Clinical and Experimental Gastroenterology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Costs, Demographics, and Causative Agents in Patients Hospitalized for Drug Induced Liver Injury: Trends in a Large Academic Healthcare System

Megan Kozar[1], Yunisse Gonzalez[2], Dina Halegoua-DeMarzio[3]

[1]Department of Medicine, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA; [2]Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA, USA; [3]Department of Medicine, Division of Gastroenterology and Hepatology. Thomas Jefferson University Hospital at Sidney Kimmel Medical College, Philadelphia, PA, USA

Correspondence: Megan Kozar, Department of Medicine, Sidney Kimmel Medical College at Thomas Jefferson University, 132 S 10th Street Main Building, Suite 480, Philadelphia, PA, 19107, USA, Email megankozar@gmail.com

Clinical and Experimental Gastroenterology downloaded from https://www.dovepress.com/
For personal use only.

Purpose: Drug-induced liver injury (DILI) is an uncommon but potentially life-threatening condition. To date, the burden of DILI on a single, large healthcare system has not been investigated, preventing adequate resource allocation. This study aims to quantify DILI-related healthcare utilization within the Jefferson Health System (JHS) and identify case-related factors associated with high resource requirements; such information is crucial to focus efforts toward resource reduction.

Patients and Methods: This study characterizes trends of 48 DILI cases within JHS, including demographics, payer status, causative agent, and DILI pattern. These variables were correlated with length of stay (LOS) and cost relating to the treatment encounter. Patient-level observed LOS and cost were then subtracted from their respective expected values from the Vizient Clinical Database, a platform that provides clinical outcome data from more than 1300 healthcare facilities in the United States.

Results: Treatment of DILI cases at JHS required higher than expected cost compared to the Vizient Clinical Database. We found high resource utilization in females, those identifying as black, and in cases where the implicated agent was uncertain. Mixed pattern DILI required the highest healthcare utilization, whereas herbal and dietary supplements (HDS) cases were relatively resource minimal.

Conclusion: This study indicates that high clinical suspicion of DILI in historically marginalized populations and improved causative agent identification are key to minimizing the healthcare burden of DILI.

Keywords: hepatotoxicity, clinical patterns, healthcare utilization, risk factors, patient characteristics

Introduction

Drug-induced liver injury (DILI) is a complication resulting from medications, herbal supplements, or dietary supplements. Due to its wide spectrum of clinical presentations (from asymptomatic transaminitis to acute liver failure (ALF), its lack of biomarkers, and the need to exclude other causes of transaminitis, it is difficult to diagnose.[1] Population studies have estimated an incidence of 14–19 per 100,000 persons, with a higher incidence of 32.8 per 100,000 persons in hospitalized patients.[1–3] DILI is further characterized as intrinsic versus idiosyncratic.[4] Intrinsic is attributed to culprit drugs with known liver toxicity in a dose-dependent manner with predictable outcomes, such as acetaminophen. Idiosyncratic refers to drugs that do not have a linear relationship with dosing and are dependent on host susceptibility and variation in presentation. The latter results in delays in diagnosis, owing to the lack of standardized biomarkers and clinical guidelines.

While DILI is considered a rare phenomenon, its consequences can be life threatening. DILI is associated with substantial morbidity and mortality, with a study estimating 9.4% of patients with DILI either dying or requiring a liver transplant within 6 months of DILI onset.[5] In a prospective cohort study of 17 tertiary centers, Goldberg et al estimated that ALF was secondary to acetaminophen overdose in 39% of cases and idiosyncratic drug reactions in 13% of cases, thus surpassing viral hepatitis as the most apparent cause of ALF.[6]

https://doi.org/10.2147/CEG.S572371
Received: 22 October 2025
Accepted: 1 March 2026
Published: 8 April 2026

© 2026 Kozar et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

Common drug classes that cause DILI based on the DILIrank dataset (a ranking of drugs based on their potential of causing DILI) include nonsteroidal anti-inflammatory drugs (NSAIDs), antigout, antimycotics, antineoplastics, psychoanaleptics, immunostimulants, and antivirals.[7] Interestingly, antibiotics are a common culprit of DILI, but this study did not find it represented a significantly higher hepatotoxic risk as a class due to many antibiotic drugs not being classified as a DILI concern. Other studies, however, have found antimicrobials to be the most common etiology of DILI.[8,9]

Overall, DILI can result in serious complications and can arise from a multitude of medications. However, the estimated healthcare expenditures from DILI have not been well described. It has been found that DILI is a major cause of withdrawal of medications from the market.[10] One study estimates that the typical cost for the research and development of a new therapeutic drug now costs $800 million, therefore a withdrawal from the market can be costly.[11] The aim of this study is to characterize DILI healthcare utilization within a single, large hospital system, correlating demographics and culprit medications to LOS and admission costs. These parameters were then compared to expected benchmarks derived from the Vizient Clinical Database.

