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# Does gastric tonometry-guided therapy reduce total mortality in critically ill patients?

Michael G Mythen

See related research by Zhang *et al.*,http://ccforum.com/content/19/1/22

**Abstract**

Zhang and colleagues have recently published a systematic review and meta-analysis of six studies and conclude that 'gastric tonometry guided therapy can reduce total mortality in critically ill patients'. So why did gastric tonometry come and go, and what can we learn from this piece of modern history?

Gastric tonometry measures the balance between alveolar ventilation, gastric blood flow, and metabolism [1,2]. In the 1990s, gastric tonometry was a fashionable clinical monitor and was incorporated into numerous laboratory and clinical trials [3-6]. Then, soon after a small randomised controlled trial (RCT) of just over 200 patients reported no impact on ICU mortality when gastric tonometry was used to guide therapy, it seemed to disappear as a clinical tool [7]. However, Zhang and colleagues have recently published a systematic review and meta-analysis of these six studies and conclude that 'gastric tonometry guided therapy can reduce total mortality in critically ill patients' [1]. So why did gastric tonometry come and go, and what can we learn from this piece of modern history?

Hollow viscus tonometry is a long-established technique. Lavaging a hollow viscus such as the gall bladder or gastrointestinal tract allows an estimate of the partial pressure of gas tension in the wall of the viscus by analysis of the lavage. It was deployed in the stomach over decades, evolving from sampling gastric juice to the use of condoms attached to nasogatric tubes and eventually bespoke modified nasogatric tubes that incorporated a silicone balloon and sampling line. Manual saline tonometry required the balloon to be filled with 2.5 mL saline and, following a dwell time of up to 90 minutes, sampling and analysis using a blood-gas analyser [3-6]. Attention was initially focused on the calculation of 'gastric intra-mucosal pH' (or 'pHi') by using the gut lumen carbon dioxide ($CO_2$) measured by tonometry and the calculated arterial bicarbonate concentration from an arterial sample drawn at the same time. The theory was that, during periods of reduced gastric blood flow, a critical level would be reached below which anaerobic metabolism would be the dominant metabolic pathway for the generation of energy. Anaerobic metabolism generates lactic acid and causes the accumulation of $CO_2$.

The first bespoke gastric tonometer was probably launched prematurely as a number of technical glitches, such as the impact of poor sampling technique and temperature on $CO_2$ tension, needed to be resolved post-launch. Despite these glitches, 'pHi' measurement became popular in clinical observational studies and was demonstrated in major surgery, trauma, and the ICU to be a highly sensitive but less specific predictor of a poor outcome [3-6]. Doubt was cast on the utility of 'pHi' as it incorporated both global acid–base balance and regional partial pressure of $CO_2$ ($PCO_2$) [1,8]. Thus, a metabolic acidosis without an excess accumulation of gastric $CO_2$ could result in a low 'pHi' that was simply a repackaging of base excess [2,8]. Finally, automated air tonometry was launched [9]. The bespoke tonometer tube was unchanged but now air rather than saline was used to fill the balloon. This facilitated quicker full equilibration and automated sampling and measurement by using a modified end-tidal $CO_2$ infra-red analyser [9]. The calculation of 'pHi' was abandoned and interest turned to the rise in gastric partial pressure of $CO_2$ compared with either the arterial partial pressure of $CO_2$ or end-tidal partial pressure of $CO_2$, referred to as the $PCO_2$ 'gap' or 'gradient'. This again proved to be highly predictive of a poor outcome, particularly in major surgery [9]. So now, at last, we thought we had a user-friendly, automated, robust surrogate measure of 'end-organ perfusion' and a growing understanding of the technique and the separation between global haemodynamic variables and splanchnic blood flow. It

Correspondence: m.mythen@ucl.ac.uk
The Institute of Sport Exercise and Health, University College London, 170 Tottenham Court Road, London W1T 7HA, UK

was demonstrated, for example, that haemorrhage in adult volunteers could be detected by gastric tonometry when commonly measured haemodynamic variables remained unchanged [10] and that if critically ill patients had an abnormal $PCO_2$ 'gap' they failed to produce gastric acid following pentagastrin stimulation [11]. Furthermore, gut-directed therapy could maintain or correct $PCO_2$ 'gap' [4,12]. So where did it all go wrong?

I think there were a number of factors. Gastric tonometry was made commercially available before all of the methodological issues had been resolved and this resulted in negative press. Furthermore, evidence-based medicine and the demand for 'proof' of safety and efficacy from large RCTs were just emerging. How one should apply these standards to monitors of physiological variables was not and has probably still not been completely resolved. Where should the burden of proof lie? With manufacturers or the clinical community? What would be the cost implications of demanding the equivalent of phase III level of evidence for monitors? Gastric tonometry was caught up in this emerging debate and came off second best. Perhaps the burden lies with the clinical trials, although noble efforts in their day would now be regarded as inadequately designed to answer the question 'does gastric tonometry guided resuscitation improve ICU survival?' [1]. The largest of the six studies randomly assigned just 260 patients—some 10- to 20-fold fewer than the numbers one might expect to have to recruit today to answer the same question [1,4]. The recent meta-analysis by Zhang and colleagues concludes (among other things) that 'in critical care patients, gastric tonometry guided therapy can reduce total mortality' [1]. On reviewing the results, one can see that six small RCTs were conducted on a diverse range of populations (surgery, trauma, and the ICU). All of the trials were grossly underpowered to determine a possible impact on mortality. However, the point estimates for impact on mortality (Figure three [1]) all favour the intervention, but the confidence intervals are large and cross the line of unity.

I suggest that if we were starting from this point today, we would conclude that there is equipoise, significant uncertainty, and enough evidence to justify asking the question 'does gastric tonometry-guided therapy reduce total mortality in critically ill patients?' This question could be answered by a pragmatic, high-quality RCT with patient-centred outcomes, but I doubt it will be.

**Abbreviations**

$CO_2$: Carbon dioxide; $PCO_2$: Partial pressure of carbon dioxide; pHi: Gastric intra-mucosal pH; RCT: Randomised controlled trial..

**Competing interests**

The author declares that he has no competing interests.

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# Gastric tonometry guided therapy in critical care patients: a systematic review and meta-analysis

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Xin Zhang (dr_xzhang@163.com)
Wei Xuan (muthaxw@163.com)
Ping Yin (ping_y2000@163.com)
Linlin Wang (Linlinw.cool@163.com)
Xiaodan Wu (dr_xdwu@163.com)
Qingping Wu (wqp1968@126.com)

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# Gastric tonometry guided therapy in critical care patients: a systematic review and meta-analysis

Xin Zhang[1,2]
Email: dr_xzhang@163.com

Wei Xuan[1,2]
Email: muthaxw@163.com

Ping Yin[3]
Email: ping_y2000@163.com

Linlin Wang[1,2]
Email: Linlinw.cool@163.com

Xiaodan Wu[1,2]
Email: dr_xdwu@163.com

Qingping Wu[1,2,*]
[*] Corresponding author
Email: wqp1968@126.com

[1] Department of Anesthesiology and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

[2] Institutional address: Surgery Building, Union Hospital, No. 1277, Jiefang Road, Wuhan City, Hubei Province 430022, China

[3] Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, No. 13, Hangkong Road, Wuhan City, Hubei Province 430030, China

## Abstract

### Introduction

The value of gastric intramucosal pH (pHi) can be calculated from the tonometrically measured partial pressure of carbon dioxide ( $P_{CO_2}$ ) in the stomach and the arterial bicarbonate content. Low pHi and increase of the difference between gastric mucosal and arterial $P_{CO_2}$ ( $P_{CO_2}$ gap) reflect splanchnic hypoperfusion and are good indicators of poor prognosis. Some randomized controlled trials (RCTs) were performed based on the theory that normalizing the low pHi or $P_{CO_2}$ gap could improve the outcomes of critical care patients. However, the conclusions of these RCTs were divergent. Therefore, we performed a systematic review and meta-analysis to assess the effects of this goal directed therapy on patient outcome in Intensive Care Units (ICUs).

**Methods**

We searched PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov for randomized controlled trials comparing gastric tonometry guided therapy with control groups. Baseline characteristics of each included RCT were extracted and displayed in a table. We calculated pooled odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes. Another measure of effect (risk difference, RD) was used to reassess the effects of gastric tonometry on total mortality. We performed sensitivity analysis for total mortality. Continuous outcomes were presented as standardised mean differences (SMDs) together with 95% CIs.

**Results**

The gastric tonometry guided therapy significantly reduced total mortality (OR, 0.732; 95% CI, 0.536 to 0.999, $P = 0.049$; $I^2 = 0\%$; RD, −0.056; 95% CI, −0.109 to −0.003, $P = 0.038$; $I^2 = 0\%$) when compared with control groups. However, after excluding the patients with normal pHi on admission, the beneficial effects of this therapy did not exist (OR, 0.736; 95% CI 0.506 to 1.071, $P = 0.109$; $I^2 = 0\%$). ICU length of stay, hospital length of stay and days intubated were not significantly improved by this therapy.

