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Population-representative Incidence of Drug-induced Acute Liver Failure Based on an Analysis of an Integrated Healthcare System

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Abstract

Background and Aims—Medications are a major cause of acute liver failure (ALF) in the US, but no population-based studies have evaluated the incidence of ALF from drug-induced liver injury. We aimed to determine the incidence and outcomes of drug-induced ALF in an integrated healthcare system that approximates a population-based cohort.

Methods—We performed a retrospective cohort study using data from the Kaiser Permanente Northern California (KPNC) healthcare system between January 1, 2004 and December 31, 2010. We included all KPNC members 18 y old with 6 months of membership and hospitalization for potential ALF. The primary outcome was drug-induced ALF (defined as coagulopathy and hepatic encephalopathy without underlying chronic liver disease), determined by hepatologists who reviewed medical records of all KPNC members with inpatient diagnostic and laboratory criteria suggesting potential ALF.

Results—Among 5,484,224 KPNC members between 2004 and 2010, 669 had inpatient diagnostic and laboratory criteria indicating potential ALF. After medical record review, 62 (9.3%) were categorized as having definite or possible ALF, and 32 (51.6%) had a drug-induced etiology (27 definite, 5 possible). Acetaminophen was implicated in 18 events (56.3%), dietary/herbal supplements in 6 (18.8%), antimicrobials in 2 (6.3%), and miscellaneous medications in 6 (18.8%). One patient with acetaminophen-induced ALF died (5.6%; .06 events/1,000,000 person-years) compared to 3 patients with non-acetaminophen induced ALF (21.4%; .18/1,000,000 person-years). Overall, 6 patients (18.8%) underwent liver transplantation, and 22 patients (68.8%) were discharged without transplantation. The incidence rates of any definite drug-induced ALF and acetaminophen-induced ALF were 1.61 events/1,000,000 person-years (95% confidence interval, 1.06–2.35) events and 1.02 events/1,000,000 person-years (95% confidence interval, 0.59–1.63), respectively.

Conclusions—Drug-induced ALF is uncommon, but over-the-counter products and dietary/herbal supplements are its most common causes.

Keywords

drug-induced liver injury; acetaminophen; acute liver failure

Acute liver failure is defined by the rapid onset of coagulopathy and hepatic encephalopathy in patients without underlying liver disease. Among patients hospitalized with acute liver failure at tertiary care centers, the transplant-free survival rate is less than 50%.^{1–3} In the United States, nearly 60% of reported cases of acute liver failure are related to drug-induced

liver injury, with many “indeterminate” cases thought to have an underlying drug-induced etiology.^{1,3–5} However, these prior data have been derived only from tertiary care centers.

Despite widely publicized cases of drug-induced acute liver failure related to acetaminophen and other medications,^{4,6–10} there are no population-based studies specifically evaluating the incidence of acute liver failure arising from drug-induced liver injury.¹¹ Published data primarily consist of case reports and case series from liver transplant and/or tertiary care centers^{2,3,12–17} or adverse event reports to regulatory agencies.^{5,18–20} As a result, the most common culprit medications, incidence, characteristics, and outcomes of drug-induced acute liver failure in real-world settings are unknown.

The objective of this study was to conduct an assessment of the incidence and outcomes of drug-induced acute liver failure within a large, integrated healthcare system that approximates a population-based cohort (“population-representative” cohort).

METHODS

Study Design and Data Source

We conducted a retrospective cohort study within Kaiser Permanente Northern California (KPNC) between January 1, 2004 and December 31, 2010.²¹ KPNC is an integrated health care organization consisting of 21 medical centers and 160 outpatient medical offices that provide comprehensive inpatient and outpatient services to approximately 3.2 million Northern California residents. Its membership is racially/ethnically, geographically (urban, suburban, and semi-rural areas), and socioeconomically diverse and approximates the region’s underlying population compared with census data; thus, studies in this setting closely approximate population-based research.^{22,23} Data collected by KPNC include: demographic information; outpatient and hospital diagnoses; procedures; inpatient and outpatient laboratory results; emergency and referral services at non-Kaiser Permanente facilities; and dispensed medications, including dosage, instructions for use, and days’ supply. Prescription drug benefits are utilized by more than 90% of members, and prior analyses have established the accuracy of pharmacy data.²⁴ Mortality databases integrate death certificate data from the California Department of Health Services and Social Security Administration Death Master File. The study was approved by the KPNC and University of Pennsylvania Institutional Review Boards.