Materials and Methods

Study Design

This retrospective cohort study was conducted at JHS between October 2020 and January 2025. JHS is a large healthcare network comprised of 32 hospitals that provide inpatient and outpatient services to the Mid-Atlantic region. Data collected by JHS includes demographic information, diagnoses, laboratory data, referral services, medications, and insurance status.

Study Patients and Confirmation of DILI

Potential DILI patients at JHS 18 years or older were identified using ICD codes, a standardized code used to classify diseases, symptoms, injuries, and causes of death. Cases are assigned an ICD code during or after a patient encounter based on a provider's judgement of patient diagnosis, symptoms, or reason for the visit. While no ICD code specifically indicating DILI exists, cases suggesting potential DILI include K710 (toxic liver disease with cholestasis), K711 (toxic liver disease with hepatic necrosis), K712 (toxic liver disease with acute hepatitis), K716 (toxic liver disease with hepatitis, not elsewhere classified), K719 (toxic liver disease, unspecified), K720 (acute and subacute hepatic failure), K729 (hepatic failure, unspecified), K759 (inflammatory liver disease, unspecified), and K762 (post-procedural hepatic failure). Relevant JHS sites included those utilizing Epic electronic health record (EHR). Cases included in this study were diagnosed at nine JHS sites.

All JHS patients with potential DILI had their records reviewed by a trained study contributor. For each patient, medical records, laboratory results, gastroenterologist/hepatologist consultation notes, and hospital discharge notes were examined. Due to the reliance on clinical suspicion and exclusion of other etiologies for DILI diagnosis, only cases explicitly noting DILI were included. All exclusion criteria are shown in Figure 1, including shock liver, graft versus host disease, and cases where a relevant identifying ICD code was observed outside of the time period for the study. Furthermore, cases in which there was high clinical suspicion for an etiology other than DILI were excluded. Included cases were then classified as cholestatic, hepatic, or mixed based on appropriate laboratory values per clinical practice guidelines.[12,13]

Vizient Database

Vizient Clinical Database is a platform that provides clinical benchmarks indicating hospital quality and financial performance. It provides data on patient outcomes compared with peer institutions. Based on patient data submitted to the database, Vizient calculates expected values for key healthcare system performance parameters, namely length of stay (LOS), in-hospital mortality, admission cost, and readmission rates. More specifically, expected values for cost are generated in the Vizient platform through proprietary models that aggregate pharmacy, service, and supply cost data from all contributing institutions and incorporate regional factors such as labor availability, patient population, and facility characteristics. Similarly, expected LOS is estimated from past similar encounters among contributing institutions. Through these models, the Vizient database provides healthcare utilization estimates for patient cases given a patient's

