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Primary small cell neuroendocrine carcinoma of the right posterior tongue

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Abstract

Small cell neuroendocrine carcinoma (SNEC) is an extremely aggressive tumor and mainly occurs in the lung. Primary extra-pulmonary SNEC is rare. To date, only 11 primary SNECs occurring in the oral cavity have been reported in the English literature. We describe a case of primary SNEC of the right posterior tongue in a 46-year-old man. The patient had stage IVA disease and received adjuvant chemotherapy, followed by radical surgery and radiotherapy. He remained tumor-free for 20 mo before death due to gastrointestinal metastasis. The relevant literature on the 11 previously reported patients was reviewed, and the clinical features, histopathological characteristics, differential diagnosis and therapeutic strategies of this rare tumor were analyzed.

Key Words: Small cell carcinoma; Neuroendocrine carcinoma; Oral cavity; Head and neck; Extrapulmonary

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Core Tip: Primary extra-pulmonary small cell neuroendocrine carcinoma (SNEC) is extremely rare. There are only 11 primary SNECs occurring in the oral cavity reported in the English literature. This time, we describe a case of primary SNEC of the right posterior tongue in a 46-year-old man. The treatment of this patient is described in detail. The relevant literature of the 11 previously reported patients was reviewed, and the clinical features, histopathological characteristics, differential diagnosis and therapeutic strategies

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of this rare tumor were analyzed.

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INTRODUCTION

Small cell neuroendocrine carcinoma (SNEC) is the most common type of pulmonary neoplasm and is an aggressive malignant tumor with a high tendency for regional and distant metastasis. Extra-pulmonary SNECs account for 2.5%-5% of all SNECs, of which head and neck SNECs account for 10%-15%^[1]. The first case of SNEC in the head and neck was reported in 1963, and the larynx is the most common site, followed by the salivary glands and the sinonasal region^[2]. Primary SNEC in the oral cavity is extremely rare and to date only 11 primary SNECs occurring in the oral cavity have been reported in the English literature^[3-13].

The management of extra-pulmonary SNECs has not been standardized, but is extrapolated from pulmonary SNEC due to their similar clinicopathologic features^[14,15]. In addition to chemotherapy as an effective therapeutic modality, radical surgery and radiation therapy may also play an important role depending on the primary site and clinical stage of the tumor^[16]. The current report presents a rare case of primary SNEC arising in the right posterior tongue. The clinicopathologic characteristics of this rare tumor are discussed and the relevant literature is reviewed.

NEW CASE OF SCNC

A 46-year-old man, who had a 30-year history of smoking and alcohol consumption, presented to the oral and maxillofacial department in September 2013 with a painful mass which grew rapidly of the right posterior tongue during the previous 3 mo and a painful mass in the contralateral upper jugular area for 1 mo. Physical examination identified a hard polypoid mass of the right posterior tongue, measuring 2.5 cm × 2.5 cm, with obvious tenderness and low mobility (Figure 1). A painful mass with low mobility, measuring 2.0 cm × 3.0 cm, in the contralateral upper jugular area was also identified.

Computerized tomography (CT) scanning showed an ill-defined mass with heterogeneous enhancement in the right posterior tongue and contralateral cervical lymph node enlargement (Figure 2). A CT scan of the chest and abdomen and a positron emission tomography-CT scan revealed no abnormalities. Findings from laboratory examinations, including routine blood, blood biochemistry and urine analysis, were within normal limits. An incision biopsy under local anesthesia was performed. Microscopically, round and spindly small cells presented with ovoid or spindle shaped nuclei, fine granular chromatin, inconspicuous nucleoli and scant cytoplasm, forming broad nests, sheets or cord shapes (Figure 3). Immunohistochemically, these cells were positive for synaptophysin (referred to as syn), N-CAM (CD56), chromogranin A and cytokeratin AE1/AE3 (Figure 4). The proliferation index evaluated by Ki-67 labeling was 90% (Figure 5). The cells were negative for human melanoma black45 (referred to as HMB-45), cytokeratin 20 (referred to as CK20), vimentin, S100 protein, leucocyte common antigen, CD99, smooth muscle actin and thyroid transcription factor1.

A combined modality therapy was approved by multidisciplinary discussion. After two cycles of chemotherapy (cisplatin 75 mg/m², day 1 and etoposide 100 mg/m², day 1-3, 3 wk per cycle), the primary tumor and cervical lymph nodes partially decreased according to the Response Evaluation Criteria in Solid Tumors. Radical resection, including extensive resection of the primary tumor with contralateral radical and homolateral functional neck dissection and reconstruction of the tongue with a left free forearm flap was performed. The diagnosis of SCNC was confirmed by postoperative pathology. A 60 Gy dose of radiotherapy was administered after surgery. The patient remained tumor-free for 20 mo before his death due to gastrointestinal metastasis.

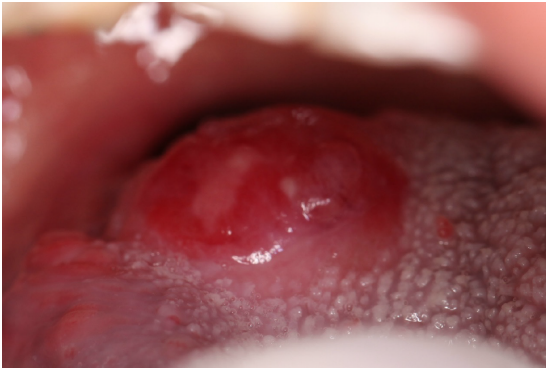


Figure 1 Clinical photograph showing the gross appearance of tumor in the right root of tongue.

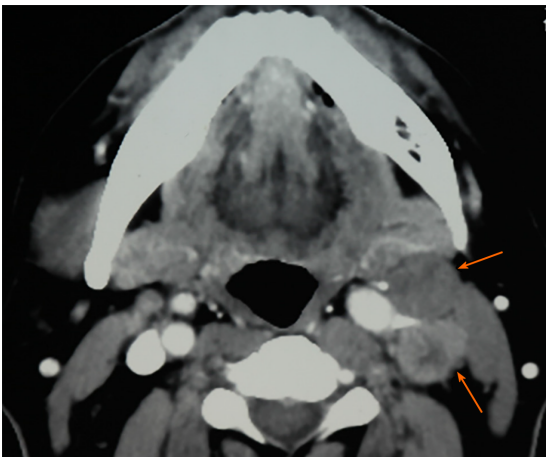


Figure 2 Preoperative computerized tomography scan showing contralateral cervical lymph nodes enlargement (orange arrows).

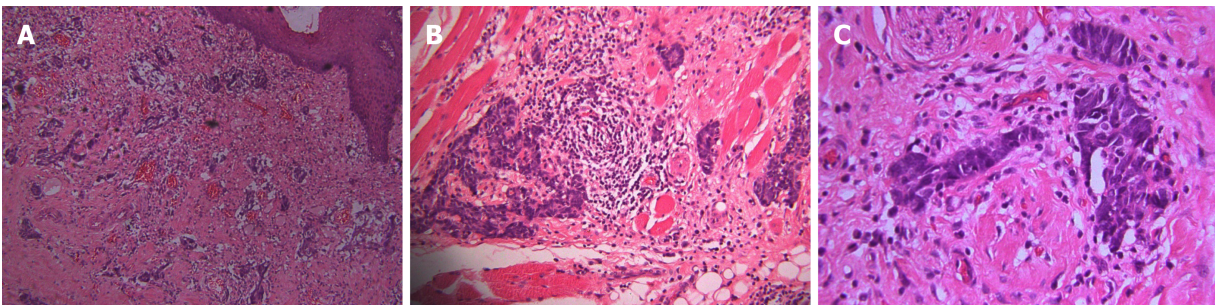


Figure 3 Microscopically, round and spindle small cells with ovoid- or spindle-shaped nuclei, fine granular chromatin, inconspicuous nucleoli and scant cytoplasm formed broad nests, sheets or cord shapes. A: The tumor cells were located in the fiber and striated muscle tissues below the mucous membrane, arranging in nest, sheet and cord shapes ($\times 100$); B: The tumor cells were found to infiltrate the fiber and striated muscle tissues, secondary inflammatory reactions were also found in the interstitial fiber, vascular tissue and nerve tissue, and infiltrating lymphocytes and neutrophils were present ($\times 200$); C: The nucleolus of the tumor cells were unsuspicious but heteromorphosis and nuclear mitosis were obvious ($\times 200$).

DISCUSSION

According to the World Health Organization Blue Book 2017, neuroendocrine carcinomas (NECs) are now classified into three categories: Well-differentiated, moderately-differentiated and poorly-differentiated, which is additionally divided into two subtypes: SNEC and large cell NEC^[17]. Primary NECs in the oral cavity have been subclassified into typical carcinoid, atypical carcinoid, large cell NEC and SNEC^[18]. The synonyms for SNEC include “small cell carcinoma”, “oat cell carcinoma” and “anaplastic small cell carcinoma”^[19]. Primary SNEC occurring in the oral cavity is extremely rare and has a poor prognosis. Positron emission tomography-CT and CT

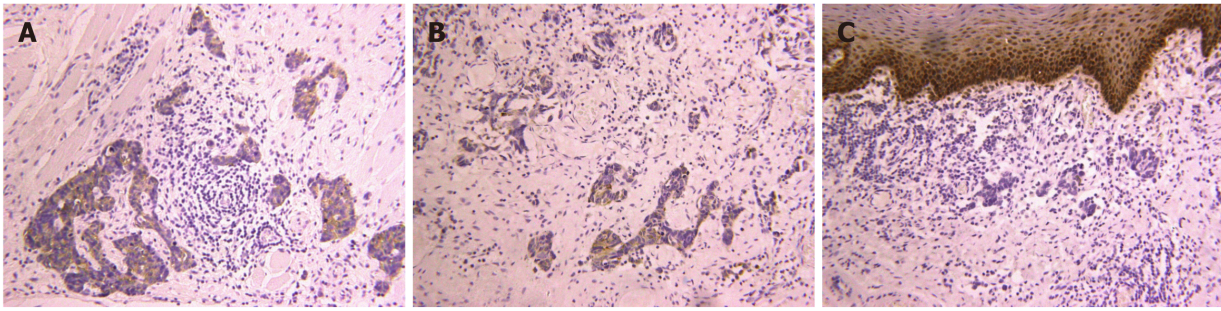


Figure 4 Immunohistochemical analysis showed positivity for (A) synaptophysin, (B) chromogranin A, and (C) cytokeratin AE1/AE3. Magnification: $\times 200$.

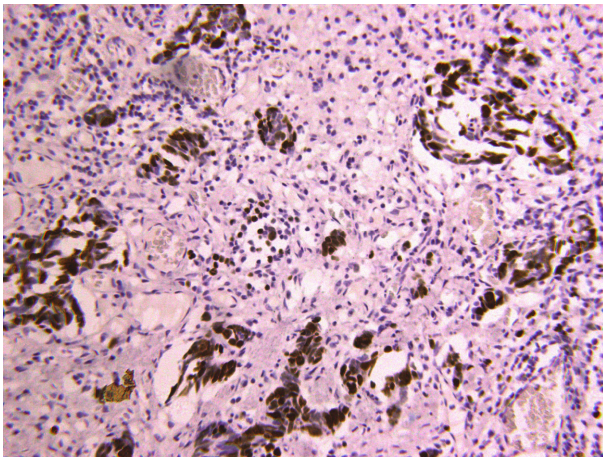


Figure 5 About 90% of the tumor cells showed Ki67+ nuclear staining, suggesting a high proliferation activity.

images confirmed that the current patient had a rare primary SNEC of the oral cavity, and not a metastatic SNEC arising from the lung.

The clinical characteristics of these rare cases reported in the English literature are shown in Table 1. Most of the patients were men (81.8%). The median age of the patients was 67.5 years (range: 40-83 years). Smoking and alcohol abuse, as the major risk factors, were also common among these patients. These results are similar to those of NEC in the head and neck^[10]. The tongue was the most common subsite (63.6%). Minor salivary glands may be the prevailing origin of primary SNEC in the oral cavity^[11]. Most of the patients had lymph node and distant metastasis with stage III, IVA, IVB and IVC tumors (72.7%), which are also similar to the results of previous studies on extra-pulmonary SNEC in the head and neck. In patients with positive cervical lymph nodes, the recurrence rate is high and distant metastasis frequently occurs. In addition, these patients have a poor median survival of 10.0 mo and a 2-year survival rate of 15.7%^[16]. Therefore, a comprehensive examination is mandatory to exclude distant metastasis. The outcomes of the previously reported 11 patients were as follows: 3 died of tumor, 1 died from other causes, 6 showed no evidence of disease, and the status of 1 patient was unknown.

The definite diagnosis of SNEC depends on histopathology and immunohistochemistry analyses. Morphological examination showed extensive proliferation of round and spindly small cells with ovoid-to-spindle shaped nuclei, fine granular chromatin, inconspicuous nucleoli and scant cytoplasm, which could help in the differential diagnosis of typical and atypical carcinoids and large cell NEC^[8]. These small cells formed broad nests, sheets or cord shapes. Necrosis is typically extensive and the mitotic count is high. The presence of electron-dense and neurosecretory granules is distinctive in SNEC^[20]. The cells are distinctively positive for neuroendocrine markers including syn, N-CAM (CD56) and chromogranin A^[17]. High Ki-67 labeling (90%) indicates high proliferative activity of tumor cells^[8].

Immunohistochemical staining is crucial for the differential diagnosis of SNEC from other malignancies. Extensive mitotic index and necrosis can distinguish SNEC from typical and atypical carcinoids. In contrast to SNEC, large cell NEC contains cells with

Table 1 Clinical characteristics of the primary small cell neuroendocrine carcinomas in the oral cavity

Publication year	Age in yr	Sex	Smoking	Alcohol	Primary subsite	Disease stage	Therapy	RT dose in Gy	CM	Follow-up time in mo	RE	DM	Patient status ¹
1984	62	M	+	+	Tongue	IVA	S + RT + CM	Un	C+A+O	10	-	+	Died of DM
1995	76	M	+	+	Tongue	IVA	RT	72	-	2	-	-	Died of debility
2001	62	M	+	+	Mandible	IVA	-	-	-	3	-	+	Died of DM
2013	75	M	Un	Un	Tongue	III	S + RT	Un	-	Un	Un	Un	Un
2013	85	M	Un	Un	Cheek	III	CRT + S	40	CA	2.5	-	+	Died of DM
2013	59	M	Un	Un	Cheek	IVC	CM	Un	CI	16	-	+	Alive
2014	55	F	+	-	Tongue	IVA	S + CM	Un	Un	Un	-	-	Alive
2015	73	M	+	+	Lower gingiva	II	S + CM	-	CI + E	14	-	-	Alive
2015	54	M	Un	Un	Tongue	I	S + CM + RT	66	CI + E	Un	-	-	Alive
2015	40	F	Un	Un	Tongue	I	S + CM + CRT + CM	60	CI + E	52	-	-	Alive
2017	74	M	Un	Un	Tongue	IVC	CM	-	CA + E	9	-	-	Alive

¹As of publication. C + A + O: Cytosin + Adriamycin + Oncovin; CA: Carboplatin; CA + E: Carboplatin + Etoposide; CI: Cisplatin; CI + E: Cisplatin + Etoposide; CM: Chemotherapy; CRT: Chemoradiotherapy; CT: Computerized tomography; DM: Distant metastasis; M: Male; F: Female; RE: Recurrence; RT: Radiotherapy; S: Surgery; Un: Unknown.

a relatively large cytoplasm and vesicular chromatin and prominent nucleoli. Primary cutaneous high-grade NEC, which mainly develops due to ultraviolet light exposure, is termed Merkel cell carcinoma. Primary mucosal high-grade NEC, which typically develops because of heavy smoking and alcohol abuse, is called SNEC. In addition, CK20 is commonly positive in Merkel cell carcinoma, and is negative in SNEC^[21]. HMB45 and S100 are special markers for malignant melanoma and malignant lymphoma. They can be used for detecting metastatic squamous cell carcinoma of the lung when thyroid transcription factor1 is positive^[11]. Cytokeratin AE1/AE3 and P63 staining is helpful in identifying a basal cell carcinoma or a squamous cell-originated tumor^[6,10,11].

