excluded opioid-involved deaths with codes associated with therapeutic adverse effects, underdosing of prescribed narcotics, or remission (T40.2X5, T40.2X6, T40.4X5, T40.4X6, T40.605, F11.21; this only applies to patients that had more than one related opioid exposure code), patients diagnosed with cancer who only had a diagnosis of opioid-use disorder (F11) but no T40 codes, and patients with only one clinical sign of opioid overdose.⁸⁻¹¹

RESULTS

From 2016 to 2019, the hospital and CCME datasets identified 4,936 unique opioid-involved deaths among residents of Cook County, IL. During the 4-year period, 1,174 patients died from opioid-involved overdoses in Cook County hospitals. However, only 239 (20%) of these hospital decedents were identified as having an autopsy. Of the hospital cases, heroin was reported in 252 cases along with the following nonopioids commonly associated with substance use disorders: stimulants (*n* = 233); sedatives, hypnotics, or anxiolytics (*n* = 64); and ethanol (*n* = 192). We identified an additional 3,762 unique deaths from opioid-involved overdoses in the CCME data.

The constellation of clinical signs and procedures related to opioid overdose are presented in Table 1; as a comparison group, the prevalence of each sign or procedure among all deaths occurring in the general hospital population are also presented (i.e., not limited to opioid-involved deaths). Among the decedents without an autopsy, 93% had two or more clinical signs of opioid overdose compared to 79% of decedents with an autopsy. The opioid cases identified using the CSTE case definition had substantially higher proportion of all clinical signs of opioid overdose compared to all deaths occurring in the general hospital population. Persons without an autopsy had a mean of 4.0 (SD = 1.8) clinical diagnoses related to the opioid overdose constellation compared to 4.1 (SD = 2.4) among those with an autopsy, while all hospital deaths had an average of 2.0 (SD = 1.7) clinical signs. When restricting the clinical signs to only those strongly associated with in-hospital mortality (e.g., respiratory signs, hepatitis, HIV, sepsis, neurologic conditions, and rhabdomyolysis), 71% of those without an autopsy and 71% of those with an autopsy

TABLE 1. Clinical Signs and Procedures Associated With the Opioid Overdose Toxidrome (Cook County, Illinois Residents Who Died Between 2016 and 2019)^a

Clinical Signs	All Hospital Deaths (all causes) ^b	Deaths Identified	
		in Hospital Data Only (N=935) ^c	in both Hospital and Medical Examiner Data (Linked Cases; N=239) ^d
Respiratory			
Respiratory depression	54%	728 (78%)	176 (83%)
Hypoxia	32%	419 (45%)	105 (44%)
Anoxia	6%	254 (27%)	111 (46%)
Aspiration pneumonia	15%	195 (21%)	56 (23%)
Cardiovascular			
Moderate to severe hypotension, transient	11%	154 (17%)	40 (17%)
Infective endocarditis	2%	33 (4%)	4 (2%)
Aneurysms, Embolisms, and Thrombosis			
Peripheral and pulmonary embolism	4%	56 (6%)	13 (5%)
Blood borne diseases and Infections			
Hepatitis B	0%	16 (2%)	2 (1%)
Hepatitis C	1%	129 (14%)	21 (9%)
HIV	0%	19 (2%)	3 (1%)
Sepsis due to Staphylococcus infection	2%	30 (3%)	7 (3%)
Sepsis due to Pseudomonas	1%	9 (1%)	0 (0%)
Sepsis due to Streptococci infection	1%	21 (2%)	0 (0%)
Neurologic			
Seizure	7%	129 (14%)	33 (14%)
Toxic encephalopathy	6%	92 (10%)	20 (8%)
Coma	10%	116 (12%)	43 (18%)
Anoxic brain damage NOS	28%	403 (43%)	125 (52%)
Gastrointestinal			
Drug-induced fecal impaction or constipation	1%	87 (9%)	0 (0%)
Other			
Rhabdomyolysis	2%	63 (7%)	27 (11%)
Drug-induced hypothermia	1%	12 (1%)	6 (3%)
Procedure			
Patient Required Intubation	37%	714 (76%)	186 (78%)