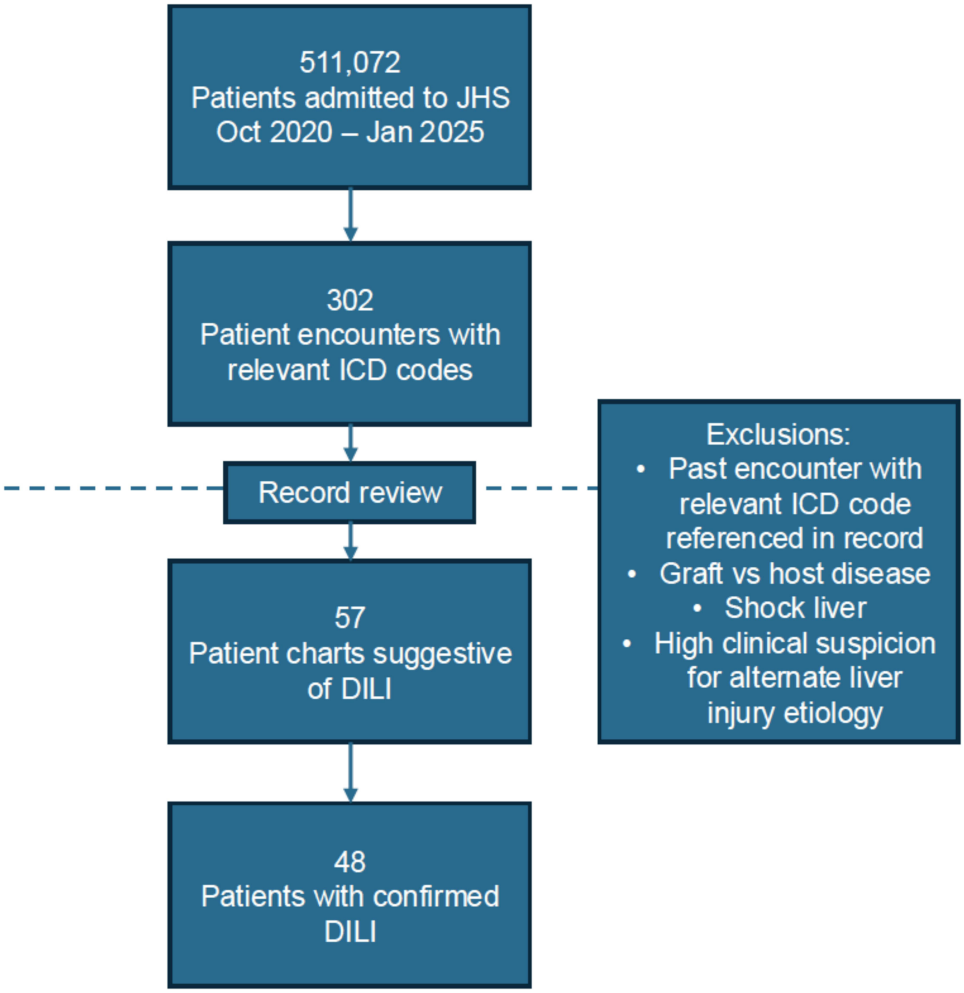

Figure 1 Flow Diagram of DILI Cases Included in the Study.
Note: some cases met more than one exclusion criteria.
Abbreviation: ICD, International Classification of Diseases.

diagnosis and demographic characteristics. The present study subtracted observed values for LOS and cost from their respective expected values from the Vizient database and reported differences in these key healthcare utilization parameters for analysis.

Statistical Analysis

Incidence rates for DILI within JHS were calculated by dividing the number of confirmed DILI inpatient cases by the total number of inpatient cases at relevant JHS sites. Among all confirmed DILI cases, the differences between expected and observed cost and LOS were compared using paired *t*-tests. The normality of the distribution for cost and LOS differences was confirmed visually. Median differences between observed and expected values were reported when individual cases were grouped for further analysis. For LOS and cost, positive results indicate higher than expected utilization, and negative results represent lower than expected utilization. JMP Pro version 18.0.2 was used for all statistical analyses.

Ethical Considerations

This study was evaluated by Institutional Review Board (IRB) #153 at Thomas Jefferson University and was determined to be exempt from review (2024–3026). This was a retrospective study, and patient consent was not required by our IRB

as patient interaction was not required; individual informed consent was waived because the study data was de-identified or originated from a registry. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Relevant patient characteristics and healthcare utilization parameters for the included DILI cases are detailed in Tables 1 and 2. The incidence of DILI at JHS was 9.19 per 100,000 hospitalized persons during the study period. In Table 3, a statistically significant increase in treatment cost was noted when comparing cases at JHS with benchmarks provided by

Table 1 Characteristics of 48 Inpatient Members Confirmed to Have DILI at JHS During the Time Period

Case Identifier	Demographics			Peak Laboratory Values			Implicated Medication(s)	Cholestatic, Hepatocellular, or Mixed Pattern
	Age [years]	Sex	Race	AST Level [U/L]	ALT Level [U/L]	ALP Level [U/L]		
1	47	Male	White	291	543	248	Lisdexamfetamine	Hepatocellular
2	39	Female	Black	121	63	394	Tacrolimus	Cholestatic
3	40	Female	Black	236	287	154	Norethindrone acetate	Hepatocellular
4	58	Female	Black	850	498	292	Dantrolene	Hepatocellular
5	55	Male	Black	349	227	109	Casarca	Hepatocellular
6	54	Female	White	260	281	255	Doxycycline	Mixed
7	43	Male	Black	359	857	249	Nugenix	Hepatocellular
8	58	Male	White	172	179	1887	Amoxicillin/Ketamine	Cholestatic
9	50	Female	Black	338	72	306	Mirtazapine	Cholestatic
10	42	Female	Black	700	600	294	Methimazole	Hepatocellular
11	39	Female	Black	295	154	493	Risperidone	Cholestatic
12	53	Female	White	2641	2762	396	Indeterminate[a]	Hepatocellular
13	68	Female	White	265	199	153	Octreotide	Hepatocellular
14	68	Male	White	250	351	1075	Nivolumab	Cholestatic
15	58	Male	Black	156	210	222	SMX-TMP	Mixed
16	67	Female	Other	555	775	179	Albendazole	Hepatocellular
17	52	Male	White	93	38	84	Daptomycin/Cefepime	Cholestatic
18	73	Male	White	225	191	388	Radioembolization	Cholestatic
19	82	Female	White	106	161	286	Vimodegib	Mixed
20	57	Female	White	55	75	582	Cephalexin	Cholestatic
21	40	Female	White	449	1821	125	Ipilimumab/Nivolumab	Hepatocellular
22	61	Female	White	45	36	388	SMX-TMP	Cholestatic
23	21	Female	White	1987	2850	71	Tylenol/Venlafaxine/Quetiapine	Hepatocellular
24	58	Male	White	374	192	924	Nivolumab	Cholestatic
25	73	Female	White	1012	1109	242	Levofloxacin	Hepatocellular
26	30	Male	White	719	2424	144	Acetaminophen	Hepatocellular
27	97	Male	White	424	269	125	Nitrofurantoin/Ciprofloxacin/SMX-TMP	Hepatocellular

(*Continued*)

Table 1 (Continued).