Study Patients

KPNC members aged 18 years or older with at least 6 months of membership were identified as having a hospitalization with potential acute liver failure if they had: 1) a hospital International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis suggestive of acute liver failure or drug-induced hepatitis (Supplementary Table 1)^{25–27}, and 2) an inpatient international normalized ratio (INR) ≥ 1.5 (off warfarin) and peak total bilirubin ≥ 5.0 mg/dL within 182 days before or after the index date (defined below). Prior data suggested that these ICD-9-CM diagnoses are typically recorded for patients with severe liver injury.^{25–27} The peak total bilirubin cutoff for identifying potential acute liver failure cases for further abstraction was based on the very

low likelihood of acute liver failure occurring in the absence of a peak bilirubin level 5.0mg/dL.^{5,28} The index date was defined as the date of hospital admission with potential acute liver failure.

Since by definition, patients with pre-existing liver disease or medication-related coagulopathy are not eligible to be classified as having acute liver failure, we excluded from further review patients with: 1) an ICD-9-CM diagnosis of a pre-existing liver disease (Supplementary Table 2) prior to the index date; 2) serologic or virologic evidence of hepatitis B, C, or D prior to the index date; 3) serologic evidence of acute hepatitis A or E in the 30 days before through 30 days after the index date; or 4) warfarin prescribed within 182 days before through 182 days after the index date.

Confirmation of Drug-Induced Acute Liver Failure Events

All KPNC members with potential acute liver failure had their hospital medical records abstracted by two trained data abstractors. For each patient, data collected from these medical records (reviewed for all data listed in Supplementary Table 3), in addition to the hospital discharge summary and gastroenterologist/hepatologist consultation notes, were independently reviewed by two transplant hepatologists (K.A.F. and D.G.), who classified acute liver failure as: 1) definite, 2) possible, or 3) no event. Disagreement resulted in review by a third hepatologist (K.R.R.) to adjudicate the event.

A *definite* diagnosis of acute liver failure, based on American Association for the Study of Liver Diseases criteria,²⁹ was defined as: 1) the absence of pre-existing liver disease, 2) coagulopathy (INR ≥ 1.5) in the absence of warfarin, and either 3a) hepatic encephalopathy (altered mentation due to liver dysfunction), or 3b) liver transplant with the stated indication of “acute liver failure/Status 1—the highest waitlist priority,” without mention of hepatic encephalopathy in the available medical record (since United Network for Organ Sharing transplant policy requires hepatic encephalopathy as part of the classification of Status 1 criteria for acute liver failure)³⁰. A *possible* diagnosis was confirmed if a patient met criteria 1 and 2 (above) and had either: 1) altered mentation in the absence of a recorded diagnosis of hepatic encephalopathy but with encephalopathy treatment (e.g., lactulose, rifaximin) and no other explanatory central nervous system abnormality (e.g., acute intracranial ischemia), or 2) liver transplant during the index admission due to an acute etiology without specification of “acute liver failure/Status 1.” Patients with documented chronic alcohol abuse based on medical record review and who had laboratory (e.g., thrombocytopenia), radiographic, and/or clinical evidence of chronic liver disease or portal hypertension were not classified as having acute liver failure. The final diagnosis of acute liver failure did not require a peak total bilirubin ≥ 5.0 mg/dL at the time of encephalopathy and coagulopathy.