^aCounts and percentages of clinical signs and procedures are not mutually exclusive.
^bAll hospital deaths—includes all patient who died after admission to an Illinois hospital between January 1, 2016, and December 31, 2019 for any reason not restricted to opioid-involved deaths; excluding signs not associated with mortality (e.g., miosis).
^cDeaths identified in only hospital data did not receive an autopsy from the medical examiner.
^dDeaths identified in both hospital and medical examiner data are hospital decedents that received an autopsy from the medical examiner identified through data linkage.
Respiratory signs ICD-10 codes: J80, R09.2, J96.2, J96.9, R06.3, J96.01, J96.91, G93.1, and J69.0.
Cardiovascular signs ICD-10 codes: I95.2, I33.0, I33.9, I38, I35.8, B37.6; T82.6, I05.9, I05.9, I01.1, I08.0, I08.3, I08.9, I37.8, I07.9, and I26.9.
Blood borne diseases and infections signs ICD-10 codes: K71.1, B16, B18.0, B18.1, B19.1, B17, B18.2, B19.2, B20, A41.0; A41.1; A41.2, A41.52, and A40.
Neurologic signs ICD-10 codes: R56.9, G40.5, G40.89, G40.9, G92, R40.2, G93.1, and G93.4.
Gastrointestinal signs ICD-10 codes: K59.03, and K56.4.
Other clinical signs ICD-10 codes: M62.82, and R680.
Procedures ICD-10 codes: 0BH13, 0BH14, 0BH17EZ, 0BH18EZ, 5A19, and 5A09.

TABLE 2. Characteristics of Opioid-involved Decedents Captured in Hospital and Medical Examiner Data (Cook County, Illinois Residents Who Died Between 2016 and 2019)

Characteristics	Deaths Identified		Deaths	
	in Hospital Data Only (N = 935) ^a	in both Hospital and Medical Examiner Data (Linked Cases; N = 239) ^b	in Medical Examiner Data Only (N = 3,762)	Total Deaths (N = 4,936)
Gender, n(%)				
Male	566 (61%)	150 (63%)	2857 (76%)	3,573 (72%)
Female	369 (40%)	89 (37%)	904 (24%)	1,362 (28%)
Unspecified	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Age; mean (SD)	56.6 (14.5)	47.3 (14.7)	45.2 (12.6)	47.5 (13.8)
Age in years, n(%)				
0–4	5 (1%)	1 (0%)	1 (0%)	7 (0%)
5–9	1 (0%)	0 (0%)	0 (0%)	1 (0%)
10–14	1 (0%)	0 (0%)	1 (0%)	2 (0%)
15–19	4 (0%)	2 (1%)	32 (1%)	38 (1%)
20–24	9 (1%)	13 (5%)	182 (5%)	204 (4%)
25–34	53 (6%)	39 (16%)	681 (18%)	773 (16%)
35–44	84 (9%)	38 (16%)	757 (20%)	879 (18%)
45–54	197 (21%)	58 (24%)	1,087 (29%)	1,342 (27%)
55–64	340 (36%)	65 (27%)	850 (23%)	1,255 (25%)
65–74	166 (18%)	20 (8%)	156 (4%)	342 (7%)
75 and older	75 (8%)	3 (1%)	12 (0%)	90 (2%)
Unspecified	0 (0%)	0 (0%)	3 (0%)	3 (0%)
Race-Ethnicity				
White, Non-Hispanic	269 (29%)	90 (38%)	1,566 (42%)	1,925 (39%)
Hispanic/Latino	67 (7%)	16 (7%)	481 (13%)	564 (11%)
Black/African American	492 (53%)	113 (47%)	1,685 (45%)	2,290 (46%)
Asian/Pacific Islander	4 (0%)	2 (1%)	19 (1%)	25 (1%)
American Indian/Alaska Native	2 (0%)	0 (0%)	3 (0%)	5 (0%)
Other/Unspecified	101 (11%)	18 (8%)	8 (0%)	127 (3%)

^aDeaths identified in only hospital data did not receive an autopsy from the medical examiner.
^bDeaths identified in both hospital and medical examiner data are hospital decedents that received an autopsy from the medical examiner identified through data linkage.

had two or more of these diagnoses compared to only 20% of all hospital deaths that includes deaths not involving opioids.