Case Identifier	Demographics			Peak Laboratory Values			Implicated Medication(s)	Cholestatic, Hepatocellular, or Mixed Pattern
	Age [years]	Sex	Race	AST Level [U/L]	ALT Level [U/L]	ALP Level [U/L]		
28	73	Female	Black	1068	1404	337	Turmeric/Elderberry supplement	Hepatocellular
29	30	Female	White	486	489	275	Acetaminophen	Hepatocellular
30	72	Female	White	1162	2013	377	Leflunomide/Valacyclovir	Hepatocellular
31	30	Female	White	177	259	417	OCP/Bupropion/Sertraline	Mixed
32	62	Female	Black	601	951	741	Dapsone	Hepatocellular
33	75	Male	Asian	1166	491	123	Cefdinir	Hepatocellular
34	79	Female	White	167	225	921	Pembrolizumab/Atorvastatin	Cholestatic
35	65	Female	White	2942	1369	467	Duvalumab	Hepatocellular
36	30	Male	Other	637	662	469	Rivaroxaban/Amoxicillin	Hepatocellular
37	31	Female	White	127	144	198	Posiconazole	Mixed
38	32	Female	White	1039	1021	305	Cetirizine/Valcyclovir	Hepatocellular
39	58	Male	White	709	550	792	Sertraline	Mixed
40	62	Male	White	90	95	824	Turmeric	Cholestatic
41	22	Female	White	13300	10610	92	Clindamycin/Acetaminophen	Cholestatic
42	53	Male	Other	112	81	2246	Indeterminate[a]	Hepatocellular
43	53	Male	Other	65	100	2813	Indeterminate[a]	Cholestatic
44	60	Male	Black	433	268	177	Valproic acid	Hepatocellular
45	92	Male	White	45	57	593	Naproxen/Neuriva	Cholestatic
46	82	Female	White	89	121	515	Ceftriaxone	Cholestatic
47	34	Male	White	840	509	73	SMX-TMP	Hepatocellular
48	45	Male	Asian	2708	2272	135	Indeterminate[a]	Hepatocellular

Notes: [a]No clear DILI-causing agent identified. Diagnosis of DILI made by excluding all other possibilities.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SMX-TMP, sulfamethoxazole-trimethoprim; OCP, oral contraceptive pill.

Table 2 Healthcare Utilization Parameters of 48 Inpatient Members Confirmed to Have DILI at JHS During the Time Period

Case Identifier	LOS [Days]			Cost [USD]		
	Observed LOS	Expected LOS	LOS Difference (Observed - Expected)	Observed Cost	Expected Cost	Cost Difference (Observed - Expected)
1	10	4.20	5.80	9263	5729	3534
2	4	4.19	−0.19	10,589	5232	5357
3	3	7.22	−4.22	4137	11,481	−7344
4	2	4.20	−2.20	4860	5922	−1062
5	2	4.68	−2.68	2155	6411	−4256

(*Continued*)

https://doi.org/10.2147/CEG.S572371

Table 2 (Continued).

Case Identifier	LOS [Days]			Cost [USD]		
	Observed LOS	Expected LOS	LOS Difference (Observed - Expected)	Observed Cost	Expected Cost	Cost Difference (Observed - Expected)
6	1	5.09	−4.09	4615	7310	−2695
7	5	3.94	1.06	4503	5283	−780
8	10	5.03	4.97	12,554	7847	4707
9	4	4.68	−0.68	3706	5788	−2082
10	1	3.15	−2.15	3496	4319	−823
11	14	6.00	8.00	14,522	6212	8310
12	2	3.15	−1.15	2535	4319	−1784
13	15	4.87	10.13	22,021	6790	15,231
14	3	3.73	−0.73	2910	5026	−2116
15	15	5.26	9.74	17,135	9099	8036
16	5	3.71	1.29	6583	4707	1876
17	3	3.92	−0.92	3200	5406	−2206
18	4	3.75	0.25	3716	4914	−1198
19	6	3.15	2.85	11,000	4610	6390
20	1	3.76	−2.76	3592	4948	−1356
21	3	3.15	−0.15	2240	4319	−2079
22	5	4.78	0.22	6365	6711	−346
23	7	4.43	2.57	6037	5740	297
24	3	4.42	−1.42	6151	6244	−93
25	4	3.70	0.30	4466	5286	−820
26	1	3.88	−2.88	2140	5340	−3200
27	3	5.27	−2.27	5153	7154	−2001
28	9	3.15	5.85	15,114	4319	10,795
29	5	4.27	0.73	12,370	6195	6175
30	36	15.06	20.94	56,702	20,525	36,177
31	4	3.51	0.49	7337	5126	2211
32	13	5.06	7.94	45,584	6887	38,697
33	3	4.42	−1.42	2736	5716	−2980
34	1	3.15	−2.15	2370	4319	−1949
35	10	5.56	4.44	13,820	8565	5255
36	3	6.25	−3.25	4954	6209	−1255
37	7	4.53	2.47	9853	9679	174

(*Continued*)

Table 2 (Continued).

