

# Effect of HELLP syndrome on acute kidney injury in pregnancy and pregnancy outcomes: a systematic review and meta-analysis

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## Research article

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# Abstract

## Background

HELLP syndrome is a common complication during pregnancy, especially among those who with gestational hypertension. At present, the impact of HELLP syndrome on AKI (acute kidney injury) and maternal and infant outcomes is controversial. Thus, we conducted a meta-analysis to find out more about the relationship between HELLP syndrome and acute kidney injury during pregnancy and pregnancy outcomes.

## Methods

We systematically searched PubMed, Embase and Cochrane Databases for cohort studies to assess the effect of HELLP syndrome on P-AKI (acute kidney injury in pregnancy) and maternal and infant outcomes. Using odds ratio (OR) with 95% confidence interval (CI) were pooled with a random- or fixed-effect models when appropriate.

## Results

This meta-analysis included 11 cohort studies with a total of 6333 Participants, including 355 cases of pregnant women with HELLP syndrome and 5979 cases that without. HELLP syndrome has been associated with relatively higher risk of AKI during pregnancy (OR 4.87 95% CI 3.31-7.17,  $P < 0.001$ ), fetal mortality (OR 1.56 95% CI 1.45-2.11,  $P < 0.001$ ) and Maternal death (OR 3.70 95% CI 1.72-7.99,  $P < 0.001$ ).

## Conclusions

HELLP syndrome has been associated with relatively higher risk of P-AKI, fetal mortality and Maternal death.

# Background

HELLP syndrome has been considered a serious complication of pre-eclampsia. It is characterized by the occurrence of hemolysis, elevated liver enzymes and thrombocytopenia. The effect of HELLP syndrome on pregnancy is enormous. A large number of studies have shown that HELLP syndrome is associated with acute kidney injury during pregnancy and pregnancy outcomes. Pregnant women with HELLP syndrome have a higher incidence of AKI and fetal mortality [1]. However, some studies have opposite conclusions [2]. Therefore, a systemic analysis of the relationship between HELLP syndrome and acute kidney injury during pregnancy and pregnancy outcomes is necessary.

# Methods

We have registered on PROSPERO and the code is CRD42018112333. We performed a systematic review of the literature based on the approach recommended by the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement for reporting meta-analysis [3]. Without language restrictions, the literature about Cohort studies or RCT that reported HELLP syndrome, AKI and pregnancy outcomes. from the inception to May 2019 was searched in PubMed, EMBASE and Cochrane. The following search terms were used: HELLP syndrome/pregnant women/AKI or P-AKI/Neonatal outcomes /Fetal outcomes/ stillbirth/perinatal outcomes. Furthermore, we reviewed the reference lists in the retrieved articles and recent reviews to identify other potential relevant studies. We excluded studies that were cross-sectional, descriptive or case series/reports.

# Data extraction and quality assessment

The following information was abstracted from all the included studies by using a standardized data collection form: study name (together with the first author's name and publication year), study design, country, Definition of acute kidney

injury, Definition of HELLP syndrome, Number of patients with HELLP syndrome vs Number of patients without HELLP syndrome, Pregnancy outcomes, major clinical outcomes, and quantity score. We also checked the supplementary files, and contacted the authors for more detailed information when it's necessary. The literature search, data extraction and quality assessment (Grading of Recommendations Assessment, Development and Evaluation system) were performed independently by two investigators (LQ and LGJ), Any discrepancy between the two investigators was adjudicated by a third reviewer (ZSQ). We assessed the authenticity and quality of the included studies by Newcastle-Ottawa scales (NOS)[4], 6 points or more is defined as high quality research.

## Statistical analysis

The odds ratio (OR) and 95% confidence interval (CI) for each outcomes was calculated before pooling by the random-effects model. Heterogeneity across the included studies was analyzed using the I<sup>2</sup> to describe the percentage of variability (greater than 50% as evidence of a significant level)[5]. The appropriate pooling method was decided according to the value of the I<sup>2</sup> statistic: fixed-effects models for I<sup>2</sup> < 50% and random-effects models for I<sup>2</sup> ≥ 50%[5–7]. Subgroup analysis was conducted to assess the effect of adjustment for the key covariates. Potential publication bias was assessed with the Begg's test and represented graphically with Begg funnel plots of the natural log of the OR versus its standard error (SE). A two-tailed P value less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata 12.0.

## Results

The literature search yielded 340 articles, with 11 studies identified according to the inclusion criteria (Fig.1).[1, 2, 8–16]. Table 1–2 summarized the characteristics of these included studies. These studies were performed between 1993 to 2011 with sample sizes ranging from 60 to 1099. The primary disease in all the studies was gestational hypertension, the patients were divided into HELLP syndrome group and no HELLP syndrome group and the study was conducted between the two groups. The study-design types were as follows: retrospective studies 9 items[1, 2, 8, 9, 11–13, 15, 16], and prospective studies 2 items[10, 14].

