Significant Medical Comorbidities Are Associated With Lower Causality Scores in Patients Presenting With Suspected Drug-Induced Liver Injury

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INTRODUCTION: **Drug-induced liver injury (DILI) is a diagnosis of exclusion, and it can be challenging to adjudicate when there are multiple comorbidities and concomitant medications. In this study, we tested the hypothesis that comorbidity burden impacts the causality adjudication in patients with suspected DILI.**

METHODS: **We studied consecutive patients with suspected DILI enrolled in the Drug-Induced Liver Injury Network Prospective Study at 2 centers between 2003 and 2017. The comorbidity burden at presentation was determined using the Charlson Comorbidity Index (CCI). We analyzed the association between significant comorbidity (CCI > 75th percentile) and (i) the adjudication of DILI by expert consensus as definite, highly likely, or probable (high-confidence DILI) and (ii) the Roussel Uclaf Causality Assessment Method (RUCAM) scores.**

RESULTS: **Our cohort consisted of 551 patients who were classified as "no comorbidity" (54%, CCI = 0), "mild comorbidity" (29%, CCI = 1 or 2), and "significant comorbidity" (17%, CCI > 2). The probability of high-confidence DILI was significantly lower in patients with significant comorbidity compared with those with mild or no comorbidities (67% vs 76% vs 87%, respectively, $P < 0.001$). The mean RUCAM scores decreased with increasing comorbidity (no comorbidity 6.6 ± 2, mild comorbidity 6 ± 2.4, and significant comorbidity 5.6 ± 2.7, $P < 0.001$). In the multiple logistic regression, significant comorbidity had an independent inverse relationship with DILI (odds ratio: 0.37, 95% confidence interval: 0.2–0.69, $P = 0.001$).**

DISCUSSION: **Higher comorbidity burden impacts the causality assessment in patients with suspected DILI. Further studies are needed to investigate the utility of comorbidity burden as a variable in the DILI causality instruments.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A230

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INTRODUCTION

Drug-induced liver injury (DILI) is an important cause of liver-related morbidity and mortality, but it lacks a gold standard diagnostic test. Establishing the occurrence of DILI requires maintaining a low threshold of suspicion and the exclusion of alternative causes of liver injury. Little is known about the impact of medical comorbidities on the likelihood of assessing causality of possible DILI either by expert panel or by accepted causality instruments. A number of comorbidities may predispose to liver injury because of specific agents, such as pre-existing liver disease, HIV infection, and diabetes, but most medical comorbidities are generally not thought to predispose to DILI, although they negatively impact survival after DILI (1,2). Severe comorbidity may be associated with increased risk for non-drug-related liver injury, which may cloud the diagnosis of DILI. The presence of increasing comorbidities and concomitant medications may make it more difficult to confidently exclude competing etiologies for liver injury and incriminate a specific drug or an herbal and dietary supplement (HDS). Thus, diminished confidence in diagnosing DILI may be directly associated with the multiplicity and complexity of comorbid conditions.

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The Drug-Induced Liver Injury Network (DILIN) Prospective Study adjudicates DILI and implicated agents based on expert consensus (3). Following the causality assessment, approximately 82% of patients with suspected DILI who are enrolled in the DILIN Prospective Study are adjudicated to have definite, highly likely, or probable (high-confidence DILI) (4). We conducted a study to test the hypothesis that comorbidity burden impacts the causality assessment of DILI in patients presenting with suspected DILI using the data from 2 centers participating in the DILIN.