Case Identifier	LOS [Days]			Cost [USD]		
	Observed LOS	Expected LOS	LOS Difference (Observed - Expected)	Observed Cost	Expected Cost	Cost Difference (Observed - Expected)
38	4	3.15	0.85	4587	4319	268
39	5	5.30	−0.30	7783	8329	−546
40	5	8.81	−3.81	6706	11,712	−5006
41	8	4.27	3.7257	18,652	6327	12,325
42	18	6.67	11.33	13,910	10,868	3042
43	7	8.56	−1.56	9322	12,234	−2912
44	9	5.65	3.35	15,471	6917	8554
45	6	5.66	0.34	6091	8259	−2168
46	8	8.08	−0.08	10,100	10,328	−228
47	2	4.47	−2.47	8627	6422	2205
48	4	4.28	−0.28	5312	5740	−428

Abbreviations: LOS, length of stay; USD, US dollars.

Table 3 Mean Aggregated Healthcare Utilization Parameters of 48 Patients Confirmed to Have DILI at JHS During the Time Period, Compared to Vizient Benchmarks

	Mean Observed Value Reported at JHS	Mean Expected Value as Predicted by Vizient Database	Mean Difference Observed - Expected Value	95% Confidence Interval (p-value)
Cost [USD]	9521.77	6898.79	2622.98	99.36, 5146.60 (0.042)
LOS [days]	6.31	4.94	1.37	−0.02, 2.76 (0.054)

Abbreviations: JHS, Jefferson Health System, LOS, length of stay.

Vizient. LOS also showed an increase at JHS versus Vizient benchmarks, although statistical significance was not reached. These results indicate high resource utilization at JHS compared to national trends. However, two cases were identified that required particularly high LOS and cost, indicating the need for caution in result interpretation.

Analysis of demographic trends in DILI revealed substantial healthcare utilization in key populations (Table 4). Females required higher than expected median LOS and cost, while males required lower than expected LOS and cost. A higher incidence of DILI was also noted in females. Treatment for those identifying as black involved the highest

Table 4 Median Aggregated Healthcare Utilization Parameters of 48 Patients Confirmed to Have DILI at JHS During the Time Period, By Demographic Variables

Demographic Variables	Median (IQR) LOS Difference: Observed - Expected in Vizient [Days]	Median (IQR) Cost Difference: Observed - Expected in Vizient [USD]
Female (N=27)	+0.48 (−1.15, 3.73)	+268.00 (−1345.00, 6390.00)
Male (N=21)	−0.73 (−2.37, 2.20)	−1198.00 (−2559.00, 2623.5)
Black (N=12)	+0.43 (−2.19, 7.41)	+2288.50 (−1827, 8493)

(*Continued*)

Table 4 (Continued).

Demographic Variables	Median (IQR) LOS Difference: Observed - Expected in Vizient [Days]	Median (IQR) Cost Difference: Observed - Expected in Vizient [USD]
White (N=30)	+0.23 (−1.61, 2.64)	−287.00 (−2020.50, 3827.25)
Asian (N=2)	−0.85[a]	−1704.00[a]
Other Race (N=4)	−0.14 (−2.823, 8.82)	+310.50 (−2497.15, 2750.5)

Notes: [a]IQR not reported due to insufficient sample size.

Table 5 Median Aggregated Healthcare Utilization Parameters of 48 Patients Confirmed to Have DILI at JHS During the Time Period, By Payer Status

Primary Payer[a]	Median (IQR) LOS Difference: Observed - Expected in Vizient [Days]	Median (IQR) Cost Difference: Observed - Expected in Vizient [USD]
Commercial/Private Payer (N=17)	−0.15 (−1.79, 1.77)	−346.00 (−1570.00, 1251.00)
Medicare (N=20)	+0.28 (−1.52, 5.63)	−683.00 (−2155.00, 6106.25)
Medicaid (N=9)	−0.19 (−2.73, 3.54)	1876.00 (−1668.50, 8432.00)

Notes: [a]One patient with uninsured/self-pay and one patient with unknown insurance status were not included.
Abbreviation: LOS, length of stay.

median difference in LOS and cost even though DILI was most common in those identifying as white. Collectively, these results indicate higher than expected healthcare utilization in historically marginalized populations.

As noted in Table 5, individuals with Medicare had the longest median LOS difference, aligning with known trends of increased DILI severity in elderly populations.[14] However, increased LOS did not translate to higher-than-expected median cost. The commercial/private payer and Medicaid groups showed comparable median LOS differences, although there was greater variation in LOS in the Medicaid group. The highest cost difference was observed in treating those with Medicaid.