## Kidney outcomes

8 studies reported 79 cases of AKI in 556 Pregnant women with HELLP syndrome and 58 cases of AKI in 1158 Pregnant women without HELLP syndrome, producing a 4.87 fold (95% CI 3.31 to 7.17, P = 0.000) higher likelihood in Pregnant women with HELLP syndrome compared with those without [1, 2, 8–13] with Very low evidence of heterogeneity (I<sup>2</sup> = 0%, P = 0.429 Fig. 2).

## Pregnancy outcomes

4 studies reported 11 cases of Maternal death in 280 Pregnant women with HELLP syndrome and 32 cases of Maternal death in 1149 Pregnant women without HELLP syndrome, producing a 3.70 fold (95% CI 1.72 to 7.99, P = 0.001) higher likelihood in Pregnant women with HELLP syndrome compared with those without HELLP syndrome[1, 9–11] with Very low evidence of heterogeneity (I<sup>2</sup> = 0%, P = 0.616 Fig. 3). 8 studies reported 87 cases of stillbirth in 612 Pregnant women with HELLP syndrome and 163 cases of stillbirth in 1997 Pregnant women without HELLP syndrome[8–11, 13–16], producing a 1.56 fold (95% CI 1.45 to 2.11, P = 0.005) higher likelihood in Pregnant women with HELLP syndrome compared with those without HELLP syndrome with Very low evidence of heterogeneity (I<sup>2</sup> = 12.4%, P = 0.333 Fig. 4). There is not enough evidence that Pregnant women with HELLP syndrome are associated with an increased incidence of Neonatal death (OR,

1.41; 95% CI 0.94 to 2.13; P = 0.098( Fig. 5). When a single study was removed in sequence, the heterogeneity did not decrease significantly and the conclusion did not change.

## Publication bias

The Newcastle-Ottawa scales (NOS) evaluation indicated that The incidence rate of AKI had low-quality evidence (Table 1). Funnel plot of Begg's test was used to show evidence of the publication bias, and found there were no bias in the incidence rate of AKI among the studies (Begg's test, P = 0.38) (Figure 6).

## Discussion

### Main findings

HELLP syndrome has a significant impact on acute kidney injury during pregnancy and pregnancy outcomes. Unfortunately, the exact definition of HELLP syndrome and AKI employed in different studies didn't reach a consensus. It is currently believed that the diagnosis of HELLP syndrome proposed by Sibai et al. is stricter and more widely used[17]. AKIN and RIFLE are currently widely used[18]in the assessment of acute kidney injury.

To the best of our knowledge, this is the first meta-analysis to explore the effect of HELLP syndrome on acute kidney injury during pregnancy and pregnancy outcomes. The analysis of the 11 included studies of 6333 pregnancies showed the relationship between HELLP syndrome during pregnancy and acute kidney injury and pregnancy outcomes. This study suggests that Pregnant women with HELLP syndrome was associated with higher risk of AKI (4.87 fold), stillbirth (3.70 fold), and Maternal death (1.56 fold). The effect of HELLP syndrome on neonatal mortality was not statistically significant in this study, but our data on this subject was less,an in-depth study with more data is necessary.

### Possible mechanism

Traditionally, HELLP syndrome was considered to be a variant of preeclampsia, but it is, in fact, a distinct disease, since 20% of pregnant women with HELLP syndrome do not have a history of hypertension or proteinuria [19, 20]. The pathogenesis of HELLP syndrome is not fully understood. Studies have shown that levels of anti-angiogenic factors (sFlt-1 and sEng) elevated and concentrations of pro-angiogenic mediators (PlGF) decreased in pregnant women with HELLP syndrome[21]. HELLP syndrome seems to be a TMA-like disorder, there are several clinical similarities between them:mechanical hemolysis, thrombocytopenia, and AKI[22].A recent study suggests that there maybe a link between HELLP syndrome and complement dysregulation,[23]. In our study, the stillbirth rate of pregnant women with HELLP syndrome was 49.5%, which was higher than the stillbirth birth rate reported in the Serdar study(7.4–34%)[24]. Premature birth and placental abruption are the main causes of stillbirth.Moreover, the maternal mortality rate in our study was 2.5% higher than that in the Sibai (1%)literature[25].