Due to the paucity of primary SNECs in the oral cavity, the lack of definitive treatment recommendations is a challenge for clinicians. The appropriate treatment strategies for extra-pulmonary SNECs are extrapolated from their pulmonary counterparts^[14]. A variety of therapeutic modalities, including surgery, chemotherapy, radiotherapy and chemoradiotherapy, are thought to be appropriate treatments^[16,22]. Surgery could be curative when SNECs are limited within the primary sites. In addition, surgery is the main treatment of NECs at different body sites and has been

reported to significantly improve overall survival, over other single-modality treatments. To decrease local recurrence of SNECs, a wide excision is mandatory (up to 3 cm)^[7]. In our case, the patient underwent extensive surgical excision of the primary tumor.

As SNEC is an extremely aggressive malignancy with high rates of local recurrence and distant metastasis, multimodal therapy is required. For patients without distant metastasis, chemotherapy can reduce tumor size and decrease the risk of distant metastasis. In early and locally advanced SNECs of the head and neck, chemoradiotherapy is also an effective treatment^[16]. In patients with extensive SNEC, chemotherapy is recommended to prolong survival and improve prognosis^[6,12]. The combination of cisplatin and etoposide is the first-line chemotherapy regimen for SNEC^[23]. In recent research, chemotherapy in combination with first-line atezolizumab prolonged survival rate compared with chemotherapy alone in the treatment of extrapulmonary SNECs with distant metastases^[2].

Furthermore, a few novel therapeutic strategies for small cell carcinoma of the lung which are unsuccessful, including mammalian target of rapamycin inhibitors, breakpoint cluster region–Abelson tyrosine kinase inhibitors, epidermal growth factor receptor tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, deoxyribonucleic acid repair inhibitors, immunotherapies, and anti-delta-like protein 3 antibody-drug conjugates, have been introduced^[24,25]. Of the 11 patients with primary SNEC in the oral cavity, 1 patient received radiotherapy only, due to his poor physical condition. Chemotherapy was the most common treatment in the majority of patients (75%). In the current case, the patient showed partial remission after two cycles of adjuvant chemotherapy. However, the patient died when gastrointestinal metastasis occurred 20 mo after treatment.

CONCLUSION

Primary SNEC occurring in the oral cavity represents a rare clinical entity, and is aggressive with a poor prognosis. The diagnosis of SNEC requires morphology and immunohistochemistry analyses. Due to its highly metastatic characteristics, a comprehensive clinical examination of the neck, chest, abdomen and bone is mandatory in SNEC patients. Multimodal therapy may be an effective treatment strategy for SNEC of the oral cavity. However, more effective treatments to improve the survival rate of patients with SNEC in the oral cavity are required.

REFERENCES

- 1 **Galanis E**, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. *Cancer* 1997; **79**: 1729-1736 [PMID: 9128989]
- 2 **Wakasaki T**, Yasumatsu R, Masuda M, Matsuo M, Tamae A, Kubo K, Kogo R, Uchi R, Taura M, Nakagawa T. Small Cell Carcinoma in the Head and Neck. *Ann Otol Rhinol Laryngol* 2019; **128**: 1006-1012 [PMID: 31161776 DOI: 10.1177/0003489419853601]
- 3 **Hull MT**, Eble JN, Warfel KA. Extrapulmonary oat-cell carcinoma of the tongue: an electron-microscopic study. *J Oral Pathol* 1984; **13**: 489-496 [PMID: 6090621 DOI: 10.1111/j.1600-0714.1984.tb01449.x]
- 4 **Yoshida H**, Onizawa K, Hirohata H. Neuroendocrine carcinoma of the tongue: report of a case. *J Oral Maxillofac Surg* 1995; **53**: 823-827 [PMID: 7595799 DOI: 10.1016/0278-2391(95)90342-9]
- 5 **Kim SG**, Jang HS. Small cell carcinoma of the oral cavity: report of a case. *J Oral Maxillofac Surg* 2001; **59**: 680-684 [PMID: 11381395 DOI: 10.1053/joms.2001.23402]
- 6 **Nishihara K**, Nozoe E, Hirayama Y, Miyawaki A, Semba I, Nakamura N. A case of small cell carcinoma in the buccal region. *Int J Oral Maxillofac Surg* 2009; **38**: 1000-1003 [PMID: 19464148 DOI: 10.1016/j.ijom.2009.04.010]
- 7 **Cymerman JA**, Kulkarni R, Goulesbrough D, McCaul J. Small cell neuroendocrine tumour of the anterior tongue: A case report. *Int J Surg Case Rep* 2013; **4**: 753-755 [PMID: 23835197 DOI: 10.1016/j.ijscr.2013.04.028]
- 8 **Terada T**. Small cell carcinoma of the oral cavity (cheek mucosa): a case report with an immunohistochemical and molecular genetic analysis. *Int J Clin Exp Pathol* 2013; **6**: 780-787 [PMID: 23573327]
- 9 **Singla A**, Singla A, Gallagher R. A rare case and literature review of primary neuroendocrine carcinoma of the tongue†. *J Surg Case Rep* 2014; **2014** [PMID: 25148834 DOI: 10.1093/jscr/rju084]
- 10 **Zeng M**, Yang SD, Zhang JL, Chen XM. Primary small cell neuroendocrine carcinoma of the oral cavity: A case report and review of the literature. *Oncol Lett* 2015; **10**: 887-890 [PMID: 26622589 DOI: 10.3892/ol.2015.3298]
- 11 **Gumusay O**, Yilmaz G, Aydil U, Ozet A, Tufan G, Erdem O, Kizil Y, Benekli M. Small cell neuroendocrine carcinoma of the posterior tongue. *J Cancer Res Ther* 2015; **11**: 651 [PMID: 26458628 DOI: 10.4103/0973-1482.140778]

- 12 **Esmati E**, Babaei M, Matini A, Ashtiani MS, Hamed EA, Nosrati H, Razi F, Ganjalikhani M. Neuroendocrine carcinoma of the tongue. *J Cancer Res Ther* 2015; **11**: 659 [PMID: [26458666](#) DOI: [10.4103/0973-1482.139395](#)]
- 13 **Xue LW**, Chen X, Yin DD, Wang XX. Report: Small cell neuroendocrine carcinoma (SCNEC) of the tongue: A case report. *Pak J Pharm Sci* 2017; **30**: 1191-1194 [PMID: [28671105](#)]
- 14 **Yasumatsu R**, Nakashima T, Yamauchi M, Toh S, Komune S. Extrapulmonary small cell carcinoma in head and neck. *J Laryngol Otol* 2015; **129** Suppl 2: S83-S85 [PMID: [25706169](#) DOI: [10.1017/S002221511400245X](#)]
- 15 **Walenkamp AM**, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. *Cancer Treat Rev* 2009; **35**: 228-236 [PMID: [19068273](#) DOI: [10.1016/j.ctrv.2008.10.007](#)]
- 16 **Pointer KB**, Ko HC, Brower JV, Witek ME, Kimple RJ, Lloyd RV, Harari PM, Baschnagel AM. Small cell carcinoma of the head and neck: An analysis of the National Cancer Database. *Oral Oncol* 2017; **69**: 92-98 [PMID: [28559027](#) DOI: [10.1016/j.oraloncology.2017.04.009](#)]
- 17 **Gale N**, Poljak M, Zidar N. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: What is New in the 2017 WHO Blue Book for Tumours of the Hypopharynx, Larynx, Trachea and Parapharyngeal Space. *Head Neck Pathol* 2017; **11**: 23-32 [PMID: [28247231](#) DOI: [10.1007/s12105-017-0788-z](#)]
- 18 **Mahomed F**. Neuroendocrine cells and associated malignancies of the oral mucosa: a review. *J Oral Pathol Med* 2010; **39**: 121-127 [PMID: [20002872](#) DOI: [10.1111/j.1600-0714.2009.00834.x](#)]
- 19 **Renner G**. Small cell carcinoma of the head and neck: a review. *Semin Oncol* 2007; **34**: 3-14 [PMID: [17270660](#) DOI: [10.1053/j.seminoncol.2006.10.024](#)]
- 20 **Roy S**, Das I, Nandi A, Roy R. Primary Merkel cell carcinoma of the oral mucosa in a young adult male: report of a rare case. *Indian J Pathol Microbiol* 2015; **58**: 214-216 [PMID: [25885137](#) DOI: [10.4103/0377-4929.155318](#)]
- 21 **Lewis JS Jr**, Duncavage E, Klonowski PW. Oral cavity neuroendocrine carcinoma: a comparison study with cutaneous Merkel cell carcinoma and other mucosal head and neck neuroendocrine carcinomas. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **110**: 209-217 [PMID: [20659699](#) DOI: [10.1016/j.tripleo.2010.04.007](#)]
- 22 **van der Laan TP**, Plaat BE, van der Laan BF, Halmos GB. Clinical recommendations on the treatment of neuroendocrine carcinoma of the larynx: A meta-analysis of 436 reported cases. *Head Neck* 2015; **37**: 707-715 [PMID: [24596175](#) DOI: [10.1002/hed.23666](#)]
- 23 **Barker JL Jr**, Glisson BS, Garden AS, El-Naggar AK, Morrison WH, Ang KK, Chao KS, Clayman G, Rosenthal DI. Management of nonsinonasal neuroendocrine carcinomas of the head and neck. *Cancer* 2003; **98**: 2322-2328 [PMID: [14635065](#) DOI: [10.1002/cncr.11795](#)]
- 24 **Horn L**, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu SV; IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med* 2018; **379**: 2220-2229 [PMID: [30280641](#) DOI: [10.1056/NEJMoa1809064](#)]
- 25 **Srivastava R**, Lebowicz Y, Jamil MO. Targeted agents in the management of small cell lung cancer - present and future. *Drugs Today (Barc)* 2018; **54**: 479-488 [PMID: [30209442](#) DOI: [10.1358/dot.2018.54.8.2833977](#)]

Treatment of *Helicobacter pylori* infection in children: A systematic review

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) infection is predominantly acquired in childhood. When indicated, the most accepted treatment for *H. pylori* eradication in this age group is first-line triple therapy. However, the increasing resistance to clarithromycin and nitroimidazoles has been associated with treatment failure, and thus, alternative treatment regimens have been proposed.

AIM

To perform a systematic review of randomized controlled trials on treatment regimens for *H. pylori* infection in children.

METHODS

We surveyed relevant articles published in English from 2010 to April 2020 in the PubMed and MEDLINE databases. Keywords included "*Helicobacter pylori*" / "children or childhood" / "treatment or eradication." The risk of bias was evaluated according to the Cochrane Handbook of Systematic Reviews for Interventions.

A PRISMA checklist was used to guide the development of the systematic review.

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RESULTS

Among the 1144 records identified through the database, 20 articles were selected. Four studies compared the eradication rates of *H. pylori* infection between standard triple therapies, changing only the main antibiotic used. Seven studies evaluated the effectiveness of standard triple therapy with the addition of probiotics. One study investigated the relationship between the effectiveness in the eradication rates of standard triple therapy and vitamin E levels. Six studies analyzed the eradication rates of sequential therapy.

CONCLUSION

The findings suggest that although standard triple therapy is the most recommended regimen for children by the current guidelines, other therapeutic schemes have shown promising results and may also be recommended for clinical practice in the future.

Key Words: *Helicobacter pylori*; Children; Pediatric treatment; Standard triple therapy; Probiotics; Sequential therapy; Eradication therapies

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Core Tip: *Helicobacter pylori* (*H. pylori*) is a bacterium that infects more than 50% of the population worldwide. In the last several years, no significant changes in the treatment of infected children have been observed, mainly due to a lack of studies with satisfactory scientific evidence to support the indication of therapies in clinical practice. We performed a systematic review of randomized controlled trials on treatment regimens for *H. pylori* infection in children.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative spiral bacterium that colonizes the gastric mucosa of more than 50% of the population worldwide. The infection is acquired predominantly in childhood, and is more prevalent in developing countries where about 70% of children are infected until 15-years-old^[1,2], whereas it is disappearing in developed countries. Once acquired, the bacterium is rarely eliminated without adequate antibiotic therapy and individuals remain infected throughout life^[3]. Most infected individuals do not develop complications, but gastric colonization can progress to chronic gastritis, duodenal ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma, and bacterial eradication is associated with the prevention of such diseases^[4]. *H. pylori* infection has also been implicated in the pathogenesis of extra-gastric diseases, including iron deficiency anemia and chronic immune thrombocytopenic purpura.

The mechanisms by which the infection progresses to the above-mentioned diseases are not completely understood and depend on the relationship between host genetics and factors regarding the environment and bacterial virulence.

Severe *H. pylori*-associated diseases are more common in adults than in children. This phenomenon can be explained, in part, by the differences in immune response between the two age groups, which seems to be a relevant factor influencing mucosal damage and clinical outcomes^[5]. In general, *H. pylori* infection induces a T helper type 1 (Th1)-polarized response with high levels of interferon- γ that stimulate gastric inflammation and mucosal damage in adults. Moreover, Th17 cells and interleukin (IL)-17 levels are important in that process because they stimulate the recruitment and activation of neutrophils in the gastric mucosa, increasing the inflammatory environment against the bacterium. In contrast to the pro-inflammatory response

found in adults, children tend to exhibit an immune response pattern with a predominance of regulatory T cells that contribute to the persistence of the infection and milder clinical manifestations^[6,7]. Children tend to have lower levels of Th1- and Th17-related cytokines as well as overexpression of IL-10 and transforming growth factor- β , resulting in a lower degree of polymorphonuclear cell activation in the acute phase of infection^[8,9] and prominent mononuclear cell infiltration in chronic infection compared with adults^[10].

H. pylori virulence factors also play an important role in the pathogenesis of infection in childhood. It is well documented that genes such as cytotoxin gene A (*cagA*) and vacuolating cytotoxin gene A (*vacA*) increase the risk of severe gastric diseases such as duodenal ulcer and gastric cancer^[11].

H. pylori eradication prevents duodenal ulcer recurrence and prevention of gastric cancer. In addition, *H. pylori* eradication in children induces platelet and iron recovery in immune thrombocytopenic purpura and iron deficiency anemia, respectively.

Since eradication therapies show variable failure rates, retesting for *H. pylori* infection after an antimicrobial regimen is recommended to ensure that patients have been successfully treated^[12]. There are various available therapeutic options aimed toward *H. pylori* eradication, and clarithromycin-based triple therapy, sequential therapy, bismuth-containing quadruple therapy or triple therapy, and hybrid therapy are the regimens most often used^[13]. Moreover, various alternative approaches have been attempted in order to improve bacterial eradication such as susceptibility-guided therapies, probiotics, and vaccines^[14-16]. In that context, a number of factors influence the choice of appropriate treatment, including antimicrobial susceptibility profile, economic factors, and importantly, individual characteristics such as previous exposure to antibiotics and age^[17].

Performing *H. pylori* eradication in children demands specific precautions, of which avoiding regimens with unacceptable rates of adverse events (AEs) for this population is very important^[18]. In this context, the number of treatment options usually available for children tends to be significantly lower compared to the range of treatments at hand for adults. Clarithromycin-based triple therapy is the most used therapeutic scheme for children, although other standard therapies have also been tried^[19]. Moreover, to reduce the frequency and severity of side effects as well as to improve eradication rates, probiotics in association with standard therapy have been tested in children^[20].

Therefore, we reviewed the randomized controlled trials (RCTs) of treatments for *H. pylori* eradication children.

MATERIALS AND METHODS

In this systematic review, the criteria recommended by the PRISMA checklist were used^[21].

Types of studies

Prospective RCTs, published in peer-reviewed journals from 2010 to April 2020 and reporting the results of antibiotic therapy and/or supplementation with other drugs for the *H. pylori* eradication in infected children under 18-years-old, were included. There was no restriction regarding the therapeutic schemes used. Excluded studies were those including adults or lacking their complete or free full text. Only English language studies were included. The inclusion criteria are outlined in [Table 1](#).

Types of participants

H. pylori-positive patients under 18-years-old diagnosed by any validated test accepted by the scientific community for *H. pylori* detection. Patients who had previous failed antibiotic therapies were included.

Types of intervention

Prospective RCTs evaluating *H. pylori* eradication rates in children.

Types of outcome measures

We collected outcomes of intention-to-treat (ITT), per protocol (PP), and simple percentages of *H. pylori* infection eradication.

Table 1 Inclusion criteria

Criteria	Description
Date range	January 2010 to April 2020
Language	Only English published articles
Location	No restriction of localization
Population	Children (< 18-years-old)
Type of study	Randomized controlled trials

Information sources

We surveyed the relevant articles published in English language from 2010 to April 2020 in the PubMed and MEDLINE databases. The term strategies used for the search at both databases were: ((*Helicobacter pylori* [and] children [and] treatment) [OR] eradication) and (*Helicobacter pylori* [and] childhood [and] (treatment [OR] eradication)).

