Published in final edited form as:

Hepatology. 2021 July ; 74(1): 28–40. doi:10.1002/hep.31645.

Factors Associated With Hepatitis A Mortality During Person-to-Person Outbreaks: A Matched Case–Control Study—United States, 2016-2019

Megan G. Hofmeister[1], **Jian Xing**[1], **Monique A. Foster**[1], **Ryan J. Augustine**[1], **Cole Burkholder**[2], **Jim Collins**[2], **Shannon McBee**[3], **Erica D. Thomasson**[3,4], **Douglas Thoroughman**[4,5], **Mark K. Weng**[1], **Philip R. Spradling**[1]

[1]Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, GA

[2]Division of Communicable Diseases, Michigan Department of Health and Human Services, Lansing, MI

[3]Bureau for Public Health, West Virginia Department of Health and Human Resources, Charleston, WV

[4]Career Epidemiology Field Officer Program, Division of State and Local Readiness, Centers for Disease Control and Prevention, Atlanta, GA

[5]Kentucky Department for Public Health, Frankfort, KY

Abstract

BACKGROUND AND AIMS: During 2016-2020, the United States experienced person-to-person hepatitis A outbreaks that are unprecedented in the vaccine era, during which case–fatality ratios reported by some jurisdictions exceeded those historically associated with hepatitis A.

APPROACH AND RESULTS: To identify factors associated with hepatitis A–related mortality, we performed a matched case–control study (matched on age [±5 years] and county of residence in a 1:4 ratio) using data collected from health department and hospital medical records of outbreak-associated patients in Kentucky, Michigan, and West Virginia. Controls were hepatitis A outbreak–associated patients who did not die. There were 110 cases (mean age 53.6 years) and 414 matched controls (mean age 51.9 years); most cases (68.2%) and controls (63.8%) were male. Significantly ($P < 0.05$) higher odds of mortality were associated with preexisting nonviral liver disease (adjusted odds ratio [aOR], 5.2), history of hepatitis B (aOR, 2.4), diabetes (aOR, 2.2), and cardiovascular disease (aOR, 2.2), as well as initial Model for End-Stage Liver Disease (MELD) score ≥ 30 (aOR, 10.0), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio >

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO: Megan G. Hofmeister, M.D., M.S., M.P.H., Division of Viral Hepatitis, Centers for Disease Control and Prevention, 1600 Clifton Road, US12-3, Atlanta, GA 30333, lxn7@cdc.gov.

Author Contributions: M.G.H. was responsible for conceptualization, investigation, methodology, project administration, writing–original draft, writing–review and editing; J.X. was responsible for formal analysis, writing–review and editing; M.A.F. was responsible for conceptualization, investigation, methodology, writing–review and editing; R.J.A., C.B., J.C., S.M., E.D.T., D.T., and M.K.W. were responsible for investigation, writing–review and editing; P.R.S. was responsible for conceptualization, investigation, methodology, supervision, writing–original draft, writing–review and editing.

Potential conflict of interest: Nothing to report.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31645/suppinfo.

2 (aOR, 10.3), and platelet count < 150,000/μL (aOR, 3.7) among hepatitis A outbreak–associated patients in the independent multivariable conditional logistic regression analyses (each model adjusted for sex).

CONCLUSIONS: Preexisting liver disease, diabetes, cardiovascular disease, and initial MELD score ≥ 30, AST/ALT ratio ≥ 1, and platelet count < 150,000/μL among hepatitis A patients were independently associated with higher odds of mortality. Providers should be vigilant for such features and have a low threshold to escalate care and consider consultation for liver transplantation. Our findings support the recommendation of the Advisory Committee on Immunization Practices to vaccinate persons with chronic liver disease, though future recommendations to include adults with diabetes and cardiovascular disease should be considered.

Hepatitis A virus (HAV) infection typically results in a mild, self-limited illness; however, serious complications do occur in rare instances and are more frequent among adults.[1,2] Historically, hepatitis A mortality in the United States was thought to be low overall (approximately 0.3%-0.6%) but higher in older age groups (approximately 1.8% among adults aged >50 years).[3] More recently, according to the National Notifiable Diseases Surveillance System, all-age mortality for hepatitis A in the United States ranged between 0.7% and 1.0% during 2013-2016 among those reported cases with complete information on death.[4] During that same time period, hepatitis A–related mortality in adults aged 45-64 years consistently exceeded the US overall hepatitis A–related mortality rate, with even higher rates recorded among adults aged >65 years.[5]

In prior studies, older age has been the characteristic most commonly associated with hepatitis A–related mortality.[6–10] In 2010, the highest mortality rates among decedents with hepatitis A in the United States were observed among persons aged ≥45 years old.[8] The mean age at death among decedents with HAV infection increased in the United States from 48.0 years in 1999 to 76.2 years in 2011.[9] Investigators have identified a variety of additional characteristics, including chronic liver disease, male sex, extended hospitalizations, homelessness, and elevated bilirubin levels associated with hepatitis A-related mortality in the literature.[6,7,9–13] Additional studies have developed prognostic models aimed at predicting the risk of transplant or death in patients with hepatitis A–related acute liver failure.[14,15] These studies have identified combinations of presenting features such as age, abnormal laboratory results (e.g., alanine aminotransferase [ALT], ammonia, bilirubin, creatinine, hemoglobin, international normalized ratio), intubation status, and administration of vasopressors as components of models that accurately predict outcomes in patients with acute liver failure caused by hepatitis A.[14,15]

Multiple US states are experiencing person-to-person hepatitis A outbreaks that are unprecedented in the vaccine era. The infections are spreading primarily through close contact among persons who use drugs, persons experiencing homelessness, and men who have sex with men (MSM).[16] Between July 1, 2016, and October 16, 2020, state health departments publicly reported >35,500 outbreak-associated patients, >21,700 hospitalizations, and >335 deaths.[17]

During these ongoing person-to-person hepatitis A outbreaks, several jurisdictions reported high numbers of hepatitis A–related deaths and case–fatality ratios higher than those

historically associated with hepatitis A surveillance and outbreak data in the United States. Given the high number of deaths reported in recent outbreaks, we sought to identify risk factors for hepatitis A–related mortality in the setting of person-to-person transmission outbreaks. The aims of this study were to identify patient characteristics that could guide clinical decision-making and to identify findings that could inform new hepatitis A vaccination recommendations or support existing ones. We conducted a matched case–control study in three states, selecting Kentucky, Michigan, and West Virginia to maximize the study's impact as these three states accounted for 56% of the person-to-person hepatitis A–related deaths that had been publicly reported nationwide at the end of the study period.