### Clinical implications and limitations

The strength of this systematic review and meta-analysis lies in the instruction significance for clinical question, large volume of data that included and rigorous methodology that used. However, our study had some limitations: Firstly, the number of cases in some studies is small, leading to the possibility of bias;Secondly, because there is no unified definition of AKI and HELLP syndrome in each study, some patients with AKI and HELLP syndrome may be missed.

## Conclusion

HELLP syndrome during pregnancy has been associated with relatively higher risk of AKI, fetal mortality and Maternal death. Although some conclusions require more research to support, this study resolves the dispute.

## Abbreviations

CC, indicates case–control; RC, retrospective cohort; PC prospective cohort; CV cardiovascular

The criteria of Sibai: hemolysis, elevated lactate dehydrogenase (LDH >600 IU/L), aspartate (AST > 40 IU/L), and/or alanine aminotransferase (ALT > 40 IU/L) and low platelet (Plt) count as class III (Plt: 100–150 × 10<sup>3</sup> /mL), class II (Plt: 50–99 × 10<sup>3</sup> /mL), and class I (Plt < 50 × 10<sup>3</sup> /mL).

AKI :Acute kidney injury.

## Declarations

## Ethics approval and consent to participate

Not applicable

## Consent for Publication

Not applicable.

## Availability of data and material

All data generated or analysed during this study are included in this published article. All literature reviewed in the study was publicly available.

## Competing interests

Not applicable.

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## Authors' contributions

LQ and LGJ conceived the study, LQ, LGJ, ZSQ and ZWQ designed and planned the study, were involved in acquisition of data, carried out the literature search and data extraction. LQ, LGJ, CYJ and YJC analyzed the data. All authors drafted the manuscript, participated in the interpretation of the data and critical review of the manuscript, and approved the version to be published.

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Not applicable

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## Tables

Table 1

Characteristics of the included studies

Author,Year	Study Design	Country	HELLP was defined	AKI (ARF) was defined	Sample size of patients with AKI in patients with HELLP <sup>a</sup>	Sample size of patients with AKI in patients without HELLP <sup>a</sup>	Major clinical outcomes	Quality score
gul2004	RC	Turkey	The criteria of Sibai	creatinine level $\geq 1.2$ mg/dL	132 (20/112)	156 (10/146)	Kidney outcome <sup>¶</sup>	6
Zuberi1998	RC	Pakistan	The criteria of Sibai	and/or oliguria $< 400$ mL/24 hr Not clear	38 (4/34)	38 (1/37)	Kidney outcome <sup>¶</sup> Fetal outcome <sup>¶</sup>	5
yildirim2011	RC	Turkey	Not clear	a creatinine clearance $\leq 20$ mL/min	196 21/175	903 14/889	Kidney outcome <sup>¶</sup> Fetal outcome	6
F. Abroug1992	PC	Tunisia	hemolysis, increased liver enzymes and thrombocytopenia.	Not clear	12 ¶8/4¶	50 ¶15/35¶	Kidney outcome <sup>¶</sup> Fetal outcome	6
haddad2000	RC	USA	The criteria of Sibai	oliguria or anuria in association with creatinine clearance $\leq 20$ mL/min and an elevated serum creatinine level $\geq 2$ mg/dL	30 ¶1/29¶	30 ¶0/30¶	Kidney outcome	6
liu2006	RC	China taiwan	Hemolysis, elevated liver enzymes, low platelet count	severe reduction in renal function with elevated serum creatinine greater than $120 \mu\text{mol/L}$ ( $> 1.4$ mg/dL). Not clear	52 ¶14/38¶	212 ¶7/205¶	Kidney outcome	7
martin1993	RC	USA	the presence of thrombocytopenia , hepatic dysfunction <sup>¶</sup> and haemolysis	Not clear	62 ¶2/60¶	55 ¶0/55¶	Kidney outcome	6
Turgut 2010	RC	Turkey	the presence of thrombocytopenia , hepatic dysfunction <sup>¶</sup> and haemolysis	creatinine clearance of $\leq 20$ mL/min and an elevated serum creatinine level of $\geq 2$ mg/dL	111 ¶9/102¶	467 ¶11/456¶	Kidney outcome	6

*Abbreviations:* CC, indicates case-control; RC, retrospective cohort; PC prospective cohort; CV cardiovascular

The criteria of Sibai: hemolysis, elevated lactate dehydrogenase (LDH >600 IU/L), aspartate (AST > 40 IU/L), and/or alanine aminotransferase (ALT > 40 IU/L) and low platelet (Plt)count as class III (Plt:100-150×10<sup>3</sup> /mL), class II (Plt:50-99×10<sup>3</sup> /mL), and class I (Plt < 50×10<sup>3</sup> /mL).