**Conclusions**

In critical care patients, gastric tonometry guided therapy can reduce total mortality. Patients with normal pHi on admission partially drive the ultimate result of this outcome; it may indicate that these patients may be more sensitive to this therapy.

# Introduction

Gastric tonometry is a kind of equipment designed to measure partial pressure of carbon dioxide ( $P_{CO_2}$ ) in the stomach. Carbon dioxide ($CO_2$) produced by mucosa can easily diffuse to the lumen of stomach to gain balance of $P_{CO_2}$ between mucosa and lumen. The change of $P_{CO_2}$ in the stomach can reflect variation of the blood flow [1]. When the perfusion of gastric mucosa reduces, $CO_2$ will accumulate in the mucosa due to the reduction removal of it [1]. Gastric intramucosal pH (pHi) is an index being calculated from the tonometrically measured $P_{CO_2}$ and the arterial bicarbonate content (assuming mucosa bicarbonate equals to arterial bicarbonate) using the Henderson-Hasselbalch equation. It is also an index to evaluate the adequacy of gastrointestinal mucosal perfusion, a fall in which may reflect the reduction of splanchnic blood flow [2-4]. More specifically, the pHi variables are indicators of blood flow to demand ratio [4]. A recently published study showed that exercise-induced splanchnic hypoperfusion could lead to measurable small intestinal injury [5]. Transient normotensive hypovolemia may result in splanchnic vasoconstriction [6] and this early change could be detected by the measurement of tonometry [7]. Inadequate intestinal perfusion may result in increased permeability, endotoxin translocation, gut wall inflammation and this may cause some patients to develop multiple organ dysfunction syndrome [8-11]. Nordin et al. performed an in vivo study, which indicated that the pHi was valuable for early outcome assessment of resuscitation of hemorrhagic shock [12]. Another study claimed the prediction value of pHi on survival rate of 20 children was better than traditional assessments (base

deficit, blood lactate level, arterial pH and so on) [13]. Perilli et al. performed a study showed that gastric tonometry could predict poor graft function in patients undergoing liver transplantation [14].

Based on the evidence mentioned above, it is reasonable for us to suggest the hypothesis that normalizing pHi or $P_{CO_2}$ gap could improve outcome of critical care patients. In some published RCTs, patients were randomized into experiment and control groups. In the intervention groups, the value of pHi was determined in regular intervals. If the pHi values were lower than the normal value, the patients would receive treatments according to the predefined methods such as fluid infusion, vasoactive agent administration, blood transfusion etc. to improve the pHi. The patients in control groups were treated without the guidance of pHi. Gutierrez et al. [15] studied 260 patients in ICU and discovered that gastric tonometry guided therapy could increase survival rate of patients whose pHi values were normal on admission to ICU. However, five other RCTs failed to demonstrate patients benefiting from this therapy [16-20]. Hence, we undertook a meta-analysis to explore whether the gastric tonometry guided therapy yielded measurable benefits in critical care patients.

# Materials and methods

## Data sources and searches

Three authors (XZ, WX, XDW) independently searched PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov using this search strategy: "gastric tonometry" OR "intramucosal pH" OR "gastrointestinal pH" OR "gut intramucosal pH" OR "gastric $PCO_2$" OR "gastric intramucosal-arterial $PCO_2$" OR "gastric mucosal pH", confining the article type to RCT or trial. There was no language restriction in our search strategy. The search scope for these databases was from their inception to May 2014.

## Study selection

Three authors (XZ, WX and PY) discussed and defined the inclusion and exclusion criteria. The inclusion criteria were: adult patients admitted to ICU; studies in which patients were randomly divided into at least two groups, including a group of patients being treated with the intent to normalize the value of pHi or $P_{CO_2}$ gap. During the process of article selection, three authors (XZ, WX and XDW) came to an agreement on the divergence by discussing with another two authors (PY and QPW). We excluded research that was updated in a latter published paper or was designed as a historical controlled trial.

## Data extraction and quality assessment

Baseline characteristics (population, mean age, APACHE II scores on admission, intervention, current treatment, number of patients, outcomes used in the meta-analysis) of included RCTs were extracted independently by three authors (XZ, WX and XDW) and the final results were displayed in a table (Table 1).

**Table 1 Baseline characteristics of included RCTs**

| Author | Population | Mean age (Mean ± SD) | APACHE II scores on admission (Mean ± SD) | Intervention | Current treatment | Number of patients | Outcomes used in the meta-analysis |
|---|---|---|---|---|---|---|---|
| **Gutierrez et al.** [15] 1992 | **Inclusion criteria:** Medical and surgical patients consecutively admitted to ICUs with APACHE II scores of 15–25.<br>**Exclusion criteria:** Patients with oesophageal varices or oesophageal or nasopharyngeal obstructions. | **pHi guided:** 65.98(15.77)<br>**Control:** 63.22(17.07) | **pHi guided:** 18.85(2.93)<br>**Control:** 19.10(2.75) | **pHi guided:** If the pHi was below 7.35 or had fallen by 0.10 units or more from the previous reading, normal saline, dobutamine was used according to a precedure in the study.<br>**Control:** Patients were treated according to the conventional practices of each participating ICU. | All patients received histamine-receptor-blocking agents throughout their ICU stay. | **pHi guided:** 135<br>**Control:** 125 | ICU survival, hospital survival |
| **Ivatury et al.** [17] 1996 | **Inclusion criteria:** Any patient with trauma injury who had substantial and prolonged hypotension in the prehospital period, emergency department, or operating room, an Injury Severity Score (ISS) greater than 25, an initial base deficit greater than 5 mol/L, or an initial blood lactate level greater than 4 mmol/L.<br>**Exclusion criteria:** Patients who died of exsanguinating hemorrhage within 24 hours of injury were excluded from the study. | **pHi guided:** 27(11.1)<br>**Control:** 27.8(10.4) | **pHi guided:- Control:-** | **pHi guided:** The oxygen delivery index ($DO_2I$) was increased progressively by crystalloid and blood infusion to a pulmonary capillary wedge pressure of 18 mm Hg and a hematocrit of 35 percent. If pHi was not corrected, inotropic therapy with dobutamine hydrochloride (5 to 10 μg/kg/minute) started.<br>**Control:** The goal of therapy was to achieve and maintain a $DO_2I$ of 600 mL/minute/$m^2$ or greater, or an oxygen consumption index ($VO_2I$) of 150 mL/minute/$m^2$ or greater, or both. | All patients in both groups received a low-dose dopamine (2 to 5 μg/kg/minute) infusion as a renal vasodilator. An $H_2$-receptor antagonist (cimetidine) was administered routinely to all the patients. | **pHi guided:** 30<br>**Control:** 27 | Overall survival |
| **Pargger et al.** [20] 1998 | **Inclusion criteria:** Patients scheduled for elective repair of infrarenal abdominal aortic aneurysms.<br>**Exclusion criteria:** Not mentioned. | **pHi guided:** 64(10)<br>**Control:** 67(9) | **pHi guided:** 11(4)<br>**Control:** 12(5) | **pHi guided:** pHi values lower than 7.32 were treated by the attending physician according to a predefined treatment flow chart (The study's Figure 1).<br>**Control:** Treatment was performed according to the usual clinical guidelines: hemodynamics were stabilized primarily by means of intravenous fluids (Hetastarch, Ringer's lactate). | Starting on the day of surgery, each patient was given 40 mg omeprazole intravenously at 24-h intervals. | **pHi guided:** 29<br>**Control:** 26 | Hospital mortality, days on SICU, total days in hospital, days intubated. |
| **Gomersal et al** [16] 2000 | **Inclusion criteria:** A total of 210 adult patients, with a median Acute Physiology and Chronic Health Evaluation II score of 24 (range, 8–51).<br>**Exclusion criteria:** A primary admission diagnosis of cardiogenic pulmonary edema, asthma, isolated neurologic trauma, intracerebral hemorrhage, or active gastrointestinal bleeding or contraindications to the insertion of a nasogastric tube or to the use of dobutamine. | **pHi guided:** 54(17.5)<br>**Control:** 56(18.5) | **pHi guided:** 24(7.167)<br>**Control:** 24(6.667) | **pHi guided:** After achieve the basic targets, if the pHi < 7.35,patients were given additional colloid and then a dobutamine infusion at 5 and then 10 μg/kg/min, titrated against pHi (The paper's Figure 2 and Figure 3).<br>**Control:** Achieve the basic targets. (The paper's Figure 2). | Specific therapy to treat the patients' underlying disease and other forms of organ dysfunction were prescribed as indicated clinically according to standard ICU treatment protocols. | **pHi guided:** 104<br>**Control:** 106 | ICU and hospital mortality, duration of ICU stay, duration of hospital stay. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Hameed et al.** [18] 2005 | **Inclusion criteria:** Trauma patients admitted to the TICU met entry criteria for the study by definition.<br><br>**Exclusion criteria:** Patients arrived more than 12 hours post injury, were pronounced brain dead in the TICU, were pronounced dead in the resuscitation area or operating room, were burn patients, or if they underwent gastroenterostomy. | **pHi guided:** − <br> **Control:** − | **pHi guided:** − <br> **Control:** − | **pHi guided:** If pHi was lower than 7.25, active interventions to treat hypoperfusion including infusion of crystalloids, colloids, blood products and pressors (The study's Figure 1).<br><br>**Control:** Patients were resuscitated based on conventional physiologic parameters such as blood pressure, urine output, cardiac output, or systemic indicators of hypoperfusion such as lactate, base deficit, pH, or mixed venous oxygenation, crystalloid, colloid, blood products. | Immediately after randomization, subjects received 600 mg of cimetidine intravenously. An additional 600 mg were administered every 12 hours. | **pHi guided:** 50 <br><br> **Control:** 54 | Ventilator days, ICU length of stay, hospital length of stay, mortality. |
| **Palizas et al.** [19] 2009 | **Inclusion criteria:** Adult patients fulfilling criteria for septic shock according to the ACCP/SCCM Consensus Conference within 48 hours of ICU admission were considered and selected if they were in a 12-hour time window.<br><br>**Exclusion criteria:** Terminal illness with the patient expected to die within 28 days, irreversible neurologic impairment, and contraindication for nasogastric tube placement. | **pHi guided:** 59.9(15.9) <br> **Control:** 57.4(15.9) | **pHi guided:** 19.4(5.6) <br> **Control:** 18.5(3.8) | **pHi guided:** After achieving the basic goal, if the pHi was lower than 7.32, crystalloids/colloids, dobutamine were used to make the pHi > 7.32 (The study's Figure 1).<br> **Control:** Using the common hemodynamic protocol to reach the common physiological objectives, making the CI $\geq$ 3.4 L/min/$m^2$ (The study's Figure 1) | All patients received $H_2$-receptor antagonists, and enteral feeding was avoided throughout the study period. | **pHi guided:** 64 <br><br> **Control:** 66 | Twenty-eight day mortality, ICU length of stay. |