Methods

We performed a matched case–control study using data collected from state health department and hospital medical records for hepatitis A outbreak–associated patients with onset between July 1, 2016, and June 10, 2019. Individuals eligible for study participation were residents of Kentucky, Michigan, or West Virginia and had been designated by the respective state health department as a person-to-person outbreak-associated hepatitis A patient. We obtained deidentified hepatitis A outbreak records from the Kentucky Department for Public Health, the Michigan Department of Health and Human Services, and the West Virginia Bureau for Public Health, current as of June 11, 2019; August 16, 2019; and June 13, 2019, respectively. We defined study cases as hepatitis A outbreak–associated patients who died and whose deaths were determined to be associated with hepatitis A by the respective state health department. Study controls were hepatitis A outbreak–associated patients who had not died and were matched to cases on age (±5 years) and county of residence in a 4:1 ratio. If insufficient controls were available in a case's county of residence, we attempted to identify additional controls from randomly selected contiguous counties. If all potential controls in immediately contiguous counties were exhausted, we ended enrollment for that case even if fewer than four controls were identified. We reviewed all available hospital medical records and state health department outbreak records using a standardized data abstraction instrument. If discrepancies existed between the medical and health department records, investigators recorded the positive response.

We obtained demographic (age, sex, race, ethnicity, county and state of residence), risk factor (drug use [injection and noninjection], homelessness, unstable housing, transient living, MSM status, incarceration, international travel, epidemiological linkage), clinical (comorbid medical conditions, pregnancy status, signs or symptoms consistent with hepatitis A, laboratory results), and outcome (hospitalization, acute liver failure, liver transplant, death) data for study participants. Risk factors were assessed based on their presence or absence during a participant's exposure period (i.e., the 15-50 days prior to symptom onset). Epidemiological linkage was defined as being a close contact of a known hepatitis A outbreak–associated patient.

We assessed the following comorbid medical conditions: history of hepatitis B (laboratory evidence of prior exposure or current infection or hepatitis B diagnosed in the medical record), history of hepatitis C (laboratory evidence of prior exposure or current infection or hepatitis C diagnosed in the medical record), other preexisting liver disease (e.g.,

alcohol-associated liver disease, nonalcoholic fatty liver disease, cirrhosis), diabetes, immunosuppression (e.g., HIV/AIDS; hemodialysis; recipient of solid organ, bone marrow, or stem cell transplant; recipient of high-dose steroids, chemotherapy, or immunomodulators at the time of hepatitis A diagnosis; primary immunodeficiency condition), and cardiovascular disease (e.g., coronary artery disease, hypertension, congestive heart failure, valvular heart disease, dyslipidemia, arrhythmia, peripheral artery disease, stroke). For laboratory results, we abstracted the result most temporally proximal to the collection time of the specimen that produced the HAV immunoglobulin M (IgM)–positive result. The Model for End-Stage Liver Disease (MELD) score was calculated in accordance with current Organ Procurement and Transplantation Network guidance and was based on laboratory results closest in time to admission for the hepatitis A hospitalization.[18]

We categorized participants as having been hospitalized if they had evidence of an inpatient hospital admission, evidence of an admission order from an emergency department physician if a patient had left against medical advice, or evidence of >24 hours of observation. Participants who were evaluated in an outpatient clinic, who were discharged to home from the emergency department with a duration of stay ≤24 hours, or whose hospitalization status was unknown were not considered hospitalized. If a participant was hospitalized more than once for hepatitis A, we combined the days from each hospitalization and reported the total. We categorized participants as having acute liver failure if the diagnosis was documented in the medical record or there was evidence of concurrent coagulopathy and hepatic encephalopathy in a patient with previously stable liver function.

Abstracted data were entered into a REDCap database.[19,20] A second author independently reviewed and verified the accuracy of each participant record in the database. We calculated descriptive statistics among participants with available data and conducted multivariable conditional logistic regression analyses to determine factors associated with hepatitis A–related mortality in the setting of person-to-person transmission outbreaks. We adjusted the multivariable models by sex, except for the MSM and pregnancy variables. We included all liver-related comorbidities as well as comorbidities that were identified as significantly associated with hepatitis A–related mortality in the initial multivariable analyses, in additional conditional logistic regression analyses examining the association of diabetes and mortality (after controlling for sex, history of hepatitis B, history of hepatitis C, other preexisting liver disease, and cardiovascular disease), and the association of cardiovascular disease and mortality (after controlling for sex, history of hepatitis B, history of hepatitis C, other preexisting liver disease, and diabetes). All ORs presented are matched ORs. We conducted all analyses using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

As this study was determined not to be human subjects research by the Centers for Disease Control and Prevention and the Michigan Department of Health and Human Resources Institutional Review Board (IRB), it was exempt from IRB review.

Results

CHARACTERISTICS AND OUTCOMES

We identified 110 cases (59 from Kentucky, 30 from Michigan, and 21 from West Virginia) and 414 matched controls (223 from Kentucky, 109 from Michigan, and 82 from West Virginia) for our study sample. Cases had a mean age of 53.6 years, while controls had a mean age of 51.9 years. Most cases and controls were male (68.2% and 63.8%, respectively). Among those with available information, 52.2% versus 55.1% reported drug use; 11.2% versus 10.8% reported homelessness, unstable housing, or transient living; 7.5% versus 16.7% reported current or recent incarceration at the time of hepatitis A diagnosis; and 51.9% versus 50.4% had an epidemiological link to a known hepatitis A outbreak-associated patient (cases vs. controls, respectively) (Table 1).

Compared to controls, higher proportions of cases had medical comorbidities including history of hepatitis B, history of hepatitis C, other preexisting liver disease, diabetes, immunosuppression, and cardiovascular disease. Jaundice/icterus (85.2% vs. 76.7%), nausea (79.0% vs. 78.7%), and abdominal pain (70.9% vs. 70.9%) were the most frequently reported signs and symptoms (cases versus controls, respectively) (Table 1). Among those with available data on hospitalization status, 95.4% of cases were hospitalized for a mean of 13.1 days, while 61.2% of controls were hospitalized for a mean of 5.8 days. Among hospitalized patients, 39.8% of cases and 7.7% of controls had multiple hepatitis A–related hospitalizations (Table 1). Demographic, risk factor, clinical, and outcome characteristics of the study sample stratified by state are described in the accompanying Supporting Information.