The highest number of DILI cases were due to antimicrobials, multiple agents, or agents not otherwise categorized (Table 6). DILI due to HDS was the least resource intensive to treat, although the greatest variation in cost was observed

Table 6 Median Aggregated Healthcare Utilization Parameters of 48 Patients Confirmed to Have DILI at JHS During the Time Period, By Causative Agent

Causative Agent	Median (IQR) LOS Difference: Observed - Expected in Vizient [Days]	Median (IQR) Cost Difference: Observed - Expected in Vizient [USD]
Antimicrobial (N=13)	−0.08 (−2.37, 1.88)	−346.00 (−2103.50, 2040.50)
HDS (N=4)	−0.81 (−3.53, 4.65)	−2518.00 (−4814.50, 7901.25)
Immunotherapy (N=5)	−0.15 (−1.08, 3.64)	−93.00 (−2097.50, 5822.50)
Indeterminant (N=4)[a]	−0.72 (−1.47, 8.43)	−1106.00 (−2630.00, 2174.50)
Multiple agents (N=9)[b]	+0.85 (−0.91, 4.35)	+297.00 (−1602.00, 8516.00)
Acetaminophen (N=2)	−1.07[c]	+1487.50[c]
Antidepressant (N=2)	−0.49[c]	−1314.00[c]
Other Agent (N=9)[d]	+0.25 (−2.18, 6.90)	+3534.00 (−1130.00, 8432.00)

Notes: [a]No clear DILI-causing agent identified. Diagnosis of DILI made by excluding all other possibilities. [b]Multiple agents implicated in DILI. [c]IQR not reported due to insufficient sample size. [d]Implicated agent did not align with any drug category previously included. Other drugs include lisdexamfetamine dimesylate, tacrolimus, norethindrone acetate, dantrolene, methimazole, risperidone, octreotide, radioembolization, and valproic acid.
Abbreviations: HDS, Herbal and dietary supplements; LOS, length of stay.

Table 7 Median Aggregated Healthcare Utilization Parameters of 48 Patients Confirmed to Have DILI at JHS During the Time Period, by DILI Pattern

DILI Pattern	Median (IQR) LOS Difference: Observed - Expected in Vizient [Days]	Median (IQR) Cost Difference: Observed - Expected in Vizient [USD]
Cholestatic (N=16)	−0.43 (−1.52, 0.32)	−1277.00 (−2155.00, 2258.25)
Hepatocellular (N=26)	+0.52 (−2.22, 3.90)	−80.00 (−1838.25, 6769.75)
Mixed (N=6)	+1.48 (−1.25, 4.57)	+1192.50 (−1083.25, 6801.50)

Notes: DILI pattern determined according to clinical practice guidelines[12,13].

in the HDS group. Cases with unclear causative agents, whether the "multiple agent" or "other agent" categories, yielded the highest median LOS and cost difference.

Hepatic pattern DILI was the most commonly observed in the present study, followed by cholestatic and mixed pattern as indicated in Table 7. Both hepatocellular and mixed patterns exhibited a higher than expected LOS difference, while cholestatic was lower than expected. The mixed pattern yielded a median cost that was higher than expected, while both hepatic and cholestatic patterns had lower than expected cost.

Discussion

In this study, we measured the economic burden of a relatively rare drug reaction to elucidate its impact on an academic, single hospital system in comparison to national trends. As shown in Table 3, we found an increased mean cost of admission for DILI compared with the mean expected cost from the national Vizient database. The length of stay, while higher than expected, was not statistically significant. This observed difference could be due to trainees ordering more advanced testing at academic medical centers in response to ambiguity of presentation. This result corresponds with a cross-sectional study in 2018 that found that major teaching hospitals ordered significantly more lab tests per day for pneumonia and cellulitis in comparison to non-teaching hospitals, even when adjusting for severity and demographics.[14] A study in 1998 also found academic teaching hospitals were 63% more costly per inpatient case than non-teaching hospitals.[15]

Another hypothesis could be the attraction of more complex cases or administration of more expensive treatments, as seen in a study comparing costs between teaching and non-teaching hospitals for cancer treatment.[16] When reviewing the results in the present study, two cases were significantly more expensive than the others. Both cases initially presented with transaminitis but had co-morbid conditions that predisposed them to develop severe infections, complicating their hospital course. This supports the theory that cases of DILI within JHS can be complicated and broad in clinical presentation, requiring high resource utilization.

Interestingly, when comparing cost and LOS among sexes, females were found to have a higher than expected admission cost and LOS than males (Table 4). This corroborates previous descriptions of sex differences in DILI, with females reportedly having an increased severity and mortality, and a 1.5–1.7 fold increased risk for developing an adverse drug reaction.[17–19] While cost is not a direct measurement of severity, it is expected to increase proportionally with case severity. Another demographic with higher than expected costs was black patients. Results showed that they had the highest median difference in LOS and cost despite the greater frequency of DILI in Caucasian patients. This supports studies that have shown a higher rate of hospitalization, liver transplantation, and mortality from DILI in black compared to white patients.[20]

When categorizing based on payer status in Table 5, patients with Medicare and private insurance had lower than expected costs, whereas patients with Medicaid had higher than expected costs. Therefore, the relationship between private and public insurance is unclear but may point to insurance not being an accurate indicator of resource utilization.