The RCT quality assessment was performed by three authors (XZ, WX and XDW) according to the table 8.5.d of Cochrane Handbook for Systematic Reviews of interventions [21]. We arrived at a consensus over the disagreements by discussion with another two authors (PY and QPW). The final results were displayed in Table 2.

**Table 2 Summary of risk of bias of included trials**

| Author | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of the pHi of the control group (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|---|---|---|---|---|---|---|
| **Gutierrez et al.** [15] 1992 | Low risk | Low risk | Low risk | Low risk | low risk | Unclear risk |
| **Ivaturyet al.** [17] 1996 | Low risk | Low risk | Low risk | Low risk | low risk | Unclear risk |
| **Pargger et al.** [20] 1998 | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk |
| **Gomersal et al.** [16] 2000 | Low risk | Low risk | Unclear risk | Low risk | low risk | Unclear risk |
| **Hameed et al.** [18] 2005 | Low risk | Low risk | Unclear risk | Low risk | low risk | Unclear risk |
| **Palizas et al.** [19] 2009 | Unclear risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk |

## Outcome

Primary outcomes were hospital mortality, total mortality and ICU mortality. The secondary outcomes were ICU length of stay, hospital length of stay and days intubated. All the included RCTs provided survival rate or mortality rate (Table 1). We transformed the survival rates into mortality rates. Two studies reported survival data or mortality data without stating explicitly which survival measure or mortality measure (30-day survival or hospital survival or 30-day mortality or hospital mortality) was used; we find the 30-day mortality was very similar to hospital mortality in Gomersall's [16] article, so we at last integrated all the mortality data of included RCTs and call it "total mortality" to obtain a larger sample size; hospital mortality provided by Gomersall et al. was used in the combination. We found some continuous data's standard deviation (SD) values of these included RCTs exceeded their mean values and this may indicate the data was not normally distributed. As the published studies reported data in the format of mean (SD), data was pooled assuming it was normally distributed. We extracted and analyzed the ICU length of stay, hospital length of stay for the purpose of roughly estimating of consumption of medical resources. Sensitivity analysis for total mortality and subgroup (patients with or without normal admission pHi) analysis for ICU mortality and hospital mortality were performed to explore whether the gastric tonometry guided therapy had significant effects on specific group of patients.

## Data synthesis

Data was analyzed using R3.1.0 and a P value of <0.05 was considered as significant. For dichotomous outcomes, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated based on the Mantel-Haenszel method for random-effects models. Continuous outcomes were presented as standardised mean differences (SMDs) together with 95%CIs using the inverse variance method for random-effects models. The baseline mortality of ICU patients in different hospitals was not the same and has been decreasing significantly over time, so we used another measure of effect (risk difference, RD) to reassess the effect of gastric tonometry on total mortality (the only positive outcome). The mean value and SD of trial which only median, range, and sample size were reported were calculated according to the formula provided by Hozo et al. [22]. Using the formula provided by the Cochrane Handbook for Systematic Reviews of interventions in table 7.7.a [21], we calculated the combining mean value and SD from two groups. We used the $I^2$ statistic to evaluate statistical heterogeneity and significant heterogeneity was predefined as $I^2 > 50\%$. In all the forest plots, leftward favors gastric tonometry and rightward favors control, the letter "W" represents weight of each study. We assumed the anticipated total mortality of population of non-gastric-tonometry-guided therapy was equal to the combined control groups statistics provided by total mortality analysis and used a formula

$$\left(n = \frac{\left[Z_\alpha\sqrt{2\bar{P}\left(1-\bar{P}\right)} + Z_\beta\sqrt{P_E\left(1-P_E\right)+P_C\left(1-P_C\right)}\right]^2}{\delta^2},\ \delta = P_E - P_C,\ \bar{P} = \frac{\left(P_E + P_C\right)}{2},\ \alpha = 0.05,\ \beta = 0.1\right)$$

[23] to evaluate the proper sample to detect 10% mortality reduction in the protocol group comparing with the control group.

### Publication bias

According to Cochrane Handbook for Systematic Reviews of interventions, when the number of included studies in the meta-analysis was <10, the power of traditional method to assess publication bias was very low [21], so we did not evaluate the publication bias using traditional method.

## Results

### Search result

We identified 11014 citations. After restricting article type to RCT or trial, 10413 studies were excluded. According to the inclusion and exclusion criteria, 23 RCTs were selected for further evaluation. Of these, 14 were duplicate studies, one was designed as a historical controlled trial, one RCT was updated in a latter published paper and one trial was performed in children. This resulted in a total of 6 RCTs being selected for our meta-analysis (Figure 1).

**Figure 1 Flow chart of study selection.**

### Primary outcomes

#### *Hospital mortality*

Three studies reported hospital mortality of pHi groups when compared with control groups [15,16,20]. The pooled data revealed that gastric tonometry guided therapy did not significantly reduce the hospital mortality (OR, 0.741; 95%CI, 0.516 to 1.064, P=0.104) (Figure 2). There was no significant heterogeneity in these studies ($I^2$=0%).

**Figure 2 Effects of gastric tonometry guided therapy versus control groups on hospital mortality.**

### Total mortality

The combining data showed that gastric tonometry guided therapy significantly reduced total mortality (OR, 0.732; 95%CI, 0.536 to 0.999; P=0.049) (Figure 3). There was no heterogeneity ($I^2$=0%). Using RD as the measure of effect yielded similar result (RD, −0.056; 95%CI, −0.109 to −0.003, P=0.038; $I^2$=0) (Figure 4).

**Figure 3 Effects of gastric tonometry guided therapy versus control groups on total mortality.**

**Figure 4 Effects of gastric tonometry guided therapy versus control groups on total mortality.**

Two trials [15,16] reported patients with normal pHi on admission, so a sensitivity analysis was performed to exclude these patients. The pooled results showed that gastric tonometry guided therapy could not reduce the total mortality (OR, 0.736; 95%CI 0.506 to 1.071, P=0.109; $I^2$=0%) (Figure 5).

**Figure 5 Sensitivity analysis of total mortality.**

## ICU mortality

Two trials reported ICU mortality [15,16] and the aggregation of them showed gastric tonometry guided therapy could not reduce ICU mortality (OR, 0.704; 95%CI, 0.402 to 1.235, P=0.221) (Figure 6). Significant heterogeneity was observed ($I^2$=56.5%).