FACTORS ASSOCIATED WITH MORTALITY

Clinical factors were identified as significantly associated ($P < 0.05$) with higher odds of mortality among hepatitis A outbreak–associated patients through multivariable conditional logistic regression (adjusted for sex). Preexisting conditions and symptoms of hepatitis A that were associated with higher odds of mortality included other preexisting liver disease (adjusted odds ratio [aOR], 5.2, 95% CI 2.0-13.9), history of hepatitis B (aOR, 2.4; 95% CI, 1.3-4.4), diabetes (aOR, 2.2; 95% CI, 1.2-3.8), cardiovascular disease (aOR, 2.2; 95% CI, 1.2-3.9), and fever (aOR, 1.6; 95% CI, 1.0-2.4). Initial laboratory indicators were also associated with higher odds of mortality: MELD score ≥ 30 (aOR, 10.0; 95% CI, 3.7-26.7, compared to MELD score 20-29), aspartate aminotransferase (AST)/ALT ratio ≥1 (aOR, 3.6; 95% CI, 2.2-6.1 for AST/ALT ratio 1-2 and aOR, 10.3; 95% CI, 4.7-22.3 for AST/ALT ratio >2, compared to AST/ALT ratio <1), platelet count <150,000/μL (aOR, 3.7; 95% CI, 2.1-6.5), HBsAg-positive (aOR, 3.2; 95% CI, 1.5-7.1), AST >3,000 IU/L (aOR, 2.6; 95% CI, 1.2-5.6, compared to AST ≤200 IU/L), total bilirubin >9 mg/dL (aOR, 2.1; 95% CI, 1.1-4.2, compared to <3 mg/dL), and anti-HCV-positive (aOR, 1.7; 95% CI, 1.0-2.8). Additionally, clinical outcomes were associated with higher odds of mortality: acute liver failure (aOR, 218.9; 95% CI, 27.8-1,721.2), intensive care unit admission (aOR, 45.3; 95% CI, 14.1-144.9), hospitalization (aOR, 17.1; 95% CI, 6.1-47.7), hospital length of stay >7 days (aOR, 4.7; 95% CI, 2.1-11.0 for 8-14 days and aOR, 16.4; 95% CI, 5.7-47.3 for ≥15 days, compared to 1-3 days), and two or three hepatitis A–related hospitalizations (aOR,

6.9; 95% CI, 3.2-14.8 and aOR, 11.8; 95% CI, 1.3-105.3, respectively, compared to one hepatitis A–related hospitalization). MELD score ≤19 (aOR, 0.1; 95% CI, 0.0-0.4, compared to MELD score 20-29) and African American/non-Hispanic race/ethnicity (aOR, 0.2; 95% CI, 0.0-0.8, compared to Caucasian/non-Hispanic) were significantly associated with lower odds of mortality (Table 1).

Diabetes (aOR, 5.3; 95% CI, 1.2-23.0) remained significantly associated ($P < 0.05$) with higher odds of mortality among hepatitis A outbreak–associated patients through multivariable conditional logistic regression even after adjusting for history of hepatitis B, history of hepatitis C, other preexisting liver disease, cardiovascular disease, and sex. Cardiovascular disease (aOR, 3.1; 95% CI, 0.9-11.2) was also associated with higher odds of hepatitis A–related mortality after adjusting for history of hepatitis B, history of hepatitis C, other preexisting liver disease, diabetes, and sex; however, the association was not statistically significant (Table 2).

Discussion

We performed a matched case–rontrol study of hepatitis A outbreak–associated patients from three states that experienced extensive person-to-person outbreaks and found significantly higher odds of mortality associated with certain comorbidities and initial laboratory indicators. We identified patient characteristics that could guide clinical decision-making, findings that support existing Advisory Committee on Immunization Practices (ACIP) hepatitis A vaccination recommendations, and findings that could inform new vaccination recommendations.

Abnormal laboratory results for tests commonly performed in the setting of hepatitis A were associated with mortality. We found that a serum AST/ALT ratio ≥1 was associated with higher odds of hepatitis A–related mortality, with the odds increasing with increasing AST/ALT ratio. In the setting of acute viral hepatitis infections, ALT is usually higher than AST, resulting in AST/ALT ratios <1.[21] However, AST/ALT ratios >1 can occasionally occur in the setting of hepatitis A infection and typically represent cases of acute liver failure with poor prognosis.[22] AST/ALT ratios >1 have also been associated with chronic viral hepatitis that has progressed to fibrosis and cirrhosis, while ratios >2 have been associated with alcohol-associated hepatitis.[22–24] In our study, compared to a total bilirubin <3 mg/dL, total bilirubin >9 mg/dL was associated with higher odds of mortality. Similarly, in a single-center study of patients with hepatitis A hospitalized in France during 1987-2000, a high bilirubin level was significantly related to the risk of death or transplantation.[13] Platelet counts <150,000/μL were also significantly associated with higher odds of hepatitis A–related mortality. Lower-than-normal platelet counts have been associated with cirrhosis and progression to hepatic decompensation among patients with chronic hepatitis C.[25] Additionally, bleeding complications and decreasing platelet counts after admission for acute liver failure of any etiology have been associated with systemic inflammation and poor prognosis.[26,27] Further research is needed to determine whether the observed hepatitis A–related mortality associations with AST/ALT ratio ≥1 and thrombocytopenia are indicative of preexisting liver disease or an acute manifestation of hepatitis A infection. We also found that MELD scores ≥30 were associated with higher odds of mortality, while MELD scores

≤19 were associated with 90% lower odds of mortality, compared with scores 20-29. This is consistent with research that prospectively validated the MELD score among patients awaiting liver transplantation with a variety of liver diseases.[28] MELD scores ≥30 have been associated with ≥50% estimated 3-month mortality.[28] Additionally, we analyzed the MELD score as a continuous variable and found that the odds of hepatitis A–related mortality significantly increased with increasing MELD score (aOR, 1.2; 95% CI, 1.2-1.3). While hepatitis A–related mortality was not specifically assessed, an analysis of San Diego, California, hepatitis A outbreak–associated cases hospitalized at a single medical center demonstrated that a higher MELD-sodium score independently predicted acute liver failure.[29]

