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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 maximumlikelihood 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.

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Author contributions

Conceptualization: CG Son. Methodology: NH Lee. Software: YC Ahn. Validation: JH Cho. Formal Analysis: NH Lee. Investigation: NH Lee. Resources: GY Lee, CR Park, and SK Kim. Data Curation: YC Ahn. Writing the original draft: NH Lee. Writing the review & editing: GY Lee, CR Park, and SK Kim. Visualization: JH Cho. Supervision: CG Son. Project Administration: CG Son. Funding acquisition: CG Son.

Conflict of interest

The authors declare no conflicts of interest.

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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.

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Study	Cases of HILI Cases	of Total	Incidence	Rate	F	ate	95%-CI	(fixed)	(random)											
Paeck et al	0	160 F	11		ſ	00 00 0	0.0 021	0.0%	1 9%											
Yun et al	100	237	-			42 10 3	5.0.51	2.0%	15 3%	D									Weight	Weight
leono et al	600	313		_		92 117	7.2.081	12.0%	15.8%	Study	Cases of HILI	Total		Incidenc	e Rate		Rate	95%-CI	(fixed)	(random)
Cho et al	600	1001	-			60 0 5	5.0.651	12.0%	15.8%											
Koh et al	0	39				01 00	0.0201	0.0%	1 9%	Prospective				1.1						
Ron et al	0	59				01 10.0	0.0.14	0.0%	1.970	Paeck et al	0	160	+				0.00	10.00: 0.051	0.0%	1.9%
Kine et al	500	000			2	50 10.0	4.0.041	40.0%	45.00/	Yun et al	1	237					0.42	10.35: 0.511	2.0%	15.3%
Kim et al	500	692				50 [0.5	T, 0.0 IJ	10.0%	15.0%	Jeong et al	6	313					1.92	[1.77: 2.08]	12.0%	15.8%
Lee et al	2700	4/09				10.57 [0.5	5, 0.59]	54.0%	15.9%	Cho et al	6	1001		-			0.60	[0.55: 0.65]	12.0%	15.8%
woo et al	500	1150				.43 [0.4	0, 0.47]	10.0%	15.8%	Fixed effect model					\$		1.00	[0.55; 1.05]	26.0%	-
										Random effects mod	el						0.51	[0.21; 1.25]	-	48.8%
Fixed effect model			, v			.64 [0.6	2; 0.65]	100.0%		Heterogeneity: /2 = 99%.	$\tau^2 = 0.6755 \rho < 0.01$									
Random effects mode	1		<u>~</u>		-	.49 [0.3	3; 0.74]		100.0%											
Heterogeneity: /* = 99%, *	t" = 0.2702, p < 0.01	0	0.5 1	15	2					Retrospective										
		v	0.0	1.0	-					Koh et al	0	39					0.01	(0.00: 0.20)	0.0%	1.9%
-										Rhee et al	0	58	←				0.01	[0.00; 0.14]	0.0%	1,9%
В							2	Weight	Weight	Kim et al	5	892					0.56	[0.51; 0.61]	10.0%	15.8%
Study	Cases of HILI Cases	of Male	Incidence	Rate	R	ate	95%-CI	(fixed)	(random)	Lee et al	27	4769					0.57	[0.55: 0.59]	54.0%	15,9%
										Woo et al	5	1156		*			0.43	[0.40; 0.47]	10.0%	15.8%
Paeck et al	0	120 +			0	.00 [0.0	0; 0.07]	0.0%	3.9%	Fixed effect model				0			0.54	[0.53; 0.56]	74.0%	-
Yun et al	100	78	÷.		1	28 [1.0	5: 1.561	3.7%	16,7%	Random effects mod	el						0.50	[0.41; 0.60]	-	51.2%