Characteristics of decedents are presented in Table 2. Of the 1,174 hospital deaths, 1,104 (94%) were inpatient cases. Among those that died while in a hospital, persons who did not have an autopsy were disproportionately female, 55 years and older, Black/African American and other race-ethnicity (Table 2). Furthermore, the proportion of cases receiving an autopsy were lower in homeless individuals (with autopsy vs without autopsy; 1% vs 2%), decedents having Medicare insurance (17% vs 30%), decedents admitted as inpatient

cases (83% vs 97%), persons undergoing a surgical intervention (38% vs 49%) and cases treated in a hospital with a level 1 or 2 trauma unit (39% vs 52%). Additionally, decedents that did not receive an autopsy demonstrated longer lengths of hospitalization (Mean ± SD: 8.8 ± 12.3 days vs 3.7 ± 6.4 days).

However, those who did not have an autopsy demonstrated lower identified exposures to heroin (16% vs 42%), and concurrent exposures to stimulants (17% vs 32%); sedatives, hypnotics, and anxiolytics (5% vs 9%); and ethanol (16% vs 19%). The type and number of comorbidities differed among those with and without autopsies after dying in a hospital (Table 3). A lower proportion of hospital decedents who subsequently had an autopsy performed were identified as having congestive heart failure, complicated hypertension, complicated diabetes, malignant cancer, renal failure, and coagulopathy (Table 3).

Table 4 presents the results of the multivariable logistic regression for the main and sensitivity models evaluating selected factors associated with not having an autopsy performed by the medical examiner after dying in a hospital following exposure to opioids. The main model confirms that decedents with the following characteristics have a higher odds of not receiving an autopsy: over the age of 50 years (50–64 years, aOR = 2.0; 95% CI = 1.4, 2.9; 65+ years, aOR = 3.2; 95% CI = 1.9, 5.5), identifying as other race-ethnicity (aOR = 2.3; 95% CI = 1.3, 4.3), those who died in more recent years (aOR = 1.2; 95% CI = 1.0, 1.4), inpatient cases (aOR = 3.7; 95% CI = 2.1, 6.5), decedents hospitalized for 4+ days (aOR = 2.2; 95% CI = 1.5, 3.1), those treated in hospitals with a level I or II trauma unit (aOR = 1.6; 95% CI = 1.1, 2.2), and decedents with malignant cancer (aOR = 4.3; 95% CI = 1.8, 10.1). However, the model demonstrates that decedents exposed to heroin and the group of synthetic opioids that includes fentanyl (T40.4; aOR = 0.39; 95% CI = 0.28, 0.55), as well as concurrent exposure to stimulants (aOR = 0.44; 95% CI = 0.31, 0.64), had substantially lower odds of not receiving an autopsy (i.e., were more likely to have an autopsy). In the first sensitivity model that excluded patients who died within 3 days of receiving anesthesia, predictors of not having an autopsy were similar to the main model. In the second sensitivity model, the parameter estimates remained nearly identical to the main model with the exception of inpatient cases and decedents with cancer comorbidities. These changes were driven by the near elimination of outpatient and cancer cases from the model.