Etiology of acute liver failure

The etiology of each acute liver failure event was ascertained by medical record review, and required the exclusion of other causes of acute liver failure, along with supporting clinical and laboratory information. Determination of the cause of acute liver failure and any implicated drugs or dietary/herbal supplements was based on consensus opinion among trained hepatologists with expertise in adjudicating drug-induced liver injury. There is no

accepted international gold-standard for determining causality and classifying patients as having drug-induced liver injury. Although consensus opinion is widely used in the US for research purposes, it is not practical from a clinical perspective. Further, investigators from Europe and pharmaceutical companies are supportive of the RUCAM.³¹ We relied on consensus opinion in order for a patient to be classified as drug or supplement-induced acute liver failure, and required documentation of a potential etiologic drug or medication, in addition to exclusion of other potential etiologies based on laboratory or medical record review, including: 1) autoimmune hepatitis, based on consistent serologies and/or histology;^{32–34} 2) ischemic acute liver failure, based on acute elevations in liver aminotransferases in the context of a documented hypoperfusion event (e.g., septic, hypovolemic, or cardiogenic shock); 3) acute viral hepatitis confirmed by serologic or virologic tests (including hepatitis E virus and herpes simplex virus, when tested); 4) acute alcoholic hepatitis based on liver enzyme elevation pattern and clinical history given the presence of underlying fibrosis/chronic liver disease in such patients; and 5) vascular/structural abnormalities (i.e. Budd-Chiari syndrome) based on available imaging reports. Acetaminophen was designated as the causative agent if there was documented excess ingestion of acetaminophen or acetaminophen-containing products and/or an elevated serum acetaminophen level (when available). A similar methodology for determination of a drug-induced etiology for acute liver injury has been employed by the U.S. Drug-Induced Liver Injury Network.^{35,36} Cases were deemed indeterminate in the absence of any potential causative drug, medication, or any other identifiable etiology.

Although the Roussel Uclaf Causality Assessment Method (RUCAM) is an instrument that was developed to quantify the strength of the association between liver injury and an implicated medication,^{37,38} it was not used in this study because it: 1) has not been validated outside of clinical trials settings, 2) is unable to ascertain causality when two or more drugs may be implicated, and 3) is primarily applicable for idiosyncratic (non-acetaminophen-based) liver injury and cannot be used to identify dietary/herbal supplement-induced liver injury.³⁹

The time from onset of jaundice (defined as the first date of a serum total bilirubin ≥ 2.0 mg/dL²) to date of first clinical manifestation of hepatic encephalopathy was determined for each patient with drug-induced acute liver failure.

Data Analysis

Incidence rates of drug- and acetaminophen-induced acute liver failure were determined by dividing the number of KPNC members with confirmed events by the total person-years of follow-up. Person-years within the underlying KPNC population were estimated using the mid-year population for each year during the study period.⁴⁰ Characteristics between patients with acetaminophen and non-acetaminophen-induced acute liver failure were compared using the Wilcoxon rank-sum test. Data were analyzed using Stata 13 (Stata Corporation, College Station, TX).

RESULTS

Between January 1, 2004 and December 31, 2010, there were 5,484,224 unique members enrolled in KPNC, of whom 4,281,530 were aged 18 years or older. This corresponded to an average mid-year population over the age of 18 years of approximately 2.4 million (range: 2.35–2.45 million) members who contributed an estimated 16,731,307 person-years. Of these, 669 members had a hospitalization with potential acute liver failure, lacked pre-existing liver disease based on recorded diagnoses or viral hepatitis serologic/virologic laboratory tests, and were not dispensed warfarin (Figure 1). Among these 669 members, 62 (9.3%) were confirmed to have acute liver failure (45 definite, 17 possible) by medical record review. There was 93% agreement in acute liver failure case arbitration between the two adjudicators, with a third hepatologist required to break disagreements in 7% of cases. Among the 607 classified as not having acute liver failure, 228 (37.6%) were excluded due to pre-existing liver/biliary disease that was not detected by prior clinical, serologic, or virologic diagnosis (186 due to pre-existing alcoholic liver disease, 14 due to pre-existing autoimmune hepatitis, and 28 due to pre-existing cirrhosis), and 379 (62.4%) had severe liver injury but no evidence of hepatic encephalopathy.