We found that persons with diabetes or cardiovascular disease had 2.2 times higher odds of hepatitis A–related mortality. Neither of these comorbidities is currently recognized by the ACIP as an independent risk factor for adverse consequences of HAV infection.[30] However, a previous analysis of the 2013 US foodborne hepatitis A outbreak associated with frozen pomegranate arils found that the presence of comorbidities, such as diabetes and cardiovascular disease, was associated with hospitalization.[31] When we further examined the associations of diabetes and cardiovascular disease with hepatitis A–related mortality after controlling for other comorbidities, we found that the strength of the mortality associations between diabetes (aOR, 5.3; 95% CI, 1.2-23.0) and cardiovascular disease (aOR, 3.1; 95% CI, 0.9-11.2) increased. However, the association between cardiovascular disease and hepatitis A–related mortality was no longer statistically significant. We expect that the results for both diabetes and cardiovascular disease are conservative estimates of the actual associations with hepatitis A–related mortality. We compared fatal hepatitis A cases to nonfatal hepatitis A controls. Had we used an approach that included patients without hepatitis A as controls, the associations with hepatitis A–related mortality might have been even stronger. This further supports future consideration of diabetes and cardiovascular disease by the ACIP as indications for adult hepatitis A vaccination.

As might be expected, acute liver failure and several hospitalization-related indicators of disease severity were significantly associated with higher odds of hepatitis A–related mortality in this study. Acute liver failure had the strongest association with hepatitis A–related mortality of any variable examined in this study (aOR, 218.9; 95% CI, 27.8-1,721.2). Historically, acute liver failure due to HAV infection has been rare in the United States, occurring in <1% of cases.[2] However, acute liver failure occurred in 4.3% of a random sample of person-to-person hepatitis A outbreak–associated patients in Kentucky, Michigan, and West Virginia during 2016-2019.[32] Participants who were hospitalized had higher odds of dying than those who were not hospitalized. Among hospitalized participants, longer hospitalizations, multiple hospitalizations, and intensive care unit admission were associated with mortality. Although these factors were associated with hepatitis A–related mortality in our study, these associations are not useful to providers from a prognostic standpoint at patient presentation; hospitalization and escalation of care should not be avoided if clinically indicated.

Consistent with previous studies, chronic liver disease was associated with higher odds of hepatitis A–related mortality.[7,10,11] In this study, participants with a history of hepatitis

B, participants who were HBsAg-positive, participants who were anti-HCV-positive, and participants with other preexisting liver disease (e.g., alcohol-associated liver disease, nonalcoholic fatty liver disease, cirrhosis) had higher odds of hepatitis A–related mortality. Although the proportion of cases with a history of hepatitis C was higher than that for controls (aOR, 1.6; 95% CI, 1.0-2.6), the finding was not statistically significant. The significant association between alcohol-associated liver disease, nonalcoholic fatty liver disease, or cirrhosis and mortality is notable given the potential for those preexisting liver diseases to be underascertained. Detection of nonalcoholic fatty liver disease and cirrhosis was dependent on whether providers ordered ultrasound or computed tomographic imaging studies, whether medical records departments included imaging results while fulfilling records requests, and whether abstractors noticed imaging results consistent with these conditions.

We suspect that alcohol played a more significant role in hepatitis A–related mortality than we were able to discern through our study. Alcohol use was rarely documented in the medical records reviewed for this study; even in the rare instances when it was documented, insufficient details on quantity and frequency of alcohol consumption were present to accurately determine the presence of alcohol use disorder. The National Survey on Drug Use and Health is conducted annually by the US Substance Abuse and Mental Health Services Administration and provides national data on tobacco, alcohol, and drug use.[33] In 2018, during the most recent year for which data are available, approximately 32% of people (aged 12 and older) with illicit drug use disorder in the past year also had alcohol use disorder in the past year.[33] Given the high prevalence of drug use in our study, it is possible that a substantial proportion of participants could have had compromised liver function as a result of alcohol use disorder.

None of the risk factors for HAV infection (e.g., drug use, homelessness, unstable housing, transient living, MSM, incarceration, international travel, epidemiological linkage) that we examined were significantly associated with hepatitis A–related mortality. However, people experiencing homelessness had 3.9 times higher odds of hepatitis A–related mortality than those not experiencing homelessness in the 2016-2018 person-to-person hepatitis A outbreak in San Diego County, California.[12] This discrepancy may be attributable to the fact that the San Diego study used controls who were negative for HAV infection, while our study used nonfatal HAV-infected controls, 61% of whom were sufficiently ill to warrant hospitalization.

African American/non-Hispanic race/ethnicity, compared to Caucasian/non-Hispanic race/ethnicity, was associated with 80% lower odds of hepatitis A–related mortality in this study. In contrast, US Multiple Cause of Death data show that age-adjusted hepatitis A mortality rates have historically been higher among non-Hispanic black persons than non-Hispanic white persons (0.49 versus 0.35 per 1,000,000 population, respectively, during 1990-1995; 0.36 versus 0.24, per 1,000,000 population, respectively, during 2000-2004).[7] More recently, however, there has been increased parity in hepatitis A mortality rates in the Multiple Cause of Death database; in 2010, the age-adjusted mortality rate among non-Hispanic black persons was 0.04 per 100,000 population, while the rate among non-Hispanic white persons was 0.03 per 100,000 population.[8] In our matched case-control study, there

were only three African American/non-Hispanic cases; all three were residents of Michigan. Thus, our findings in this regard may have limited relevance.

Although the matched case–control design used in our study precludes exploration of the effect of age on hepatitis A–related mortality, we explored the age distribution of study cases versus all those hepatitis A patients who did not die (i.e., potential controls). Consistent with the body of literature that guided our *a priori* decision to match study cases and controls on age, the mean and median ages for study cases were older than the mean and median ages for all potential controls in each participating state.[6–10] In Kentucky, study cases were on average 49.7 years old (median 47.0 years old), while all potential controls were on average 37.5 years old (median 36.0 years old). In Michigan, study cases were on average 61.2 years old (median 58.5 years old), while all potential controls were on average 42.1 years old (median 39.0 years old). And in West Virginia, study cases were on average 53.7 years old (median 56.0 years old), while all potential controls were on average 38.8 years old (median 37.0 years old).