Based on the reported number of opioid deaths by the CDC MCODE, there were 4,303 residents of Cook County with opioid-involved deaths between 2016 and 2019. In our data linkage analysis, we identified 633 more cases than reported by the CDC, representing an undercount of 15%. However, it appears that the CDC is primarily missing cases that die after admission to a hospital. The number of inpatient deaths (place of death “Medical Facility—Inpatient”) reported by the CDC was 413 compared to 1,104 in our dataset. Our analysis

TABLE 3. Comorbidities of Opioid-involved Decedents Captured in the Hospital Data (Cook County, Illinois Residents Who Died Between 2016 and 2019)^a

Comorbidities	Deaths Identified in Hospital Data Only (N = 935) ^b	Deaths Identified in both Hospital and Medical Examiner Data (Linked Cases; N = 239) ^c	Total (N = 1,174)
Number of comorbidities; Mean (SD)	6.1 (2.2)	4.9 (2.6)	5.8 (2.4)
Number of decedents with 3+ comorbidities, n(%)	884 (95%)	193 (81%)	1109 (91%)
Type of comorbidity ^d , n(%)			
Congestive heart failure	278 (30%)	45 (19%)	323 (28%)
Cardiac arrhythmia	356 (38%)	80 (34%)	436 (37%)
Valvular disease	48 (5%)	7 (3%)	55 (5%)
Pulmonary circulation disorders	120 (13%)	19 (8%)	139 (12%)
Peripheral vascular disorders	67 (7%)	12 (5%)	79 (7%)
Hypertension uncomplicated	251 (27%)	72 (30%)	323 (28%)
Hypertension complicated	274 (29%)	31 (13%)	305 (26%)
Paralysis	29 (3%)	5 (2%)	34 (3%)
Other neurological disorders ^e	448 (48%)	135 (57%)	583 (50%)
Chronic pulmonary disease	329 (35%)	71 (30%)	400 (34%)
Diabetes uncomplicated	79 (8%)	16 (7%)	95 (8%)
Diabetes complicated	137 (15%)	14 (6%)	151 (13%)
Hypothyroidism	51 (6%)	8 (3%)	59 (5%)
Renal failure	217 (23%)	33 (14%)	250 (21%)
Liver disease	285 (31%)	80 (34%)	365 (31%)
Peptic ulcer disease ex. bleeding	4 (0%)	0 (0%)	4 (0%)
AIDS/HIV	19 (2%)	3 (1%)	22 (2%)
Lymphoma	17 (2%)	1 (0%)	18 (2%)
Metastatic cancer	163 (17%)	4 (2%)	167 (14%)
Solid tumor without metastasis	167 (18%)	4 (2%)	171 (15%)
Rheumatoid arthritis/collagen	24 (3%)	2 (1%)	26 (2%)
Coagulopathy	263 (28%)	46 (19%)	309 (26%)
Obesity	84 (9%)	14 (6%)	98 (8%)
Weight loss	242 (26%)	23 (10%)	265 (23%)
Fluid and electrolyte disorders	689 (74%)	79 (33%)	849 (72%)
Blood loss anemia	8 (1%)	4 (2%)	12 (1%)
Deficiency anemia	52 (6%)	7 (3%)	59 (5%)
Alcohol abuse	161 (17%)	45 (19%)	206 (18%)
Drug abuse	683 (73%)	29 (12%)	893 (76%)
Psychoses	32 (3%)	4 (2%)	36 (3%)
Depression	79 (8%)	13 (5%)	92 (8%)

^aMedical examiner data had sparse information on comorbidities and was not presented.

^bDeaths identified in only hospital data did not receive an autopsy from the medical examiner.

^cDeaths identified in both hospital and medical examiner data are hospital decedents that received an autopsy from the medical examiner identified through data linkage.

^dCounts presented in table are not independent. A single patient can have multiple diagnoses, including across cancer categories.

^eUsing the Elixhauser comorbidity index, other neurological disorders included in this analysis were unspecified cerebral degeneration, Parkinson’s disease, Huntington’s chorea and other chorea’s, spinocerebellar disease and anterior horn cell disease, multiple sclerosis and other demyelinating diseases, epilepsy, anoxic brain damage, unspecified encephalopathy, convulsions, and aphasia.