Of the 62 patients with confirmed acute liver failure, 32 (51.6%) had a drug-induced etiology, with 27 (84.4%) meeting criteria for definite acute liver failure (all with documented hepatic encephalopathy). Acetaminophen was implicated in 18 (56.3%) events (17 definite), dietary/herbal supplements in 6 (18.8%; four classified as definite), antimicrobials in two (6.3%), and other medical products in 6 (18.8%; Table 1). Among the 18 patients with acetaminophen-induced acute liver failure, 1 (5.6%; .06 events/1,000,000 person-years) died, compared with 3/14 (21.4%; .18/1,000,000 person-years) who died after developing non-acetaminophen induced acute liver failure.

Of the 32 patients with confirmed drug-induced liver failure, 12 (37.5%) were transferred to a liver transplant center. When stratified by etiology of drug-induced acute liver failure (acetaminophen versus non-acetaminophen), the peak total bilirubin did not differ by transfer status in either group. However, the peak INR was significantly higher ($P=.01$) in acetaminophen-induced acute liver failure patients who were transferred (median: 4.9, IQR: 3.9–5.7 versus 3.1, IQR: 2.1–3.8), but not among those with non-acetaminophen induced acute liver failure. Six (50.0%) of the 12 transfers were transplanted, and 6 (50.0%) were discharged alive without requiring a transplant. Of the remaining 20 patients who were not transferred, 4 (20.0%) died in the hospital (3 of the 4 deaths categorized as “definite” acute liver failure), while 16 (80.0%) were discharged alive without a transplant. Transplantation-free survival was more common among patients with drug-induced acute liver failure from acetaminophen (88.9%) than from other agents (42.9%; $P=.005$; Tables 1 and 2).

In the 18 cases of acetaminophen-induced acute liver failure, four (22.2%) had an intentional acetaminophen overdose alone, 3 (16.7%) had unintentional overdoses in the setting of preceding alcohol abuse, 1 (5.6%) had an intentional overdose with preceding alcohol abuse, and the remaining 10 (55.6%) had an unintentional overdose without any evidence of alcohol abuse (2 of whom died).

The incidence rate of any drug-induced acute liver failure (definite or possible) was 1.91 (95% CI: 1.31–2.70) events per 1,000,000 person-years and the incidence rate of acetaminophen-induced acute liver failure (definite or possible) was 1.07 (95% CI: 0.64–1.70) events per 1,000,000 person-years. Among only those with definite acute liver failure, the incidence rates of any drug-induced acute liver failure and acetaminophen-induced acute liver failure were 1.61 (95% CI: 1.06–2.35) and 1.02 (95% CI: 0.59–1.63) events per 1,000,000 person-years, respectively.

Patients with acute liver failure due to acetaminophen were younger (median: 39 versus 63 years; $P=.008$), had higher peak levels of alanine aminotransferase (median: 4,588 versus 707 U/L; $p<0.001$) and aspartate aminotransferase (median: 6,839 versus 1,044 U/L; $p<0.001$), had lower peak levels of total bilirubin (7.4 versus 20.6 mg/dL; $P=.01$; Table 2), and had shorter median times from jaundice to encephalopathy (median: 2 versus 8 days; $P<.001$). The time from onset of jaundice to hepatic encephalopathy was longest in patients with drug-induced acute liver failure resulting from dietary/herbal supplements or antimicrobials (Table 2). Twenty-two (68.8%) patients with drug-induced acute liver failure had time from jaundice to hepatic encephalopathy within 7 days (“hyperacute” acute liver failure²).

In the 30 cases of non-drug-induced acute liver failure, the etiologies were: ischemia due to hypoperfusion (15/30); indeterminate etiology without any potential culprit drugs (6/30); malignancy (4/30); autoimmune hepatitis (2/30); and acute fatty liver of pregnancy, acute hepatitis B, and Wilson’s disease (1/30 for each).