Study selection

The eligibility of the articles was evaluated by two independent reviewers (Da Silva FAF and de Brito BB). Duplicate articles were excluded. The abstracts of the articles were evaluated and studies that were not prospective RCTs and/or did not evaluate *H. pylori* eradication rate in children were excluded. A third reviewer (de Melo FF) resolved disagreements between the two reviewers. To verify if the articles met all previously established criteria, each article was individually analyzed. To statistically evaluate the agreement between the reviewers, the Kappa coefficient (K) was calculated, which indicated a $K = 0.752$, considered as a substantially strong degree of agreement between the reviewers.

Data collection process

We developed a structured data extraction spreadsheet specifically for this review based on the criteria recommended by the Cochrane Handbook of Systematic Reviews for Interventions^[42]. We independently reviewed the relevant study data and results of interest such as rates of eradication of *H. pylori* infection in childhood.

Data items

Information was extracted from each study including: General characteristics of the participants and studies, type of intervention, therapeutic regimen used, type of outcome measure, and positive and negative outcomes.

Risk of bias

To assess the validity of RCTs, two authors independently analyzed the risk of bias criteria recommended by the Cochrane Handbook of Systematic Reviews for Interventions^[42]: Generation of the random sequence, concealment of allocation, blinding of participants and professionals, blinding of outcome evaluators, incomplete outcomes, and reporting of the selective outcome. Then the risk of bias was categorized as high, low, or uncertain.

RESULTS

Study selection

Of the 1144 articles reviewed (861 in NCBI and 283 in MEDLINE), 1118 were excluded using previously established inclusion criteria. Twenty-six articles were selected for complete analysis; however, eight were duplicate and thus were excluded. Finally, 2 studies were an additional reference list and 20 articles were included. **Figure 1** shows the selection and distribution of articles according to the databases searched, from the first search to the application of all of the selection criteria.

Study characteristics

The characteristics of the 20 selected studies are summarized in **Table 2**. A total of 2261 children aged 22 mo to 18 years were included. Regarding the geographic distribution

Table 2 Summary of included studies

Ref.	Year	Country	Study design	Patients, n	Age range	Follow-up	Goal
Moubri <i>et al</i> ^[22]	2018	Algeria	RCT	272	5-16 yr	8-12 wk	To compare efficacy, side effects and influence of resistance of <i>H. pylori</i> strains between two different treatments in Algerian children.
Namkin <i>et al</i> ^[23]	2016	Iran	RCT	28	9-12 yr	4-8 wk	To evaluate the effect of <i>S. boulardii</i> supplementation on the eradication of <i>H. pylori</i> in children in the region.
Akcam <i>et al</i> ^[24]	2015	Turkey	RCT	61	7-18 yr	6 wk	To evaluate the effect of probiotics on eradication rates and side effects in association with standard triple therapy in <i>H. pylori</i> -positive children.
Tolone <i>et al</i> ^[25]	2012	Italy	RCT	68	4-11 yr	4 wk	To evaluate if addition of probiotics increases eradication rates and reduces side effects in children.
Farahmand <i>et al</i> ^[26]	2016	Iran	RCT	66	7-15 yr	4 wk	To compare the effect of ciprofloxacin and furazolidone on <i>H. pylori</i> eradication in combination with amoxicillin and omeprazole.
Ahmad <i>et al</i> ^[27]	2013	Iran	RCT	66	3-14 yr	4-8 wk	To evaluate the effect of probiotic supplementation with the combination of seven microorganisms on the treatment of <i>H. pylori</i> infection in childhood.
Bin <i>et al</i> ^[28]	2015	China	RCT	205	22 mo-16 yr	2 wk	To investigate the effects of <i>Saccharomyces boulardii</i> CNCM I-745 on eradication of <i>H. pylori</i> in children.
Kasiri <i>et al</i> ^[29]	2017	Iran	RCT	82	1-15 yr	4 wk	To compare the effect of amoxicillin and metronidazole in the triple therapy regimen to eradicate <i>H. pylori</i> infection in children aged 1 to 15 yr.
Iwańczak <i>et al</i> ^[30]	2016	Poland	RCT	69	5-17 yr	6-8 wk	To compare the efficacy of sequential therapy for 10 d with triple therapy for 7 d (PPI, amoxicillin and clarithromycin or PPI, amoxicillin and metronidazole) in children.
Tümgör <i>et al</i> ^[31]	2014	Turkey	RCT	90	10-17 yr	6 wk	To compare the treatment with lansoprazole, amoxicillin and clarithromycin (LAC) and with the combination of LAC + vitamin E (LACE) in Turkish children.
Ali Habib <i>et al</i> ^[32]	2013	India	RCT	18	12-15 yr	6 wk	To investigate which sequential or standard eradication regimen has the most effective improvement in the status of associated iron and iron deficiency in children.
Ustundag <i>et al</i> ^[33]	2017	Turkey	RCT	69	6-16 yr	4-6 wk	To evaluate the effects of the use of the symbiotic <i>Bifidobacterium lactis</i> B94 + inulin, together with standard triple therapy on the eradication rate, adherence, as well as in the symptoms of <i>H. pylori</i> infection in children.
Huang <i>et al</i> ^[34]	2013	China	RCT	360	3-16 yr	4 wk	To compare 10 d sequential therapy and standard triple therapy in Chinese children with <i>H. pylori</i> infection.
N Şirvan <i>et al</i> ^[35]	2017	Turkey	RCT	104	5-17 yr	4 wk	To evaluate the addition of symbiotics containing <i>Bifidobacterium lactis</i> to triple therapeutics in the rates of side effects, dyspeptic symptoms and <i>H. pylori</i> eradication in children.
Baysoy <i>et al</i> ^[36]	2013	Turkey	RCT	61	4-18 yr	6-8 wk	To compare ornidazole-based sequential therapy with standard triple therapy for the eradication of <i>H. pylori</i> in children.
Esmaili-Dooki <i>et al</i> ^[37]	2015	Iran	RCT	64	2-15 yr	4-6 wk	To evaluate the effect of the classic triple therapy and azithromycin eradication regimen against <i>H. pylori</i> in children.
Laving <i>et al</i> ^[38]	2013	Kenya	RCT	71	2-15 yr	2-6 wk	To determine the effectiveness of a new 10 d sequential therapy compared to the standard 10 d triple therapy for the treatment of <i>H. pylori</i> infection in children.
Prieto-Jimenez <i>et al</i> ^[39]	2011	United States of America	RCT	110	3-11 yr	6 wk	To evaluate the efficacy of sequential quadruple eradication therapy for 10 d and observe the iron levels of positive <i>H. pylori</i> children.
Nguyen <i>et al</i> ^[40]	2012	Vietnam	RCT	232	3-15 yr	4 wk	To investigate the role of antibiotic resistance, drug dosage, and administration frequency in treatment of <i>H. pylori</i> infection in Vietnamese children.
Bontems <i>et al</i> ^[41]	2011	Belgium, France and Italy	RCT	165	2,7 a 17 yr	8 wk	To compare sequential <i>vs</i> tailored triple therapy regimens on <i>H. pylori</i> eradication rate and to assess the effect of antimicrobial susceptibility in children.

RCTs: Randomized controlled trials. *H. pylori*: *Helicobacter pylori*; PPI: Proton pump inhibitor.

of the studies, 25% of the articles were from Iran; 25% from Turkey; 10% from China;



Figure 1 Summary of the study selection process.

and 40% from Algeria, Italy, Poland, India, Kenya, United States, Belgium, and France. The studies had a follow-up average of 6 wk. In addition, the articles evaluated conventional eradication therapies, probiotics, or sequential therapies as well as the eradication rates of *H. pylori* infection in childhood.

Results of individual studies

All patients were *H. pylori*-positive children diagnosed by validated methods. Randomization methods and loss of follow-up were highlighted for analysis of the risk of bias. All articles were classified according to the criteria of the Oxford Center for Evidence-based Medicine - Levels of Evidence^[43] (Table 3). Standard triple therapy was the main therapeutic scheme evaluated. The studies compared conventional triple therapy alone to triple therapy containing probiotics and to sequential therapies (Table 4).

Synthesis of results

Table 5 summarizes the positive and negative outcomes of the studies.

Risk of bias assessment

Using the Cochrane risk of bias tool^[44], seven RCTs^[23,26,27,34,37-39] had a low risk of bias for the following criteria: Generation of the random sequence, allocation concealment, blinding of participants and professionals, and blinding of outcome evaluators. Only the work by Akcam *et al*^[24] was classified as high risk of bias for generating the random sequence. All other RCTs had an uncertain or low rating for all of the criteria mentioned above. In general, we observed some risks of biases through deviations from the intended interventions, represented by the concealment of how the drugs were distributed and how the researchers made recommendations to the participants. In addition, interaction with a healthcare professional can improve symptoms and treatment adherence, becoming a possible bias for all the analyzed results.

Table 3 Criteria analyzed individually in the studies

Ref.	Specific disease	Diagnosis	Groups	Randomization	Loss of follow-up	Level of evidence
Moubri <i>et al</i> ^[22]	No	Biopsy, RUT, culture, HpSA and ¹³ C-UBT/(Biopsy, RUT, culture, HpSA and ¹³ C-UBT)	2	The method chosen was to classify closed envelopes, which were randomly assigned to treatment	12 patients	1b
Namkin <i>et al</i> ^[23]	No	HpSA/(HpSA)	2	Limited information on the method used	4 patients	2b
Akcam <i>et al</i> ^[24]	No	Biopsy, histology, RUT and ¹³ C-UBT/(¹³ C-UBT)	2	Admission order	5 patients	1b
Tolone <i>et al</i> ^[25]	No	Biopsy, histology, RUT and ¹⁴ C-UBT/(¹³ C-UBT)	2	No reported	No loss	2b
Farahmand <i>et al</i> ^[26]	No	Biopsy, RUT and HpSA/(HpSA)	2	Table of aleatory numbers	No loss	1b
Ahmad <i>et al</i> ^[27]	No	RUT, histology, and HpSA/(HpSA)	2	Limited information on the method used	No loss	1b
Bin <i>et al</i> ^[28]	No	Immunoglobulin G Antibody, histology and ¹³ C-UBT/(¹³ C-UBT)	2	No reported	14	1b
Kasiri <i>et al</i> ^[29]	Dyspepsia, epigastric pain and GB	Biopsy, histology and RUT/(HpSA)	2	Limited information on the method used	3	1b
Iwańczak <i>et al</i> ^[30]	Dyspepsia and gastric and/or duodenal ulcer	Histology and/or culture/(Biopsy and culture)	3	No reported	No loss	1b
Tümgör <i>et al</i> ^[31]	Dyspepsia.	¹⁴ C-UBT and histology/(¹³ C-UBT)	2	No reported	2	2b
Ali Habib <i>et al</i> ^[32]	No	Immunoglobulin G Antibody and ¹³ C-UBT/(¹³ C-UBT)	2	No reported	2	2b
Ustundag <i>et al</i> ^[33]	Gastrointestinal symptoms, severe regurgitation, gastrointestinal bleeding, unexplained weight loss or chronic diarrhea	Histology/(¹⁴ C-UBT)	2	Double-blind randomization list	5	2b
Huang <i>et al</i> ^[34]	No	RUT, HpSA, histology and culture/(HpSA)	3	Limited information on the method used	42	1b
N Şirvan <i>et al</i> ^[35]	Chronic diseases, abdominal pain and dyspepsia	Histology/(HpSA)	2	Limited information on the method used	No loss	2b
Baysoy <i>et al</i> ^[36]	No	Histology, RUT, ¹³ C-UBT/(HpSA or Biopsy and histology)	2	Limited information on the method used	8	1b
Esmaili-Dooki <i>et al</i> ^[37]	No	Biopsy, histology and HpSA/(¹³ C-UBT)	2	Table of aleatory numbers	No loss	1b
Laving <i>et al</i> ^[38]	No	Histology and HpSA/(HpSA)	2	Computer-generated random numbers	33	1b
Prieto-Jimenez <i>et al</i> ^[39]	No	¹³ C-UBT and urine antibody	6	Computer-generated random numbers	20	1b
Nguyen <i>et al</i> ^[40]	No	Biopsy, RUT, histology and culture	3	No reported	10	1b
Bontems <i>et al</i> ^[41]	Abdominal pain, nausea, vomiting, heartburn and anemia	Biopsy, histology and culture/(HpSA)	2	No reported	15	1b

The levels of evidence were based in the Oxford Centre for Evidence-based Medicine – Levels of Evidence^[43]. All diagnostic methods in brackets were used after treatment to verify *Helicobacter pylori* (*H. pylori*) eradication. RUT: Rapid urease test; HpSA: *H. pylori* monoclonal stool antigen test;

¹³C-UBT: ¹³C-urea breath test;

¹⁴C-UBT: ¹⁴C-urea breath test; GB: Gastrointestinal bleeding.