AKI :Acute kidney injury,

a Expressed as total number of patients (number in HELLP group/number in control group)

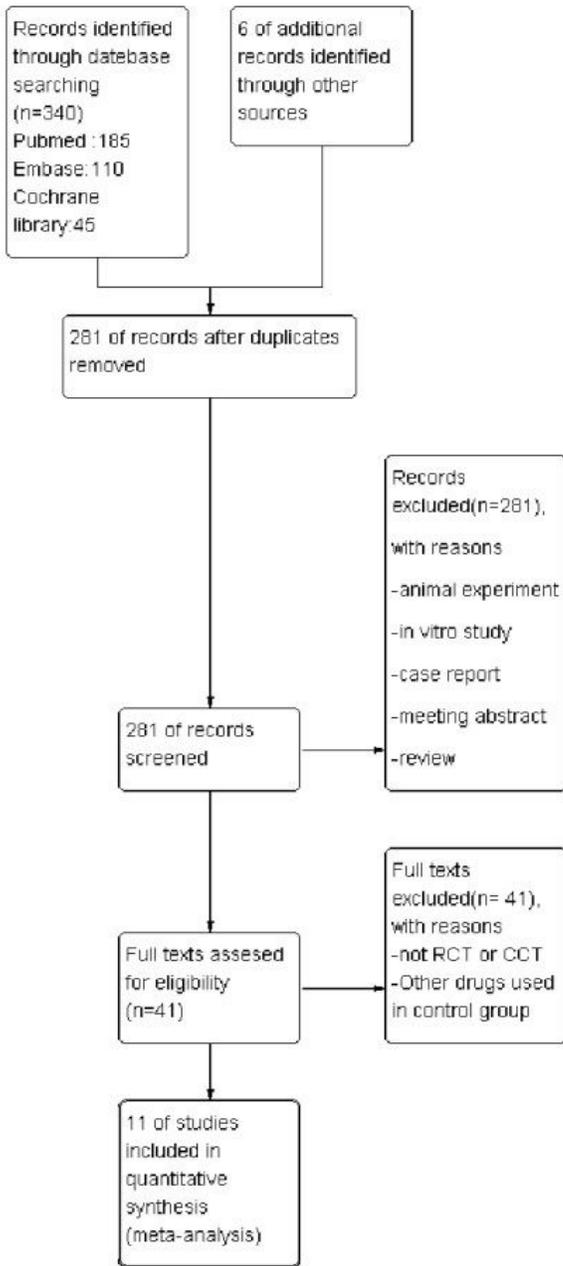
Table 2

Characteristics of the included studies

Author,Year	Study Design	Country	HELLP was defined	Sample size of patients with stillbirth in patients with HELLP <sup>a</sup>	sample size of patients with stillbirth in patients without HELLP <sup>a</sup>	Major clinical outcomes	Quality score
gul2005	PC	Turkey	The criteria of Sibai	106	261	Fetal outcome	6
abramovici	RC	Pakistan	The criteria of Sibai	(11/95) 133	(12/249) 141	Fetal outcome	6
1999 Osmanağaoğlu2004	RC	Turkey	Hemolysis, elevated liver enzymes, low platelet count	(10/123) 51 27/24	(5/136) 52 19/23	Fetal outcome	5