Jeong et al	400	87	1	_	x 4	60 [4.1	7: 5.071	14.8%	16.9%	Heterogeneity: /2 = 91%,	$\tau^2 = 0.0267 \rho < 0.01$		_	11						
Cho et al	0	360 >			0	00 00	0.0021	0.0%	3.9%				ò	0.5	1 1.	52				
Koh et al	0	18 ↔			0	03 10 0	0.0441	0.0%	3.9%											
			i																	
NU00 01 31	n	31 ⊷	1		0	02 [0.0]	0.0 581	0.0%	3 9%											
Kinee et al	500	31 ← 422	: #		0	02 [0.0	0; 0.26]	0.0%	3.9%	F									Moight	Moight
Kinee et al Kim et al	500 1400	31 ← 422 1652	÷		1	.02 [0.0	0; 0.26] 9; 1.29] 0: 0.89]	0.0% 18.5% 51.8%	3.9% 16.9%	E	Cases of HILL	Total		Incidence	o Roto		Bata	05% CI	Weight	Weight
Rhee et al Kim et al Lee et al	500 1400 300	31 ← 422 1652 506			1	.02 [0.0] .18 [1.0] .85 [0.8]	0; 0.26] 9; 1.29] 0; 0.89] 3: 0.66]	0.0% 18.5% 51.8%	3.9% 16.9% 16.9%	\mathbf{E}_{study}	Cases of HILI	Total		Incidence	e Rate		Rate	95%-CI	Weight (fixed)	Weight (random)
Rhee et al Kim et al Lee et al Woo et al	500 1400 300	31 ← 422 1652 506			0 1 0 0	.02 [0.00 .18 [1.09 .85 [0.80 .59 [0.53	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66]	0.0% 18.5% 51.8% 11.1%	3.9% 16.9% 16.9% 16.9%	E study	Cases of HILI	Total		Incidence	e Rate		Rate	95%-CI	Weight (fixed)	Weight (random)
Knee et al Kim et al Lee et al Woo et al	500 1400 300	31 ← 422 1652 506			0	.02 [0.0) .18 [1.0] .85 [0.8] .59 [0.5]	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66]	0.0% 18.5% 51.8% 11.1%	3.9% 16.9% 16.9% 16.9%	E Study Outpatients	Cases of HILI	Total		Incidence	e Rate		Rate	95%-CI	Weight (fixed)	Weight (random)
Rhee et al Kim et al Lee et al Woo et al Fixed effect model Bandom effect model	0 500 1400 300	31 ← 422 1652 506			0 1 0 0	.02 [0.00 .18 [1.09 .85 [0.80 .59 [0.53 .13 [1.08	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17]	0.0% 18.5% 51.8% 11.1%	3.9% 16.9% 16.9% 16.9%	E Study Outpatients Paeck et al	Cases of HILI	Total	۲	Incidence	e Rate		Rate	95%-CI [0.00; 0.05]	Weight (fixed) 0.0%	Weight (random) 1.9%
Rhee et al Kim et al Lee et al Woo et al Fixed effect model Random effects mode	0 500 1400 300	31 ⊢ 422 1652 506			0 1 0 0 1	.02 [0.00 .18 [1.09 .85 [0.80 .59 [0.55 .13 [1.08 .57 [0.30	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 0; 1.06]	0.0% 18.5% 51.8% 11.1% 100.0%	3.9% 16.9% 16.9% 16.9% 100.0%	E Study Outpatients Paeck et al Yun et al	Cases of HILI 0 1	Total 160 237	۲	Incidence	e Rate		Rate 0.00 0.42	95%-Cl [0.00; 0.05] [0.35; 0.51]	Weight (fixed) 0.0% 2.0%	Weight (random) 1.9% 15.3%