**Figure 6 Effects of gastric tonometry guided therapy versus control groups on ICU mortality.**

## Secondary outcomes

### *ICU length of stay*

The effects of gastric tonometry guided therapy on the ICU length of stay were reported in four trials [16,18-20]. Three reported mean (SD) stay [18-20] and one reported median (range) [16]. The combined data suggested that gastric tonometry guided therapy could not significantly reduce the days on ICU (SMD, 0.104; 95%CI, −0.072 to 0.280, P=0.247; $I^2$=0%) (Figure 7).

**Figure 7 Effects of gastric tonometry guided therapy versus control groups on ICU length of stay.**

## Hospital length of stay

Three studies evaluated the impact of gastric tonometry guided therapy on hospital length of stay [16,18,20]. No differences between two protocols were observed (SMD, 0.049; 95%CI, −0.155 to 0.253, P=0.637; $I^2$=0%) (Figure 8).

**Figure 8 Effects of gastric tonometry guided therapy versus control groups on hospital length of stay.**

## Days intubated

Two trials investigated the duration of mechanical ventilation [18,20]; the combining data showed gastric tonometry guided therapy could not diminish the days intubated (SMD, −0.031; 95%CI, −0.342 to 0.280, P=0.846; $I^2$=0%) (Figure 9).

**Figure 9 Effects of gastric tonometry guided therapy versus control groups on days intubated.**

## Subgroup analysis

Two RCTs performed subgroup analysis for ICU and hospital mortality based on the admission pHi of patients [15,16]. The pooled data revealed gastric tonometry guided therapy could not diminished the ICU mortality (OR, 0.597; 95%CI, 0.145 to 2.468, P=0.476; $I^2$=64.4%) (Figure 10) or hospital mortality (OR, 1.049; 95%CI, 0.216 to 5.091; P=0.953; $I^2$=77.8%) (Figure 11) of patients with normal admission pHi. Obvious heterogeneity was

observed between the two trials. The combined results of patients without normal admission pHi showed similar results for the two outcomes (ICU mortality, OR, 0.926; 95%CI, 0.571 to 1.502; P=0.755; $I^2$=0%; hospital mortality, OR, 0.771; 95%CI, 0.475 to 1.251; P=0.293; $I^2$=0%) (Figure 12 and 13).

**Figure 10 Subgroup analysis of ICU mortality for patients with normal admission gastric intramucosal pH.**

**Figure 11 Subgroup analysis of hospital mortality for patients with normal admission gastric intramucosal pH.**

**Figure 12 Subgroup analysis of ICU mortality for patients without normal admission gastric intramucosal pH.**

**Figure 13 Subgroup analysis of hospital mortality for patients without normal admission gastric intramucosal pH.**

### Sample size evaluation

The proper sample size of each group was 469, the number of total patients was about 938, none of the six RCTs meet this requirement. The sample size of total mortality data was 816, approaching to the requirement, so the combining result may be more persuasive than any of the six RCTs.

### Publication bias

As Figure 3 and 4 show, all the 95%CIs of ORs (or RDs) of included studies cross with the vertical solid line, which means none of the included RCTs showed significant results, so the publication bias could be excluded [24].

## Discussion

This meta-analysis showed that gastric tonometry guided therapy reduced total mortality of critical care patients when compared with control groups. However, there was no difference in hospital mortality, ICU mortality, ICU length of stay, hospital length of stay or intubation days. This may be the case that the effects of gastric tonometry guided therapy are not apparent and require a relative big sample size to be detected.

Gutierrez et al. [15] reported the survival rate in a form of dividing patients of both experiment and control groups into two subgroups based on the admission pHi; they demonstrated that patients with normal admission pHi had significantly higher survival rate in the experimental group. Another study [16] using mortality rate as the outcome performed similar subgroup analysis and failed to demonstrate this benefit. We transformed the survival rate of the first study into mortality rate and pooled the results of two articles; the combining data showed gastric tonometry guided therapy could not reduce the mortality of patients with normal admission pHi and statistical heterogeneity was observed between the two trials (Figure 10 and 11). However, we could not conclude that gastric tonometry guided therapy has no beneficial effects on the patients with normal admission pHi. For one thing, the sample size of patients with normal admission pHi in the second study [16] was too small and

the combining sample size (Figure 10 and 11) was also relatively small, it may make it underpowered to detect the effects of gastric tonometry guided therapy and result in statistical heterogeneity. For another the difference of pathophysiological states of patients of two studies may also contribute to the outcome heterogeneity; the effect of gastric tonometry guided therapy may be different in various disease/health conditions. We performed a sensitivity analysis excluding these patients using total mortality as outcome and the pooled result (Figure 5) showed the beneficial effects disappeared. This may indicate that the patients with normal admission pHi drove to the ultimate combining results of total mortality and these patients may be more sensitive to gastric tonometry guided therapy.

The methodology of gastric tonometry has been severely debated. The calculated value of pHi is a combination of locally ( $P_{CO_2}$ , partial pressure of carbon dioxide in the stomach) and systemic (atrial bicarbonate content) derived indexes; the calculation is based on the assumption that the atrial bicarbonate content is equal to the mucosal content. However, the bicarbonate concentration of ischemic mucosa may not equal that in arterial blood [25], so the pHi may not reflect the actual pH of mucosa layer. An animal study demonstrated that increase of $P_{CO_2}$ gap(the difference of partial pressure of carbon dioxide between gastric mucosa and artery) was highly correlated with reduction of gastric blood flow [26], it suggested that the $P_{CO_2}$ gap was a better index than pHi to reflect the splanchnic hypoperfusion. Another research also favoured using $P_{CO_2}$ gap as a marker of tissue ischemia [27]. But Jakob et al. [28] performed a research included 22 patients after cardiac surgery and concluded that an increase in the $P_{CO_2}$ gap may be explained partly or totally by the Haldane effect, so the $P_{CO_2}$ gap may also be flawed in reflecting the perfusion state of mucosa. In general, the exact physiology meaning of pHi and $P_{CO_2}$ gap need further investigation to elucidate.

Despite the methodology arguments of gastric tonometry, through this meta-analysis, we found improving pHi could reduce total mortality in critical care patients. One RCT reported their failure to improve the outcome may be caused by inability to produce a significant change of pHi [16]. Therefore, exploring which kind of method could improve the pHi or $P_{CO_2}$ gap is important. Levy et al. [29] did a research demonstrating that $P_{CO_2}$ gap of septic shock patients treated with norepinephrine could be inconsistently improved by low dose of dobutamine and dopexamine. We could conclude that different patients have different sensitivity to dobutamine and dopexamine; the use of them should be individual. Other research showed levosimendan, olprinone, enalaprilat and rapid volume infusion could improve the pHi values or $P_{CO_2}$ gap [30-33]. However, all the authors of mentioned studies performed their experiments in particular groups of patients; whether these treatments could produce significant effects on all critical care patients was unknown.

Now few institutions use gastric tonometry in clinical practice for it has been severely questioned in the aspect of its methodology and physiology meaning. As our study provided some evidence supporting the use of this technique, it may indicate the pHi and $P_{CO_2}$ gap represent a physiology state which change could affect the prognosis of critical care patients. The current explanations of the physiology meaning of this technique are divergent, we believe the pHi or $P_{CO_2}$ gap is not a simplex index indicating a simplex meaning but a compound index of multiple physiology or pathophysiology state. If convinced and profound

interpretation for gastric tonometry is raised by future researchers, this technique may return to the clinical practice.

Some limitations in this meta-analysis deserved discussion. First of all, though the heterogeneity of most outcomes was not significant, the clinical baseline characteristics of included patients were not the same among the six studies (Table 1); it may make this study underpowered to detect concealed but important difference between gastric tonometry guided therapy and controls, but it may also indicate that gastric tonometry guided therapy is universal for various kinds of patients. Second, these RCTs defined different normal values of pHi and the treatment guidelines of experimental and control groups were also differential; it could result in heterogeneous outcomes of patients and then underestimated or exaggerated the conclusion of this study. Another limitation was that one study did not mention whether their patients received gastric acid inhibition [16], so the precise of the value of pHi may be affected in a degree. At last, Correa-Martin et al. performed two studies and demonstrated that tonometry was sensitive to the increase of intra-abdominal pressure (IAP) [34,35], but none of the included six studies excluded patients with high IAP.

# Conclusions

Gastric tonometry guided therapy can reduce total mortality of critical care patients. Treatments that improve organ microcirculation may be recommended to resuscitation of critical care patients if not contraindicated. Gastric tonometry guided therapy may be more effective in some specific critical care patients. Further investigation needs to be done to interpret the physiology meaning of gastric tonometry.

# Key messages

- Gastric tonometry guided therapy can reduce total mortality of critical patients.
- Some specific critical care patients may be more sensitive to gastric tonometry guided therapy.