METHODS

We studied consecutive patients with suspected DILI enrolled in the DILIN Prospective Study at 2 centers (Indiana University and University of North Carolina) between 2003 and 2017. The DILIN Prospective Study is a multicenter observational study of patients 2 years or older with suspected drug-induced liver injury meeting the predefined biochemical criteria for liver test abnormalities (3). Enrolled patients were clinically characterized in a standardized manner, and the likelihood of DILI was adjudicated by expert consensus, as were alternate etiologies for liver injury when DILI was determined to be either only possible or unlikely (3). For the purposes of this study, we analyzed the demographic and clinical data, including implicated agents, and the outcomes of DILI. The pattern of liver injury at presentation was defined using the R value (ratio of alanine aminotransferase (measured value divided by the upper limit of normal) to alkaline phosphatase (measured value divided by the upper limit of normal)) as cholestatic ($R < 2$), mixed ($R = 2–5$), or hepatocellular ($R > 5$). The primary outcome of interest is the adjudication of the liver injury event to a drug or an HDS as high-confidence DILI, defined as definite, highly likely, or probable causality scores. The Roussel Uclaf Causality Assessment Method (RUCAM) score assigned by the enrolling investigator in all cases and for all implicated agents since high suspicion of DILI was the key reason for enrollment in the DILIN (5). Individuals who are included in the study have been included in other papers published by the DILIN (2,4). In particular, this cohort served as the basis for our recent observation that the Charlson Comorbidity Index (CCI) is an independent predictor of overall mortality in individuals presenting with suspected DILI (2).

The medical comorbidity burden at presentation was quantified using the CCI (6). Patients were grouped by the CCI as no, mild ($CCI > 0$ but $\leq$ 75th percentile), and significant comorbidity ($CCI >$ 75th percentile) corresponding to ($CCI = 0$), ($CCI = 1–2$), and ($CCI > 2$), respectively. Descriptive analyses included a comparison of clinical characteristics according to the CCI study groups. We compared the proportions of high-confidence DILI (probable, very likely, or definite) vs low-confidence DILI (possible or unlikely) across the patient groups who belonged to the no, mild, or significant comorbidity category. Alternate etiologies of liver injury were also compared among the comorbidity groups, with attention to cases adjudicated as non-DILI but without an identifiable competing etiology. Comparisons of categorical variables between the study groups were performed using the χ^2 or Kruskal–Wallis test. Comparisons of continuous variables among the study groups were performed using the Mann–Whitney test or analysis of variance. Statistical significance was defined as a P value < 0.05 for all analyses.

RESULTS

Patient and liver injury characteristics

The study cohort consisted of 551 patients, mean age 49 ± 18 years, and 46% were men. This cohort combines 2 previously described cohorts used to derive and validate a model using the CCI, model for end-stage liver disease, and albumin to predict 6-month mortality in patients with suspected DILI (2). The median CCI was 0 (interquartile range 0–2), with 53% having no comorbidity ($CCI = 0$), 30% mild comorbidity ($CCI = 1–2$), and 17% significant comorbidity ($CCI > 2$). The most frequent conditions contributing to the CCI were diabetes (15%), pulmonary disease (13%), and malignancy (10%). We compared patient and liver injury characteristics in patients with suspected DILI according to the categories of comorbidity (Table 1). Compared with the patients with no or mild comorbidity, those with significant comorbidity were older and more frequently men. The pattern of liver injury in patients with significant comorbidity was more frequently cholestatic and less frequently hepatocellular. The most common class of implicated agents was antimicrobials in all the groups. However, HDS was predominantly implicated in patients with no comorbidities, whereas antineoplastic agents were predominantly implicated in patients with significant comorbidity. Increasing comorbidity burden was associated with a greater number of concomitant medications and lower RUCAM scores.

Comorbidity and likelihood of DILI

On DILIN causality assessment, 442 patients (80.2%) were adjudicated as having DILI (definite, highly likely, or probable), whereas 109 (19.8%) were adjudicated as having non-DILI (see Supplemental Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A230). Increasing comorbidity burden was associated with a significantly lower probability of DILI confidence by expert consensus (Figure 1). Thirty-four percent patients with significant comorbidity were adjudicated as non-DILI compared with 24% and 13% for patients with mild or no comorbidity, respectively ($P <$ 0.001). We compared the medical comorbidities comprising the CCI in patients with possible or unlikely DILI vs high-confidence DILI (Table 2). The conditions with a significantly higher frequency in patients with possible or unlikely DILI included diabetes mellitus, chronic pulmonary disease, stroke or transient ischemic attack, congestive heart failure, myocardial infarction, peripheral vascular disease, renal disease, AIDS, and lymphoma. The burden of liver disease and malignancy was similar between the 2 groups.