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Kine et al Kine et al Lee et al Woo et al Fixed effect model Random effects mode Heterogenety: i [*] = 99%, 1 C Study Paeck et al Yun et al Jeong et al	0 500 1400 300 H I cases of HILI Cases 0 0 200	$31 \vdash$ 422 1652 506 0 of Female $40 \leftarrow$ $159 \vdash$ 226 226	Incidenc	1 1 3 4 e Rate	0 1 0 0 1 0 5	.02 [0.01 .18 [1.01 .85 [0.84 .59 [0.5] .13 [1.03 .57 [0.30 .57 [0.30 .64 .57 [0.30 .00 [0.1 0.88 [0.]	95%-C1 90; 0.20] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 0; 1.06] 95%-C1 00; 0.20] 00; 0.20] 77; 1.02]	0.0% 18.5% 51.8% 11.1% 100.0% Weight (fixed) 0.0% 8.7%	3.9% 16.9% 16.9% 16.9% 	E Study Outpatients Paeck et al Yun et al Koh et al Fixed effect model Random effects model Heterogeneby: 1 ² = 89 %. Inpatients Jeong et al Cho et al Rhee et al	Cases of HILI 0 1 0 H $t^2 = 8.0399 \rho < 0.01$ 6 6 0	Total 160 237 39 313 1001 58	. 1 U 1	Incidence	e Rate	-3	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01	95%-Cl [0.00; 0.05] [0.03; 0.51] [0.00; 0.20] [0.33; 0.49] [0.40; 0.98] [0.40; 0.98] [0.55; 0.65] [0.00; 0.14]	Weight (fixed) 0.0% 2.0% - - 12.0% 12.0% 0.0%	Weight (random) 15.3% 1.9% - 19.1% 15.8% 15.8% 1.9%
Kine et al Kine et al Lee et al Vivo et al Fixed effect model Random effects model Heterogenety: J ² = 95%, J C Study Paeck et al Yun et al Jeong et al Cho et al	0 500 1400 300 i i cases of HILL Cases - 0 0 200 600	31 ← 422 1652 506 0 of Female 40 ← 226 641	Incidence	1 1 3 4 e Rate 	0 1 0 0 1 0 5	.02 [0.01 .18 [1.01 .85 [0.8] .59 [0.5] .13 [1.02 .57 [0.30 .57 [0.30 .57 [0.30 .57 [0.30 .57 [0.30 .57 [0.30] .57 [0.30] .59 [0.50] .57 [0.30] .57 [0.30]	95%-C1 90; 0.20] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 0; 1.06] 95%-C1 00; 0.20] 00; 0.20] 00; 0.05] 77; 1.02] 36; 1.01]	0.0% 18.5% 51.8% 11.1% 100.0% Weight (fixed) 0.0% 8.7% 26.1%	3.9% 16.9% 16.9% 16.9% 	E Study Outpatients Pack et al Yun et al Koh et al Fixed effect model Random effects model Heterogeneb: / ³ = 89 %. Inpatients Jeong et al Cho et al Rhee et al Kim et al	Cases of HILI 0 1 0 2 = 8.0399 p < 0.01 6 6 0 5	Total 160 237 39 313 1001 58 892	· 1 U 1	Incidence	e Rate	-#	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.56	95%-Cl [0.05; 0.05] [0.05; 0.51] [0.00; 0.20] [0.30; 0.20] [0.40; 0.98] [0.40; 0.98] [0.40; 0.98] [0.55; 0.65] [0.00; 0.14] [0.51; 0.61]	Weight (fixed) 0.0% 2.0% - 12.0% 12.0% 0.0% 10.0%	Weight (random) 1.9% 15.3% - 19.1% 15.8% 15.8% 1.9% 15.8%
Kine et al Kine et al Lee et al Woo et al Fixed effect model Random effects mode Heterogenety: i ² = 99%, C Study Paeck et al Yun et al Jeong et al Cho et al Koh et al	0 500 1400 300 H Cases of HLI Cases 0 200 600 0	31 ← 422 1652 506 0 0 0 0 0 0 0 0 0 0 0 0	Incidenc	1 1 3 4 e Rate 	0 1 0 0 1 0 5	.02 [0.01 .18 [1.01 .85 [0.8] .59 [0.5] .13 [1.03 .57 [0.30 .57 [0.30] .57	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 0; 1.06] 95%-Cl 00; 0.20] 00; 0.05] 77; 1.02] 36; 1.01] 00; 0.38]	0.0% 18.5% 51.8% 11.1% 100.0% Weight (fixed) 0.0% 8.7% 26.1% 0.0%	3.9% 16.9% 16.9% 16.9% 100.0% Weight (random) 2.9% 2.9% 21.5% 2.1.5%	E Study Outpatients Paeck et al Yun et al Koh et al Fixed effect model Heterogenety: I ² = 89 %. Inpatients Jeong et al Cho et al Rhee et al Kim