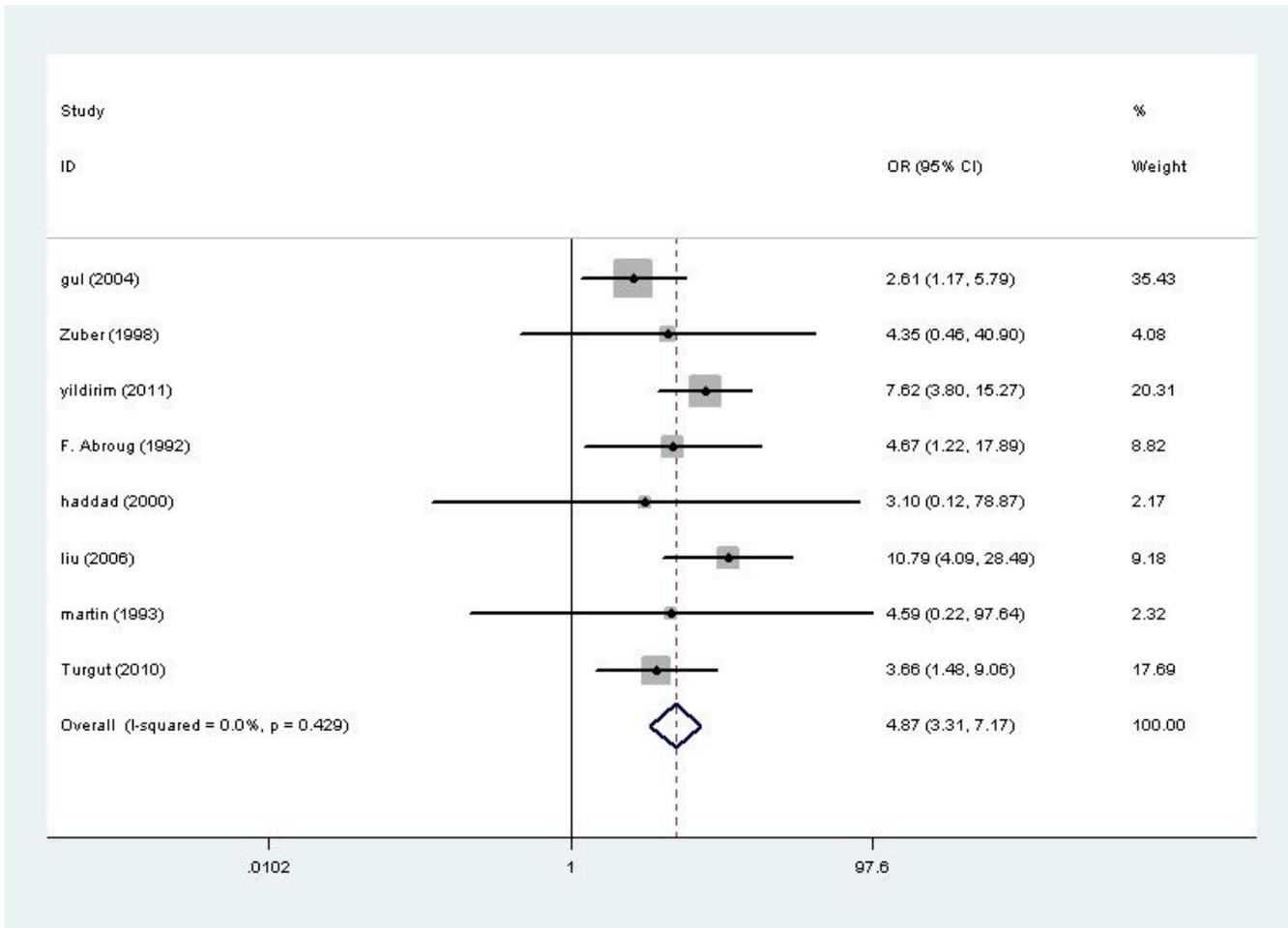
a:Expressed as total number of patients (number in PR-AKI group/number in control group)