CONCLUSIONS

Nearly 50% of Americans take one or more prescription medications every month,⁴¹ 15% consume over-the-counter analgesics daily,⁴² and almost 20% use dietary or herbal supplements regularly.⁴³ Untoward effects of medication and supplement use are an important public health concern, particularly as the population ages and medication usage increases. In this study, we report an incidence of definite drug-induced acute liver failure of 1.61 per million person-years in an integrated healthcare system that approximates a population-based cohort, with the overwhelming majority related to over-the-counter medications or products. These data provide a better understanding of the true population-representative incidence of drug-induced acute liver failure, the most severe form of drug-induced hepatotoxicity, and its associated morbidity and mortality in an integrated health care organization.

An important observation was the role of over-the-counter medications and supplements. Dietary/herbal supplements were implicated in 18.8% of drug-induced acute liver failure cases. Combined with acetaminophen, 75% of drug-induced acute liver failure cases in this study were attributed to over-the-counter products, with over one-half of the acetaminophen overdoses being unintentional. Such results stand in stark contrast to data from countries where acetaminophen is infrequently combined with other painkillers, and is not a cause of acute liver failure (e.g., no cases of acetaminophen-induced acute liver failure reported in a six and a half-year period in Argentina⁴⁴). Stricter regulation of co-formulation of

acetaminophen with other painkillers or limiting the number of acetaminophen tablets available for over-the-counter purchase might help to decrease the number of acetaminophen-related acute liver failure cases. Additionally, while acetaminophen has proven health benefits, most dietary/herbal supplements do not have demonstrated efficacy for the treatment or prevention of particular diseases, and these products currently do not undergo pre-marketing safety assessments by the Food and Drug Administration.⁴⁵ These data suggest that standard prescription medications are a rare source of acute liver failure; although there is an ongoing need for continued vigilant reporting and prospective studies of hepatotoxicity and acute liver failure among users of these products, consideration should also be given to additional pre-marketing regulatory oversight of dietary supplements and herbal products, as well as additional post-marketing efforts to identify drug-, herbal-, and dietary supplement-induced liver injury. Furthermore, given that over one-half of cases of acetaminophen-induced acute liver failure were from unintentional overdoses, consideration should be given to laws that limit the size of packs of acetaminophen, and/or require acetaminophen packages to use blister packs. Such legislation enacted in the United Kingdom in 1988 resulted in a significant reduction in cases of acute liver failure from acetaminophen.⁴⁶

Although prescription drugs were a rare cause of drug-induced acute liver failure in this cohort, the medications that were implicated were consistent with previously published reports. Isoniazid and amoxicillin/clavulanate have been implicated as two of the most common antimicrobial agents that lead to drug-induced liver injury and acute liver failure.^{47–51} Similarly, chemotherapeutic and immunosuppressant agents^{52–54}, as well as antiretroviral drugs^{55–57}, have also been reported as causes of severe drug-induced liver injury and acute liver failure. In clinical practice, the risks and benefits of prescribing such medications should be made on a case-by-case basis and in the context of the exceedingly rare risk of drug-induced acute liver failure.

These data allow for a better understanding of the incidence, etiology, and outcomes of acute liver failure in a community-based population. Approximately 25% of Northern California residents have KPNC health insurance, thus these data capture a large proportion of the adult population in Northern California. Based on data derived from the California Health Interview Study, the KPNC membership is similar to the broader Northern California population with regards to socio-demographic and health characteristics.²⁴

The transplant-free survival of the patients with acetaminophen- versus non-acetaminophen-induced acute liver failure was not significantly different. However, when put in the context of previously reported data, the transplant-free survival in the non-acetaminophen group was similar to that previously reported by the US Acute Liver Failure Study Group, the transplant-free survival of nearly 90% in acetaminophen-induced acute liver failure was substantially higher in the current study.^{3,9} While a potential explanation is the nature of these data, such that nearly two-thirds of our subjects with drug-induced acute liver failure never received care at a tertiary care center despite being critically ill, this alone cannot account for the higher survival given that patients with acetaminophen-induced acute liver failure who were not transferred to a tertiary care center had INR and total bilirubin values comparable to those previously reported by the US Acute Liver Failure Study Group.^{1,3} Yet

the current patients had substantially higher transplant-free survival than those previously reported.^{1,3,9,58} While the degree of encephalopathy in non-transferred patients may have been less severe than those that were transferred, which cannot be evaluated retrospectively, all of these patients nevertheless met criteria for possible or definite acute liver failure. Although it cannot be directly proven in the context of this study, one hypothesis for the higher transplant-free survival rate in these patients may, in part, be related to being cared for in a coordinated health care network that links patients, doctors, and hospitals together to optimize patient care. Nevertheless, the risk of mortality from APAP-related ALF and non-APAP related ALF was small, at less than 1 event per 1,000,000 person-years, respectively.