et al Lee et al	Cases of HILI 0 1 0 $P^{2} = 8.0359 p < 0.011$ 6 6 6 0 5 27	Total 160 237 39 313 1001 58 892 4769	. I U I	Incidence	e Rate	-3	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.56 0.57	95%-Cl [0.00; 0.05] [0.35; 0.51] [0.00; 0.20] [0.33; 0.49] [0.40; 0.98] [1.77; 2.08] [0.55; 0.65] [0.00; 0.14] [0.55; 0.59]	Weight (fixed) 0.0% 2.0% - 12.0% 12.0% 12.0% 0.0% 54.0%	Weight (random) 1.9% 15.3% 19.1% 15.8% 15.8% 15.8% 15.8% 15.9%
Kine et al Kine et al Lee et al Fixed effect model Random effects model Heterogenety: i ² = 99%, ¹ C Study Paeck et al Yun et al Jeong et al Cho et al Koh et al Rhee et al	0 500 1400 300 I Cases of HILL Cases 0 0 200 600 600 0 0	31 ← 422 506 506 0 of Female 40 ← 226 641 21 ← 27 ← 27 ←	Incidenc	1 1 3 4 e Rate	0 1 0 1 5	.02 [0.0] .18 [1.0] .85 [0.8] .59 [0.5] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .59 [0.5] .57 [0.3] .59 [0.5] .59 [0.5] .50 [0.5]	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 95%-Cl 0; 0.20] 00; 0.20] 00; 0.05] 77; 1.02] 36; 1.01] 00; 0.38] 00; 0.30]	0.0% 18.5% 51.8% 11.1% 100.0% (fixed) 0.0% 8.7% 26.1% 0.0%	3.9% 16.9% 16.9% 16.9% 100.0% Weight (random) 2.9% 2.1.5% 2.9% 2.9%	E Study Outpatients Paeck et al Yun et al Kixed effect model Random effects model Heterogeneby: /² = 89 %. Inpatients Jeong et al Cho et al Kim et al Lee et al Woo et al	Cases of HILI 0 1 c ² = 8.0399 p < 0.01 6 6 0 5 27 5	Total 160 237 39 313 1001 58 892 4769 1156	. 1 U 1	Incidence	e Rate	-#-	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.56 0.57 0.43	95%-Cl [0.00; 0.05] [0.35; 0.51] [0.00; 0.20] [0.33; 0.49] [0.40; 0.98] [1.77; 2.08] [0.55; 0.65] [0.00; 0.14] [0.55; 0.61] [0.55; 0.51] [0.40; 0.47]	Weight (fixed) 0.0% 2.0% - 12.0% 12.0% 0.0% 10.0% 54.0%	Weight (random) 1.9% 15.3% 1.9% 15.8% 15.8% 15.8% 15.8%
Kine et al Kine et al Lee et al Woo et al Fixed effect model Random effects mode Heterogenety: <i>i</i> ² = 99%, ' C Study Paeck et al Yun et al Long et al Koh et al Rhee et al Kin et al	0 500 1400 300 I Cases of HILI Cases - 0 Cases of HILI Cases - 0 200 600 0 0 0 0	31	Incidence	T T 3 4 e Rate — x — x	0 1 0 1 5	.02 [0.0] .18 [1.0] .85 [0.8] .59 [0.5] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .13 [1.0] .57 [0.3] .59 [0.5] .57 [0.3] .57 [0.3]	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 95%-Cl 0; 0.20] 0; 0.20] 0; 0.20] 0; 0.20] 0; 0.30] 0; 0.30] 0; 0.30] 0; 0.30]	0.0% 18.5% 51.8% 11.1% 100.0% Weight (fixed) 0.0% 0.0% 8.7% 26.1% 0.0% 0.0%	3.9% 16.9% 16.9% 16.9% 100.0% Weight (random) 2.9% 2.1.3% 2.1.5% 2.9% 2.9%	E Study Outpatients Paeck et al Yun et ai Kich et al Fixed effect model Random effects model Heterogenety: I ² = 89 % Impatients Jeong et al Cho et al Rhee et al Kine et al Lee et al Vico et al Fixed effect model	Cases of HILI 0 1 0 4 * = 8.0399 p < 0.01 6 6 6 0 5 27 5	Total 160 237 39 313 1001 58 892 4769 1156	. 