Our study has other limitations. First, the states involved in this study did not use an identical hepatitis A–related death case definition, which might have resulted in differential classification of deaths as being hepatitis A–related or not. Upon medical record review —after the point in time at which case and control eligibility had been determined— coauthors identified six controls who died and whose deaths were hepatitis A–related. We proceeded with the analysis using an intention-to-treat approach, maintaining the originally assigned case and control status based on the information that had been available to the state health departments at the time the study assignments were made. We did, however, conduct a sensitivity analysis excluding the 6 controls who died; the only difference in the multivariable conditional logistic regression models was that anti-HCV positivity was no longer statistically significantly associated with hepatitis A–related mortality (data not shown). Second, behavioral risk data were primarily self-reported and subject to recall and social desirability bias. Third, a substantial proportion of data was missing for many of the variables in the study. The populations most impacted by the ongoing person-to-person outbreaks are often difficult to reach, creating challenges for public health to conduct case investigation interviews and resulting in relatively high rates of loss to follow-up. While rates of loss to follow-up have varied widely between states affected by the person-to-person outbreaks, the rates were similar among the state participants in this study.[34,35] Finally, the generalizability of the study might be limited as only three states were involved. However, in June 2019, at the end of the study period, Kentucky, Michigan, and West Virginia accounted for 40% of the person-to-person hepatitis A outbreak–associated patients that had been publicly reported nationwide.

Given the relatively high number of hepatitis A–related deaths reported by Kentucky, Michigan, and West Virginia during their respective person-to-person hepatitis A outbreaks, we sought to characterize factors associated with hepatitis A–related mortality. We found that nonviral preexisting liver disease, history of hepatitis B, diabetes, cardiovascular disease, MELD score ≥ 30, AST/ALT ratio ≥ 1, and platelet count < 150,000/μL were independently significantly associated with higher odds of mortality. Patients with hepatitis A who have these comorbidities and laboratory abnormalities should prompt providers to

have a low threshold to escalate care and consider consultation with transplant specialists. Our findings support the current ACIP recommendation to vaccinate all persons with chronic liver disease and highlight missed opportunities for prevention given that at least 75% of cases who died had some form of preexisting liver disease. In 2017, self-reported adult hepatitis A vaccination coverage among persons with chronic liver conditions with two or more doses was only 20.8%.[36] It is incumbent on health care providers of persons with chronic liver disease to improve hepatitis A vaccination coverage rates in accordance with the ACIP recommendations. The findings from our study suggest that adults with diabetes and cardiovascular disease could be considered for inclusion in future ACIP hepatitis A vaccination recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

The authors extend their gratitude to Yuna Zhong for assistance with additional analysis (Division of Viral Hepatitis, Centers for Disease Control and Prevention); the Kentucky Department for Public Health (KDPH), Division of Epidemiology and Health Planning, Reportable Disease Section; Diana Carrier (KDPH); the Michigan Department of Health and Human Services, Surveillance and Infectious Disease Epidemiology Section; Terrie Lee (Infection Prevention & Employee Health, Charleston Area Medical Center); the West Virginia Bureau for Public Health Hepatitis A Outbreak Response Team; and local health department and hospital medical record department staff in Kentucky, Michigan, and West Virginia.

Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations:

ACIP	Advisory Committee on Immunization Practices
ALT	alanine aminotransferase
aOR	adjusted odds ratio
AST	aspartate aminotransferase
HAV	hepatitis A virus
MELD	Model for End-Stage Liver Disease
MSM	men who have sex with men

REFERENCES

1). Lednar WM, Lemon SM, Kirkpatrick JW, Redfield RR, Fields ML, Kelley PW. Frequency of illness associated with epidemic hepatitis A virus infections in adults. Am J Epidemiol 1985;122:226–233. [PubMed: 3860002]

2). Kemmer NM, Miskovsky EP. Hepatitis A. Infect Dis Clin North Am 2000;14:605–615. [PubMed: 10987112]

3). Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55:1–23.

4). Centers for Disease Control and Prevention. Viral hepatitis surveillance—United States. https://www.cdc.gov/hepatitis/statistics/SurveillanceRpts.htm. Published April 2018. Accessed April 3, 2020.

5). Centers for Disease Control and Prevention. Viral hepatitis surveillance, United States, 2017. https://www.cdc.gov/hepatitis/statistics/2017surveillance/pdfs/2017HepSurveillanceRpt.pdf. Published November 2019. Accessed April 3, 2020.

6). Wise ME, Sorvillo F. Hepatitis A-related mortality in California, 1989-2000: analysis of multiple cause-coded death data. Am J Public Health 2005;95:900–905. [PubMed: 15855472]

7). Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis 2008;197:1282–1288. [PubMed: 18422440]

8). Ly KN, Xing J, Klevens RM, Jiles RB, Holmberg SD. Causes of death and characteristics of decedents with viral hepatitis, United States, 2010. Clin Infect Dis 2014;58:40–49. [PubMed: 24065331]

9). Ly KN, Klevens RM. Trends in disease and complications of hepatitis A virus infection in the United States, 1999-2011: a new concern for adults. J Infect Dis 2015;212:176–182. [PubMed: 25637352]

10). Chen CM, Chen SC, Yang HY, Yang ST, Wang CM. Hospitalization and mortality due to hepatitis A in Taiwan: a 15-year nationwide cohort study. J Viral Hepat 2016;23:940–945. [PubMed: 27386835]

11). Keeffe EB. Hepatitis A and B superimposed on chronic liver disease: vaccine-preventable diseases. Trans Am Clin Climatol Assoc 2006;117:227–237. [PubMed: 18528476]

12). Peak CM, Stous SS, Healy JM, Hofmeister MG, Lin Y, Ramachandran S, et al. Homelessness and hepatitis A—San Diego County, 2016-2018. Clin Infect Dis 2020;71:14–21. [PubMed: 31412358]

13). Rezende G, Roque-Afonso AM, Samuel D, Gigou M, Nicand E, Ferre V, et al. Viral and clinical factors associated with the fulminant course of hepatitis A infection. HEPATOLOGY 2003;38:613–618. [PubMed: 12939587]

14). Taylor RM, Davern T, Munoz S, Han SH, McGuire B, Larson AM, et al. Fulminant hepatitis A virus infection in the United States: incidence, prognosis, and outcomes. HEPATOLOGY 2006;44:1589–1597. [PubMed: 17133489]

15). Kim JD, Cho EJ, Ahn C, Park SK, Choi JY, Lee HC, et al. A model to predict 1-month risk of transplant or death in hepatitis A-related acute liver failure. HEPATOLOGY 2019;70:621–629. [PubMed: 30194739]

16). Foster MA, Hofmeister MG, Kupronis BA, Lin Y, Xia GL, Yin S, et al. Increase in hepatitis A virus infections—United States, 2013-2018. MMWR Morb Mortal Wkly Rep 2019;68:413–415.