# Abbreviations

CI, Confidence intervals; $CO_2$, Carbon dioxide; IAP, Intra-abdominal pressure; ICU, Intensive Care Unit; OR, Odds ratios; pHi, Intramucosal pH; $P_{CO_2}$, Partial pressure of carbon dioxide; $P_{CO_2}$ gap, The difference between gastric mucosal and arterial $P_{CO_2}$; RCT, Randomized controlled trial; RD, Risk difference; SD, Standard deviation; SMD, Standardised mean difference

# Competing interests

The authors declare that they have no competing interests.

# Authors' contributions

XZ and QPW conceived the study and participated in the design. XZ, WX and XDW performed the search and extracted the data from the included RCTs. XZ, WX, LLW and PY

analyzed the data. XZ and LLW drafted the manuscript. QPW, PY and LLW provided valuable advice and reviewed the manuscript. All authors have read and approved the final version of the manuscript.

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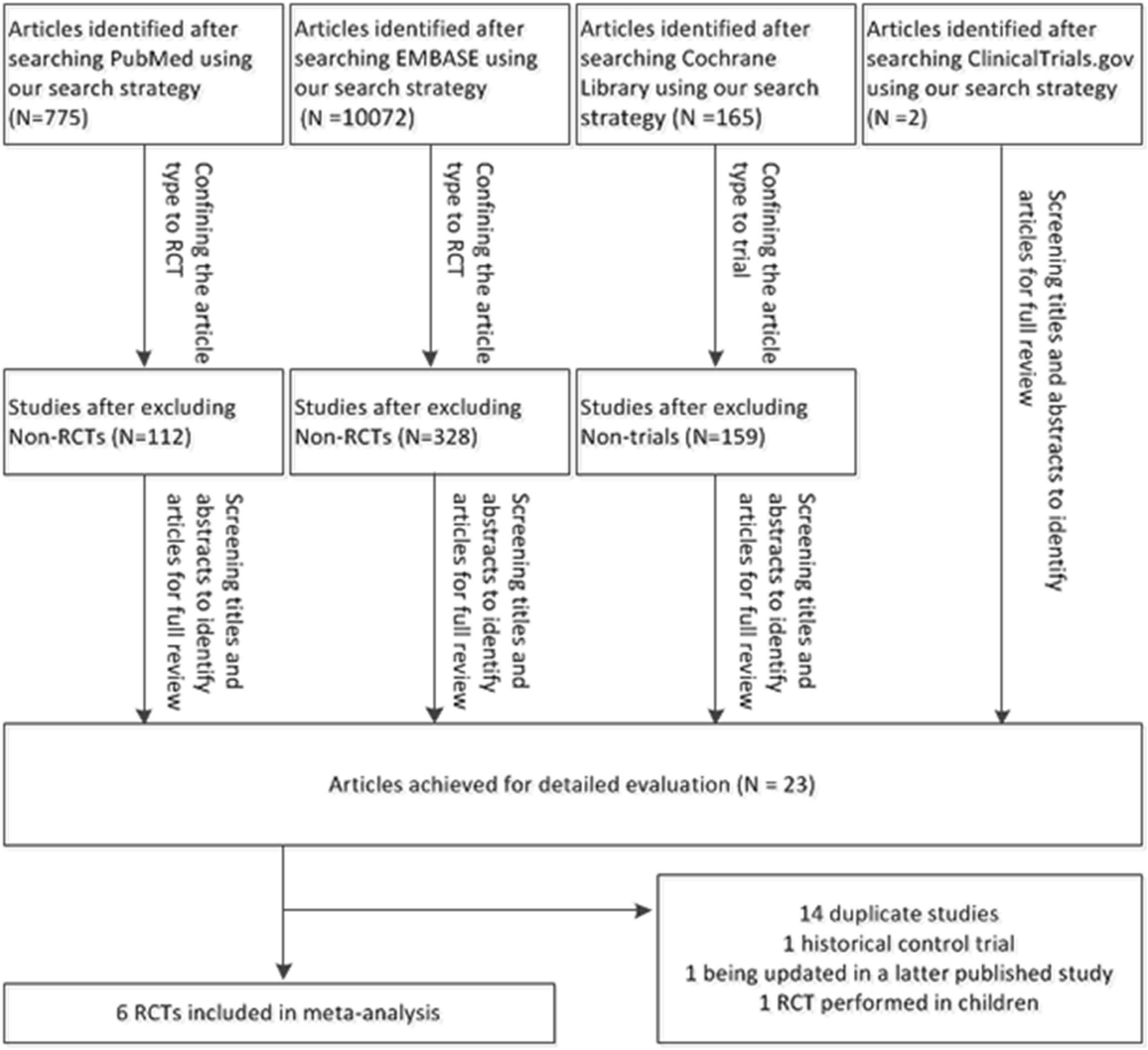
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Confining the article type to RCT
Confining the article type to RCT
Confining the article type to trial
Screening titles and abstracts to identify articles for full review
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Studies after excluding Non-RCTs (N=328)
Studies after excluding Non-trials (N=159)
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Screening titles and abstracts to identify articles for full review
Screening titles and abstracts to identify articles for full review
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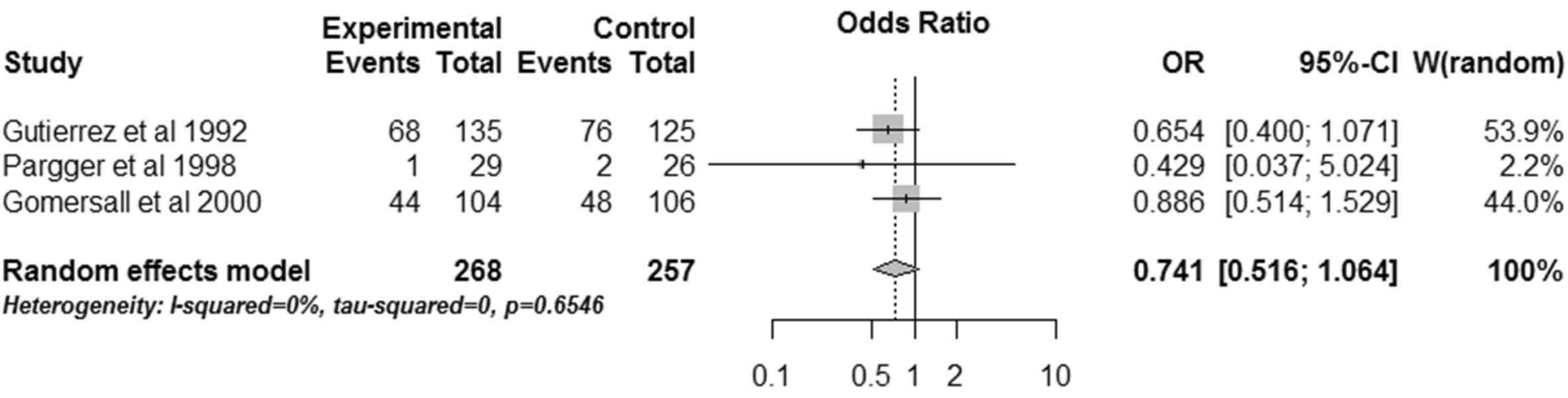
1 historical control trial
1 being updated in a latter published study
1 RCT performed in children