## Figures



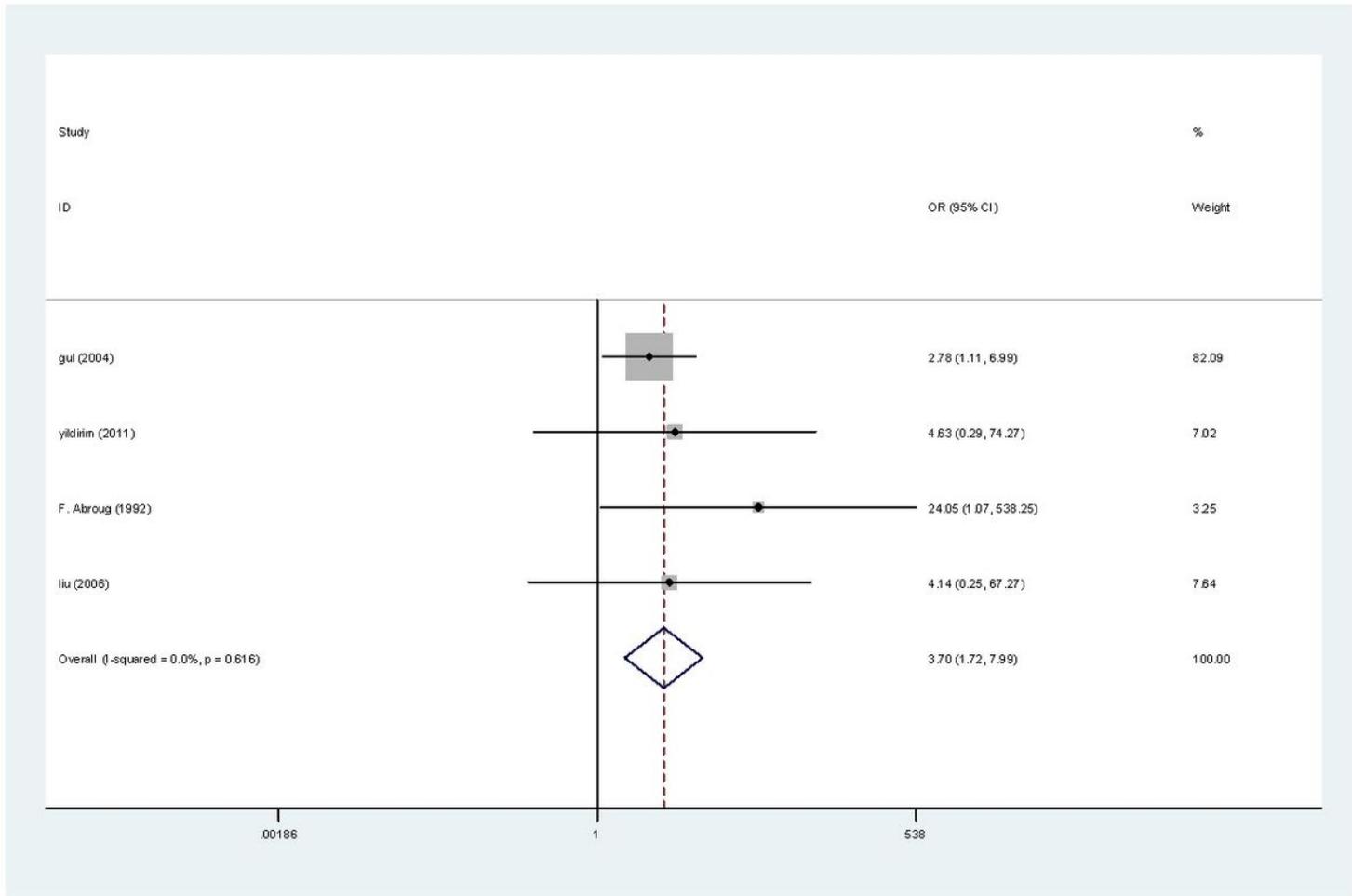
**Figure 1**

Process for identifying studies eligible for the meta-analysis



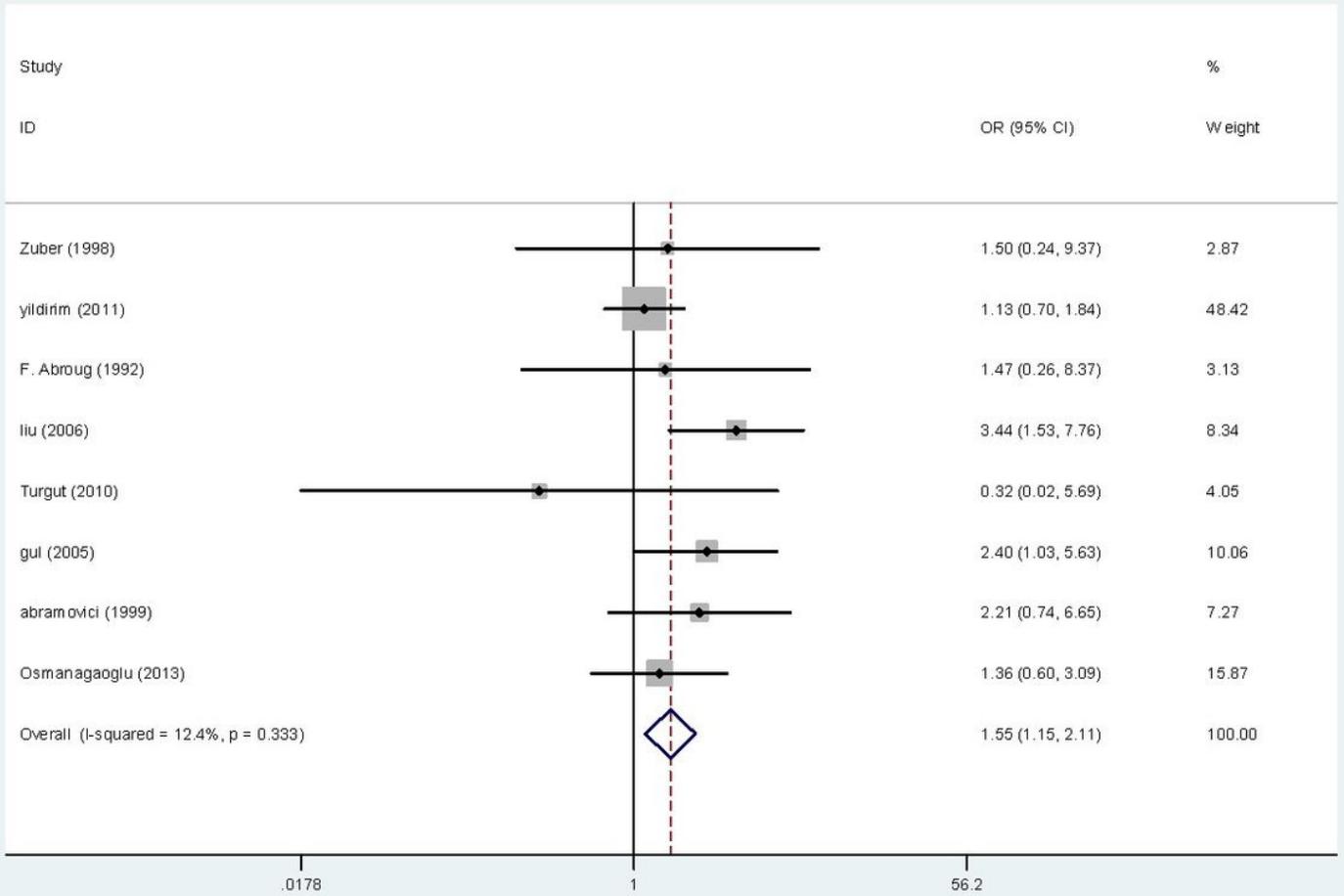
**Figure 2**

Comparison of the incidence