17). Centers for Disease Control and Prevention. Widespread person-to-person outbreaks of hepatitis A across the United States. https://www.cdc.gov/hepatitis/outbreak/2017March-HepatitisA.htm. Published September 2020. Accessed October 19, 2020.

18). Organ Procurement and Transplantation Network. OPTN/UNOS policy notice. Clerical changes for implementation of adding serum sodium to the MELD score. https://optn.transplant.hrsa.gov/media/1575/policynotice_20151101.pdf. Published November 2015. Accessed April 3, 2020.

19). Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–381. [PubMed: 18929686]

20). Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208. [PubMed: 31078660]

21). De Ritis F, Coltorti M, Giusti G. An enzymic test for the diagnosis of viral hepatitis; the transaminase serum activities. Clin Chim Acta 1957;2:70–74. [PubMed: 13447217]

22). Botros M, Sikaris KA. The De Ritis ratio: the test of time. Clin Biochem Rev 2013;34:117–130. [PubMed: 24353357]

23). Cohen JA, Kaplan MM. The SGOT/SGPT ratio—an indicator of alcoholic liver disease. Dig Dis Sci 1979;24:835–838. [PubMed: 520102]

24). Alves PS, Camilo EA, Correia JP. The SGOT/SGPT ratio in alcoholic liver disease. Acta Med Port 1981;3:255–260. [PubMed: 7331882]

25). Xu F, Moorman AC, Tong X, Gordon SC, Rupp LB, Lu M, et al. All-cause mortality and progression risks to hepatic decompensation and hepatocellular carcinoma in patients infected with hepatitis C virus. Clin Infect Dis 2016;62:289–297. [PubMed: 26417034]

26). Stravitz RT, Ellerbe C, Durkalski V, Reuben A, Lisman T, Lee WM. Thrombocytopenia is associated with multi-organ system failure in patients with acute liver failure. Clin Gastroenterol Hepatol 2016;14:613–620. [PubMed: 26453953]

27). Stravitz RT, Ellerbe C, Durkalski V, Schilsky M, Fontana RJ, Peterseim C, et al. Bleeding complications in acute liver failure. HEPATOLOGY 2018;67:1931–1942. [PubMed: 29194678]

28). Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for End-Stage Liver Disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91–96. [PubMed: 12512033]

29). Jiang AA, Greenwald HS, Sheikh L, Wooten DA, Malhotra A, Schooley RT, et al. Predictors of acute liver failure in patients with acute hepatitis A: an analysis of the 2016-2018 San Diego County hepatitis A outbreak. Open Forum Infect Dis 2019;6:ofz467. [PubMed: 31777757]

30). Nelson NP, Weng MK, Hofmeister MG, Moore KL, Doshani M, Kamili S, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69:1–38.

31). Epson EE, Cronquist A, Lamba K, Kimura AC, Hassan R, Selvage D, et al. Risk factors for hospitalisation and associated costs among patients with hepatitis A associated with imported pomegranate arils, United States, 2013. Public Health 2016;136:144–151. [PubMed: 27156991]

32). Hofmeister MG, Xing J, Foster MA, Augustine RJ, Burkholder C, Collins J, et al. Hepatitis A person-to-person outbreaks: epidemiology, morbidity burden, and factors associated with hospitalization—multiple states, 2016–2019. J Infect Dis 2021;223:426–434. [PubMed: 33097935]

33). Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health. HHS Publication no. PEP19-5068, NSDUH Series H-54. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2019. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf. Published August 2019. Accessed April 24, 2020.

34). Michigan Department of Health and Human Services. Michigan hepatitis A outbreak. https://www.michigan.gov/mdhhs/0,5885,7-339-71550_2955_2976_82305_82310-447907--,00.html. Published 2020. Accessed April 4, 2020.

35). Kentucky Department for Public Health. Hepatitis A outbreak. https://chfs.ky.gov/agencies/dph/dehp/idb/Pages/hepAoutbreak.aspx. Published 2020. Accessed April 4, 2020.

36). Centers for Disease Control and Prevention. Vaccination coverage among adults in the United States. National Health Interview Survey, 2017: hepatitis A vaccination. https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/NHIS-2017.html#box2. Published 2019. Accessed February 22, 2020.

TABLE 1.

Multivariable Associations With Mortality During Person-to-Person Hepatitis A Outbreaks—Kentucky, Michigan, and West Virginia, 2016-2019

Characteristic	Cases, n (%) (n = 110)*	Controls, n (%) (n = 414)*	aOR (95% CI)†	*P*
Demographic				
Age, year				
Mean (SE)	53.6 (1.4)	51.9 (0.7)	—	—
Median (range)	55.0 (24.0-87.0)	53.0 (21.0-90.0)	—	—
Age categories				
20-29	6 (5.5)	21 (5.1)	—	—
30-39	11 (10.0)	51 (12.3)	—	—
40-49	28 (25.5)	104 (25.1)	—	—
50-69	47 (42.7)	189 (45.7)	—	—
≥70	18 (16.4)	49 (11.8)	—	—
Sex				
Male	75 (68.2)	264 (63.8)	1.2 (0.6-2.1)	0.660
Female	35 (31.8)	150 (36.2)	REF	—
Race/ethnicity (n = 318)				
Caucasian/NH	85 (96.6)	195 (84.8)	REF	—
African American/NH	3 (3.4)	33 (14.3)	**0.2 (0.0-0.8)**	**0.022**
Other‡	0 (0.0)	2 (0.9)	N/A	N/A
Risk factor§				
Drug use (n = 431)				
Yes	47 (52.2)	188 (55.1)	1.0 (0.6-1.8)	0.990
No	43 (47.8)	153 (44.9)	REF	—
Injection drug use (n = 389)‖				
Yes	31 (39.2)	122 (39.4)	1.1 (0.5-2.4)	0.770
No	48 (60.8)	188 (60.6)	REF	—
Noninjection drug use (n = 333)‖				
Yes	23 (33.8)	109 (41.1)	0.7 (0.3-1.4)	0.290
No	45 (66.2)	156 (58.9)	REF	—
Homelessness, unstable housing, or transient living (n = 451)				

Hepatology. Author manuscript; available in PMC 2024 April 15.