6 RCTs included in meta-analysis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Study
Events Total Events Total
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Pargger et al 1998 1 29 2 26 0.429 [0.037; 5.024] 2.2%
Gomersall et al 2000 44 104 48 106 0.886 [0.514; 1.529] 44.0%
Random effects model 268 257 0.741 [0.516; 1.064] 100%
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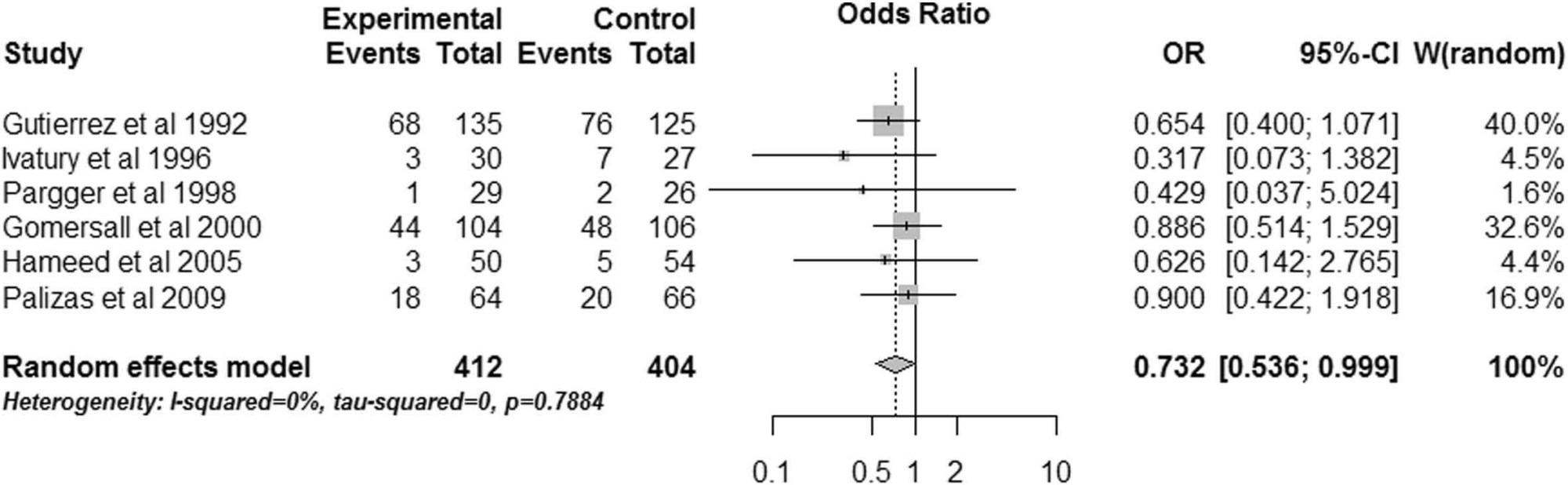
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Study
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Pargger et al 1998 1 29 2 26 0.429 [0.037; 5.024] 1.6%
Gomersall et al 2000 44 104 48 106 0.886 [0.514; 1.529] 32.6%
Hameed et al 2005 3 50 5 54 0.626 [0.142; 2.765] 4.4%
Palizas et al 2009 18 64 20 66 0.900 [0.422; 1.918] 16.9%
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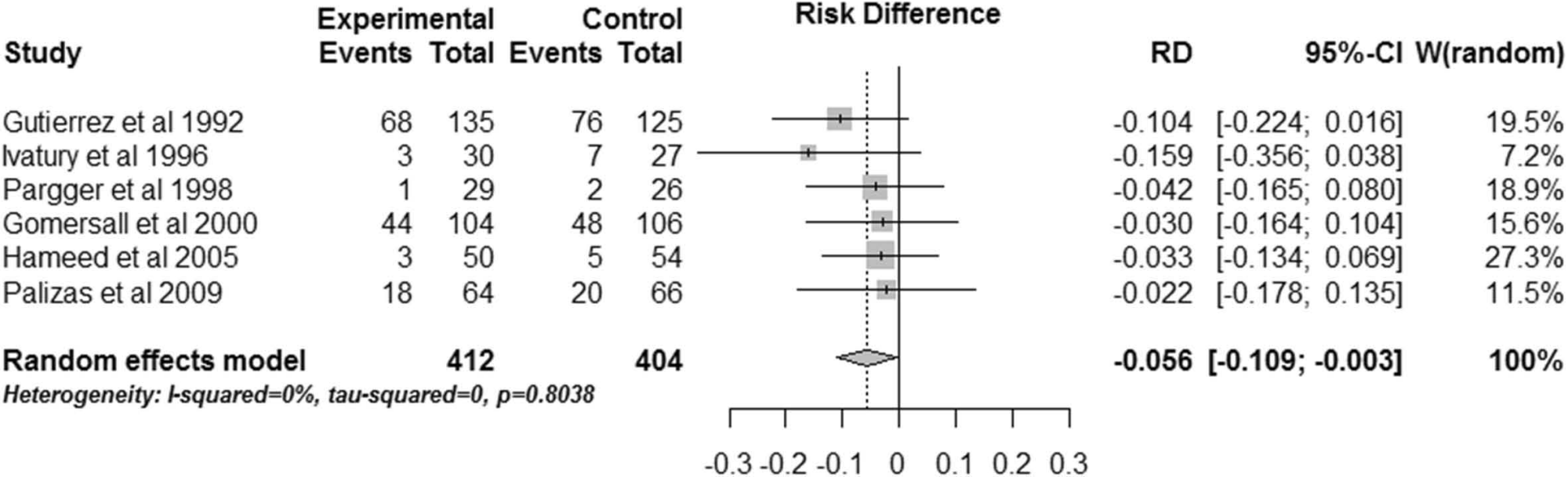
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Events Total Events Total
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Pargger et al 1998 1 29 2 26 -0.042 [-0.165; 0.080] 18.9%
Gomersall et al 2000 44 104 48 106 -0.030 [-0.164; 0.104] 15.6%
Hameed et al 2005 3 50 5 54 -0.033 [-0.134; 0.069] 27.3%
Palizas et al 2009 18 64 20 66 -0.022 [-0.178; 0.135] 11.5%
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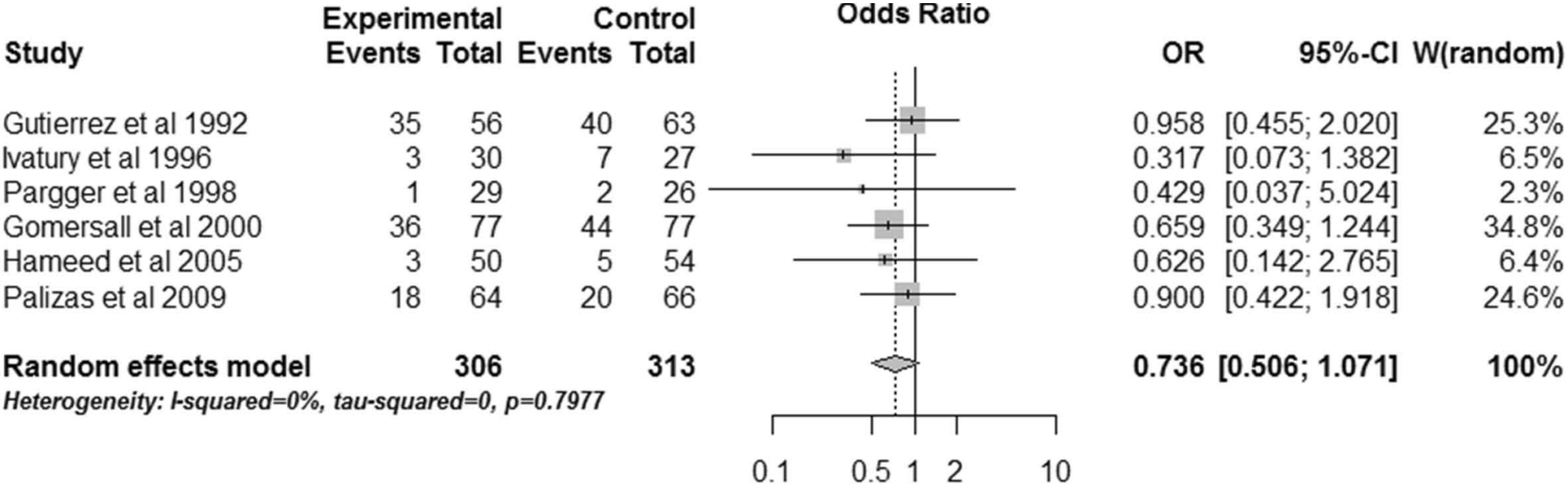
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Control
Odds Ratio
Study
Events Total Events Total
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Gutierrez et al 1992 35 56 40 63 0.958 [0.455; 2.020] 25.3%
Ivatury et al 1996 3 30 7 27 0.317 [0.073; 1.382] 6.5%
Pargger et al 1998 1 29 2 26 0.429 [0.037; 5.024] 2.3%
Gomersall et al 2000 36 77 44 77 0.659 [0.349; 1.244] 34.8%
Hameed et al 2005 3 50 5 54 0.626 [0.142; 2.765] 6.4%