When grouping admission costs and LOS by causative agents in Table 6, cases in the "multiple agents" and "other agents" categories were the most resource intensive. This is possibly due to diagnostic uncertainty in the absence of a clear causative agent, resulting in increased testing. DILI secondary to HDS was found to have the lowest associated cost and LOS. There has been a rising prevalence of usage of HDS with associated DILI.[21,22] The lower cost of HDS-associated DILI may be secondary to the type of patients who consume HDS, which tend to be health-conscious

individuals, although one study found HDS-induced DILI tends to be more severe than other types of DILI.[23] Similarly, while antimicrobials were the most frequent causative agent implicated in DILI, they were also found to have low median cost and LOS difference. This may be due to the well-known risk of hepatotoxicity associated with antibiotics leading to prompt diagnosis. Lastly, DILI due to acetaminophen required shorter than expected median hospital stays, but higher than expected median costs. This again points to familiarity of acetaminophen toxicity, but the increase in cost may highlight a difference in management compared to national trends that necessitates more resources.

Some studies in the literature have correlated the pattern of injury with severity, with hepatocellular injury being associated with more severe DILI prognosis.[19] In Table 7, we found that hepatocellular injury was the most common form of DILI, but it was not correlated with higher costs. In fact, a mixed injury pattern was the only one that resulted in higher costs. This may be due to delays in diagnosis, presumably because of ambiguity in interpreting liver function tests.

This study identifies several areas in which DILI has a higher than expected financial impact. Within the JHS hospital system, female patients, black patients, and DILI secondary to multiple possible agents were found to have a higher than expected cost compared to national trends. Further focus on these groups is necessary to identify the reasons for increased resource utilization. We hypothesize that the spectrum of disease, lack of familiarity of certain culprit medications, and complexity of the patient population with individualized risk factors may contribute to the unexpected cost differential. Studies have evaluated the efficacy of emerging biomarkers in combination with diagnostic scoring systems to enhance diagnostic and prognostic parameters, and it would be interesting to verify whether these new tools would reduce the cost of DILI.[24]

A major limitation of this study is the small sample size, which is attributed to the uncommon prevalence of DILI in a single hospital system. Use of diagnostic codes to identify DILI has been shown to have reduced sensitivity in capturing DILI cases, likely leading to underreporting of cases within the timeframe.[25] Furthermore, DILI incidence at JHS was 9.39 cases per 100,000 hospitalized patients, which is lower than others reported in the literature.[1–3] Additional work is required to expand the cohort of DILI patients for more robust analysis. As mentioned above, we noted two cases that were more expensive than the median cost by nature of their complicated hospital course, which could contribute to the higher than expected costs in a small cohort. Lastly, while cost would presumably be higher in severe cases of DILI, we did not directly measure DILI severity for each case. Thus, further analysis is needed to determine whether cost is mostly dictated by severity, or if there are other individual or systemic factors that contribute to the financial impact of DILI.

Conclusion

The present study characterized DILI healthcare utilization trends at JHS, compared key parameters to benchmarks from Vizient Clinical Database, and correlated demographics, payer status, and causative agents with LOS and cost. At JHS, certain subgroups of patients with DILI required more resources than expected compared with Vizient benchmarks. Historically marginalized groups, including females and those identifying as black, required higher than expected resources to treat, although insurance status was not strongly associated with healthcare utilization. Cases involving multiple agents or agents not included in a DILI-causing category were the most resource expensive, likely due to additive drug effects and lack of familiarity with uncategorized therapeutics. Mixed pattern DILI required the highest healthcare utilization, whereas HDS cases were found to be relatively resource minimal. This study collectively suggests that clinical suspicion for DILI and swift determination of the offending agent are key to minimizing resources required for treatment. Social determinants of health likely contribute to healthcare utilization in DILI, although expansion of the cohort is required to further elucidate these trends.

Abbreviations

ALF, acute liver failure; ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DILI, drug induced liver injury; EHR, electronic health record; ICD, International Classification of Diseases; IQR, interquartile range; JHS, Jefferson Health System; HDS, herbal and dietary supplements; LOS, length of stay; NSAID, nonsteroidal anti-inflammatory drug; OCP, oral contraceptive pill; SMX-TMP, sulfamethoxazole-trimethoprim.