Table 4 Summary of therapeutic schemes used in included studies

Ref.	Treatment schemes
Moubri <i>et al</i> ^[22]	<p>Group A - Amoxicillin-based triple therapy: (1) Children > 30 kg: Omeprazole 40 mg/d, amoxicillin 50 mg/kg/d with a maximum of 2 g/d and clarithromycin 15 mg/kg/d for 7 d. All given in two daily doses; and (2) Children < 30 kg: omeprazole 2 × 10 mg/d b.i.d., amoxicillin 50 mg/kg/d b.i.d. with a maximum of 2 g/d, and clarithromycin 15 mg/kg/d b.i.d. for 7 d.</p> <p>Group B - Metronidazole-based triple therapy: (1) Children > 30 kg: Omeprazole 2 × 20 mg/d, amoxicillin 50 mg/kg/d b.i.d. with a maximum of 2 g/d and metronidazole 40 mg/kg/d b.i.d. for 10 d; and (2) Children < 30 kg: omeprazole 2 × 10 mg/d, amoxicillin 50 mg/kg/d b.i.d. with a maximum of 2 g/d and metronidazole 40 mg/kg/d b.i.d., for 10 d, with a maximum of 1.5 g/d in children above 30 kg and 1 g/d in children below 30 kg body weight.</p>
Namkin <i>et al</i> ^[23]	<p>Probiotic group: Yomogi® 250 mg lyophilizate - 1 capsule daily for 30 d.</p> <p>Placebo group: placebo capsule 250 mg - lactose and powdered wheat starch - 1 capsule daily for 30 d.</p>
Akcam <i>et al</i> ^[24]	<p>Standard triple therapy group: Omeprazole 1 mg/kg, before breakfast, amoxicillin 50 mg/kg b.i.d. after meals, clarithromycin 15 mg/kg b.i.d. after meals for 7 d.</p> <p>Standard triple therapy group + probiotics: Omeprazole 1 mg/kg, before breakfast + amoxicillin 50 mg/kg b.i.d. after meals, clarithromycin 15 mg/kg b.i.d. after meals, PROBINUL® 5 g once a day for 7 d.</p>
Tolone <i>et al</i> ^[25]	<p>Standard triple therapy group - lansoprazole 30 mg, before breakfast, amoxicillin 50 mg/kg/d b.i.d., clarithromycin 15 mg/kg/d b.i.d. for 14 d.</p> <p>Standard triple therapy group + probiotics: Lansoprazol 30 mg, before breakfast + amoxicillin 50 mg/kg/d b.i.d., clarithromycin 15 mg/kg/d b.i.d., Maflor® plus 1 capsule, b.i.d. for 14 d.</p>
Farahmand <i>et al</i> ^[26]	<p>Group A - Ciprofloxacin-based triple therapy: Ciprofloxacin 30 mg/kg/d b.i.d. and amoxicillin 50 mg/kg/d b.i.d. for 1 wk. Omeprazole 1 mg/kg/d b.i.d. for 4 wk.</p> <p>Group B - Furazolidone-based triple therapy: furazolidone 6 mg/kg/d single-dose over and amoxicillin 50 mg/kg/d b.i.d. for 1 wk. omeprazole 1 mg/kg/d b.i.d. for 4 wk.</p>
Ahmad <i>et al</i> ^[27]	<p>Group A - Triple therapy + placebo: Amoxicillin 50 mg/kg/d b.i.d., as syrup or capsule, and furazolidone 6 mg/kg/d b.i.d. as syrup or tablet for 1 wk. Omeprazole 1 mg/kg/d plus placebo for 4 wk.</p> <p>Group B - Triple therapy + probiotics: Amoxicillin 50 mg/kg/d b.i.d., as syrup or capsule, and furazolidone 6 mg/kg/d b.i.d. as syrup or tablet, for 1 wk. Omeprazole 1 mg/kg/d plus placebo for 1 sachet/d for 4 wk.</p>
Bin <i>et al</i> ^[28]	<p>Group A - Triple therapy + <i>Saccharomyces boulardii</i>: Amoxicillin, omeprazole, clarithromycin and 2 sachet <i>S. boulardii</i> 250 mg per day, for 2 wk. Allergic to penicillin: metronidazole + omeprazole, clarithromycin and <i>S. boulardii</i> (dosages not reported).</p> <p>Group B - Only triple therapy: Amoxicillin, omeprazole, clarithromycin. Allergic to penicillin: metronidazole + omeprazole, clarithromycin (dosages not reported).</p>
Kasiri <i>et al</i> ^[29]	<p>Group A - Amoxicillin-based triple therapy: Omeprazole 1–2 mg/kg b.i.d. for 1 mo. Amoxicillin 50 mg/kg and clarithromycin 15 mg/kg b.i.d. for 2 wk.</p> <p>Group B - Metronidazole-based triple therapy: Omeprazole 1 mg/kg b.i.d. divided into two doses for 1 mo. Metronidazole 15 mg/kg and clarithromycin 15 mg/kg b.i.d. for 2 wk.</p>
Iwańczak <i>et al</i> ^[30]	<p>Group I - Amoxicillin-based triple therapy: Omeprazole, amoxicillin and clarithromycin for 7 d (dosages not reported).</p> <p>Group II - Metronidazole-based triple therapy: Omeprazole, amoxicillin and metronidazole for 7 d (dosages not reported).</p> <p>Group III - Sequential therapy: omeprazole 1 mg/kg of body weight/d, max 20 mg b.i.d. and amoxicillin 50 mg/kg of body weight/d, max 1000 mg/24 h for 5 d, b.i.d. followed by 5 d treatment with omeprazole 1 mg/kg of body weight/d, max 20 mg/24 h twice daily, clarithromycin 15 mg/kg of body weight/d, max 500 mg/24 h twice daily and metronidazole 20 mg/kg of body weight/d, max 500 mg/24 h twice daily.</p>
Tümgör <i>et al</i> ^[31]	<p>Group A - Clarithromycin-based triple therapy: Lansoprazole 1 mg/kg/d, amoxicillin 50 mg/kg/d, and clarithromycin 14 mg/kg/d, all medications b.i.d. for 14 d.</p> <p>Group B - Clarithromycin-based triple therapy + vitamin E: Lansoprazole 1 mg/kg/d b.i.d., amoxicillin 50 mg/kg/d b.i.d., and clarithromycin 14 mg/kg/d b.i.d., vitamin E 200 IU/d for 14 d.</p>
Ali Habib <i>et al</i> ^[32]	<p>Group A - Standard therapy: Rabeprazole 20 mg, clarithromycin 250 mg, and amoxicillin 500 mg each administered orally twice daily for 10 d.</p> <p>Group B - Sequential therapy: Rabeprazole 20 mg and amoxicillin 500 mg for 5 d, followed by rabeprazole 20 mg clarithromycin 250 mg and tinidazole 500 mg for another 5 d, twice daily.</p>
Ustundag <i>et al</i> ^[33]	<p>Group A - Standard triple therapy: Amoxicillin 50 mg/kg/d, clarithromycin 15 mg/kg/d twice daily for 14 d and omeprazole 1 mg/kg/d once daily for 1 mo.</p> <p>Group B - Standard triple therapy + symbiotic: Amoxicillin 50 mg/kg/d and clarithromycin 15 mg/kg/d twice daily for 14 d. Omeprazole 1 mg/kg/d once daily for 1 mo and Maflor® a single dose for 14 d concurrently.</p>
Huang <i>et al</i> ^[34]	<p>Group A - 1 d sequential therapy: Omeprazole 0.8–1.0 mg/kg/d, amoxicillin 30 mg/kg/d for the first 5 d, followed by omeprazole 0.8–1.0 mg/kg/d, clarithromycin 20 mg/kg/d, and metronidazole 20 mg/kg/d for the remaining 5 d.</p>

	Group B – 7 d triple standard therapy: Omeprazole 0.8–1.0 mg/kg/d, amoxicillin 30 mg/kg/d, and clarithromycin 20 mg/kg/d.
	Group C – 10 d triple standard therapy: Omeprazole 0.8–1.0 mg/kg/d, amoxicillin 30 mg/kg/d, and clarithromycin 20 mg/kg/d.
N Şirvan <i>et al</i> ^[35]	Group 1 - Standard triple therapy + symbiotic: Amoxicillin 50 mg/kg/d b.i.d. for 7 d, clarithromycin 15 mg/kg/d b.i.d. for 14 d, and lansoprazole 1 mg/kg/d - single dose, in the morning for 14 d. Maflor [®] sachet - single dose for 14 d.
	Group 2 - Standard triple therapy: Amoxicillin 50 mg/kg/d b.i.d. for 14 d, clarithromycin 15 mg/kg/d b.i.d. for 14 d, and lansoprazole 1 mg/kg/d - single dose, in the morning for 14 d.
Baysoy <i>et al</i> ^[36]	Group A - Standard triple therapy: Amoxicillin 50 mg/kg/d, clarithromycin 15 mg/kg/d, and lansoprazole 1 mg/kg/d for 14 d.
	Group B - Sequential therapy group: Amoxicillin 50 mg/kg/d and lansoprazole 1 mg/kg/d for the first 5 d and clarithromycin 15 mg/kg/d, ornidazole 30 mg/kg/d and lansoprazole 1 mg/kg/d for another 5 d.
Esmaili-Dooki <i>et al</i> ^[37]	Group 1 - Clarithromycin-based triple therapy: Clarithromycin 7.5 mg/kg/d b.i.d. and amoxicillin 50 mg/kg/d every b.i.d. for 10 d, and omeprazole 1 mg/kg/d b.i.d. for 2 wk.
	Group 2 - Amoxicillin-based triple therapy: Azithromycin 10 mg/kg/d once a day, before meal, for 6 d along with amoxicillin and omeprazole.
Laving <i>et al</i> ^[38]	Conventional therapy group: Omeprazole plus 1 mg/kg/d, amoxicillin plus 50 mg/kg/d and clarithromycin 15 mg/kg/d for 10 d.
	10 d sequential therapy group: Omeprazole plus 1 mg/kg/d, amoxicillin plus 50 mg/kg/d for 5 d followed by omeprazole plus 1 mg/kg/d, clarithromycin 15 mg/kg/d, and tinidazole 20 mg/kg/d for the next 5 d.
Prieto-Jimenez <i>et al</i> ^[39]	Group I - Quadruple sequential eradication and placebo: Lansoprazole, once per day before breakfast, plus an oral solution containing amoxicillin 50 mg/kg/d for 5 d followed by lansoprazole, once per day, plus an oral solution containing clarithromycin 15 mg/kg/d and an oral solution containing tinidazole 20 mg/kg/d for another 5 d. 6 wk of a placebo matched to iron supplementation.
	Group II - Quadruple sequential eradication and iron: Lansoprazole, once per day before breakfast, plus an oral solution containing amoxicillin 50 mg/kg/d for 5 d followed by lansoprazole, once per day, plus an oral solution containing clarithromycin 15 mg/kg/d and an oral solution containing tinidazole 20 mg/kg/d for another 5 d. 6 wk of iron supplementation.
	Group III: Iron and placebo: A 10 d course of a placebo matched to <i>H. pylori</i> sequential eradication therapy plus 6 wk of iron supplementation.
	Group IV: Placebo alone: A 10 d course of placebo matched to <i>H. pylori</i> sequential eradication therapy plus 6 wk of a placebo matched to iron supplementation.
Nguyen <i>et al</i> ^[40]	Group A: Lansoprazole, amoxicillin and clarithromycin: (1) Children weighing 13–22 kg: lansoprazole 15 mg once daily, amoxicillin 500 mg twice daily and clarithromycin 250 mg once daily; and (2) Children weighing 23–45 kg: lansoprazole 15 mg, amoxicillin 750 mg and clarithromycin 250 mg, all given twice daily.
	Group B: Lansoprazole, amoxicillin and metronidazole: (1) Children weighing 13–22 kg: lansoprazole 15 mg once daily, amoxicillin 500 mg and metronidazole 250 mg twice daily; and (2) Children weighing 23–45 kg: Lansoprazole 15 mg, amoxicillin 750 mg and metronidazole 500 mg, all given twice daily.
Bontems <i>et al</i> ^[41]	Group A: 10 d sequential treatment: 5 d therapy with a combination of omeprazole (10 mg b.i.d. below 30 kg body weight or 20 mg b.i.d. above 30 kg) and amoxicillin 25 mg/kg b.i.d. – maximum 2 g/d), followed by 5 d of omeprazole, clarithromycin (7.5 mg/kg b.i.d. – maximum 1 g/d), and metronidazole (10 mg/kg b.i.d. – maximum 1.5 g/d).
	Group B: 7 d triple therapy: 7 d treatment tailored comprising omeprazole and amoxicillin with clarithromycin in cases of <i>H. pylori</i> strains susceptible to clarithromycin or with clarithromycin in cases of <i>H. pylori</i> strains susceptible to metronidazole and resistant to clarithromycin.

H. pylori: *Helicobacter pylori*.

DISCUSSION

In pediatric clinical practice, *H. pylori* infection is common, especially in developing countries and certain populations such as ethnic minorities and migrant communities living in developed countries. In this systematic review, standard triple therapies, given for 7, 10, or 14 d were compared with sequential, third-line, and quadruple therapies for *H. pylori* eradication. In addition, some studies evaluated the efficacy of probiotics as adjuvant therapy for triple therapy.

Currently, triple therapies recommended by the main guidelines for *H. pylori* eradication include a proton pump inhibitor (PPI) or ranitidine, amoxicillin, and either clarithromycin or metronidazole, considered the first-line regimen, and bismuth, administered for 7, 10, or 14 d^[45]. The desirable target of anti-*H. pylori* treatment regimens is to reach an eradication rate of at least 90% in the per-protocol analysis whereas antibiotic use eradication rate below 80% is considered unacceptable^[46]. However, few studies have achieved this goal. The low efficacy of triple therapy observed in diverse geographic areas has been attributed to the rising resistance of *H. pylori* strains to clarithromycin and metronidazole, poor compliance, duration of treatment, and inadequate dosage and number of daily doses. The growing *H. pylori* resistance is due to the previous exposition of children to these antimicrobials that are

Table 5 Synthesis of results from included studies

Ref.	Adverse events	Deaths	Eradication rates	Conclusion
Moubri <i>et al</i> ^[22]	Mild and moderate symptoms, mainly gastrointestinal.	No	(1) ITT: Group A - Amoxicillin - based triple therapy: 68%; Group B - Metronidazole - based triple therapy: 80%; and (2) PP: Group A - Amoxicillin - based triple therapy: 71%; Group B - Metronidazole - based triple therapy: 88%.	The group B eradication rates were higher than Group A rates. The differences were only significant for PP ($P < 0.03$).
Namkin <i>et al</i> ^[23]	Loss of appetite.	No	Probiotic group: 0.40 ± 0.32 to 0.21 ± 0.27 average HpSA title; $P = 0.005$. Placebo group: 0.24 ± 0.2 to 0.24 ± 0.27 average HpSA title; $P = 0.89$.	There was no significant difference between the two groups in relation to the eradication rate of <i>H. pylori</i> infection ($P = 0.16$), however the decrease in the concentration of HpSA was significantly greater in the group treated with probiotics ($P = 0.005$ vs $P = 0.89$).
Akcam <i>et al</i> ^[24]	Abdominal pain, nausea, vomiting, constipation, belching, changes in taste, poor appetite and diarrhea.	No	Standard triple therapy group: 68.9%; Standard triple therapy group + probiotics: 66.6%; $P = 0.78$.	There was no statistically significant difference between the two groups.
Tolone <i>et al</i> ^[25]	Epigastric pain, nausea, vomiting, diarrhea and constipation.	No	Group A standard therapy group: 76.4%; Group B standard therapy + probiotics: 88.2%; $P = 0.1$.	There was no significant difference in the rate of <i>H. pylori</i> eradication between group A and group B, however, the side effects were significantly greater ($P < 0.05$) in group A than in group B.
Farahmand <i>et al</i> ^[26]	Vomiting, abdominal pain, iron deficiency, anemia and gastrointestinal bleeding.	No	Group A - Ciprofloxacin-based triple therapy: 87.9%; Group B - Furazolidone-based triple therapy: 60.6%; $P = 0.011$.	This study concludes that triple therapy consisting of ciprofloxacin, amoxicillin and omeprazole is highly valuable as <i>H. pylori</i> is not resistant to the antimicrobials.
Ahmad <i>et al</i> ^[27]	Diarrhea, nausea, vomiting and abdominal swelling.	No	Group A - Triple therapy + placebo: 69.69%; Group B - Triple therapy + probiotics: 90.09%; $P = 0.04$.	The group treated with the combination of probiotic and standard therapeutic regimen showed a more significant eradication rate. Supplementation with probiotics has a positive effect on <i>H. pylori</i> and decreases adverse events and effectiveness.
Bin <i>et al</i> ^[28]	Diarrhea.	11	Group A - Triple therapy + <i>S. boulardii</i> : 71.4%; Group B - Only triple therapy: 61.9%; $P = 0.51$	The probiotic prevented diarrhea associated with triple <i>H. pylori</i> eradication therapy. In addition, when diarrhea developed, it was less severe and of shorter duration in the <i>S. boulardii</i> group. The probiotic increased the adherence to <i>H. pylori</i> eradication therapy, which may be related to a small increase in <i>H. pylori</i> eradication by 10 percent.
Kasiri <i>et al</i> ^[29]	Intolerance to clarithromycin.	No	Group A - Amoxicillin-based triple therapy: 87.2%; Group B - Metronidazole-based triple therapy: 92.5%; $P = 0.43$.	There was no significant difference in the complete recovery and eradication of <i>H. pylori</i> between the two regimens. Both therapeutic regimens were considered to be effective, since both have similar rates of eradication, recovery and side effects.
Iwańczak <i>et al</i> ^[30]	-	-	Group I - Amoxicillin-based triple therapy: 78.2%; Group II Metronidazole-based triple therapy: 78.2%; Group III - Sequential therapy: 91.3%; $P > 0.5$.	For strains susceptible to clarithromycin: treatment with amoxicillin-based triple therapy was the most effective. For regions with clarithromycin resistance greater than 20%, quadruple therapy or therapy based on the susceptibility of the strains is recommended.
Tümçör <i>et al</i> ^[31]	Nausea, headache, vomiting, abdominal pain and diarrhea.	-	Group A - Clarithromycin-based triple therapy: 46.6%; Group B - Clarithromycin-based triple therapy + vitamin E: 64.4%; $P = 0.13$.	Although, Group B showed a higher rate of eradication, no statistically significant difference was observed between the two groups.
Ali Habib <i>et al</i> ^[32]	-	No	Group A - Standard therapy: 55.6%; Group B - Sequential therapy: 57.1%; $P = 0.949$.	The rates of <i>H. pylori</i> eradication were not significantly different in sequential vs standard therapy. In addition, serum ferritin was not significantly different between the two therapies and in the same therapy group before and after treatment.