1 U 1	Incidence	e Rate	-#	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.56 0.57 0.43 0.64 0.64	95%-Cl [0.00; 0.05] [0.35; 0.51] [0.00; 0.20] [0.40; 0.38] [0.40; 0.38] [1.77; 2.08] [0.55; 0.65] [0.00; 0.14] [0.55; 0.65] [0.00; 0.14] [0.55; 0.59] [0.40; 0.47] [0.40; 0.47]	Weight (fixed) 0.0% 2.0% - 12.0% 12.0% 12.0% 10.0% 54.0% 10.0% 98.0%	Weight (random) 1.9% 15.3% - 19.1% 15.8% 15.8% 15.8% 15.8% 15.8%
Kine et al Kim et al Lee et al Woo et al Fixed effect model Random effects model Heterogenety: i ² = 95%, 1 C Study Paeck et al Yun et al Jeong et al Cho et al Kho et al Kho et al Kho et al Lee et al Lee et al	0 500 1400 300 4 4 cases of HILI Cases 0 200 600 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	31 ← 422 1652 506 0 of Female 40 ← 159 ← 226 641 21 ← 27 ← 3117	Incidenc	1 1 3 4 e Rate — x	0 1 0 5	0.2 [0.0] 18 [1.0] 85 [0.8] 59 [0.5] 13 [1.0] 57 [0.3] Rate 0.01 [0.1 0.00 [0.1 0.94 [0.3 0.02 [0.1 0.02 [0.1 0.02 [0.1 0.02 [0.1] 0.02	0: 0.26] 9: 1.29] 0: 0.89] 3: 0.66] 3: 1.17] 0: 1.06] 95%-Cl 0: 0.20] 00: 0.20] 00: 0.20] 00: 0.05] 77: 1.02] 36: 1.01] 00: 0.30] 00: 0.30] 00: 0.30] 00: 0.30] 00: 0.44] 00: 0.44]	0.0% 18.5% 51.8% 11.1% 100.0% Weight (fixed) 0.0% 0.0% 0.0% 0.0% 0.0% 0.0% 0.0%	3.9% 16.9% 16.9% 16.9% 	E Study Outpatients Paeck et al Yun et al Koh et al Fixed effect model Random effects model Meterogenety: I ² = 89 %. Inpatients Jeong et al Cho et al Kine et al Lee et al Vico et al Fixed effect model Random effectes model	Cases of HILI 0 1 $c^2 = 8.0399 \rho < 0.01$ 6 6 6 6 0 5 27 5	Total 160 237 39 313 1001 58 892 4769 1156		Incidence	e Rate -	-*	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.56 0.57 0.43 0.64 0.62	95%-Cl [0.00; 0.05] [0.35; 0.51] [0.00; 0.20] [0.30; 0.49] [0.40; 0.98] [0.51; 0.65] [0.00; 0.14] [0.51; 0.65] [0.54; 0.59] [0.40; 0.47] [0.40; 0.98]	Weight (fixed) 0.0% 2.0% - - 12.0% 12.0% 12.0% 10.0% 54.0% 10.0% 98.0% -	Weight (random) 1.9% 15.3% 19.1% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8%
Kine et al Kine et al Lee et al Vioo et al Fixed effect model Random effects mode Heterogenety: / ² = 59%, 1 C Study Paeck et al Yun et al Jeong et al Cho et al Kine et al Kine et al Kine et al Vioo et al	0 500 1400 300 4 Cases of HILI Cases - 0 200 600 0 0 0 1300 200	31 ← 422 1652 506 0 of Female 40 ← 159 ← 226 641 21 ← 27 ← 470 ← 3117 650	Incidence	1 1 3 4 e Rate — <u>*</u>	0 1 0 0 5 5	0.2 [0.0] 18 [1.0] 85 [0.8] 59 [0.5] 13 [1.0] 57 [0.3] Rate 0.01 [0.4] 0.00 [0.4] 0.08 [0.1] 0.02 [0.4] 0.02 [0.4] 0.03 [0.4] 0.04 [0.4]	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 0; 1.06] 95%-CI 00; 0.20] 00; 0.20] 00; 0.05] 77; 1.02] 36; 1.01] 00; 0.30] 00; 0.30] 00; 0.30] 00; 0.32]	0.0% 18.5% 51.8% 11.1% 100.0% Weight (fixed) 0.0% 0.0% 0.0% 0.0% 56.5% 8.7%	3.9% 16.9% 16.9% 16.9% 100.0% Weight (random) 2.9% 2.9% 2.9% 2.9% 2.9% 2.9% 2.9% 2.9%	E Study Outpatients Paeck et al Yun et al Koh et al Fixed effect model Random effects model Heterogenety: I ⁷ = 89 %. Inpatients Jeong et al Cho et al Rhee et al Khe et al Exe et al Voo et al Fixed effect model Fixed effect model Random effects model Heterogenety: I ⁷ = 99 %.	