In cases adjudicated as non-DILI, an alternate diagnosis was established by consensus per the DILIN protocol. Liver injury was ascribed to well-defined non-DILI etiologies in similar proportions of patients with significant vs no or mild comorbidity (73% vs 79%, $P = 0.4$, respectively). The most common alternative etiology of liver injury in all patients was viral hepatitis, but patients with significant comorbidity more frequently had sepsis, ischemia, and malignancy, whereas autoimmune hepatitis (AIH) was more frequent in patients with no or mild comorbidities (Table 3).

The factors associated with liver injury events that were assessed as high-confidence DILI cases are described in Table 4. Age, number of concomitant drugs, cholestatic (relative to hepatocellular) injury pattern, and increasing comorbidity burden were inversely associated with a lower likelihood of high-confidence DILI on simple logistic regression. On multiple logistic regression, increasing comorbidity burden was independently associated with a progressively lower likelihood of

Table 1. Comparison of patient and liver injury characteristics in patients with suspected drug-induced liver injury according to the CCI category[a]

Variable	Patients, N = 551	CCI = 0, n = 297	CCI = 1–2, n = 161	CCI > 2, n = 93	*P* value
Age (yr)	50 ± 18	44 ± 17	55 ± 18	58 ± 14	<0.001
Male (%)	46	41	47	58	0.015
Body mass index (kg/m^2)	28.2 ± 7.1	27.1 ± 6.2	29.7 ± 8.4	28.9 ± 6.9	0.002
Race/ethnicity (%)					0.2
White	79.6	79.8	83.1	73.1	
Black	13.3	11.4	11.9	21.5	
Asian	2.5	3.4	1.9	1.1	
Other	4.5	5.4	3.1	4.3	
Hispanic (%)	5.6	6.1	4.3	6.5	0.7
Latency (d)	162 ± 496	147 ± 495	125 ± 380	279 ± 645	0.18
Alanine aminotransferase (IU/L)	725 ± 921	816 ± 933	735 ± 1,064	407 ± 402	<0.001
Alkaline phosphatase (IU/L)	286 ± 280	247 ± 157	295 ± 275	398 ± 491	0.15
Bilirubin (mg/dL)	6.3 ± 5.8	6.3 ± 5.7	6.6 ± 5.9	5.5 ± 5.9	0.064
INR (at onset)	1.2 ± 0.8	1.3 ± 0.8	1.4 ± 1	1.4 ± 0.5	<0.001
INR (at peak MELD)	1.7 ± 1.5	1.4 ± 1	2 ± 2.1	2 ± 1.4	<0.001
Creatinine (mg/dL)	1.2 ± 0.5	1.1 ± 0.3	1.2 ± 0.5	1.5 ± 0.9	<0.001
MELD	15.1 ± 6.5	14.2 ± 5.5	15.8 ± 6.7	16.8 ± 8.3	0.024
Albumin (g/dL)	3.5 ± 0.7	3.7 ± 0.7	3.4 ± 0.7	3.1 ± 0.7	<0.001
R value	11.2 ± 16.9	13.5 ± 18.9	10.4 ± 16	5.4 ± 8.1	<0.001
Injury pattern (%)					<0.001
Hepatocellular	48.6	54.2	47.8	32.3	
Mixed	22.5	25.3	21.1	16.1	
Cholestatic	28.9	20.5	31.1	51.6	
Class of agents (most common) (%)					
Antimicrobial	45.2	47.1	42.9	43	0.6
Antineoplastic	6.2	1.7	5.6	21.5	<0.001
Cardiovascular	9.3	8.4	5.6	18.3	0.003
Herbal and dietary supplement	16.5	23.9	11.2	2.2	<0.001
Neurologic	7.4	7.7	9.3	3.2	0.2
No. of implicated agents	1.4 ± 0.7	1.4 ± 0.8	1.4 ± 0.6	1.5 ± 0.7	0.5
No. of concomitant drugs	7.8 ± 7.5	5.6 ± 5.3	9.1 ± 8.8	11.7 ± 8.4	<0.001
RUCAM score	6.2 ± 2.3	6.6 ± 2	6 ± 2.4	5.6 ± 2.7	0.004