Acknowledgments

We would like to acknowledge Kelley Darlington for her support in data acquisition.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Shin J, Hunt CM, Suzuki A, Papay JI, Beach KJ, Cheetham TC. Characterizing phenotypes and outcomes of drug-associated liver injury using electronic medical record data. *Pharmacoepidemiol Drug Saf*. 2013;22(2):190–198. doi:10.1002/pds.3388
2. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology*. 2002;36(2):451–455. doi:10.1053/jhep.2002.34857
3. Björnsson ES, Bergmann OM, Björnsson HK, et al. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013;144(7):1419–25,1425.e1–3; quize19–20. doi:10.1053/j.gastro.2013.02.006
4. Roth RA, Ganey PE. Intrinsic versus idiosyncratic drug-induced hepatotoxicity--two villains or one? *J Pharmacol Exp Ther*. 2010;332(3):692–697. doi:10.1124/jpet.109.162651
5. Fontana RJ, Hayashi PH, Gu J, et al; DILIN Network. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. *Gastroenterology*. 2014;147(1):96–108.e4. doi:10.1053/j.gastro.2014.03.045.
6. Ostapowicz G, Fontana RJ, Schiødt FV, et al; US Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137(12):947–954. doi:10.7326/0003-4819-137-12-200212170-00007.
7. Chen M, Suzuki A, Thakkar S, et al. DILIrank: the largest reference drug list ranked by the risk for developing drug-induced liver injury in humans. *Drug Discov Today*. 2016;21(4):648–653. doi:10.1016/j.drudis.2016.02.015
8. Rao A, Rule JA, Hameed B, et al. Secular trends in severe idiosyncratic drug-induced liver injury in North America: an update from the acute liver failure study group registry. *Am J Gastroenterol*. 2022;117(4):617–626. doi:10.14309/ajg.0000000000001655
9. Chalasani N, Bonkovsky HL, Fontana R, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology*. 2015;148(7):1340–52.e7. doi:10.1053/j.gastro.2015.03.006.
10. Wilke RA, Lin DW, Roden DM, et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. *Nat Rev Drug Discov*. 2007;6(11):904–916. doi:10.1038/nrd2423
11. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *Journal of Health Economics*. 2003;22 (2):151–185. doi:10.1016/S0167-6296(02)00126-1
12. Chalasani NP, Maddur H, Russo MW, et al; Practice Parameters Committee of the American College of Gastroenterology. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2021;116(5):878–898. doi:10.14309/ajg.0000000000001259.
13. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther*. 2011;89(6):806–815. doi:10.1038/clpt.2011.58
14. Suzuki A, Minjun Chen. Epidemiology and risk determinants of drug-induced liver injury: current knowledge and future research needs. *Liver Int*. 2025;45(4):e16146. doi:10.1111/liv.16146
15. Valencia V, Arora VM, Ranji SR, Meza C, Moriates C. A comparison of laboratory testing in teaching vs nonteaching hospitals for 2 common medical conditions. *JAMA Intern Med*. 2018;178(1):39–47. doi:10.1001/jamainternmed.2017.6032
16. Mechanic R, Coleman K, Dobson A. Teaching hospital costs: implications for academic missions in a competitive market. *JAMA*. 1998;280 (11):1015–1019. doi:10.1001/jama.280.11.1015
17. Fodero R, Bailey J. Comparing hospital costs and length of stay for cancer patients in New York State Comprehensive cancer centers versus nondesignated academic centers and community hospitals. *Health Serv Res*. 2023;58(6):1178–1188. doi:10.1111/1475-6773.14209
18. Floreani A, Bizzaro D, Shalaby S, et al; Special Interest Group Gender in Hepatology of the Italian Association for the Study of the Liver (AISF). Sex disparity and drug-induced liver injury. *Dig Liver Dis*. 2023;55(1):21–28. doi:10.1016/j.dld.2022.06.025.
19. Lucena MI, Andrade RJ, Kaplowitz N, et al; Spanish Group for the Study of Drug-Induced Liver Disease. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. *Hepatology*. 2009;49(6):2001–2009. doi:10.1002/hep.22895.
20. Stephens C, Robles-Diaz M, Medina-Caliz I, et al. Participating clinical centres. comprehensive analysis and insights gained from long-term experience of the Spanish Dili Registry. *J Hepatol*. 2021;75(1):86–97. doi:10.1016/j.jhep.2021.01.029
21. Chalasani N, Reddy KRK, Fontana RJ, et al. Idiosyncratic drug induced liver injury in african-americans is associated with greater morbidity and mortality compared to caucasians. *Am J Gastroenterol*. 2017;112(9):1382–1388. doi:10.1038/ajg.2017.215
22. Regan LB, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003–20061. *J Nutr*. 2011;141(2):261–266. doi:10.3945/jn.110.133025
23. Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the US drug-induced liver injury network. *Hepatology*. 2014;60(4):1399–1408. doi:10.1002/hep.27317
24. Medina-Caliz I, Garcia-Cortes M, Gonzalez-Jimenez A. Herbal and dietary supplement-induced liver injuries in the Spanish Dili registryspanish DILI registry et al. *Clin Gastroenterol Hepatol*. 2018;16(9):1495–1502. doi:10.1016/j.cgh.2017.12.051
25. Fu S, Wu D, Jiang W, et al. Molecular biomarkers in drug-induced liver injury: challenges and future perspectives. *Front Pharmacol*. 2020;10:1667. doi:10.3389/fphar.2019.01667

Clinical and Experimental Gastroenterology

Dovepress
Taylor & Francis Group

Publish your work in this journal

Clinical and Experimental Gastroenterology is an international, peer-reviewed, open access, online journal publishing original research, reports, editorials, reviews and commentaries on all aspects of gastroenterology in the clinic and laboratory. This journal is indexed on American Chemical Society's Chemical Abstracts Service (CAS). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/clinical-and-experimental-gastroenterology-journal