Cases of HILI 0 1 0 1 2 * = 8.0399 p < 0.01 6 6 0 5 27 5 1 4 c ² = 0.2702, p < 0.01	Total 160 237 39 313 1001 58 892 4769 1156		Incidence	e Rate -	*	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.56 0.57 0.43 0.64 0.62	95%-Cl [0.00; 0.05] [0.35; 0.51] [0.00; 0.20] [0.33; 0.49] [0.55; 0.65] [0.00; 0.14] [0.55; 0.65] [0.40; 0.14] [0.55; 0.59] [0.40; 0.47] [0.63; 0.66] [0.40; 0.98]	Weight (fixed) 0.0% 2.0% - - 12.0% 12.0% 12.0% 10.0% 54.0% 10.0% 54.0% -	Weight (random) 15.3% 15.3% 1.9% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8%
Kine et al Kim et al Lee et al Woo et al Fixed effect model Random effects mode Heterogenety: i ² = 99%, C Study Paeck et al Yun et al Jeong et al Cho et al Kim et al Lee et al Woo et al	0 500 1400 300 A A Cases of HLL Cases 0 200 600 0 0 0 0 0 1300 200	$\begin{array}{c} 31 \leftarrow \\ 422 \\ 1652 \\ 506 \\ \hline \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	Incidenc	1 1 3 4 e Rate	0 1 0 1 0 5	0.2 [0.0] 1.8 [1.0] 5.5 [0.5] 1.3 [1.04 5.7 [0.3] 1.4 [1.04 5.7 [0.3] 0.01 [0.1] 0.01 [0.1] 0.01 [0.1] 0.02 [0.1] 0	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 95%-CI 00; 0.20] 00; 00; 00; 00; 00; 00; 00; 00; 00; 00;	0.0% 18.5% 51.8% 11.1% 100.0% 	3.9% 16.9% 16.9% 16.9% 	E Study Outpatients Paeck et al Yun et al Koh et al Fixed effect model Random effects model Heterogenety: I ² = 89 %. Inpatients Jeong et al Cho et al Rhee et al Kime et al Uvo et al Fixed effect model Random effects model Heterogenety: I ² = 99 %.	Cases of HILI 0 1 $c^2 = 8.0399 \rho < 0.01$ 6 6 6 0 5 27 5 H $c^2 = 0.2702, \rho < 0.01$	Total 160 237 39 1001 58 892 4769 1156	, 1 U 1	Incidence	e Rate - 1 1.5	-#	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.56 0.57 0.43 0.64 0.62	95%-Cl [0.00; 0.05] [0.35; 0.51] [0.00; 0.20] [0.40; 0.98] [0.40; 0.98] [0.55; 0.65] [0.55; 0.65] [0.55; 0.59] [0.40; 0.79] [0.40; 0.98]	Weight (fixed) 0.0% 2.0% - 12.0% 12.0% 12.0% 10.0% 54.0% 10.0% 98.0% -	Weight (random) 1.9% 15.3% 1.9% - 19.1% 15.8% 15.8% 15.8% 15.8% 15.8% 5.5% 15.8% - 80.9%
Kine et al Kine et al Lee et al Fixed effect model Random effects mode Heterogenety: I ² = 95%, 1 C Study Paeck et al Yun et al Jeong et al Cho et al Kine et al	0 500 1400 300 1 Cases of HILL Cases of 0 200 600 0 0 1300 200	31 ← 422 506 0 of Female 40 ← 226 641 21 ← 27 ← 27 ← 3117 650	Incidence	1 1 3 4 e Rate —	0 1 0 5 5	0.2 [0.0.] 18 [1.0.] 18 [1.0.] 