The higher transplant-free survival may be attributable to other factors, including: 1) improved management of acute liver failure and critically ill patients over time; 2) earlier recognition and intervention of acetaminophen overdose with available therapy (i.e., n-acetylcysteine); or 3) unmeasured confounders. Finally, the results confirm that, even in a community-based setting, the patterns of liver test abnormalities and bilirubin elevations in the acetaminophen- and non-acetaminophen-induced acute liver failure cases are consistent with prior reports.^{3,4,8,9,12,17,42,58,59}

Our study has several limitations. First, we used ICD-9-CM diagnoses to exclude patients with non-viral chronic liver disease, and there is the potential that some patients might have been misclassified as having underlying liver disease. Second, we restricted medical record review to patients with a peak total bilirubin ≥ 5.0 mg/dL, given the low likelihood of acute liver failure developing without a peak total bilirubin reaching this value. There is the potential that we might have missed a very small number of patients with acute liver failure who never obtained this total bilirubin level, in particular those with acetaminophen-induced acute liver failure.^{5,28} However, even if the total incidence of drug-induced acute liver failure was underestimated by as much as 25%, the incidence of drug-induced acute liver failure would only increase to 2.57 cases per 1,000,000 person-years. Third, the data were reviewed retrospectively, and certain laboratory tests listed in Supplementary Table 3 (e.g., hepatitis E serologies) were missing for some patients. Nevertheless, determination of the etiology of acute liver failure was based on independent adjudication by at least two hepatologists. Additionally, there were no events deemed to be drug-induced where a competing potential etiology was considered, yet not diagnosed, because of missing laboratory testing (e.g., a case where the diagnosis was deemed drug-induced, but the patient lacked test results for other diagnoses, such as quantitative immunoglobulins for autoimmune hepatitis). Fourth, alcohol history was based on retrospective review of the medical record, which may have led to misclassification of chronic alcohol use. However, this limitation may also potentially exist in prospectively collected data if patients do not report alcohol use, and any misclassification would likely lead to under-recognition of chronic alcohol use, and thus over-estimation of true drug-induced acute liver failure in the absence of chronic alcohol use. Fifth, the exact preparation, and purchase location of the dietary/herbal supplements that led to acute liver failure were not known.

Although this study was conducted in Northern California, we believe these results are generalizable to broader populations. Previous work within the KPNC integrated health care network, which includes greater than 1 of every 100 people in the United States, has

demonstrated that the KPNC population closely reflects the broader population in Northern California.^{22,23} The estimates of the number of acute liver failure events in this cohort are also consistent with data from two other distinct cohorts of patients, which further suggests the generalizability of these data. First, according to Organ Procurement and Transplantation Network data, approximately 50 adults are transplanted each year for drug-induced acute liver failure, with an additional 40 for unknown etiologies. Given that the 2.4 million KPNC members in this analysis represent approximately 1% of the US adult population, our observation of six transplants for drug-induced acute liver failure within seven years is consistent with the reported annual average number of transplants for drug-induced acute liver failure.⁶⁰ Second, our estimates of the proportion of acute liver failure cases due to drugs are consistent with results of the multi-center US Acute Liver Failure Study Group.^{3,5} Furthermore, recent data from the Drug-Induced Liver Injury Network also suggest that an increasing proportion of cases of drug-induced liver injury in the U.S. are arising from dietary/herbal supplements.¹⁷ These lines of evidence further support the accuracy of our methods for identifying acute liver failure events.

