no implicated drug, the patient was excluded. Yet in the list of drugs contributing to death the authors mention that a number of drug details were not available. These statements are contradictory. It is difficult to understand how the researchers were able to reconcile the diagnosis of DILI when the ingredients are unknown in such a large number of patients. From a total of 27,245 cases, the authors state 25,927 had a probable or highly probable DILI. This means an astonishing 95.2% were at least probable on a retrospective analysis with no predefined criteria for DILI.

Fourth, when antituberculosis drug details were not available for a number of patients with DILI, how did the authors calculate the incidence or frequency of individual drugs or agents causing DILI; for example, single agents 60.34%, double agents 18.22%, and ≥3 agents 21.43%. Moreover, in the supplementary figure enlisting drugs causing mortality, the authors state in at least one-third of patients the details of the drug were not available.

Fifth, the study included predominantly hospitalized patients, which generally translates as severe disease. Therefore, it is difficult to explain the low mortality of 0.39%. The death rate of 0.39% and a liver transplantation rate of <1.08% is contrary to published literature. In another DILI study from China, the overall mortality was 8.6%,” which is very consistent with previous DILI studies.

Sixth, nowhere in the article are the mean bilirubin levels, transaminase levels, and international normalized ratio levels provided including in patients with jaundice, which boils down to the question how was jaundice defined? Was there a cutoff level for jaundice? Of note, 5460 hepatocellular injuries (44.40%; 95% confidence interval, 43.52–45.28) resulted in laboratory values consistent with Hy's Law (serum alanine aminotransferase of >3 and a total serum bilirubin >2 the upper limit of normal). It is thus difficult to understand the statement “that 80.76% of cases did not experience jaundice.”

Seventh, the authors state “242 centres out of 308 provided DILI cases from some but not all clinical departments. Thus, when all cases of DILI are not captured extrapolating it to the entire country is doubtful. Further, as only 66/308 centers provided details the authors claim “that a majority of patients were reevaluated” seems as contradictory.

Finally, Supplemental Figure 6 states life-threatening (“fatal cases”) were 384 DILI cases, including 280 cases of progression to hepatic failure, 2 liver transplantations, and 102 deaths. This sentence does not make sense; fatal means dead.

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diagnosis of DILI is commonly used clinically, but reports from Europe and America indicated that the misdiagnosis rate of DILI reached 47.1% and 28.5%, respectively.\(^2\)\(^-\)\(^4\) Although the Roussel Uclaf Causality Assessment Method (RUCAM) is widely documented in literature for DILI, some ambiguous questions and weaknesses influence its accuracy resulting in an update in 2015. RUCAM is more limited in assessing the causality of TCM owing to fewer warning labels and published reports regarding the hepatotoxicity and frequent polypharmacy of TCM.\(^4\) Moreover, the quality variation, adulteration, and toxin contaminants of TCM are not included in the RUCAM system. Additionally, clinical diagnosis of TCM DILI is more difficult because of the complicated compositions of formula, drug combination, misuse and unreasonable use, physique, heredity, and so on. Misuse and unreasonable use are in a large proportion in practice. For example, the radix of Gynura segetum (Lour.) Merr (Tu-San-Qi in Chinese) is a completely misused substitute and fake substitution for Panax notoginseng (Burkill) F. H. Chen (San-Qi in Chinese). Tu-San-Qi is not stipulated in Chinese Pharmacopoeia as TCM.

In summary, we suggest interpreting this study by Shen at al as a beneficial attempt in researching TCM DILI and herb-induced liver injury (HILI), which is far from a final adjudication. HILI has become a global concern due to the widespread use of products containing herbs. Fortunately, steps forward have been taken. In 2016 and 2018, the China Association of Chinese Medicine and the China Food and Drug Administration (the predecessor of National Medical Product Administration) issued Guidelines for clinical diagnosis of herb-induced liver injury and Guidance for the clinical evaluation of traditional Chinese medicine-induced liver injury respectively, developing an organized and systemic approach to HILI.\(^3\)\(^-\)\(^5\) However, it must be made clear that such guideline should be continuously revised and improved in accordance with research progress and regulatory requirements.

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Conflicts of Interest
The authors disclose no conflicts.

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Reply. We have carefully read the letters from our peers who are interested in our work, which we explain and discuss below. The diagnosis at discharge are all made as drug-induced liver injury (DILI) for the initially screened 29,478 patients. According to the protocol, all these cases needed to be reevaluated by the Roussel Uclaf causality assessment method (RUCAM) or expert opinion process, which was recognized as assessment of causality, to confirm that they were probable or highly probable DILI cases. There were 25,927 patients who were finally confirmed to be in accordance with the protocol and enrolled into the study.\(^1\) Therefore, the term “confirmed DILI cases” described in the abstract referred to the probable or highly probable DILI cases, which were confirmed by the reevaluation process. This was also the reason why the study had a high screening success rate.

According to the European DILI guideline released this year, liver biochemical threshold should meet one of the following criteria: (1) alanine aminotransferase of ≥5× the upper limit of normal (ULN); (2) alkaline phosphatase of ≥2× ULN; and (3) alanine aminotransferase of ≥3× ULN + total bilirubin (TBIL) of ≥2× ULN.\(^2\) However, in our study, inclusion criteria did not include specific cutoff levels for liver chemistries. The reason is that Chinese DILI guideline (issued in 2015 in Chinese version) emphasizes on causality assessment, without specifically recommending the liver biochemical threshold when diagnosing DILI.\(^5\) Therefore, it was inevitable that some of the mild DILI cases who might be considered as an adaptor were included. It should be noted that among the 25,927 enrolled cases in this study, 23.38% of patients had preexisting liver diseases, and were all assessed as probable or highly probable DILI at liver injury onset.

Information regarding the suspected drugs was determined according to the medical history records. Cases who had no drug information or whose causality was unable to assess owing to incomplete drug information were excluded from the study. As a large-scale retrospective study, some of the suspected drug information was not comprehensive. “Details unknown” of the drug described in the article was referring to the missing of detailed chemical/trade name of the drug; however, the information of the class of the drug were well-recorded in the medical history.

The DILI-associated mortality rate in this study was lower than we expected, as mentioned by our peers. One possible reason is that some of the patients had mild disease, which would usually be excluded in other registries. The other reason is that, the inpatients that we screened were not only hospitalized for liver disease, most of these cases came from other departments. In the study of Chen’s team (fatality rate of 8.6%), all DILI cases were from department of liver disease, whose liver injury might be more severe.\(^4\)