Palizas et al 2009 18 64 20 66 0.900 [0.422; 1.918] 24.6%
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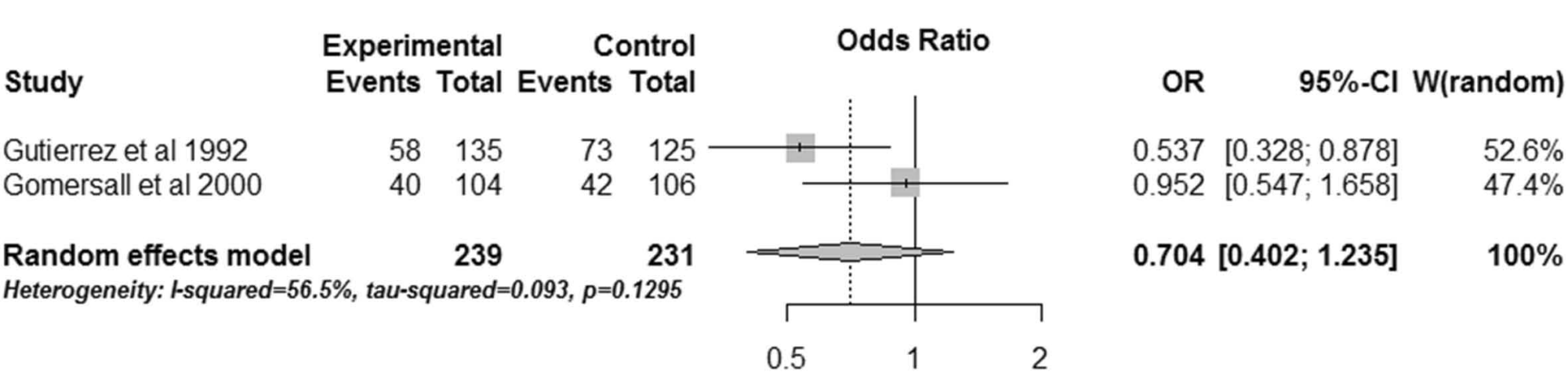
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Control
Odds Ratio
Study
Events Total Events Total
OR 95%-CI W(random)
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Gomersall et al 2000 40 104 42 106 0.952 [0.547; 1.658] 47.4%
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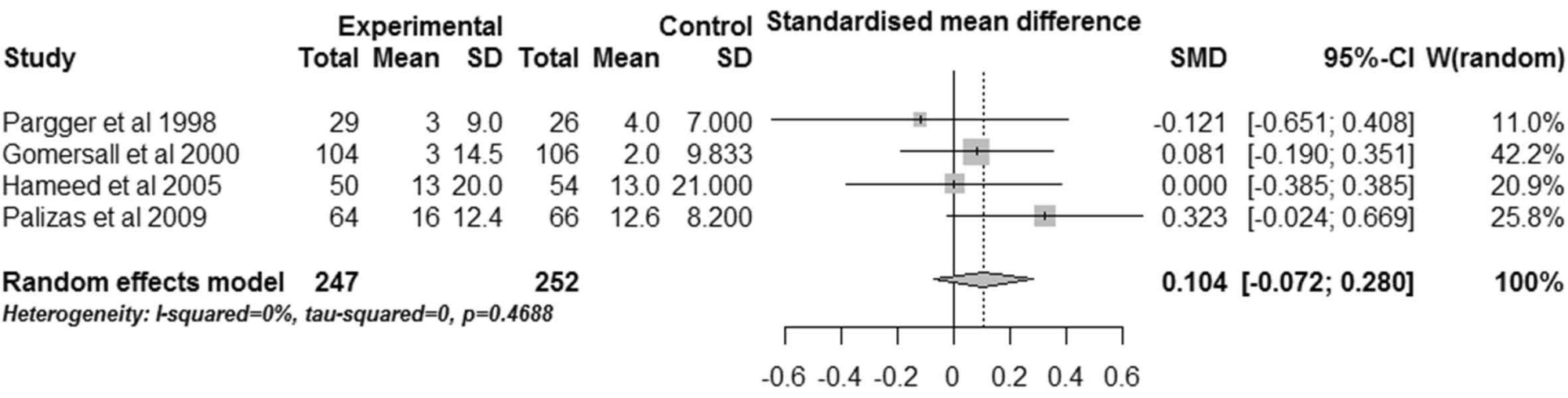
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Control
Standardised mean difference
Study
Total Mean SD Total Mean SD
SMD 95%-CI W(random)
Pargger et al 1998 29 3 9.0 26 4.0 7.000 -0.121 [-0.651; 0.408] 11.0%
Gomersall et al 2000 104 3 14.5 106 2.0 9.833 0.081 [-0.190; 0.351] 42.2%
Hameed et al 2005 50 13 20.0 54 13.0 21.000 0.000 [-0.385; 0.385] 20.9%
Palizas et al 2009 64 16 12.4 66 12.6 8.200 0.323 [-0.024; 0.669] 25.8%
Random effects model 247 252 0.104 [-0.072; 0.280] 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.4688
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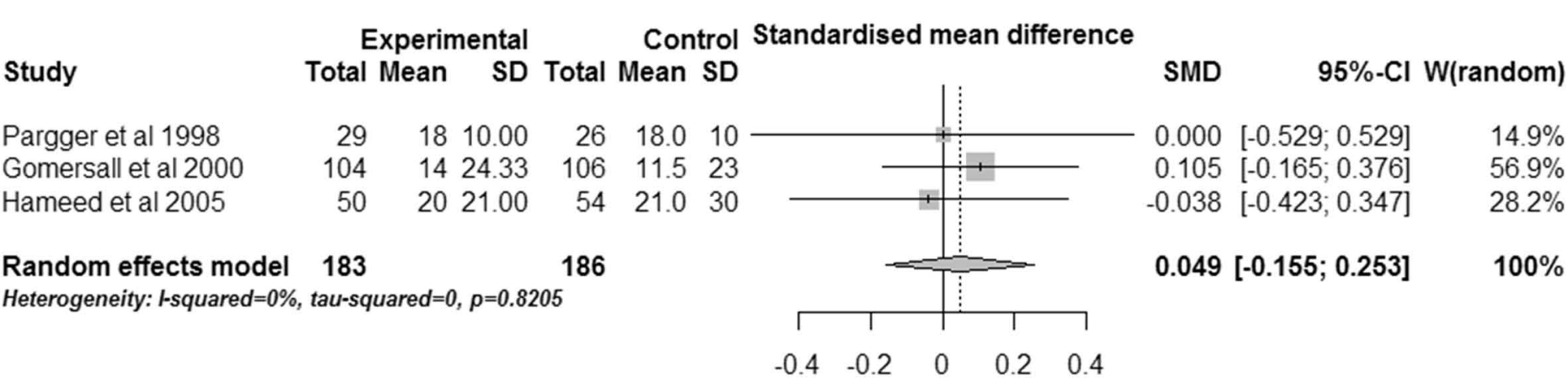
Experimental
Control
Standardised mean difference
Study
Total Mean SD Total Mean SD
SMD 95%-CI W(random)
Pargger et al 1998 29 18 10.00 26 18.0 10 0.000 [-0.529; 0.529] 14.9%
Gomersall et al 2000 104 14 24.33 106 11.5 23 0.105 [-0.165; 0.376] 56.9%
Hameed et al 2005 50 20 21.00 54 21.0 30 -0.038 [-0.423; 0.347] 28.2%
Random effects model 183 186 0.049 [-0.155; 0.253] 100%
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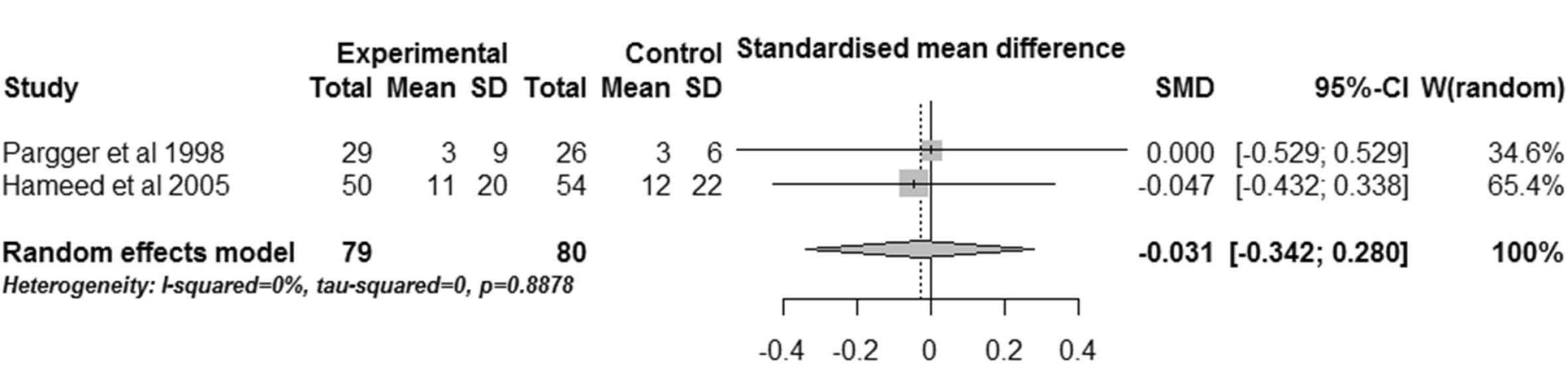
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Study
Total Mean SD Total Mean SD
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Pargger et al 1998 29 3 9 26 3 6 0.000 [-0.529; 0.529] 34.6%
