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Letter to the Editor

Risk levels of herb-induced liver injury in Korea: from a meta-analysis

Adverse drug reactions (ADRs) are very common and are experienced by approximately 10% of patients treated in hospitals in Europe.[1] Among ADRs, drug-induced liver injury (DILI) is the most important in terms of drug safety and is a major reason for acute liver failure in the US.[2]

As more people use herbal products worldwide, there has been concern about the risk of herb-induced liver injury (HILI).[3] The role of herbal drugs in DILI has been controversial in China and Korea, where herbal remedies are very popular. Many clinical studies have assessed the risk of HILI in Korea. Therefore, we conducted a meta-analysis of the incidence of hepatotoxicity due to herbal drugs. Using domestic (KMBASE, https://kmbase.medric.or.kr/) and international (PubMed) databases, we surveyed publications investigating the incidence of HILI. Ultimately, nine studies (four prospective and five retrospective) were identified, including three reports in which 2006 was the first year (Fig. 1). These involved 8625 participants (3274 males; 5351 females), including 436 outpatients (three studies) and 8189 inpatients (six studies).

Meta-analysis by random-effects model was conducted to provide point estimates (95% CI) of prevalence with subgroup analysis to account for heterogeneity. To account for the potentially high inter-study heterogeneity, the pooled outcome measures and their corresponding 95% confidence intervals were calculated using a random-effects model fitted with the restricted maximum-likelihood estimator. The I2 statistic was used to evaluate the degree of heterogeneity between studies. Statistical analyses were performed using the "meta" packages (by Guido Schwarzer) in R (Ver. 4.0.2) & R Studio (Ver. 1.3.1073) software.

The overall incidence of HILI in Korea was 0.49% (95% CI 0.33–0.74%), and it was 0.57% in males and 0.30% in females (Fig. 1A–C). The incidence of ADRs including DILI can differ markedly depending on the country and study conditions. For example, the incidence of ADRs appears to be higher in prospective studies than in retrospective studies.[4] However, we found a similar incidence of HILI in prospective (0.51%) and retrospective (0.50%) studies (Fig. 1D). As expected, the incidence of HILI was higher in inpatients (0.62%) than outpatients (0.03%) (Fig. 1E). This is a general tendency in other studies including our previous study, which analyzed hepatic ADRs in 6193 participants in 99 RCTs of herbal preparations and found an 0.08% incidence of HILI, which is comparable to our current finding for outpatients (0.03%).[5] Regarding gender, females are generally believed to be more sensitive to DILI.[6] However, there are conflicting data suggesting that in elder adults, HILI predominates in males (37.5%) and not females (10.5%),[7] similar to our results for HILI (0.57% vs. 0.30%) (Fig. 1B and C). This HILI outcome (0.62% in inpatients) seems to be at the lower level of DILI due to conventional drugs among inpatients (0.7% to 1.4%).[8,9]

The medical issues regarding the safety of herbal drugs include calculating the risks of HILI, the clinical characteristics of HILI, listing the causative herbs, and exploring genetic susceptibility.[10] Although there are limitations regarding study quality and the number of participants, we systematically estimated the risk of HILI in Korea. This information is important both for practices regarding herbal prescriptions in clinics and research on the safety of herbs.

Conflict of interest

The authors declare no conflicts of interest.

Ethical statement

Not applicable for this manuscript as this work did not involve human subjects or laboratory animals.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2020.100705.
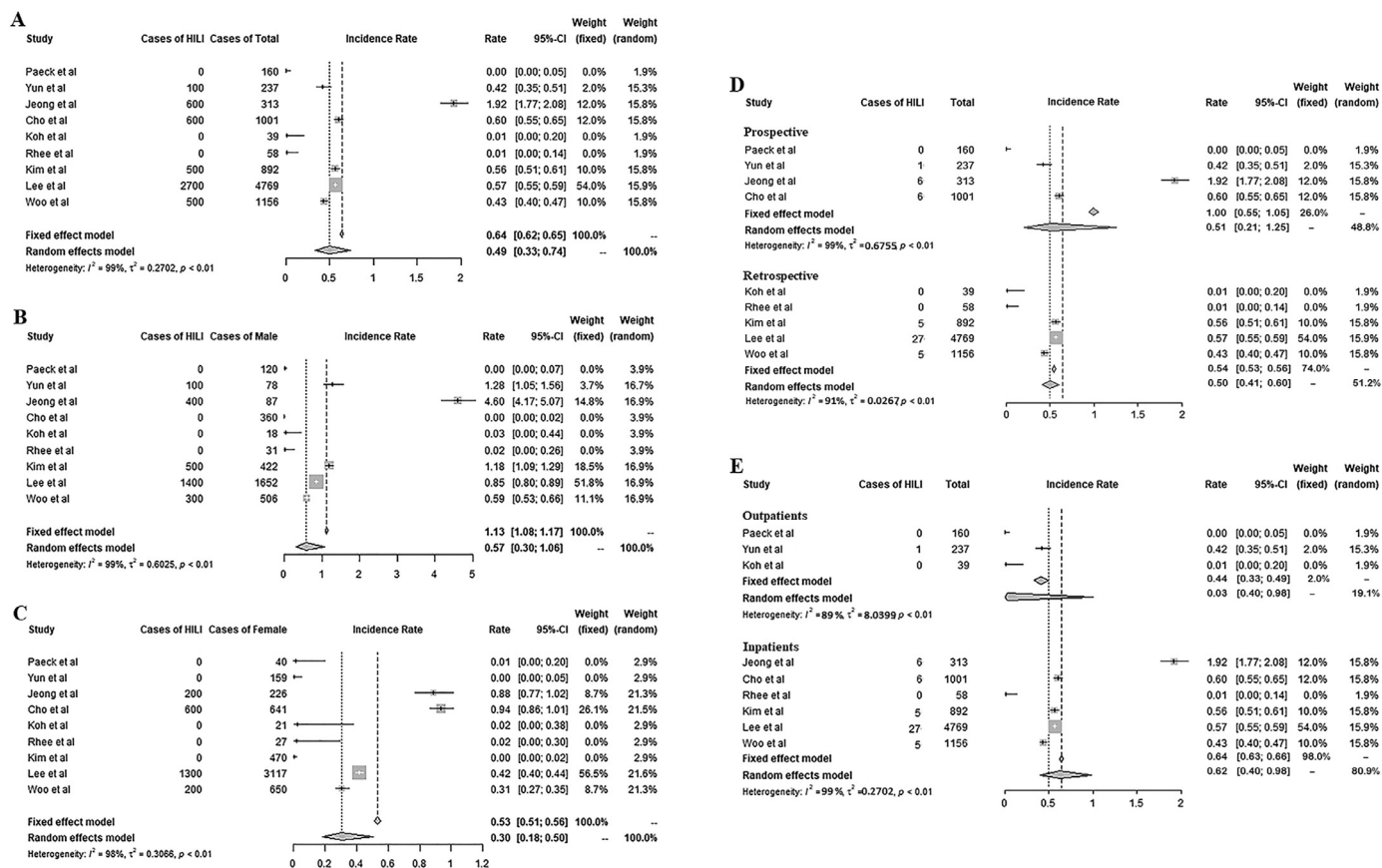
Fig. 1. Incidence rate of HILI. Total incidence rate (A), in male (B), in female (C), by methods (D), and by subjects (E) are presented.

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