Ustundag <i>et al</i> ^[33]	Abdominal pain and nausea.	No	ITT: Group A - Standard triple therapy: 58.8%; Group B - Standard triple therapy + symbiotic: 77.1%; $P = 0.16$. PP: Group A: 64.5%; Group B: 81.8%; $P = 0.19$.	The results of the study demonstrated that the addition of Bifidobacterium lactis B94 (5×10^9 CFU/dose) plus inulin once daily to standard triple therapy did not show superiority in eradication rates compared to standard triple therapy administered alone.
Huang <i>et al</i> ^[34]	Nausea, vomiting and diarrhea.	-	(1) ITT: Group A - 10-d sequential therapy: 81.4%; Group B - 7 d triple standard therapy: 61.9%; Group C - 10 d triple standard therapy: 67.7%; $P < 0.05$; and (2) PP: Group A - 10 d sequential therapy: 89.7%; Group B - 7 d triple standard therapy: 70.8%; Group C - 10 d triple standard therapy: 77.8%; $P < 0.05$.	The 10 d sequential regimen was significantly more effective than the 7 or 10 d triple regimens in eradicating Chinese children. In addition, the adverse events between the three groups were also similar, with no statistical differences $P > 0.05$.
N Şirvan <i>et al</i> ^[35]	Abdominal pain, nausea and diarrhea.	-	Group 1 - Standard triple therapy + symbiotic: 88%; Group 2 - Standard triple therapy: 72%; $P = 0.046$.	The rate of eradication was statistically higher in group I. The addition of probiotics to triple therapy is effective in eradicating <i>H. pylori</i> infection in children and is generally useful in reducing or eliminating dyspeptic symptoms, such as abdominal pain, diarrhea and vomiting.
Baysoy <i>et al</i> ^[36]	Metallic taste sensation, abdominal pain, diarrhea, vomiting, rash, itching.	-	(1) ITT: Group A - Standard triple therapy: 46.0%; Group B - Sequential therapy group: 40.9%; and (2) PP: Group A - Standard triple therapy: 54.2%; Group B - Sequential therapy group: 48.6%.	Sequential ornidazole therapy did not show superiority compared to standard triple treatment in children with <i>H. pylori</i> infection.
Esmaili-Dooki <i>et al</i> ^[37]	-	-	(1) ITT: Group 1 - Clarithromycin-based triple therapy: 62.5%; Group 2 - Amoxicillin-based triple therapy: 56.2%; $P = 0.4$; and (2) PP: Group 1 - Clarithromycin-based triple therapy: 69%; Group 1 - Amoxicillin-based triple therapy: 61.9%; $P = 0.431$.	The therapeutic response was observed in more than half of the patients treated with triple therapy of the <i>H. Pylori</i> eradication regimen, including azithromycin or clarithromycin, and there was no significant difference between the two treatment groups.
Laving <i>et al</i> ^[38]	-	-	Conventional therapy Group: 48.8%; 10 d sequential therapy Group: 84.6%; $P = 0.02$.	The sequential treatment had a significantly higher rate of <i>H. pylori</i> eradication than conventional treatment.
Prieto-Jimenez <i>et al</i> ^[39]	Abdominal pain, nausea, diarrhea, rash.	No	(1) ITT: Group I - Quadruple sequential eradication and placebo: 44.8%; Group II - Quadruple sequential eradication and iron: 43.7%; Group III: Iron and placebo: 17.4%; Group IV: Placebo alone: 7.7%; $P < 0.001$; and (2) PP: Group I - Quadruple sequential eradication and placebo: 56.5%; Group II - Quadruple sequential eradication and iron: 50%; Group III: Iron and placebo: 20%; Group IV: Placebo alone: 10.5%; $P < 0.001$.	A sequential quadruple regimen eradicated <i>H. pylori</i> in only half of asymptomatic children who received this treatment. Eradication rates did not differ between patients who received iron supplementation and those who received placebo.
Nguyen <i>et al</i> ^[40]	No reported.	No	(1) Group A: Antibiotic sensitive - 79% using high medication dosages, $P = 0.278$; 75% using lansoprazole twice daily, $P = 0.096$. Antibiotic resistant - 67.5% using high medication dosages, $P = 0.006$; 69.2% using lansoprazole twice daily, $P = 0.004$; and (2) Group B: Antibiotic sensitive - 85.2% using high medication dosages, $P = 0.278$; 87.5% using lansoprazole Twice daily, $P = 0.096$. Antibiotic resistant - 45.3% using high medication dosages, $P = 0.096$; 50.0% using lansoprazole Twice daily, $P = 0.004$.	The prevalence of resistance to clarithromycin, metronidazole, and amoxicillin was 50.9%, 65.3% and 0.5%, respectively. The two treatment regimens used did not successfully eradicate <i>H. pylori</i> in Vietnamese children, mainly because of the unexpectedly high prevalence of antibiotic resistance.
Bontems <i>et al</i> ^[41]	Abdominal pain, diarrhea, nausea and vomiting.		(1) ITT: Group A - 10 d sequential treatment: 81.9%; Group B: 7 d triple therapy: 71.9%; and (2) PP: Group B - 10 d sequential treatment: 88.3%, Group B: 7 d triple therapy: 80.8%.	The sequential treatment is greatly effective for eradicating <i>H. pylori</i> in children except in clarithromycin-resistant strains. Sequential treatment can be used as a first-line therapy, but only in areas with a low clarithromycin resistance rate.

ITT: Intention-to-treat; PP: Per protocol; *H. pylori*: *Helicobacter pylori*.

overused to treat upper and lower respiratory diseases that are very common in childhood. Eradication rates of standard triple therapies are often below 80% in various regions of the world^[47]. In this study, extremely low eradication rates were observed in China, India, Kenya, and Turkey. The frequency of *H. pylori*-resistant strains was 16.4%, 75.2%, and 0.06% to clarithromycin, metronidazole, and amoxicillin,

respectively, in children from the southeast regions of China^[48]. The resistance to clarithromycin in Turkish children ranges from 9.5% to 27%^[49]. No data are available on clarithromycin resistance in Indian and Kenyan children. Concerning resistance to metronidazole, no data are available on those countries.

Standard triple therapy

A trial comparing amoxicillin-based with metronidazole-based triple therapy, by ITT analysis, found that the latter showed a significantly higher eradication rate (68% *vs* 80%, respectively)^[22]. The 7 and 10 d triple therapy failed to eradicate *H. pylori* infection in most of the studies^[22,26,27,30,34,37-39]. In some of them, the eradication rates were less than 60%.

Esmaeili-Dooki *et al*^[37] compared a triple therapy consisting of azithromycin once daily plus amoxicillin and omeprazole given twice daily for 6 d with clarithromycin in association with amoxicillin and omeprazole twice daily for 10 d. Based on the ITT analysis, the eradication rates in the azithromycin and clarithromycin groups were 56.2% and 62.5%, respectively ($P = 0.40$)^[37]. AEs were 15.6% in the omeprazole, clarithromycin, and amoxicillin group and 3.1% in the omeprazole, azithromycin, and amoxicillin group ($P = 0.19$). Per protocol, the eradication rate was 61.9% in the azithromycin group and 69% in the clarithromycin group ($P = 0.431$).

High resistance of *H. pylori* to clarithromycin and metronidazole, poor compliance, and a short duration of treatment may explain these findings, in part. European Society for Paediatric Gastroenterology, Hepatology and Nutrition and North American Society for Paediatric Gastroenterology, and Hepatology and Nutrition guidelines recommend when antimicrobials susceptibility profiles are either unknown or *H. pylori* is susceptible to clarithromycin or metronidazole, a high-dose triple therapy with PPI, amoxicillin and triple for 14 d or bismuth-base quadruple therapy. In this review, the effectiveness of a triple therapy for 14 d was evaluated in eight studies. Eradication rate superior to 80% was observed in two of them^[29,40]. Kasiri *et al*^[29] did not observe a significant difference in the eradication rate between 14 d amoxicillin-based (87.2%) and for metronidazole-based triple therapy (92.5%) in Iranian children.

A study from Vietnam, triple therapy consisting of lansoprazole amoxicillin and either clarithromycin or metronidazole (LAM) therapy given once or twice daily for 14 d were compared^[40]. Eradication success was associated with the strain susceptibility to clarithromycin (78.2% *vs* 29.3%, $P = 0.0001$). PPI and clarithromycin given twice daily was superior to once-daily dosage for resistant strains (50.0% *vs* 14.7%, $P = 0.004$) and tended to be effective so also for sensitive strains (87.5% *vs* 65.2%, $P = 0.051$). The differences were less pronounced with LAM when PPI was given twice daily in comparison with PPI once a day (69.2% *vs* 50.0%, $P = 0.096$). The reported resistance to clarithromycin, metronidazole, and amoxicillin was 50.9%, 65.3%, and 0.5%, respectively. The authors found that resistance to clarithromycin was an important cause for treatment failure^[40]. Higher doses of PPI improve the success of eradication rate of clarithromycin and amoxicillin based-therapy^[46]. Moreover, younger children need a higher PPI dose per kg of bodyweight compared to adolescents and adults to obtain sufficient acid suppression^[46].

Eradication rate with triple therapy for 14 d ranged from 46% to 76.4% in five studies^[24,25,31,33,36].

One study evaluated the efficacy of a third-line therapy. Farahmand *et al*^[26] compared a regimen consisting of ciprofloxacin, amoxicillin, and omeprazole, third-line therapy, with the standard triple therapy, amoxicillin, and omeprazole twice a day plus furazolidone once a day. Both regimens given for 1 wk reported that the eradication rate was significantly higher ($P = 0.011$) in the group treated with ciprofloxacin (87.9%) than in that receiving furazolidone (60.6%)^[32].

Standard triple therapy and probiotics

Probiotics have been proposed as an adjuvant to triple therapy to improve the efficacy and diminish AEs in both children and adults. Diarrhea, nausea, and vomiting are the most frequent side effects of eradication therapy and are an important cause of poor compliance and treatment failure.

Several studies did not show an increase in the eradication rate when triple therapy was supplemented with probiotics^[23,24,25,33], by contrast, an increase in the *H. pylori* eradication rate was observed by others^[27,28,35]. Although the beneficial effects of probiotics depend on the strains of the microorganisms selected, more robust studies and meta-analyses on this issue should be performed to clarify these discrepant results^[50]. Of note, some studies demonstrated a statistically significant decrease in adverse gastrointestinal effects during the treatment^[25,27,28,35]. This result was also

observed in a meta-analysis using multiple strains to eradicate *H. pylori* and prevent AEs, in children and adults^[51]. Another meta-analysis observed that the addition of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* to standard triple therapy improved medication tolerance and patient compliance due to the decrease in side effects, both in children and adults^[52]. In the studies included in this review, commercial probiotics were used; however, the use in clinical practice is not economically accessible for many countries with high prevalence rates of *H. pylori*.

Standard triple therapy and antioxidant vitamins

Tümgör *et al.*^[31] evaluated the use of vitamin E with clarithromycin-based triple therapy in children and found no statistically significant difference between its eradication rate and triple therapy alone. Although the addition of antioxidant vitamins in the eradication treatments has been evaluated^[53,54], no statistically significant differences were observed. It is important to highlight that the available studies on this therapeutic alternative have a small sample size and to moderate methodological design^[53].

Sequential therapy

Sequential therapy has been related to high *H. pylori* eradication rates^[47], and some articles included here corroborated this, showing success rates of 91.3%, 81.4%, and 84.6%, whereas the effectiveness of standard triple therapy ranged from 48.8% to 78.2%^[30,34,38]. However, two studies did not observe a statistically significant increase in eradication rates when this regimen was used^[32,36]. A meta-analysis that evaluated sequential therapy compared to triple therapy in 13 RCTs also found a higher rate of *H. pylori* eradication in children when using sequential therapy, in accordance with the results of the articles analyzed in this review^[55]. Although it is a therapeutic regimen with encouraging rates of *H. pylori* eradication, more robust studies are necessary to prove its effectiveness and safety to substitute triple therapy in high clarithromycin and/or nitroimidazole resistance settings^[56].

Study limitations

This study had some limitations due to the small number of available studies evaluating each therapeutic regimen in children. The quality of included studies, the great diversity of treatment regimens, and the duration of treatment, doses, and administration frequency of the drugs as well as lack of antimicrobial susceptibility tests limit the comparison of the results. Most studies had an uncertain degree of bias for concealing the processes of allocation of patients as well as the blinding of participants, professionals, and outcome evaluators.

In summary, the eradication rate associated with current treatments is not satisfactory in many geographical areas. Unfortunately, many of the published works on *H. pylori* eradication in children have weaknesses in their methods and do not meet the ideal scientific criteria to be indicated in practice. It has to be emphasized that, because *H. pylori* is disappearing in developed, studies investigating *H. pylori* treatment are scarce in adults and children. Otherwise, a number of countries that have a high prevalence of *H. pylori* infection face difficulties in conducting research with a good level of evidence due to the lack of structural and financial supports. Finally, the studies were limited to a few countries ($n = 10$), and good results observed in some studies may not work well in other geographical areas.

CONCLUSION

In conclusion, although some studies support the use of new therapeutic regimens in the treatment of *H. pylori* infection in children, more methodologically reliable prospective studies evaluating the most promising new therapeutic regimens are needed to assess the applicability of these treatments in pediatric clinical practice.

ARTICLE HIGHLIGHTS

Research background

Helicobacter pylori (*H. pylori*) is a gram-negative microaerophilic bacterium that infects the gastric epithelium and whose acquisition occurs mainly during childhood. In the

last several years, no significant changes in the treatment of infected children have been observed, mainly due to the lack of studies with satisfactory scientific evidence to support the indication of new therapies in clinical practice. This systematic review evaluated the eradication rates of *H. pylori* infection using various therapeutic regimens and their positive and negative outcomes in pediatric patients.

Research motivation

Standard triple therapy for the eradication of *H. pylori* infection has been used as first-line treatment in children worldwide. However, the effectiveness of standard triple therapy in eradicating *H. pylori* is decreasing in various geographical areas as a consequence of increasing bacterial resistance to clarithromycin and nitroimidazoles.

Research objectives

To compare the eradication rates of *H. pylori* infection in childhood in controlled, randomized, and prospective studies evaluating different therapeutic schemes during the last 10 years.

Research methods

We systematically reviewed in PubMed and MEDLINE relevant publications from 2010 to April 2020. Twenty studies were shortlisted. This systematic review uses guidance from the PRISMA checklist.

Research results

The results were quite heterogeneous. Standard triple therapy is still the most used regimen and its eradication rates vary according to the *H. pylori* susceptibility profiles in different world regions. The addition of probiotics to therapeutic schemes shows discrepant results in eradication rate, but decrease the incidence of side effects and increases the treatment adherence. Sequential therapy has been associated with higher eradication rates than triple therapies and is a promising therapeutic regimen for this population.

Research conclusions

Currently, standard triple therapy is the most recommended *H. pylori* eradication regimen for children worldwide. However, other therapeutic schemes have shown promising results in controlled trials and in a near future may be included in the guidelines recommendations.

Research perspectives

There are still few studies with satisfactory evidence levels evaluating the eradication of *H. pylori* infection in children, mainly due to the difficulties to conduct controlled clinical trials as well as to the low availability of sources for research in many developing countries where the prevalence of *H. pylori* infection remain elevated. Well-designed studies evaluating treatments for *H. pylori* eradication in children are needed to further evaluate new therapeutic options in pediatric clinical practice in high bacterial resistance settings.