Characteristic	Cases, n (%) (n = 110)*	Controls, n (%) (n = 414)*	aOR (95% CI)†	P
Yes	11 (11.2)	38 (10.8)	1.1 (0.5-2.3)	0.830
No	87 (88.8)	315 (89.2)	REF	—
MSM (n = 134)¶				
Yes	3 (15.8)	14 (12.2)	1.3 (0.3-5.2)	0.750
No	16 (84.2)	101 (87.8)	REF	—
Incarcerated (n = 244)				
Yes	3 (7.5)	34 (16.7)	1.7 (0.3-11.3)	0.570
No	37 (92.5)	170 (83.3)	REF	—
International travel (n = 352)				
Yes	0 (0.0)	0 (0.0)	N/A	N/A
No	69 (100.0)	283 (100.0)	REF	—
Epidemiologically linked (n = 158)				
Yes	14 (51.9)	66 (50.4)	2.0 (0.5-8.9)	0.350
No	13 (48.1)	65 (49.6)	REF	—
Clinical				
History of hepatitis B (n = 434)				
Yes	22 (21.8)	36 (10.8)	**2.4 (1.3-4.4)**	**0.006**
No	79 (78.2)	297 (89.2)	REF	—
History of hepatitis C (n = 469)				
Yes	49 (46.2)	142 (39.1)	1.6 (1.0-2.6)	0.077
No	57 (53.8)	221 (60.9)	REF	—
Other preexisting liver disease (n = 186)				
Yes	60 (81.1)	55 (49.1)	**5.2 (2.0-13.9)**	**<0.001**
No	14 (18.9)	57 (50.9)	REF	—
Diabetes (n = 358)				
Yes	41 (42.7)	60 (22.9)	**2.2 (1.2-3.8)**	**0.007**
No	55 (57.3)	202 (77.1)	REF	—
Pregnancy (n = 119)#				
Yes	0 (0.0)	3 (3.3)	N/A	N/A
No	27 (100.0)	89 (96.7)	REF	—
Immunosuppression (n = 289)				

Characteristic	Cases, n (%) (n = 110)*	Controls, n (%) (n = 414)*	aOR (95% CI)†	P
Yes	7 (8.1)	12 (5.9)	1.1 (0.4-3.1)	0.880
No	79 (91.9)	191 (94.1)	REF	—
Cardiovascular disease (n = 332)				
Yes	66 (69.5)	125 (52.7)	**2.2 (1.2-3.9)**	**0.010**
No	29 (30.5)	112 (47.3)	REF	—
Signs or symptoms				
Fever (n = 490)				
Yes	50 (48.5)	141 (36.4)	**1.6 (1.0-2.4)**	**0.045**
No	53 (51.5)	246 (63.6)	REF	—
Headache (n = 400)				
Yes	16 (19.5)	48 (15.1)	1.7 (0.8-3.4)	0.168
No	66 (80.5)	270 (84.9)	REF	—
Malaise (n = 468)				
Yes	61 (64.2)	208 (55.8)	1.6 (0.9-2.8)	0.082
No	34 (35.8)	165 (44.2)	REF	—
Anorexia (n = 464)				
Yes	42 (44.7)	145 (39.2)	1.3 (0.8-2.3)	0.310
No	52 (55.3)	225 (60.8)	REF	—
Nausea (n = 503)				
Yes	79 (79.0)	317 (78.7)	1.0 (0.6-1.8)	0.890
No	21 (21.0)	86 (21.3)	REF	—
Vomiting (n = 482)				
Yes	53 (53.0)	176 (46.1)	1.5 (0.9-2.4)	0.093
No	47 (47.0)	206 (53.9)	REF	—
Diarrhea (n = 440)				
Yes	32 (34.8)	112 (32.2)	1.3 (0.8-2.2)	0.380
No	60 (65.2)	236 (67.8)	REF	—
Abdominal pain (n = 505)				
Yes	73 (70.9)	285 (70.9)	1.1 (0.7-1.9)	0.650
No	30 (29.1)	117 (29.1)	REF	—
Dark urine (n = 444)				

Characteristic	Cases, n (%) (n = 110)*	Controls, n (%) (n = 414)*	aOR (95% CI)†	P
Yes	42 (49.4)	196 (54.6)	0.9 (0.5-1.5)	0.640
No	43 (50.6)	163 (45.4)	REF	—
Acholic stool (n = 163)				
Yes	13 (41.9)	67 (50.8)	1.1 (0.4-3.1)	0.860
No	18 (58.1)	65 (49.2)	REF	—
Jaundice/icterus (n = 494)				
Yes	92 (85.2)	296 (76.7)	1.8 (1.0-3.2)	0.059
No	16 (14.8)	90 (23.3)	REF	—
Date of symptom onset (range)	9/1/2016–5/23/2019	8/17/2016–6/1/2019	N/A	N/A
Laboratory results				
ALT (IU/L) (n = 512)				
≤ 200	18 (16.7)	45 (11.1)	REF	—
201-1,500	39 (36.1)	161 (39.9)	0.7 (0.4-1.3)	0.198
1,501-3,000	23 (21.3)	122 (30.2)	**0.5 (0.2-1.0)**	**0.037**
> 3,000	28 (25.9)	76 (18.8)	0.9 (0.4-1.8)	0.710
AST (IU/L) (n = 510)				
≤ 200	14 (13.0)	70 (17.4)	REF	—
201-1,500	38 (35.2)	175 (43.5)	1.1 (0.6-2.2)	0.780
1,501-3,000	28 (25.9)	108 (26.9)	1.3 (0.6-2.6)	0.490
> 3,000	28 (25.9)	49 (12.2)	**2.6 (1.2-5.6)**	**0.013**
AST/ALT ratio (n = 510)				
< 1	42 (38.9)	297 (73.9)	REF	—
1-2	46 (42.6)	90 (22.4)	**3.6 (2.2-6.1)**	**<0.001**
> 2	20 (18.5)	15 (3.7)	**10.3 (4.7-22.3)**	**<0.001**
Total bilirubin (mg/dL) (n = 382)				
< 3	21 (20.4)	53 (19.0)	REF	—
3-6	15 (14.6)	85 (30.5)	**0.4 (0.2-0.9)**	**0.023**
6-9	12 (11.7)	67 (24.0)	0.4 (0.2-1.1)	0.066
> 9	55 (53.4)	74 (26.5)	**2.1 (1.1-4.2)**	**0.026**
Platelet count (K/μL) (n = 357)				
< 150	51 (50.5)	58 (22.7)	**3.7 (2.1-6.5)**	**<0.001**