of AKI in pregnant women with HELLP syndrome and no HELLP syndrome



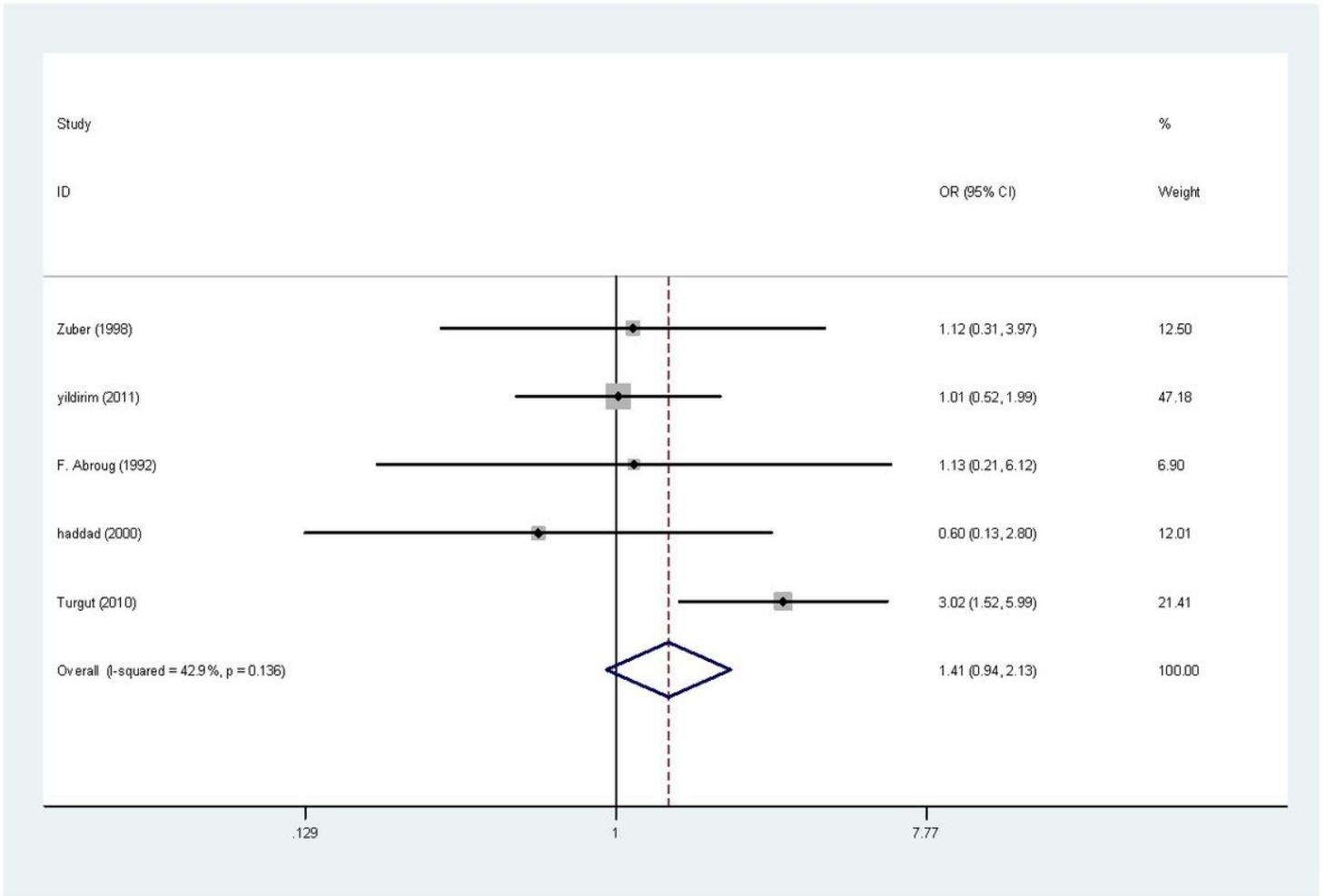
**Figure 3**

Comparison of the Maternal death in pregnant women with HELLP syndrome and no HELLP syndrome