REFERENCES

- 1 Suerbaum S, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; **347**: 1175-1186 [PMID: 12374879 DOI: 10.1056/NEJMra020542]
- 2 Sherman PM. Appropriate strategies for testing and treating Helicobacter pylori in children: when and how? *Am J Med* 2004; **117** Suppl 5A: 30S-35S [PMID: 15478850 DOI: 10.1016/j.amjmed.2004.07.015]
- 3 Kuipers EJ, Peña AS, van Kamp G, Uytendaele AM, Pals G, Pels NF, Kurz-Pohlmann E, Meuwissen SG. Seroconversion for Helicobacter pylori. *Lancet* 1993; **342**: 328-331 [PMID: 8101585 DOI: 10.1016/0140-6736(93)91473-y]
- 4 Pacifico L, Anania C, Osborn JF, Ferraro F, Chiesa C. Consequences of Helicobacter pylori infection in children. *World J Gastroenterol* 2010; **16**: 5181-5194 [PMID: 21049552 DOI: 10.3748/wjg.v16.i41.5181]
- 5 Ortiz-Princz D, Daoud G, Salgado-Sabel A, Cavazza ME. Helicobacter pylori infection in children: should it be carefully assessed? *Eur Rev Med Pharmacol Sci* 2016; **20**: 1798-1813 [PMID: 27212173]
- 6 Razavi A, Bagheri N, Azadegan-Dehkordi F, Shirzad M, Rahimian G, Rafieian-Kopaei M, Shirzad H. Comparative Immune Response in Children and Adults with H. pylori Infection. *J Immunol Res* 2015; **2015**: 315957 [PMID: 26495322 DOI: 10.1155/2015/315957]
- 7 Freire de Melo F, Rocha AM, Rocha GA, Pedrosa SH, de Assis Batista S, Fonseca de Castro LP, Carvalho SD, Bittencourt PF, de Oliveira CA, Corrêa-Oliveira R, Magalhães Queiroz DM. A regulatory instead of an IL-17 T response predominates in Helicobacter pylori-associated gastritis in children. *Microbes Infect* 2012;

- 14: 341-347 [PMID: [22155622](#) DOI: [10.1016/j.micinf.2011.11.008](#)]
- 8 **Camorlinga-Ponce M**, Muñoz L, Fuentes-Panana E, Torres J. Clinical consequences of *Helicobacter pylori* infection in children and its relation with the response of the gastric mucosa to the infection. *Boletín médico del Hospital Infantil de México* 2014; **71**: 2-7
- 9 **Queiroz DM**, Mendes EN, Carvalho AS, Rocha GA, Oliveira AM, Soares TF, Santos A, Cabral MM, Nogueira AM. Factors associated with *Helicobacter pylori* infection by a cagA-positive strain in children. *J Infect Dis* 2000; **181**: 626-630 [PMID: [10669347](#) DOI: [10.1086/315262](#)]
- 10 **Yang HR**. Updates on the Diagnosis of *Helicobacter pylori* Infection in Children: What Are the Differences between Adults and Children? *Pediatr Gastroenterol Hepatol Nutr* 2016; **19**: 96-103 [PMID: [27437185](#) DOI: [10.5223/pghn.2016.19.2.96](#)]
- 11 **Biernat MM**, Gościński G, Iwańczak B. Prevalence of *Helicobacter pylori* cagA, vacA, iceA, babA2 genotypes in Polish children and adolescents with gastroduodenal disease. *Postepy Hig Med Dosw (Online)* 2014; **68**: 1015-1021 [PMID: [25228509](#) DOI: [10.5604/17322693.1118211](#)]
- 12 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European *Helicobacter* and Microbiota Study Group and Consensus panel. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: [27707777](#) DOI: [10.1136/gutjnl-2016-312288](#)]
- 13 **Zamani M**, Zamani V, Derakhshan MH, Shokri-Shirvani J. The efficacy of first-line regimens for *Helicobacter pylori* eradication in different continents: A systematic review and network meta-analysis protocol. *Medicine (Baltimore)* 2018; **97**: e13682 [PMID: [30558078](#) DOI: [10.1097/MD.00000000000013682](#)]
- 14 **Goderska K**, Agudo Pena S, Alarcon T. *Helicobacter pylori* treatment: antibiotics or probiotics. *Appl Microbiol Biotechnol* 2018; **102**: 1-7 [PMID: [29075827](#) DOI: [10.1007/s00253-017-8535-7](#)]
- 15 **Chen Q**, Long X, Ji Y, Liang X, Li D, Gao H, Xu B, Liu M, Chen Y, Sun Y, Zhao Y, Xu G, Song Y, Yu L, Zhang W, Liu W, Graham DY, Lu H. Randomised controlled trial: susceptibility-guided therapy versus empiric bismuth quadruple therapy for first-line *Helicobacter pylori* treatment. *Aliment Pharmacol Ther* 2019; **49**: 1385-1394 [PMID: [31020673](#) DOI: [10.1111/apt.15273](#)]
- 16 **Lehours P**, Ferrero RL. Review: *Helicobacter*: Inflammation, immunology, and vaccines. *Helicobacter* 2019; **24** Suppl 1: e12644 [PMID: [31486236](#) DOI: [10.1111/hel.12644](#)]
- 17 **Thung I**, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, Valasek MA. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther* 2016; **43**: 514-533 [PMID: [26694080](#) DOI: [10.1111/apt.13497](#)]
- 18 **Okuda M**, Lin Y, Wang C, Kakiuchi T, Kikuchi S. Metronidazole for *Helicobacter pylori* eradication therapy among children and adolescents in Japan: Overcoming controversies and concerns. *Helicobacter* 2019; **24**: e12575 [PMID: [30873719](#) DOI: [10.1111/hel.12575](#)]
- 19 **Erdur B**, Ozturk Y, Gurbuz ED, Yilmaz O. Comparison of sequential and standard therapy for *Helicobacter pylori* eradication in children and investigation of clarithromycin resistance. *J Pediatr Gastroenterol Nutr* 2012; **55**: 530-533 [PMID: [22465935](#) DOI: [10.1097/MPG.0b013e3182575f9c](#)]
- 20 **Zhu XL**, Liu Z, Wu ZQ, Li D, Jiang AP, Yu GX. [Clinical effects of different therapeutic regimens for *Helicobacter pylori* infection in children]. *Zhongguo Dang Dai Er Ke Za Zhi* 2017; **19**: 672-676 [PMID: [28606235](#) DOI: [10.7499/j.issn.1008-8830.2017.06.012](#)]
- 21 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; **151**: W65-W94 [PMID: [19622512](#) DOI: [10.7326/0003-4819-151-4-200908180-00136](#)]
- 22 **Moubri M**, Kalach N, Larras R, Berrah H, Mouffok F, Guechi Z, Cadranel S. Adapted first-line treatment of *Helicobacter pylori* infection in Algerian children. *Ann Gastroenterol* 2019; **32**: 60-66 [PMID: [30598593](#) DOI: [10.20524/aog.2018.0317](#)]
- 23 **Namkin K**, Zardast M, Basirinejad F. *Saccharomyces Boulardii* in *Helicobacter Pylori* Eradication in Children: A Randomized Trial From Iran. *Iran J Pediatr* 2016; **26**: e3768 [PMID: [26848376](#) DOI: [10.5812/ijp.3768](#)]
- 24 **Akcam M**, Koca T, Salman H, Karahan N. The effects of probiotics on treatment of *Helicobacter pylori* eradication in children. *Saudi Med J* 2015; **36**: 286-290 [PMID: [25737169](#) DOI: [10.15537/smj.2015.3.10124](#)]
- 25 **Tolone S**, Pellino V, Vitaliti G, Lanzafame A, Tolone C. Evaluation of *Helicobacter Pylori* eradication in pediatric patients by triple therapy plus lactoferrin and probiotics compared to triple therapy alone. *Ital J Pediatr* 2012; **38**: 63 [PMID: [23114016](#) DOI: [10.1186/1824-7288-38-63](#)]
- 26 **Farahmand F**, Mohammadi T, Najafi M, Fallahi G, Khodadad A, Motamed F, Mahdi Marashi S, Shooran M, Nabavizadeh Rafsanjani R. Comparison of Ciprofloxacin-Based Triple Therapy with Conventional Triple Regimen for *Helicobacter pylori* Eradication in Children. *Acta Med Iran* 2016; **54**: 395-400 [PMID: [27306347](#)]
- 27 **Ahmad K**, Fatemeh F, Mehri N, Maryam S. Probiotics for the treatment of pediatric *helicobacter pylori* infection: a randomized double blind clinical trial. *Iran J Pediatr* 2013; **23**: 79-84 [PMID: [23446685](#)]
- 28 **Bin Z**, Ya-Zheng X, Zhao-Hui D, Bo C, Li-Rong J, Vandenplas Y. The Efficacy of *Saccharomyces boulardii* CNCM I-745 in Addition to Standard *Helicobacter pylori* Eradication Treatment in Children. *Pediatr Gastroenterol Hepatol Nutr* 2015; **18**: 17-22 [PMID: [25866729](#) DOI: [10.5223/pghn.2015.18.1.17](#)]
- 29 **Kasiri KA**, Khoshdel A, Karimi A, Sedehi M, Kasiri N. Comparison of amoxicillin and metronidazole effect on three-drug regimen for the treatment of *Helicobacter pylori* infection in children. *J Adv Pharm Technol Res* 2017; **8**: 63-66 [PMID: [28516058](#) DOI: [10.4103/japtr.JAPTR_162_16](#)]
- 30 **Iwańczak BM**, Borys-Iwanicka A, Biernat M, Gościński G. Assessment of Sequential and Standard Triple Therapy in Treatment of *Helicobacter pylori* Infection in Children Dependent on Bacteria Sensitivity to Antibiotics. *Adv Clin Exp Med* 2016; **25**: 701-708 [PMID: [27629844](#) DOI: [10.17219/acem/38554](#)]
- 31 **Tümgör G**, Baran M, Çakır M, Yüksekaya HA, Aydoğdu S. Comparison of standard and standard plus vitamin E therapy for *Helicobacter pylori* eradications in children. *Turk J Gastroenterol* 2014; **25** Suppl 1: 99-103 [PMID: [25910378](#) DOI: [10.5152/tjg.2014.5592](#)]

- 32 **Ali Habib HS**, Murad HA, Amir EM, Halawa TF. Effect of sequential versus standard *Helicobacter pylori* eradication therapy on the associated iron deficiency anemia in children. *Indian J Pharmacol* 2013; **45**: 470-473 [PMID: 24130381 DOI: 10.4103/0253-7613.117757]
- 33 **Ustundag GH**, Altuntas H, Soysal YD, Kokturk F. The Effects of Synbiotic "*Bifidobacterium lactis* B94 plus Inulin" Addition on Standard Triple Therapy of *Helicobacter pylori* Eradication in Children. *Can J Gastroenterol Hepatol* 2017; **2017**: 8130596 [PMID: 28656129 DOI: 10.1155/2017/8130596]
- 34 **Huang J**, Zhou L, Geng L, Yang M, Xu XW, Ding ZL, Mao M, Wang ZL, Li ZL, Li DY, Gong ST. Randomised controlled trial: sequential vs. standard triple therapy for *Helicobacter pylori* infection in Chinese children-a multicentre, open-labelled study. *Aliment Pharmacol Ther* 2013; **38**: 1230-1235 [PMID: 24117692 DOI: 10.1111/apt.12516]
- 35 **N Şirvan B**, K Usta M, U Kizilkan N, Urganci N. Are Synbiotics added to the Standard Therapy to eradicate *Helicobacter pylori* in Children Beneficial? A Randomized Controlled Study. *Euroasian J Hepatogastroenterol* 2017; **7**: 17-22 [PMID: 29201766 DOI: 10.5005/jp-journals-10018-1205]
- 36 **Baysoy G**, Saltık Temizel İN, Uslu N, Balamtekin N, Demir H, Gürkan F, Özen H, Akyön Y, Yüce A. Ornidazole-based sequential therapy is not effective in *Helicobacter pylori* eradication in children. *Turk J Gastroenterol* 2013; **24**: 382-386 [PMID: 24557960 DOI: 10.4318/tjg.2013.0575]
- 37 **Esmaili-Dooki MR**, Shirdel H, Hajiahmadi M. Eradication of *Helicobacter pylori* in Children by Triple Therapy Regimens of Amoxicillin, Omeprazole, and Clarithromycin or Azithromycin. *Iran J Pediatr* 2015; **25**: e2360 [PMID: 26635936 DOI: 10.5812/ijp.2360]
- 38 **Laving A**, Kamenwa R, Sayed S, Kimang'a AN, Revathi G. Effectiveness of sequential v. standard triple therapy for treatment of *Helicobacter pylori* infection in children in Nairobi, Kenya. *S Afr Med J* 2013; **103**: 921-924 [PMID: 24300630 DOI: 10.7196/samj.7012]
- 39 **Prieto-Jimenez CA**, Cardenas VM, Fischbach LA, Mulla ZD, Rivera JO, Dominguez DC, Graham DY, Ortiz M. Double-blind randomized trial of quadruple sequential *Helicobacter pylori* eradication therapy in asymptomatic infected children in El Paso, Texas. *J Pediatr Gastroenterol Nutr* 2011; **52**: 319-325 [PMID: 21336156 DOI: 10.1097/MPG.0b013e318206870e]
- 40 **Nguyen TV**, Bengtsson C, Yin L, Nguyen GK, Hoang TT, Phung DC, Sörberg M, Granström M. Eradication of *Helicobacter pylori* in children in Vietnam in relation to antibiotic resistance. *Helicobacter* 2012; **17**: 319-325 [PMID: 22759333 DOI: 10.1111/j.1523-5378.2012.00950.x]
- 41 **Bontems P**, Kalach N, Oderda G, Salame A, Muyschont L, Miendje DY, Raymond J, Cadranet S, Scaillon M. Sequential therapy versus tailored triple therapies for *Helicobacter pylori* infection in children. *J Pediatr Gastroenterol Nutr* 2011; **53**: 646-650 [PMID: 21701406 DOI: 10.1097/MPG.0b013e318229c769]
- 42 **Cochrane Training**. Cochrane Handbook for Systematic Reviews of Interventions. 2019 [cited 20 May 2020]. In: Cochrane website [Internet]. Cochrane Training. Available from: URL: <https://training.cochrane.org/handbook/current>
- 43 **Centre for Evidence-Based Medicine**. Oxford Centre for Evidence-based Medicine – Levels of Evidence. 2009 Mar [Cited 27 April 2020]. In: CEBM website [Internet]. Oxford: CEBM. Available from: URL: <https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
- 44 **Cochrane Training**. Assessing risk of bias in a randomized trial. 2019 [cited 20 May 2020]. In: Cochrane website [Internet]. Cochrane training. Available from: URL: <https://training.cochrane.org/handbook/current/chapter-08>
- 45 **Gold BD**, Colletti RB, Abbott M, Czinn SJ, Elitsur Y, Hassall E, Macarthur C, Snyder J, Sherman PM; North American Society for Pediatric Gastroenterology and Nutrition. *Helicobacter pylori* infection in children: recommendations for diagnosis and treatment. *J Pediatr Gastroenterol Nutr* 2000; **31**: 490-497 [PMID: 11144432 DOI: 10.1097/00005176-200011000-00007]
- 46 **Jones NL**, Koletzko S, Goodman K, Bontems P, Cadranet S, Casswall T, Czinn S, Gold BD, Guarner J, Elitsur Y, Homan M, Kalach N, Kori M, Madrazo A, Megraud F, Papadopolou A, Rowland M, ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN Guidelines for the Management of *Helicobacter pylori* in Children and Adolescents (Update 2016). *J Pediatr Gastroenterol Nutr* 2017; **64**: 991-1003 [PMID: 28541262 DOI: 10.1097/MPG.0000000000001594]
- 47 **Rajindrajith S**, Devanarayana NM, de Silva HJ. *Helicobacter pylori* infection in children. *Saudi J Gastroenterol* 2009; **15**: 86-94 [PMID: 19568571 DOI: 10.4103/1319-3767.48964]
- 48 **Kotilea K**, Bontems P, Touati E. Epidemiology, Diagnosis and Risk Factors of *Helicobacter pylori* Infection. *Adv Exp Med Biol* 2019; **1149**: 17-33 [PMID: 31016621 DOI: 10.1007/5584_2019_357]
- 49 **Güven B**, Gülerman F, Kaçmaz B. *Helicobacter pylori* resistance to clarithromycin and fluoroquinolones in a pediatric population in Turkey: A cross-sectional study. *Helicobacter* 2019; **24**: e12581 [PMID: 30950125 DOI: 10.1111/hel.12581]
- 50 **De Francesco V**, Giorgio F, Hassan C, Manes G, Vannella L, Panella C, Ierardi E, Zullo A. Worldwide *H. pylori* antibiotic resistance: a systematic review. *J Gastrointest Liver Dis* 2010; **19**: 409-414 [PMID: 21188333]
- 51 **Khurana R**, Fischbach L, Chiba N, VAN Zanten SV, Sherman PM, George BA, Goodman KJ, Gold BD. Meta-analysis: *Helicobacter pylori* eradication treatment efficacy in children. *Aliment Pharmacol Ther* 2007; **25**: 523-536 [PMID: 17305754 DOI: 10.1111/j.1365-2036.2006.03236.x]
- 52 **Homan M**, Orel R. Are probiotics useful in *Helicobacter pylori* eradication? *World J Gastroenterol* 2015; **21**: 10644-10653 [PMID: 26457024 DOI: 10.3748/wjg.v21.i37.10644]
- 53 **McFarland LV**, Huang Y, Wang L, Malfertheiner P. Systematic review and meta-analysis: Multi-strain probiotics as adjunct therapy for *Helicobacter pylori* eradication and prevention of adverse events. *United European Gastroenterol J* 2016; **4**: 546-561 [PMID: 27536365 DOI: 10.1177/2050640615617358]
- 54 **Lau CS**, Ward A, Chamberlain RS. Probiotics improve the efficacy of standard triple therapy in the eradication of *Helicobacter pylori*: a meta-analysis. *Infect Drug Resist* 2016; **9**: 275-289 [PMID: 27994474]
- 55 **Gatta L**, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol* 2009; **104**: 3069-79; quiz 1080 [PMID: 19844205 DOI: 10.1038/ajg.2009.555]
- 56 **Kate V**, Kalayarasan R, Ananthakrishnan N. Sequential therapy versus standard triple-drug therapy for

Helicobacter pylori eradication: a systematic review of recent evidence. *Drugs* 2013; **73**: 815-824 [PMID: 23625272 DOI: 10.1007/s40265-013-0053-z]

Importance of reporting quality: An assessment of the COVID-19 meta-analysis laboratory hematology literature

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Abstract

BACKGROUND

Meta-analysis, a form of quantitative review, is an attempt to combine data from multiple independent studies to improve statistical power. Because of the complexity of process involved in study selection, data analysis, and evaluation of bias and heterogeneity, checklists have been prepared by the Institutes of Medicine (IOM), Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA), and Meta-analyses of Observational Studies in Epidemiology (MOOSE) to standardize the reporting quality of a meta-analysis.