TABLE 4. Multivariable Logistic Regression Models Evaluating Predictors of Not Having an Autopsy After Dying in a Hospital From an Opioid-involved Event, Including Sensitivity Models (Cook County, Illinois Residents Who Died Between 2016 and 2019)

	Main Model (n = 1174) Adjusted Odds Ratio (95 % CI)	Sensitivity Models	
		Did not Die within 3 days of getting an anesthesia (n = 855) Adjusted Odds Ratio (95 % CI)	Excludes Deaths Related to Thera- peutic Care, Cancer or Constellation of Opioid Overdose (n = 808) Adjusted Odds Ratio (95 % CI)
Number who had an autopsy (Outcome)	239	175	191
Age category			
0–49 years	Ref	Ref	Ref
50–64 years	2.0 (1.4, 2.9)	2.3 (1.5, 3.6)	1.8 (1.2, 2.7)
65 years and up	3.2 (1.9, 5.5)	2.7 (1.5, 4.9)	2.2 (1.2, 4.1)
Race-Ethnicity			
White non-Hispanic	Ref	Ref	Ref
Black non-Hispanic	1.4 (0.93, 2.0)	1.7 (1.05, 2.6)	1.5 (0.97, 2.3)
Hispanic/Latino	1.4 (0.70, 2.7)	1.8 (0.79, 4.3)	1.5 (0.72, 3.3)
Other	2.3 (1.3, 4.3)	3.4 (1.6, 7.2)	2.3 (1.2, 4.4)
Year of death ^a	1.3 (1.0, 1.4)	1.2 (1.0, 1.5)	1.2 (1.0, 1.4)
Inpatient cases	3.7 (2.1, 6.5)	3.5 (2.0, 6.3)	0.75 (0.33, 1.7)
Length of stay greater than 4 days (median)	2.2 (1.5, 3.1)	2.3 (1.5, 3.5)	2.1 (1.4, 3.0)
Heroin and Synthetic Opioids (Fentanyl) ^b	0.39 (0.28, 0.55)	0.43 (0.29, 0.65)	0.29 (0.20, 0.42)
Stimulants ^c	0.44 (0.31, 0.64)	0.52 (0.31, 0.84)	0.43 (0.29, 0.64)
Any cancer comorbidities ^d	4.3 (1.8, 10.1)	5.6 (2.0, 16)	2.3 (0.28, 19)
Level I or II trauma unit	1.6 (1.1, 2.2)	2.0 (1.3, 3.0)	1.5 (1.0, 2.1)
Overall Model Fit (c-statistic; AUC)	C = 0.81	C = 0.83	C = 0.76

^a1-year increment between 2016-2019.

^bIncludes cases with ICD-10-CM code of T40.1 (poisoning by heroin) and T40.4 (poisoning by other synthetic narcotics) which is the code used to identify Fentanyl.

^cIncludes cases with ICD-10-CM code of T40.5 (Cocaine) and T43.6 (other psychostimulants).

^dIncludes any of the following Elixhauser Comorbidity Index cancer comorbidities: lymphoma, metastatic cancer, and solid tumor without metastasis.

^eDate of surgery identified through procedure codes was used to identify deaths occurring within three days of surgery. All surgical cases were assumed to have been exposed to anesthesia (n = 319 excluded).

^fModel excludes opioid-related deaths with codes associated with therapeutic adverse effects, underdosing or remission (T40.2X5, T40.2X6, T40.4X5, T40.4X6, T40.605, F11.21) and patients diagnosed with cancer who only had an OUD diagnosis (F11) but no T40 codes indicating toxic exposure to an opioid (n = 366 excluded).

identified 2.7 times more inpatient cases, which is almost precisely the difference between the CDC and our numbers. In addition, the difference in counts among inpatient cases (413 vs 1,104; 37.4% of total hospital deaths identified in our analysis) is close to the reported autopsy rate for all injury cases (ICD-10 S and T codes) who have been admitted to a hospital among Cook County residents between 2016 and 2019 (CDC reported autopsy rate of 25%).