Hameed et al 2005 50 11 20 54 12 22 -0.047 [-0.432; 0.338] 65.4%
Random effects model 79 80 -0.031 [-0.342; 0.280] 100%
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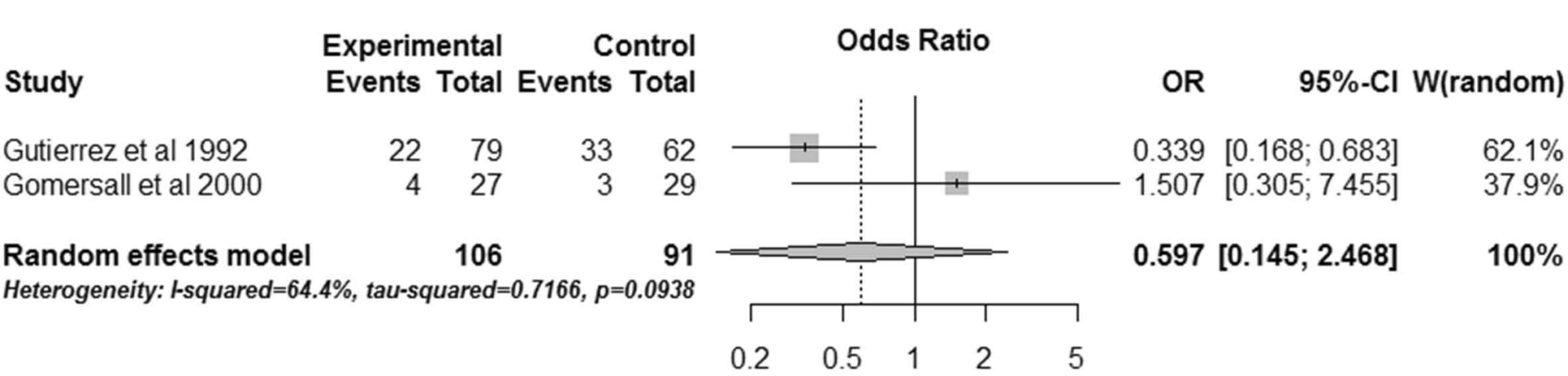
Experimental
Control
Odds Ratio
Study
Events Total Events Total
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Gutierrez et al 1992 22 79 33 62 0.339 [0.168; 0.683] 62.1%
Gomersall et al 2000 4 27 3 29 1.507 [0.305; 7.455] 37.9%
Random effects model 106 91 0.597 [0.145; 2.468] 100%
Heterogeneity: I-squared=64.4%, tau-squared=0.7166, p=0.0938
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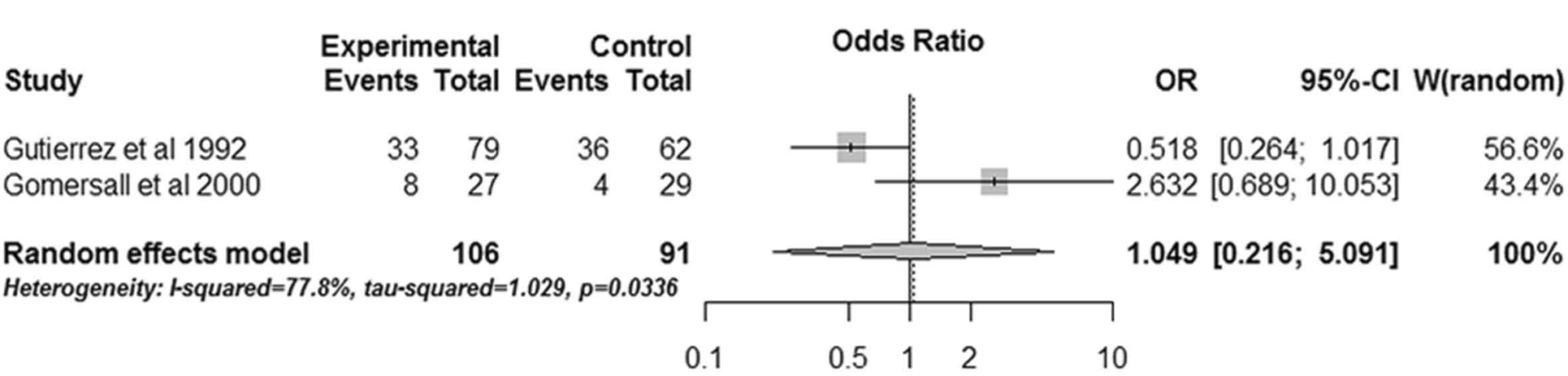
Experimental
Control
Odds Ratio
Study
Events Total Events Total
OR 95%-CI W(random)
Gutierrez et al 1992 33 79 36 62 0.518 [0.264; 1.017] 56.6%
Gomersall et al 2000 8 27 4 29 2.632 [0.689; 10.053] 43.4%
Random effects model 106 91 1.049 [0.216; 5.091] 100%
Heterogeneity: I-squared=77.8%, tau-squared=1.029, p=0.0336
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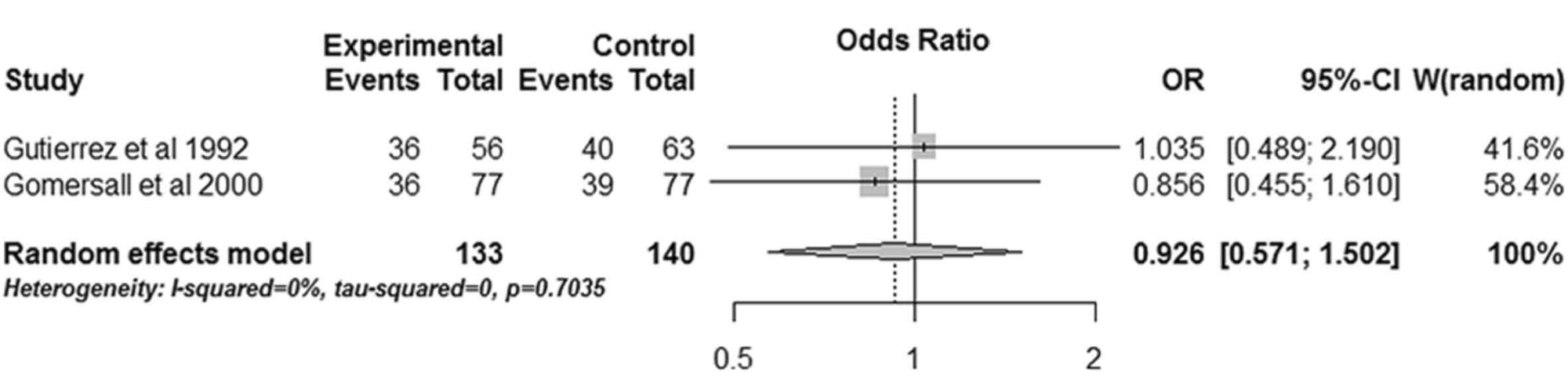
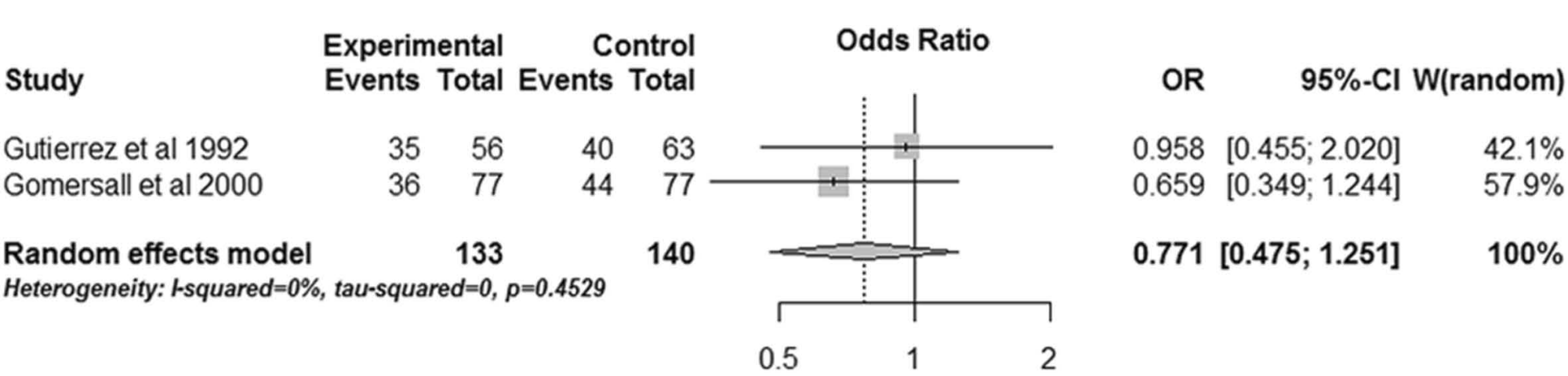

Experimental
Control
Odds Ratio
Study
Events Total Events Total
OR 95%-CI W(random)
Gutierrez et al 1992 36 56 40 63 1.035 [0.489; 2.190] 41.6%
Gomersall et al 2000 36 77 39 77 0.856 [0.455; 1.610] 58.4%
Random effects model 133 140 0.926 [0.571; 1.502] 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.7035
0.5
1
2


Experimental
Control
Odds Ratio
Study
Events Total Events Total
OR 95%-CI W(random)
Gutierrez et al 1992 35 56 40 63 0.958 [0.455; 2.020] 42.1%
Gomersall et al 2000 36 77 44 77 0.659 [0.349; 1.244] 57.9%
Random effects model 133 140 0.771 [0.475; 1.251] 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.4529
0.5
1
2