AIM

To use these checklists to assess the reporting quality of the coronavirus disease-2019 (COVID-19) meta-analysis literature relevant to laboratory hematology.

METHODS

After a search of the literature 19 studies were selected for analysis, including 10 studies appearing in the preprint literature (studies that can be identified by database search but have not yet completed peer review).

RESULTS

The average IOM (76% of required elements completed), PRISMA (75% of required elements completed), and MOOSE (60% of required elements completed) scores enumerated demonstrated a reporting quality inferior to that of earlier reports of pathology and medicine meta-analyses. There was no statistically significant difference in performance between accepted/ published and preprint studies. Comparison of the results of PRISMA and MOOSE studies demonstrated a weak positive correlation (Pearson's correlation coefficient = 0.39).

CONCLUSION

The most common deficits in the studies included sensitivity analysis, assessment for bias, and details of the search strategy. Although the COVID-19 laboratory hematology meta-analysis literature can be a helpful source of information,

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readers should be aware of these reporting quality deficits.

Key Words: COVID-19; Meta-analysis; Reporting quality

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Core Tip: The Institutes of Medicine, Preferred Reporting Items for Systemic Reviews and Meta-analyses, and Meta-analyses of Observational Studies in Epidemiology checklists were created to standardize the reporting quality of a meta-analysis. The purpose of this study was to use these checklists to assess the reporting quality of the coronavirus disease-2019 meta-analysis literature relevant to laboratory hematology.

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INTRODUCTION

Meta-analysis, the examination of data from multiple independent studies of the same subject, is a useful form of quantitative review that can provide improved statistical power compared to studies with smaller numbers of subjects and demonstrate the presence or lack of consensus regarding a specific scientific question^[1]. In recent years, the number of published meta-analyses has increased, particularly in the realm of clinical medicine, and they have become important sources of information for practitioners, especially in areas where information is rapidly evolving.

In pathology and laboratory medicine, meta-analyses are published less frequently compared to other areas of clinical medicine. Kinzler and Zhang, in their survey of the meta-analysis literature in pathology journals compared to medicine journals, note a significantly larger percentage of publication space dedicated to meta-analyses in medicine journals^[1]. This is despite the proven high quality of meta-analyses in both journal categories, as evidenced by similar adjusted citation ratios (which they defined as article's citation count divided by the mean citations for the meta-analysis, review, and original research articles published in the same journal the same year)^[1].

Because meta-analyses are an important source of information for clinicians and others, it is essential that they are formatted to easily allow the reader to assess their strengths and weaknesses. Several checklists have been established by national and international committees, including the Institutes of Medicine (IOM), Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA), and Meta-analyses of Observational Studies in Epidemiology (MOOSE)^[2-4]. A recent survey by Liu *et al*^[5] using the PRISMA criteria noted that the reporting quality for a sampling of medicine meta-analyses was higher than that of pathology meta-analyses. The overall reporting quality for laboratory hematology-focused meta-analyses was not specifically addressed^[5].

The coronavirus disease-2019 (COVID-19) pandemic, which originated in the city of Wuhan in the Hubei Province of China in December 2019 quickly spread to Europe and then to North America^[6,7]. In an effort to study the disease and improve the world health community's response, over 30000 papers have been added to the medical literature since December 2019, based on a search of the PubMed database for the keyword "COVID-19" conducted on July 16, 2020. In a situation such as this, it is essential for the practicing clinician to have access to reliable studies with good statistical power, hence the need for meta-analyses with high reporting quality. Laboratory hematology is an essential component of the medical response to COVID-19 since several biomarkers of infection derived from the complete blood count (CBC) and coagulation testing are of proven utility in assessing prognosis and likely outcome^[8-10]. As in all quickly evolving fields, a large fraction of the accessible medical COVID medical literature appears in the form of preprint publications. These are manuscripts that are indexed in services such as Google Scholar, but have not yet completed the peer-review process. The purpose of this study is two-fold; to assess the reporting quality of COVID-19 meta-analyses focused on laboratory hematology and to compare the reporting quality of published studies of COVID-19 to the preprint

literature.

MATERIALS AND METHODS

Study selection

The study selection processes is summarized in [Figure 1](#). A search was conducted in PubMed and Google Scholar using the search terms “COVID-19” OR “COVID”, “SARS-CoV-2”, OR “coronavirus” AND “meta-analysis”, which yielded 34 entries in PubMed and 3080 in Google Scholar (total = 3114 studies). Initial screening for letters to the editor, editorials, and non-meta-analysis reviews removed 3029 publications, with 85 entries remaining for further consideration. After removal of 27 duplicate entries, 58 publications remained. The full text of the remaining 58 studies were examined for content, and 39 studies that fell out of scope for further consideration were removed, leaving 19 studies for the analysis.

Checklists

The studies were separated into published studies ($n = 9$, [Table 1](#))^[11-19] and manuscripts appearing in the preprint literature ($n = 10$, [Table 1](#))^[20-28]. For the purposes of this study, preprint literature refers to manuscripts discoverable in the Google Scholar database which have been submitted for publication and are assigned an identifier through a service such as doi.org or preprints.org but have not completed the peer-review process.

The studies were then evaluated using the IOM, PRISMA, and MOOSE criteria. The IOM has compiled a list of 5 required elements that serve as recommended standards for meta-analysis ([Table 2](#))^[2]. The PRISMA group compiled a list of 27 checklist items to facilitate the assessment of the reporting quality of meta-analyses^[3]. The MOOSE criteria consist of a 34-point checklist categorized under 5 divisions^[4]. The criteria were evaluated for each study, and a numeric score was assigned based on the sum total of positive results for each element of the IOM, PRISMA and MOOSE checklists.

Statistics

The mean PRISMA and MOOSE scores for the accepted/published and preprint studies were compared using the student 2-tail t -test, with significance defined as $P < 0.05$. The PRISMA and MOOSE scores were compared using Pearson's correlation coefficient. All statistics were calculated using Excel (Microsoft, Redmond, WA, United States).

RESULTS

Qualitative aspects of the identified studies

Qualitative features of the studies are summarized in [Table 1](#). Most cases (17 of 19, 89%) were from Chinese patient populations. For the remaining 2 studies, the national origin of the patient populations was not defined, but given the affiliations of the authors, the patient cohorts were also likely from China. The number of patients in each study was highly variable, ranging from 50 to 59254. The hematology data reported in the studies was heterogeneous. The most common evaluated tests were white blood cell count (15 studies), absolute lymphocyte count (15 studies), and platelet count (10 studies).

Because of the limited number of reporting elements in the IOM checklist ([Table 2](#)), a comparison with the PRISMA ([Table 3](#)) and MOOSE ([Table 4](#)) checklists was not performed. The mean IOM score was 3.8/5 (76%) for all studies. The average scores for preprint (4.0/5, 80%) and accepted/ published (3.5, 70%) studies was similar, and there was no statistically significant difference between the two groups ($P > 0.05$). Reviewing the IOM required elements, the most common deficiencies were in explaining why a pooled estimate might be useful to decision makers and lack of sensitivity analysis.

Due to the larger number of reporting elements in the PRISMA and MOOSE checklists a more robust comparison could be performed. The average PRISMA score for all studies was 20.3/27 (75%) (median = 22/27, 81%). The average scores of the accepted/published (mean = 20.4/27, 76% median = 21.5/27, 80%) and preprint (mean = 20.2/27, 75%, median = 22/27, 81%) groups were similar (student t -test, $P > 0.05$). The most common elements which were lacking were checklist numbers 15 (methods:

Table 1 Articles considered in the analysis

Ref.	Country ¹	No. of patients	Evaluated hematologic parameters
Published studies			
Borges <i>et al</i> ^[11]	Multinational, predominantly China	59254	WBC, ANC, ALC, PLT, D-Dimer
Cao <i>et al</i> ^[12]	China	46959	WBC, ALC
Fu <i>et al</i> ^[13]	Not stated, likely all China	3600	WBC, ALC, PLT, D-dimer
Henry <i>et al</i> ^[14]	China, Singapore	2984	WBC, ANC, ALC, MONO, EOS, HGB, PT, PTT, D-dimer
Lagunes-Rangel ^[15]	China	828	Estimate of N/L ratio
Li <i>et al</i> ^[16]	China	1995	WBC
Lippi <i>et al</i> ^[17]	China, Singapore	1099	PLT
Rodriguez-Morales <i>et al</i> ^[18]	China, Australia	2874	WBC, ALC, HGB
Zhu <i>et al</i> ^[19]	China	3062	WBC, ALC, D-dimer
Preprint studies			
Arabi <i>et al</i> ^[20]	China	50	WBC
Ebrahimi <i>et al</i> ^[21]	China	2217	WBC, ANC, ALC, HGB, PLT, PT, PTT, D-Dimer
Han <i>et al</i> ^[22]	China	1208	ALC, ANC, PLT, PT, PTT, D-Dimer
Heydari <i>et al</i> ^[23]	China, S. Korea	49504	WBC, ANC, ALC, D-dimer
Ma <i>et al</i> ^[24]	China	53000	ALC, PLT, D-dimer
Nasiri <i>et al</i> ^[25]	China, Germany	4679	WBC, ANC, ALC, HGB, PLT
Pormohammad <i>et al</i> ^[26]	China	52251	WBC, ALC, ANC, PLT, HGB
Xu <i>et al</i> ^[27]	China	4062	WBC, ANC, ALC, PLT, D-dimer
Zhang <i>et al</i> ^[28]	Not stated, likely all China	275	WBC, ALC

¹Country of origin of patient population. WBC: White blood cell count; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; PLT: Platelet count; MONO: Absolute monocyte count; EOS: Absolute eosinophil count; HGB: Hemoglobin; PT: Prothrombin time; PTT: Partial thromboplastin time; N/L: Neutrophil-to-lymphocyte.

Table 2 Institutes of Medicine recommended standards for meta-analysis

Required element	Papers meeting this standard (total number and percentage)	Published/ accepted papers meeting this standard (total number and percentage)	Preprint papers meeting this standard (total number and percentage)
Explain why a pooled estimate might be useful to decision makers	9/19 (47%)	5/9 (56%)	4/10 (40%)
Use expert methodologists to develop, execute, and peer review the meta-analyses	15/19 (79%)	7/9 (78%)	8/10 (80%)
Address heterogeneity among study effects	18/19 (95%)	8/9 (89%)	10/10 (100%)
Accompany all estimates with measures of statistical uncertainty	19/19 (100%)	9/9 (100%)	10/10 (100%)
Assess the sensitivity of conclusions to changes in the protocol, assumptions, and study selection (sensitivity analysis)	12/19 (63%)	5/9 (56%)	7/10 (70%)

risk of bias across studies), 16 (methods: additional analyses), 22 (results: risk of bias across studies), and 23 (results: risk of bias across studies). The average MOOSE scores for all studies was 19.9/34, 60% (median = 20/34, 60%). The average scores of the accepted/published (mean = 20.6, 61% median = 21/34, 62%) and preprint (mean = 19.1, 56% median = 19, 56%) groups were similar (student *t*-test, *P* > 0.05). The most common elements which were lacking were II.A [Qualifications of searchers (*e.g.*,

Table 3 Preferred Reporting Items for Systemic Reviews and Meta-analyses checklist

Item number	Element	Papers meeting this standard (total number and percentage)	Published/ accepted papers meeting this standard (total number and percentage)	Preprint papers meeting this standard (total number and percentage)
1	Title	19/19 (100%)	8/9 (89%)	10/10 (100%)
2	Structured summary	18/19 (95%)	8/9 (89%)	10/10 (100%)
Introduction				
3	Rationale	16/19 (84%)	8/9 (80%)	8/10 (89%)
4	Objectives	17/19 (89%)	9/9 (90%)	8/10 (89%)
Methods				
5	Protocol/Registration	16/19 (84%)	8/9 (89%)	8/10 (78%)
6	Eligibility criteria	17/19 (89%)	8/9 (89%)	9/10 (89%)
7	Information sources	18/19 (95%)	9/9 (100%)	9/10 (89%)
8	Search	18/19 (95%)	9/9 (100%)	9/10 (89%)
9	Study selection	19/19 (100%)	9/9 (100%)	10/10 (100%)
10	Data collection process	18/19 (95%)	8/9 (89%)	10/10 (100%)
11	Data items	17/19 (89%)	8/9 (89%)	9/10 (89%)
12	Risk of bias in individual studies	10/19 (53%)	4/9 (44%)	6/10 (56%)
13	Summary measures	15/19 (79%)	6/9 (66%)	8/10 (78%)
14	Synthesis of results	16/19 (84%)	7/9 (78%)	9/10 (89%)
15	Risk of bias across studies	2/19 (11%)	2/9 (22%)	0/10 (0)
16	Additional analyses	2/19 (11%)	1/9 (11%)	1/10 (10%)
Results				
17	Study selection	19/19 (100%)	9/9 (100%)	10/10 (100%)
18	Study characteristics	19/19 (100%)	9/9 (100%)	10/10 (100%)
19	Risk of bias within studies	12/19 (63%)	5/9 (56%)	7/10 (70%)
20	Results of individual studies	11/19 (58%)	5/9 (56%)	6/10 (60%)
21	Synthesis of results	16/19 (84%)	8/9 (89%)	8/10 (80%)
22	Risk of bias across studies	9/19 (47%)	5/9 (56%)	4/10 (40%)
23	Additional analysis	0/19 (0)	0/9 (0)	0/10 (0)
Discussion				
24	Summary of evidence	19/19 (100%)	9/9 (100%)	10/10 (100%)
25	Limitations	16/19 (84%)	7/9 (78%)	9/10 (90%)
26	Conclusions	19/19 (100%)	9/9 (100%)	10/10 (100%)
Funding				
27	Funding	7/19 (37%)	3/9 (33%)	4/10 (40%)

librarians and investigators)], II.H (Method of addressing articles published in languages other than English, II.I (Method of handling abstracts and unpublished studies) and II.J (Description of any contact with authors).

To determine the degree to which the PRISMA and MOOSE scores correlated, analysis using Pearson's correlation coefficient was performed. The resulting coefficient, 0.39, suggests a weak positive correlation.