The specific drugs or supplements implicated as causing acute liver failure in this study differed from a previous report of liver transplant recipients with acute liver failure due to drug-induced liver injury published in 2004.⁶¹ This difference is likely due to the different time periods of the two studies (1990–2002 versus 2004–2010), with the first study including medications that are no longer available on the market (specifically halothane and troglitazone), as well as the spectrum of diseases in the two cohorts (transplant recipients versus patients with acute liver failure, regardless of transplant status).⁶¹

In conclusion, we found that the incidence of drug-induced acute liver failure was 1.61 per million person-years in adults in a population-representative cohort, and acetaminophen and dietary/herbal supplements were implicated in three-quarters of cases. These data highlight the rarity of this complication, and provide estimates of the true risk of acute liver failure resulting from medications, herbals, and/or dietary supplements. Furthermore, such events are rarely due to prescription medications. While continued vigilance for acute liver injury from prescription medications remains important, these data suggest that closer attention to the hepatotoxicity of over-the-counter medications, particularly dietary and herbal supplements, is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALF	Acute liver failure
KPNC	Kaiser Permanente Northern California
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
RUCAM	Roussel Uclaf Causality Assessment Method

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Figure 1. Flow diagram of study patients

KPNC=Kaiser Permanente Northern California; ALF=acute liver failure; INR=international normalized ratio; DNA=deoxyribonucleic acid; RNA=ribonucleic acid

*ICD-9 codes 573.3 or 573.8

†ICD-9 codes 570, 572.2, 572.4, 572.8, V42.7

‡Index date defined as the admission date of the hospitalization associated with the drug-induced hepatitis or ALF diagnosis code

§Patients may have had more than one exclusionary diagnosis recorded

Characteristics and outcomes of 32 members confirmed to have drug-induced acute liver failure in the Kaiser Permanente Northern California healthcare system (2004–2010).

Table 1

Age	Sex	Implicated Medication(s)	Outcome	Days from Jaundice to Hepatic Encephalopathy	Peak Laboratory Results				
					AST, (U/L)	ALT, (U/L)	ALP, (U/L)	Total bilirubin, (mg/dL)	INR
52	F	Acetaminophen	Alive	0	8,091	5,262	601	7.5	4.1
47	F	Amoxicillin/Clavulanate	Transplanted	4	1,356	523	1,287	40.2	1.9
25*	M	Acetaminophen	Alive	1	10,213	8,796	160	5.8	4.1
32	M	Acetaminophen	Alive	5	1,090	3,200	174	5.7	2.1
39	F	Isoniazid	Transplanted	21	797	850	243	7.1	4.5
31	F	Acetaminophen/ <i>Propoxyphene</i> , Erythromycin	Transplanted	1	6,340	2,480	347	25.5	2.8
72	F	Ibuprofen, Orlistat	Alive	3	5,533	3,778	181	17.0	2.1
70*	M	Cytarabine, Idarubicin	Alive	6	115	192	267	7.8	1.9
84*	M	Herbal (saw palmetto)	Alive	28	156	124	1,031	24.2	2.6
45	F	Imatinib	Alive	10	1,362	1,212	257	16.9	3.0
58	F	Leflunomide, Herbs (unspecified), Lovastatin, Pantoprazole, Tramadol	Transplanted	0	3,700	1,714	283	26.9	2.0
57	M	Acetaminophen	Alive	0	3,449	3,476	200	19.8	3.0
45	F	Chinese herbs	Transplanted	6	1,150	1,167	426	14.6	3.0
71	M	Chinese herbs	Died	7	3,012	1,126	149	25.2	9.3
58 [†]	M	Acetaminophen	Alive	-2 [†]	2,108	2,997	87	6.7	3.1
52	F	Butalbital/Acetaminophen/Caffeine, Valproic acid	Alive	0	2,152	1,193	409	5.8	1.7
35	F	Acetaminophen	Alive	0	11,912	3,893	229	10.1	4.9
23	F	Acetaminophen	Alive	0	12,675	9,310	255	7.2	5.7
24	M	Acetaminophen	Alive	0	13,503	14,470	246	57.0	6.9
31	M	Acetaminophen, Risperidone	Alive	0	16,093	8,487	216	12.3	3.8
80	M	Nicotinic acid	Died	0	427	339	292	35.3	4.9
51	F	Acetaminophen	Alive	0	2363	2285	239	24.5	3.4
56	F	Acetaminophen, Metformin	Alive	0	15,750	21,000	374	19.7	3.9
19	F	Acetaminophen	Alive	0	7,337	5,887	110	5.0	5.0
43	F	Acetaminophen	Alive	3	1,459	5,816	192	7.1	2.0