Furthermore, when comparing the age distribution of the cases identified in our analysis with those reported by the CDC, the CDC data are primarily missing decedents over the age of 45 years (Figure), which is consistent with our multivariable analysis. Even excluding opioid-involved deaths with codes associated with therapeutic adverse effects, underdosing or remission, patients diagnosed with cancer who only had a diagnosis of opioid-use disorder (F11) but no T40 codes, and those with less than two clinical signs of opioid overdose, there are 267 more cases than reported by the CDC (6% undercount).

DISCUSSION

This linkage project of hospital and medical examiner data evaluating opioid-involved deaths in Cook County Illinois demonstrates (1) overall low autopsy rates for opioid-involved deaths occurring in a hospital setting, (2) that the odds of an autopsy varies by age, clinical characteristics, and type of drug exposures, and (3) a resulting undercount of opioid-involved deaths occurring in a hospital setting. Our undercount estimate ranging between 6% and 15% is smaller than the low-end estimate in prior studies, which have only used death certificate data and focused primarily on misclassification of unspecified drug overdoses (ICD-10: T50.9).^{14–19,28} As our approach of linking hospital data to medical examiner data are unique relative to these prior studies, it is likely that the undercount identified in our analysis exists in addition to the estimated 20%–40% undercount identified within death records.^{14–19,28}

Because this analysis uses a novel approach to identify opioid-involved deaths, we assessed the inclusion of hospital opioid-involved deaths through a series of steps to improve the validity of the inclusion criteria and reduce misclassification. First, we based the inclusion criteria for hospitalized cases on national criteria developed by CSTE rather than arbitrary criteria. All of the persons included in this study had an ICD-10 code indicating opioid-use disorder with intoxication or acute opioid poisoning (T40). Second, all hospital cases presented clinical signs consistent with the recognized opioid toxidrome, and the proportion of these signs were substantially higher than the general hospital population of deaths (i.e., in-hospital mortality related to any cause). Third, as with death records, the focus is on contributing causes, not solely on the primary underlying cause. Opioids directly increase mortality by causing respiratory depression, anoxia, hypoxia,

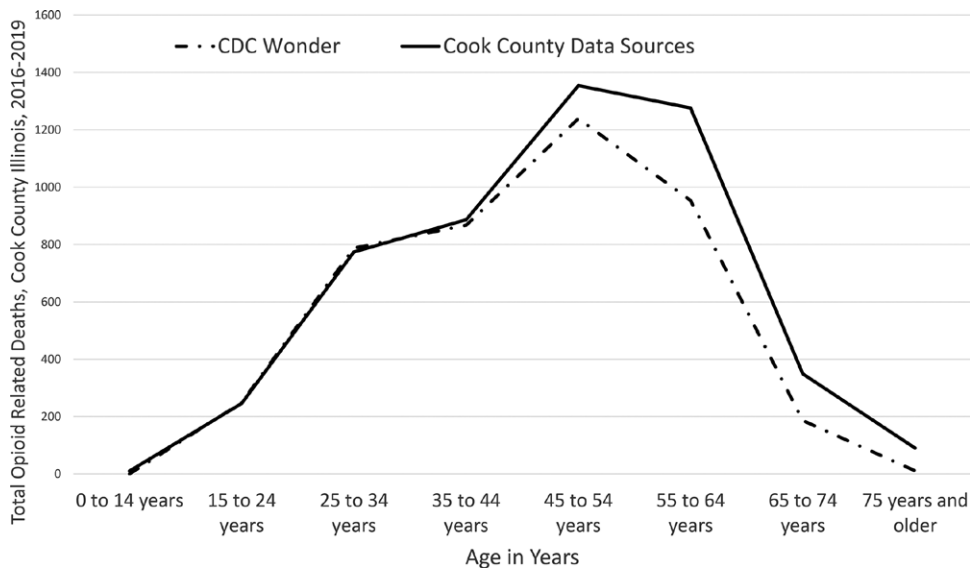


FIGURE. Comparison of opioid-involved deaths as reported by the CDC (multiple cause of death data) and Cook County hospital and medical examiner data (Cook County residents, Illinois who died between 2016 and 2019).