Characteristic	Cases, n (%) (n = 110)*	Controls, n (%) (n = 414)*	aOR (95% CI)†	P
≥ 150	50 (49.5)	198 (77.3)	REF	—
MELD score (n = 324)				
≤ 19	11 (11.1)	118 (52.4)	**0.1 (0.0-0.4)**	**<0.001**
20-29	38 (38.4)	93 (41.3)	REF	—
≥ 30	50 (50.5)	14 (6.2)	**10.0 (3.7-26.7)**	**<0.001**
HBsAg (n = 437)				
Positive/reactive	16 (15.8)	19 (5.7)	**3.2 (1.5-7.1)**	**0.004**
Negative/nonreactive	85 (84.2)	317 (94.3)	REF	—
IgM anti-HBc (n = 428)				
Positive/reactive	8 (7.9)	21 (6.4)	1.4 (0.6-3.4)	0.470
Negative/nonreactive	90 (89.1)	304 (93.0)	REF	—
Indeterminate/borderline	3 (3.0)	2 (0.6)	4.3 (0.7-26.1)	0.119
Anti-HCV (n = 446)				
Positive/reactive	47 (45.6)	129 (37.6)	**1.7 (1.0-2.8)**	**0.045**
Negative/nonreactive	56 (54.4)	214 (62.4)	REF	—
HCV RNA viral load (n = 96)				
Undetectable	18 (46.2)	28 (49.1)	REF	—
Detected but not quantifiable	5 (12.8)	9 (15.8)	0.3 (0.0-11.9)	0.520
Detected and quantifiable	16 (41.0)	20 (35.1)	0.2 (0.0-2.9)	0.230
Outcome				
Hospitalized (n = 513)				
Yes	103 (95.4)	248 (61.2)	**17.1 (6.1-47.7)**	**<0.001**
No	5 (4.6)	157 (38.8)	REF	—
Length of hospitalization, days (n = 346)**				
1-3	15 (14.9)	85 (34.7)	REF	—
4-7	28 (27.7)	110 (44.9)	1.2 (0.6-2.6)	0.630
8-14	28 (27.7)	37 (15.1)	**4.7 (2.1-11.0)**	**<0.001**
≥ 15	30 (29.7)	13 (5.3)	**16.4 (5.7-47.3)**	**<0.001**
Intensive care unit (n = 332)**				
Yes	81 (83.5)	26 (11.1)	**45.3 (14.1-144.9)**	**<0.001**

Characteristic	Cases, n (%) (n = 110)*	Controls, n (%) (n = 414)*	aOR (95% CI)†	*P*
No	16 (16.5)	209 (88.9)	REF	—
Number of hepatitis A–related hospitalizations**				
1	62 (60.2)	229 (92.3)	REF	—
2	32 (31.1)	18 (7.3)	**6.9 (3.2-14.8)**	**<0.001**
3	6 (5.8)	1 (0.4)	**11.8 (1.3-105.3)**	**0.027**
> 3	3 (2.9)	0 (0.0)	N/A	N/A
Acute liver failure (n = 354)				
Yes	74 (80.4)	14 (5.3)	**218.9 (27.8-1721.2)**	**<0.001**
No	18 (19.6)	248 (94.7)	REF	—
Liver transplant (n = 355)				
Yes	1 (1.1)	0 (0.0)	N/A	N/A
No	90 (98.9)	264 (100.0)	REF	—

Statistically significant associations are highlighted in bold.

*Percentages are calculated based on participants with available information and may not sum to 100.0% due to rounding.

†Adjusted by sex, except for MSM and pregnancy. All ORs presented are matched ORs after matching for age (±5 years) and county of residence.

‡Other: Hispanic ethnicity.

§Risk factors were assessed based on their presence or absence during a participant's exposure period (i.e., the 15-50 days prior to symptom onset).

‖Restricted to those with available information on reported drug use (n = 431).

¶Restricted to male study participants (n = 339).

#Restricted to female study participants (n = 185).

**Restricted to hospitalized study participants (n = 351).

Abbreviations: ALT, alanine aminotransferase; anti-HCV, hepatitis C antibody; AST, aspartate aminotransferase; CI, confidence interval; HBsAg, hepatitis B surface antigen; IgM anti-HBc, immunoglobulin M hepatitis B core antibody; MELD, Model for End-Stage Liver Disease; MSM, men who have sex with men; NH, non-Hispanic; OR, odds ratio; REF, reference category; SE, standard error.

TABLE 2.

Multivariable Conditional Logistic Regression Analyses of Non-Liver-Related Comorbidities Associated With Mortality During Person-to-Person Hepatitis A Outbreaks—Kentucky, Michigan, and West Virginia, 2016-2019

Characteristic	aOR (95% CI)*	*P*
Diabetes†		
Yes	**5.3 (1.2-23.0)**	**0.027**
No	REF	
Cardiovascular disease‡		
Yes	3.1 (0.9-11.2)	0.078
No	REF	

Statistically significant associations are highlighted in bold.

*All ORs presented are matched ORs after matching for age (±5 years) and county of residence.

†Adjusted by sex, history of hepatitis B, history of hepatitis C, other preexisting liver disease, and cardiovascular disease.

‡Adjusted by sex, history of hepatitis B, history of hepatitis C, other preexisting liver disease, and diabetes.

Abbreviation: REF, reference category.