50 [0.5] 13 [1.0[1.57 [0.3] Rate 0.01 [0.1] 0.00 [0.1 0.00 [0.1] 0.02 [0.1 0.02 [0.1] 0.02 [0.1] 0.02 [0.1] 0.03 [0.1] 0.33 [0.1]	0; 0.26] 9; 1.29] 9; 0.89] 9; 0.66] 9; 0.67] 9; 0.68] 9; 0.69] 9;	0.0% 18.5% 51.8% 11.1% 100.0% - Weight (fixed) 0.0% 0.0% 0.0% 0.0% 0.0% 0.0% 0.0% 0.0	3.9% 16.9% 16.9% 16.9% 16.9% 100.0% Weight (random) 2.9% 2.1.3% 2.9% 2.9% 2.9% 2.9% 2.1.6% 2.1.3%	E Study Outpatients Packet al Yun et al Koh et al Fixed effect model Random effects model Heterogeneb; / ² = 89 %. Inpatients Jeong et al Che et al Rhee et al Kim et al Lee et al Voo et al Fixed effect model Random effects model Heterogeneb;; / ² = 99 %.	Cases of HILI 0 1 1 0 1 1 0 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	Total 160 237 39 313 1001 58 892 4769 1156		Incidence	e Rate 	-1-	Rate 0.00 0.42 0.01 0.44 0.03 1.92 0.60 0.01 0.57 0.43 0.64 0.62	95%-Cl [0.00; 0.05] [0.35; 0.51] [0.00; 0.20] [0.33; 0.49] [0.40; 0.98] [1.77; 2.08] [0.55; 0.65] [0.00; 0.14] [0.51; 0.61] [0.55; 0.59] [0.40; 0.47] [0.40; 0.98]	Weight (fixed) 0.0% 2.0% - 12.0% 12.0% 10.0% 54.0% 98.0% -	Weight (random) 1.9% 15.3% 1.9% - 19.1% 15.8% 15.8% 15.8% 15.8% 15.8% 15.8% - 80.9%
Kine et al Kine et al Lee et al Woo et al Fixed effect model Random effects mode Heterogenety: <i>i</i> ² = 99%, ' C Study Paeck et al Yun et al Jeong et al Cho et al Kine et al Kine et al Kine et al Lee et al Woo et al Fixed effect model Random effects model	0 500 1400 300 4 Cases of HILI Cases of 0 200 600 0 0 1300 200 1300 200	31 ← 422 1652 506 0 of Female 40 ← 159 ← 225 641 21 ← 470 ← 3117 650	Incidence	1 1 3 4 e Rate 	0 1 0 1 5 - - -	0.2 [0.0.) 1.8 [1.0.] 1.5 [1.0.3] 1.5 [0.5] 1.3 [1.0[1.5 [0.3] 1.4 [1.0] 1.5 [0.3] 1.5 [0.3] 1.5 [0.3] 0.0 [0.1] 0.0 [0.	0; 0.26] 9; 1.29] 0; 0.89] 3; 0.66] 3; 1.17] 95%-C1 00; 0.20] 00; 0.05] 77; 1.02] 36; 1.01] 00; 0.30] 00; 0.30] 00; 0.30] 00; 0.30] 00; 0.30] 51; 0.56] 8; 0.50]	0.0% 18.5% 51.8% 11.1% 100.0% Weight (fixed) 0.0% 8.7% 26.1% 0.0% 56.5% 8.7%	3.9% 16.9% 16.9% 16.9% 100.0% Weight (random) 2.9% 21.5% 2.9% 2.9% 2.9% 2.9% 2.9% 2.9% 2.1.3%	E Study Outpatients Paeck et al Yun et ai Koh et ai Fixed effect model Random effects model Heterogeneky: I ² = 89 %. Inpatients Jeong et al Cho et al Rhee et al Kine et al Lee et al Hixed effect model Random effects model Heterogeneky: I ² = 99 %.	Cases of HILI 0 1 0 8 4 2 = 8.0399 p < 0.01 6 6 6 0 5 5 27 5 8 1 27 5 9 27 5 9	Total 160 237 39 313 1001 58 892 4769 1156		Incidence	e Rate - - 1 1.5	- <u>+</u> -	Rate 0.00 0.42 0.44 0.44 0.44 0.44 0.44 0.44	95%-Cl [0.00; 0.05] [0.3; 0.51] [0.00; 0.20] [0.30; 0.40] [0.5; 0.65] [0.00; 0.14] [0.55; 0.66] [0.00; 0.14] [0.55; 0.61] [0.55; 0.69] [0.40; 0.47] [0.40; 0.98]	Weight (fixed) 0.0% 2.0% 0.0% 2.0% - - - - - - - - - - - - - - - - - -	Weight (random) 1.9% 15.3% 19.1% 15.8% 15.8% 15.8% 15.8% 15.9% 15.8% 15.9% 15.8% 15.9%

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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