**Figure 4**

Comparison of the stillbirth in pregnant women with HELLP syndrome and no HELLP syndrome



**Figure 5**

Comparison of Neonatal death in pregnant women with HELLP syndrome and no HELLP syndrome

Begg's funnel plot with pseudo 95% confidence limits

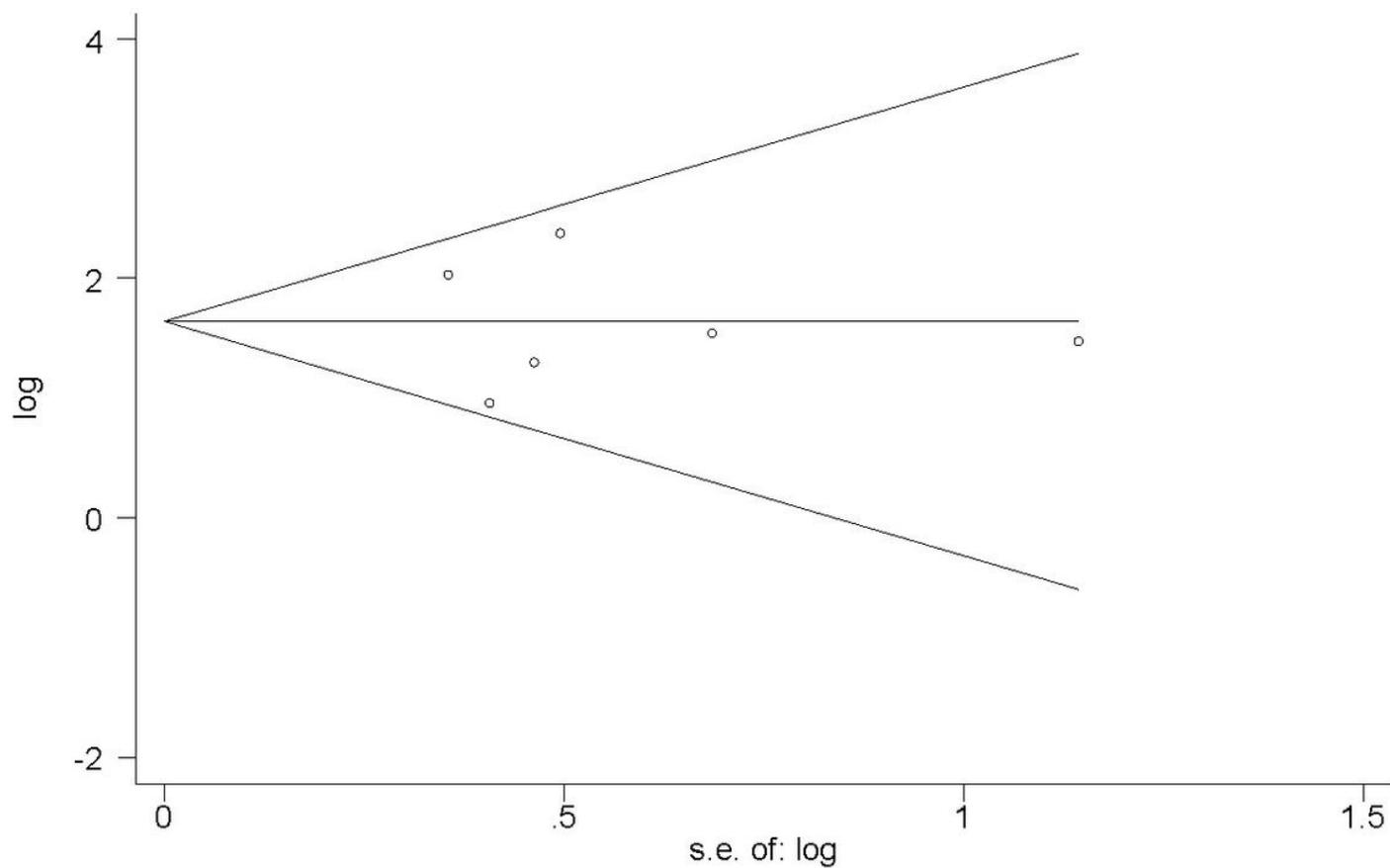


Figure 6

Begg's test about Fig2

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