CCI, Charlson Comorbidity Index; INR, international normalized ratio; MELD, model for end-stage liver disease; RUCAM, Roussel Uclaf Causality Assessment Method.
[a]Values shown as mean ± SD or percentages.

high confidence for both mild and significant comorbidities relative to no comorbidity (Table 4).

The mean RUCAM scores decreased with increasing comorbidity burden (Table 1). We assessed the impact of comorbidity burden on the diagnosis of DILI using the RUCAM (score > 5). We found that the likelihood of DILI by the RUCAM also decreased with increasing burden (73% with no comorbidity, 67% with mild comorbidity, and 58% with significant comorbidity [P = 0.006]). Among patients adjudicated to have DILI by expert consensus, the proportion of patients correctly classified as DILI by the RUCAM also decreased with increasing comorbidity burden (77% with no comorbidity, 78% with mild comorbidity, and 69% with significant comorbidity [P = 0.047]). The diagnostic accuracy of the RUCAM was 74% with no comorbidity, 75% with mild comorbidity, and 68% with significant comorbidity.

To assess for the potential impact of the CCI on the performance of the RUCAM, we performed a preliminary analysis where the RUCAM was modified to account for the CCI category. Among the 545 patients with the RUCAM scores available, we modified the RUCAM score by adding 1 point for CCI = 0, making no changes for CCI 1–2 and subtracting 1 point for CCI > 2. Compared with the standard RUCAM and using expert opinion to diagnose DILI,

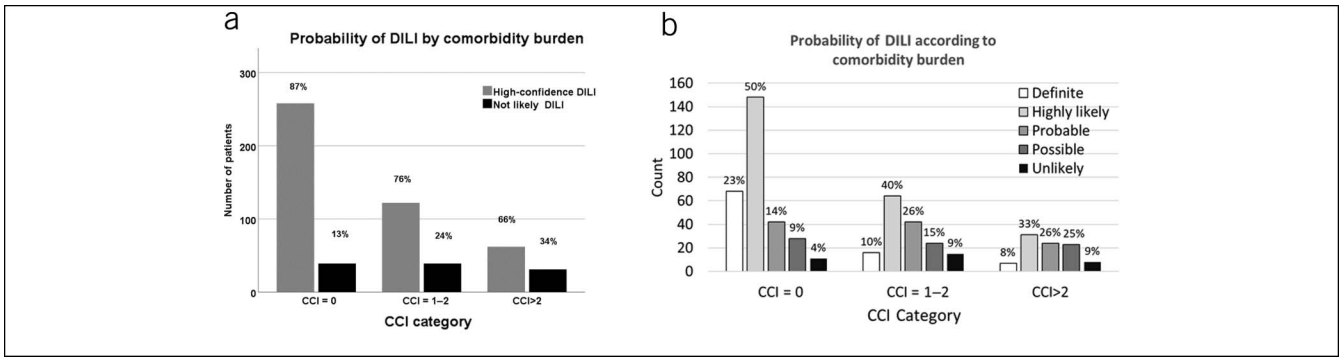

Figure 1. The probability of DILI as adjudicated by consensus of expert opinion according to comorbidity burden as measured by the CCI. (**a**) The proportion of high-confidence DILI (definite, highly likely, or probable) and not likely DILI (possible or unlikely adjudication) in patients with no (CCI = 0), mild (CCI = 1–2), and significant (CCI > 2) comorbidity burden. (**b**) The proportion of individual causality categories (definite, highly likely, probable, possible, or unlikely) in patients with no (CCI = 0), mild (CCI = 1–2), and significant (CCI > 2) comorbidity burden. CCI, Charlson Comorbidity Index; DILI, drug-induced liver injury.