Age	Sex	Implicated Medication(s)	Outcome	Days from Jaundice to Hepatic Encephalopathy	Peak Laboratory Results			
					AST, (U/L)	ALT, (U/L)	ALP, (U/L)	Total bilirubin, (mg/dL) INR
52	F	Acetaminophen	Alive	0	16,195	16,035	220	6.5 3.8
41	F	Tenofovir, Lamivudine, Zidovudine	Transplanted	30	2,309	725	236	14.2 2.4
67*	M	Simvastatin, Losartan	Died	0	138	102	1,333	7.8 1.6
89	M	Herbals (pine needle tea)	Alive	8	938	688	145	24.5 2.0
29*	M	Cisplatin, Herbals (unspecified)	Alive	112	185	144	649	34.3 2.1
32	M	Acetaminophen	Alive	0	2,520	3,914	294	5.5 2.1
48	F	Acetaminophen	Died	0	4,709	1,769	779	10.9 4.2

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; M=male; F=female

* Patient with "possible" acute liver failure, defined by international normalized ratio 1.5 with altered mentation and use of hepatic encephalopathy treatment without recorded hepatic encephalopathy diagnosis.

† Patient with hepatic encephalopathy and international normalized ratio 1.5 on hospital day 2. Total bilirubin was 1.1 mg/dL on hospital day 2, which increased to 3.7 mg/dL on hospital day 5.

Table 2

Demographic, laboratory, and clinical characteristics of 32 patients confirmed to have drug-induced acute liver failure in the Kaiser Permanente Northern California healthcare system (2004–2010), grouped by implicated causative medication

Characteristic*	Implicated causative medication			
	Acetaminophen, N=18	Herbal, N=6	Antimicrobial, N=2	Other [‡] , N=6
Age, years	39 (31–52)	65 (45–84)	43 (39–47)	49 (45–72)
Female sex, n (%)	11 (61.1)	2 (33.3)	2 (100.0)	3 (50.0)
Liver transplantation, n (%)	1 (5.6)	2 (33.3)	2 (100.0)	1 (16.7)
Alive without liver transplant, n (%)	16 (88.9)	3 (50.0)	0 (0.0)	3 (50.0)
Peak AST, U/L	6,839 (2363–12,675)	1,044 (185–3012)	1,077 (797–1,356)	895 (138–2,309)
Peak ALT, U/L	4,588 (2,997–8,796)	907 (144–1167)	687 (523–850)	532 (192–1,212)
Peak total bilirubin, mg/dL	7.4 (5.8–19.1)	24.9 (24.2–26.9)	23.7 (7.1–40.2)	15.6 (7.8–17.0)
Peak alkaline phosphatase, U/L	234 (192–347)	355 (149–649)	765 (243–1,287)	262 (236–292)
Peak international normalized ratio	3.8 (2.8–4.2)	2.4 (2.0–3.0)	3.2 (1.9–4.5)	2.3 (1.9–3.0)
Time from jaundice to encephalopathy, days [†]	2 (2–2)	10 (5–13)	8 (6–10)	6 (2–9)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; IQR=interquartile range

* Variables are reported as median with interquartile range unless otherwise specified

[†] Defined as days from total bilirubin > 2.0mg/dL to first clinical manifestation of hepatic encephalopathy²

[‡] Other drugs implicated as causes of acute liver failure included: cytarabine, idarubicin, ibuprofen, orlistat, imatinib, nicotinic acid, tenofovir, lamivudine, zidovudine, simvastatin, and losartan.