and related brain damage, but also by increasing risk of infection and other adverse systemic effects that lead to medical complications and increased in-hospital mortality.^{8–11} For this reason, the CDC uses multiple contributing causes to estimate total opioid-involved deaths, not just the underlying cause of death. Fourth, the distribution of the constellation of clinical signs associated with opioid overdose was similar for decedents without an autopsy as those confirmed by the pathologist at the medical examiner's office. Fifth, the cases that were identified by hospital staff as T40 opioid overdoses and had clinical signs of overdose were not being systematically autopsied. Only 126 (24%) of the 523 persons with a T40 code had an autopsy, despite all cases presenting with other clinical signs of the opioid toxidrome.

Past studies have shown that women and white non-Hispanics,^{19,21,29} those dying from suicide,¹⁶ residents of nonurban lower income counties,^{21,29} and people in specific age groups^{16,19,21,29} are more likely to be coded as “T50.9: unspecified drug overdose” on death records. Some studies have also identified lower general autopsy rates among white non-Hispanics, older individuals,^{30–32} and individuals having chronic diseases,³² but these studies were not specific to opioid-involved deaths. However, our study connects the evidence between death record misclassification and autopsy rates showing that a substantial number of opioid-involved deaths not involving heroin and fentanyl (i.e. prescription opioids), particularly among older patients with chronic health conditions, do not have autopsies and are missed entirely within death records. ICD-10-CM coding of opioids only has six categories. In our analysis, we focus on ICD-10 codes that had the greatest specificity in identifying a single agent or correspond to the opioids associated with “illicit street drugs” (heroin and fentanyl). Since there were very few patients testing positive for opium and methadone

alone ($n = 14$), the inverse of the heroin and synthetic opioid category almost exclusively represents prescription opioids. If the findings are representative of a national pattern, the contribution of prescription opioids to mortality is being diminished in national death data, particularly underestimating the lethality of prescription opioids in the absence of concurrent use of heroin or fentanyl. Furthermore, with data demonstrating increased opioid misuse among the elderly,³³ the low autopsy rates may indicate that we are also substantially undercounting opioid-involved deaths among the elderly.

Limitations

There are several potential limitations with this analysis. First, our analysis utilized medical examiner data which does not include all death certificates. It is possible that the death records completed by a physician at the hospital accurately recorded opioids as a contributing cause of death. However, cumulative deaths reported exclusively by the ME coincides with the count reported by CDC vital records, indicating that very few opioid-involved deaths without a subsequent autopsy had opioids included as a contributing cause on the death certificate. Second, hospital ICD-10 coding may not accurately or completely capture cases of opioid intoxication/overdose. However, two large analyses of medical record coding^{12,34} noted high positive predictive values of coding opioid poisoning in electronic health records, with 96% of opioid intoxication/overdose cases coded correctly.¹² Third, we did not include opioid-involved cases discharged to hospice because we do not have information on their dates of death (an additional 840 deaths). It is possible that many of these hospice patients are also missed on death records given the concordance between the numbers reported by the CCME and CDC MCODE vital records.

CONCLUSIONS

There is little doubt that the increase of fentanyl congeners in the illicit drug supply chain has contributed to the precipitous rise in opioid-involved deaths over the last 10 years. However, in our analysis opioid-involved deaths involving prescription opioids were less likely to have an autopsy and be captured in death certificates. It is important to characterize decedents that do and do not have autopsies in order to develop better estimates of opioid-involved deaths, and more importantly enhanced surveillance systems and overdose prevention programs to avoid undercounting individuals at risk of experiencing an opioid-involved death.

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