the CCI-modified RUCAM had increased sensitivity (76%–83.3%), no change in specificity (62% for both), and better agreement with expert opinion in identifying DILI (kappa [agreement] increased from 0.311 to 0.408). The net effect of the CCI-modified RUCAM was that among patients *with* DILI, as judged by expert opinion, 32 of 40 patients would have been reclassified as DILI (8 of 40 patients were reclassified as non-DILI). There was no net difference observed in patients *without* DILI (5 reclassified as non-DILI and 5 reclassified as DILI). As a result, 32 of 105 patients with DILI (30%) who were classified as non-DILI by the standard RUCAM were reclassified as DILI using the CCI-modified RUCAM score. A modification of the RUCAM scoring with the inclusion of comorbidity resulted in increased negative predictive value (39%–47.9%) and diagnostic accuracy (73.2%–79.1%) while maintaining a high positive predictive value (89%–90%).

DISCUSSION

This is a study of a prospectively enrolled cohort that was well characterized in whom the causality assessment of DILI was based on consensus expert opinion. The main finding was that increasing comorbidity burden was associated with a progressively lower degree of confidence in a final diagnosis of DILI. This is a novel and important finding, with potentially significant ramifications in the determination of DILI, which lacks a diagnostic gold standard biomarker or test.

Table 2. Comorbidities comprising the Charlson Comorbidity Index in the study group and compared in patients with possible or unlikely DILI vs probable, very likely, or definite DILI[a]

Comorbidity (%)	Overall, N = 551	Possible or unlikely DILI, n = 109	Probable, very likely, or definite DILI, n = 442	*P* value
Diabetes uncomplicated/complicated	10.9/4.2	14.7/8.3	10/3.2	0.02
Chronic pulmonary disease	12.9	21.1	10.9	0.004
Malignancy nonmetastatic/metastatic	6/3.3	7.3/1.8	5.7/3.6	0.5
Connective tissue disease	6.2	4.6	6.6	0.4
Liver disease mild/moderate to severe	4/1.8	4.6/1.9	3.8/2.8	0.7
Stroke or transient ischemic attack	4.5	8.3	3.6	0.04
Congestive heart failure	4.2	8.3	3.2	0.02
Myocardial infarction	4.2	8.3	3.2	0.02
Peripheral vascular disease	3.8	7.3	2.9	0.03
Renal disease (moderate to severe)	3.6	8.3	2.5	0.004
Peptic ulcer disease	3.1	5.5	2.5	0.1
Leukemia	2	3.7	1.6	0.16
AIDS	1.8	4.6	1.1	0.015
Lymphoma	1.5	5.5	0.5	<0.001
Dementia	0.9	0.9	0.9	0.99
Hemiplegia or paraplegia	0.2	None	0.2	0.6

DILI, drug-induced liver injury.
[a]Data shown as percentages.

Table 3. Alternative diagnoses ascribed to liver injury in cases adjudicated as possible or unlikely drug-induced liver injury[a]

Alternate diagnosis (%)	Patients, N = 109	CCI = 0, n = 39	CCI = 1–2, n = 39	CCI > 2, n = 31	*P* value
Viral	21.1	15.4	25.6	22.6	
AIH	15.6	23.1	17.9	3.2	
Biliary disease	11	5.1	20.5	6.5	
Other liver disease	8.3	12.8	2.6	9.7	0.3
Sepsis	7.3	5.1	2.6	16.1	
Ischemia	5.5	2.6	5.1	9.7	
Malignancy	3.7	None	5.1	9.7	
Other	2.8	2.6	2.6	3.2	
Unknown	24.8	33.3	17.9	22.6	

AIH, autoimmune hepatitis; CCI, Charlson Comorbidity Index.
[a]Data shown as percentages.

The RUCAM is commonly used as a reference scoring system to aid in the diagnosis of DILI (5). Here, we used the RUCAM for the purpose of demonstrating the potential impact of comorbidity on DILI adjudication using a system other than expert consensus as used in the DILIN. Notably, the RUCAM in this study was scored prospectively by experts in DILI, assessing cases of liver injury highly suspicious of DILI. Although the mean RUCAM scores decreased with increasing comorbidity burden (Table 1), comorbidity burden still impacted the accuracy of the RUCAM in identifying DILI, as judged by expert opinion. This confirms the main study findings and highlights the challenges of identifying DILI in the setting of increased comorbidities. The CCI-modified RUCAM was our attempt to leverage these findings to refine the causality assessment of DILI. Since expert opinion already incorporates clinical considerations, including comorbid conditions, it is difficult to modify that process with the CCI scores. In our preliminary analysis, the CCI-modified RUCAM was superior to the standard RUCAM in identifying DILI as diagnosed by expert opinion and improving the overall agreement between the RUCAM and expert opinion. Although the differences in performance of the RUCAM were relatively small, they still represent an incremental improvement (33%) in agreement with expert opinion. Some limitations of the RUCAM, including the diagnostic inaccuracy and lower reproducibility, have been reported, and some modifications have been previously suggested (7,8). The incorporation of comorbidity burden in diagnostic algorithms for DILI may potentially refine the performance of the RUCAM.

In our analysis, we used the CCI to measure comorbidity burden. However, we point out that the CCI is one of many comorbidity scales, none of which can capture all medical comorbidities. Our goal was to demonstrate the impact of comorbidity burden on the causality assessment of DILI. The CCI is a well-known index and has been validated in multiple studies. It lends itself well for the purpose of our descriptive study, and we highlight that our intent was not to redefine the CCI or compare it with other comorbidity scales. We did, however, explore specific comorbid conditions that contribute to both the CCI and possibly the severity of liver injury, namely underlying liver disease.

Underlying liver disease was noted in similar frequencies in patients with or without DILI (Table 2). Alternate liver disease–related liver injury was also found in similar proportions of patients

Table 4. Simple and multiple logistic regression analyses for predictors of drug-induced liver injury as determined by expert opinion

	Simple logistic regression		Multiple logistic regression	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.99 (0.97–0.99)	0.04	0.99 (0.98–1.01)	0.6
No. of concomitant drugs	0.97 (0.95–0.99)	0.03	0.99 (0.98–1.02)	0.6
Pattern of liver injury				
Hepatocellular (reference)				
Mixed	1.8 (0.98–3.5)	0.058	1.9 (1–3.6)	0.05
Cholestatic	0.6 (0.4–0.98)	0.04	0.8 (0.5–1.3)	0.4
CCI				
CCI = 0 (reference)				
CCI = 1–2	0.47 (0.29–0.77)	0.003	0.53 (0.31–0.89)	0.016
CCI > 2	0.3 (0.18–0.52)	<0.001	0.37 (0.2–0.69)	0.001

CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odds ratio.

without DILI, with the sole exception of AIH. A progressively higher frequency of AIH was noted inversely to comorbidity burden in patients with non-DILI (Table 3). Together, these data suggest that underlying liver disease or cirrhosis did not impact the relationship of comorbidity burden and DILI causality assessment, but a diagnosis of AIH did. The clinical presentation of AIH can be quite similar to DILI without the overt clue of being a nonliver comorbidity, such as heart failure leading to shock liver or leukemia leading to sepsis. Indeed, a liver biopsy may be needed and even that may not be definitive in separating AIH from DILI. Thus, increased scrutiny is warranted to rule out AIH in patients with suspected DILI and no or mild comorbidity burden.

The increasing frequency of cholestatic liver injury pattern in patients with increasing comorbidity burden (Table 1) and non-DILI (see Supplement Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A230) was interesting. These patients were also older and more frequently men, characteristics that have been associated with cholestatic DILI patterns overall (9,10). Cholestatic liver injury was associated with a lower likelihood of DILI but not when adjusted for other comorbid conditions and comorbidity burden. Biliary diseases were not explanatory as such diagnoses were not more common in patients with non-DILI and high comorbidity (Table 3). Therefore, the preponderance of cholestatic presentation is probably explained by the differences in other competing diagnoses, such as sepsis, which was over 3-fold more common in CCI $>$ 2 compared with CCI $=$ 0, patients with non-DILI (Table 3).

Our hypothesis that comorbidity burden could lead to a lower likelihood of DILI is clinically intuitive but has not been rigorously scrutinized. Beyond providing confirmation of this association and an element of novelty, the data presented here also carry important clinical ramifications. We previously demonstrated the impact of increasing comorbidity burden on mortality risk in suspected DILI (2) and here demonstrate its impact on the causality assessment of DILI. The latter finding is timely given the guidance from the World Health Organization for modifications to improve the RUCAM (Naga Chalasani, MD, oral communication, 2018). Our preliminary analysis suggests that a modification of the RUCAM by including the CCI as an additional variable improves its performance when compared with expert consensus as the reference adjudication method. Additional studies are warranted to confirm our findings and inform the potential modifications of the RUCAM and other DILI causality assessment tools.

The strengths of the study include the prospective design of the DILIN study and standardized phenotyping of patient factors and both the liver- and non-liver-related outcomes. The analysis of comorbidity in DILI is novel and demonstrates that although half of patients with suspected DILI have no comorbidities, a sizable number have significant comorbidities. The latter patients are less likely to have DILI as the etiology of liver injury. We would like to point out that this study was based on the data from only 2 centers of the DILIN rather than all 5 participating centers. Because the medical comorbidities comprising the CCI were not all systematically documented in the study case report forms, we had to review the source documents, which was labor intensive and prevented us from including all the DILIN centers. Finally, the lack of a gold standard to define DILI remains a challenge in this and all studies on the causality assessment of DILI.

In summary, we found increasing comorbidity to be associated with less likelihood of being given a firm diagnosis of DILI by both expert opinion and the RUCAM scoring. Further studies are needed to investigate the utility of including comorbidity burden as a potentially important element in improving the performance of the DILI causality instruments.

CONFLICTS OF INTEREST

Guarantor of the article: Naga Chalasani, MD.

Specific author contributions: M.G.: study design, data collection and analysis, manuscript preparation, and final approval. J.G.: data collection and analysis, manuscript preparation, and final approval. L.Y., L.C., A.R., and C.D.B.: study design, data collection and analysis, manuscript preparation, and final approval. R.V.: study design, data interpretation, manuscript preparation, and final approval. H.B.: data analysis, manuscript preparation, and final approval. P.H. and N.C.: study design, data collection and analysis, manuscript preparation, and final approval.

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Potential competing interests: N. Chalasani holds consulting agreements from several pharmaceutical companies for activities related to NAFLD, DILI, and liver disease in general. His institution receives research grants on his behalf from Intercept, Lilly, Cumberland, Galectin, and Exact Sciences. But none represents a conflict of interest for this paper. M.G., J.G., L.Y., L.C., L.D., and P.H.H. report no potential conflicts of interest. R. Vuppalanchi has consulting agreements and research support from pharmaceutical companies, but they do not represent potential conflict for this paper.

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Study Highlights

WHAT IS KNOWN

- ✓ DILI lacks a gold standard test and is a diagnosis of exclusion.
- ✓ Comorbidity burden may impact the causality assessment of DILI because of clinical complexity and competing etiologies of liver injury.

WHAT IS NEW HERE

- ✓ Increasing comorbidity burden as measured by the CCI is associated with a lower causality assessment of DILI by expert opinion.
- ✓ This finding was also confirmed in the assessment of DILI by the widely used scoring system of the RUCAM.

TRANSLATIONAL IMPACT

- ✓ Clinical suspicion of DILI versus competing etiologies of liver injury can be refined by consideration of an individuals comorbidity burden.
- ✓ CCI may enhance the diagnostic accuracy of RUCAM.

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