Table 4 Meta-analyses of Observational Studies in Epidemiology criteria checklist

Checklist	Number	Papers meeting this standard (total number and percentage)	Published/ accepted papers meeting this standard (total number and percentage)	Preprint papers meeting this standard (total number and percentage)
I. Reporting of background				
A. Problem definition		10/19 (53%)	7/9 (78%)	3/10 (30%)
B. Hypothesis statement		2/19 (11%)	1/9 (11%)	1/10 (10%)
C. Description of study outcome(s)		19/19 (100%)	10/9 (100%)	9/10 (90%)
D. Type of exposure or intervention used		18/19 (95%)	9/9 (100%)	8/10 (80%)
E. Type of study designs used		18/19 (95%)	9/9 (100%)	9/10 (90%)
F. Study population		18/19 (95%)	9/9 (100%)	9/10 (90%)
II. Reporting of search strategy				
A. Qualifications of searchers		0/19 (0)	0/9 (0)	0/10 (0)
B. Search strategy		17/19 (89%)	9/9 (100%)	8/10 (80%)
C. Effort to include all available studies		10/19 (53%)	7/9 (78%)	3/10 (30%)
D. Databases and registries searched		17/19 (89%)	7/9 (78%)	10/10 (100%)
E. Search software used		8/19 (42%)	4/9 (44%)	4/10 (40%)
F. Use of hand searching		2/19 (11%)	1/9 (11%)	1/10 (10%)
G. List of citations located and those excluded		10/19 (53%)	5/9 (56%)	5/10 (50%)
H. Method of addressing articles published in languages other than English		0/19 (0)	0/9 (0)	0/10 (0)
I. Method of handling abstracts and unpublished studies		0/19 (0)	0/9 (0)	0/10 (0)
J. Description of any contact with authors		0/19 (0)	0/9 (0)	0/10 (0)
III. Reporting of methods				
A. Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		8/19 (42%)	4/9 (44%)	4/10 (40%)
B. Rationale for the selection and coding of data		13/19 (68%)	7/9 (78%)	6/10 (60%)
C. Documentation of how data were classified and coded		12/19 (63%)	8/9 (89%)	4/10 (40%)
D. Assessment of confounding		1/19 (5%)	0/9 (0)	1/10 (10%)
E. Assessment of study quality		16/19 (84%)	7/9 (78%)	9/10 (90%)
F. Assessment of heterogeneity		18/19 (95%)	8/9 (89%)	10/10 (100%)
G. Description of statistical methods		19/19 (100%)	9/9 (100%)	10/10 (100%)
H. Provision of appropriate tables and graphics		18/19 (95%)	9/9 (100%)	9/10 (90%)
IV. Reporting of results				
A. Graphic summarizing individual study estimates and overall estimate		19/19 (100%)	9/9 (100%)	10/10 (100%)
B. Table giving descriptive information for each study included		16/19 (84%)	7/9 (78%)	9/10 (90%)
C. Results of sensitivity testing (e.g. subgroup analysis)		12/19 (63%)	7/9 (78%)	5/10 (50%)
D. Indication of statistical uncertainty of findings		17/19 (89%)	8/9 (89%)	9/10 (90%)
E. Reporting of discussion should include				
1. Quantitative assessment of bias (e.g. publication bias)		11/19 (58%)	4/9 (44%)	7/10 (70%)

2. Justification for exclusion (eg, exclusion of non-English-language citations)	3/19 (16%)	1/9 (11%)	2/10 (20%)
3. Assessment of quality of included studies	12/19 (63%)	4/9 (44%)	8/10 (80%)
V. Reporting of conclusions			
A. Consideration of alternative explanations for observed results	1/19 (11%)	0/9 (0)	1/10 (10%)
B. Generalization of the conclusions (<i>i.e.</i> , appropriate for the data presented and within the domain of the literature review)	19/19 (100%)	9/9 (100%)	10/10 (100%)
C. Guidelines for future research	8/19 (42%)	6/9 (66%)	2/10 (20%)

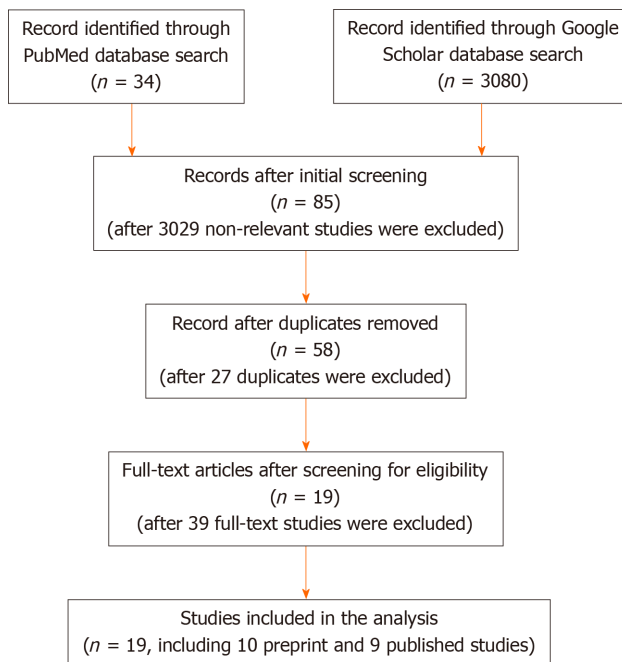


Figure 1 Study selection flow diagram.

DISCUSSION

The use of meta-analysis in the COVID-19 literature

Narrative, nonquantitative review papers have existed in the medical literature for many years and are an important source for succinctly reported and up-to-date information for clinicians and others interested in patient care and other issues. In recognition of the importance of the evidence-based approach to the dissemination of medical information, authors added increasingly rigorous approaches to their publications to provide quantitative information, minimize bias, identify knowledge gaps in the regarding a subject, and provide guidance for further growth of the area of study. This trend resulted in the development of the meta-analysis^[29].

Meta-analysis is a modification and attempted improvement of more traditional forms of review publication. Meta-analysis attempts to move beyond the narrative review process by adding numeric data synthesized from previously published data^[30]. By combining data from more than one study, there is an obvious improvement in statistical power. Meta-analysis has been widely employed in the behavioral science and clinical medicine literatures but has been underutilized in the pathology and laboratory medicine literature. Kinzler and Zhang published a study comparing the use of meta-analysis in the diagnostic pathology literature compared to the clinical medicine literature and noted that meta-analyses comprised < 1% of diagnostic pathology articles compared to 4%-6% of the clinical medicine literature^[1]. Despite their relatively low numbers, meta-analyses in the diagnostic pathology literature were highly cited, with a citation rate similar to that of meta-analyses appearing in the clinical medicine literature^[1]. This finding is also noted in the current study: although numerous studies have been published addressing the laboratory

hematologic aspects of COVID-19, the number of meta-analyses is low and comprises < 1% of the published literature in this area.

To be successful, the meta-analysis must address several elements^[29]: (1) The question must be stated unambiguously; (2) A search of the medical literature must be performed in a comprehensive way; (3) The articles identified by the search must be screened; (4) The appropriate data must be extracted from the selected papers; (5) An assessment of the quality of the information is performed, by a review of the contents of the manuscripts and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria^[30]; (6) Determine whether the data in each publication are heterogeneous; (7) Determine summary effect size as odds ratio and generate graphical depictions of data, for example as a forest plot; (8) Assess for publication bias using funnel plot or some other mechanism; and (9) Conduct subset analysis to look for subsets of groups that capture the summary effect.

Purpose of reporting quality analysis and its limits

Because of the complexity of design and execution of meta-analyses, there are numerous opportunities to introduce biases and other errors that may significantly alter the outcome. To make the reporting of data and statistical analysis in meta-analyses transparent to the reader and to clearly advertise the limits of the data used in the study, 3 checklist systems have been promulgated to list the major elements that researchers should use to structure their work.

The first of these systems, the IOM checklist, was created by a committee by the United States Institutes of Medicine. This is a relatively simple 5-point checklist that broadly addresses the reporting of the planning and execution of meta-analyses^[2]. The Institutes of Medicine, along with a large number of journals and other publishers, later endorsed the PRISMA statement, which addresses these issues in a more granular fashion^[3]. Another checklist, the MOOSE guidelines, may also be applied to evaluate reporting quality of systematic reviews including meta-analyses^[4]. In the reported literature, PRISMA guidelines are utilized more frequently than MOOSE guidelines. In a survey of the medical literature by Fleming *et al*^[31], the vast majority of publications used PRISMA guidelines, compared to MOOSE guidelines, which were cited in only 17% of reviews. Fleming *et al*^[31] note that although there is a high degree of overlap between the MOOSE and PRISMA checklists, MOOSE provides more advice about features such as the search strategy and interpretation of the results of the review, both of which may introduce bias if not adequately addressed^[31,32].

In the current study the most common deficiencies were (1) lack of an articulated rationale for why a pooled analysis is necessary; (2) lack of detail of how to address the use of data that has not been peer reviewed; (3) a lack of sensitivity analysis; and (4) a lack of assessment of studies for bias. Although the rationale for why a meta-analysis is performed is generally obvious (*e.g.*, improved statistical power, identification of a consensus/lack of consensus regarding a specific clinical question) it is not explicitly articulated in a significant number of studies included in this survey. The lack of transparency about the use of non-English language literature and preprint and other non-peer reviewed materials may be problematic, in particular in COVID-19 studies. Sensitivity analysis is a fundamental element of meta-analysis and provides an estimate of the appropriateness of the assumptions made by the analysis^[29]. Bias can be introduced into a study in many ways, most commonly by publication bias, in which the medical literature has an underrepresentation of studies with negative findings^[29].

The overall reporting of quality in the pathology literature appears to lag behind that for clinical medicine^[5]. Liu *et al*^[5] compared the reporting quality of a group of diagnostic pathology meta-analyses to a group published in clinical medicine journals using the PRISMA checklist, and found a higher average PRISMA score for the medicine studies that was statistically significant ($P < 0.01$). The average PRISMA score for the COVID-19 meta-analyses in the current study (20.3/27, 75% of items addressed) is below that for both groups analyzed by Liu *et al*^[5]. This reflects a significant weakness in the COVID-19 meta-analysis laboratory hematology literature, since the potential strengths of the meta-analysis approach as a force multiplier for evidence-based medicine requires good reporting quality^[5].

It is important to note the assessment of reporting quality is not synonymous with assessment of methodological quality of a meta-analysis. The purpose of reporting quality guidelines is to provide an appropriate framework to the authors of meta-analyses and other systematic reviews so that their data and statistical analysis is reported in an unambiguous way. The assessment of methodological quality is a separate exercise and can only proceed if the data can be unambiguously extracted from the publication. The methodological assessment of systematic reviews is addressed by other guidelines such as QUADAS and QUADAS-2^[33]. Due to the

apparent suboptimal average reporting quality of COVID-19 laboratory hematology meta-analyses literature, the ability of the reader to assess methodological quality is limited in many cases.

Preprint literature and its reporting quality

In academic publishing, a preprint is the version of a manuscript that has been submitted for publication but has not yet finished the peer review process. In recent years, publishers and others have electronically posted preprint manuscripts to rapidly disseminate scientific knowledge. In addition, studies that have been uploaded to dedicated servers but not submitted for peer review are also included in the category of preprints. Preprints are particularly useful in fields such as COVID-19, which are rapidly evolving and are of intense clinical and scientific interest.

Since preprints are widely accessible, it would be important for readers to be aware of their quality compared to studies published in the peer review literature. Although it would be assumed that the reporting quality of the peer review process would be higher than the comparable preprint literature since the purpose of peer review is to permit scrutiny of one's work by experts^[34], there have apparently been no studies in the peer review literature that directly compare the reporting quality of clinical studies in the preprint and published literature. A single study in the preprint literature (Carneiro *et al*^[35]) has attempted to address this question. The authors compared a sample of studies identified in the bioRxiv preprint server with studies identified in a Medline (PubMed interface) search. They also compared a group of preprint studies with their final versions. Carneiro *et al*^[35] identified a small increase in quality in the published studies compared to the preprint group.

In the current study, using the PRISMA and MOOSE criteria, a significant difference was not identified comparing the preprint and published studies in the COVID-19 meta-analysis literature. Taken together, these findings suggest that the peer review process itself does not guarantee an improvement in quality, and authors should take the initiative to conform to reporting quality norms.

CONCLUSION

This study represents an attempt to assess the overall reporting quality of the laboratory hematology COVID-19 meta-analysis literature. Using the IOM, PRISMA, and MOOSE, guidelines, there were consistent deficits in the reporting of bias and sensitivity. The results for the preprint and published literature were similar and suggest that the preprint literature on this subject is not decidedly inferior to the published literature. Because of the suboptimal reporting quality, it is important for clinicians and others to carefully assess the individual studies used in a given meta-analysis for evidence of bias or other methodological flaws that have not been reported by the authors. Although there is a positive correlation between the PRISMA and MOOSE guidelines, it is relatively weak. This implies that authors of meta-analyses should consider using both systems to increase the strength of the reporting quality of their studies.

ARTICLE HIGHLIGHTS

Research background

Meta-analyses, which are underutilized in pathology and laboratory medicine, combine the data from multiple studies to produce a publication with increased statistical power. It is important for readers of meta-analyses to have the information in these studies reported in a transparent fashion. Hence the Institutes of Medicine (IOM), Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA), and Meta-analyses of Observational Studies in Epidemiology (MOOSE) checklists have been promulgated to standardize the reporting of meta-analyses.

Research motivation

Several parameters evaluated by the hematology laboratory have been identified as potential biomarkers of prognosis and outcome in the coronavirus disease 2019 (COVID-19). The data from many of these studies have been pooled and published as meta-analyses. Many of these studies have been identified in the preprint literature (studies that have not yet completed peer review). The reporting quality of this body

of work is unknown.

Research objectives

The purposes of this study were to 1) evaluate the reporting quality of laboratory hematology-focused COVID-19 meta-analyses using the IOM, PRISMA, and MOOSE checklists and 2) compare the reporting quality of published vs. preprint studies.

Research methods

Based on a search of the literature, 19 studies were selected for analysis (9 published studies and 10 preprint studies). The reporting quality of the studies was evaluated using the IOM, PRISMA, and MOOSE checklists.

Research results

The reporting quality of the published and preprint studies was similar, and was inferior in quality to that described in similar studies on reporting quality of meta-analyses published in the pathology and medicine literature.

Research conclusions

Readers of COVID-19 laboratory hematology meta-analyses should be cognizant of their reporting quality problems, and critically evaluate them before using their information for patient care.

Research perspectives

The issue of reporting quality is of critical importance, and the assessment of reporting quality has been underreported in the medical literature. Studies similar to this one will emphasize that the use of the IOM, PRISMA, and MOOSE checklists is a simple strategy to optimize the overall quality of meta-analyses.

REFERENCES

- Kinzer M, Zhang L. Underutilization of Meta-analysis in Diagnostic Pathology. *Arch Pathol Lab Med* 2015; **139**: 1302-1307 [PMID: [26414474](#) DOI: [10.5858/arpa.2014-0461-OAI](#)]
- Eden J, Levit L, Berg L, Morton S. Finding what works in healthcare: standards for systematic reviews. Washington, DC.: The National Academies Press; 2011
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535 [PMID: [19622551](#) DOI: [10.1136/bmj.b2535](#)]
- Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: [10789670](#) DOI: [10.1001/jama.283.15.2008](#)]
- Liu X, Kinzer M, Yuan J, He G, Zhang L. Low Reporting Quality of the Meta-Analyses in Diagnostic Pathology. *Arch Pathol Lab Med* 2017; **141**: 423-430 [PMID: [28055241](#) DOI: [10.5858/arpa.2016-0144-OA](#)]
- Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol* 2020; **92**: 401-402 [PMID: [31950516](#) DOI: [10.1002/jmv.25678](#)]
- Perlman S. Another Decade, Another Coronavirus. *N Engl J Med* 2020; **382**: 760-762 [PMID: [31978944](#) DOI: [10.1056/NEJMe2001126](#)]
- Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. *Int J Lab Hematol* 2020; **42** Suppl 1: 11-18 [PMID: [32311826](#) DOI: [10.1111/ijlh.13229](#)]
- Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med* 2020; **58**: 1131-1134 [PMID: [32119647](#) DOI: [10.1515/cclm-2020-0198](#)]
- Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. *Clin Chem Lab Med* 2020; **58**: 1063-1069 [PMID: [32191623](#) DOI: [10.1515/cclm-2020-0240](#)]
- Borges do Nascimento IJ, Cacic N, Abdulazeem HM, von Groote TC, Jayarajah U, Weerasekara I, Esfahani MA, Civile VT, Marusic A, Jeroncic A, Carvas Junior N, Pericic TP, Zakarija-Grkovic I, Meirelles Guimarães SM, Luigi Bragazzi N, Bjorklund M, Sofi-Mahmudi A, Altujjar M, Tian M, Arcani DMC, O'Mathúna DP, Marcolino MS. Novel Coronavirus Infection (COVID-19) in Humans: A Scoping Review and Meta-Analysis. *J Clin Med* 2020; **9**: 941 [PMID: [32235486](#) DOI: [10.3390/jcm9040941](#)]
- Cao Y, Liu X, Xiong L, Cai K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. *J Med Virol* 2020; Epub ahead of print [PMID: [32242947](#) DOI: [10.1002/jmv.25822](#)]
- Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, Li P, Zhou Y, Lin YF, Duan Q, Luo G, Fan S, Lu Y, Feng A, Zhan Y, Liang B, Cai W, Zhang L, Du X, Li L, Shu Y, Zou H. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect* 2020; **80**: 656-665 [PMID: [32283155](#) DOI: [10.1016/j.jinf.2020.03.041](#)]
- Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-

- 19): a meta-analysis. *Clin Chem Lab Med* 2020; **58**: 1021-1028 [PMID: [32286245](#) DOI: [10.1515/cclm-2020-0369](#)]
- 15 **Lagunas-Rangel FA**. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. *J Med Virol* 2020; Epub ahead of print [PMID: [32242950](#) DOI: [10.1002/jmv.25819](#)]
- 16 **Lippi G**, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta* 2020; **506**: 145-148 [PMID: [32178975](#) DOI: [10.1016/j.cca.2020.03.022](#)]
- 17 **Rodriguez-Morales AJ**, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK, Franco-Paredes C, Henao-Martínez AF, Paniz-Mondolfi A, Lagos-Grisales GJ, Ramírez-Vallejo E, Suárez JA, Zambrano LI, Villamil-Gómez WE, Balbin-Ramón GJ, Rabaan AA, Harapan H, Dhama K, Nishiura H, Kataoka H, Ahmad T, Sah R; Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Electronic address: <https://www.lancovid.org>. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis* 2020; **34**: 101623 [PMID: [32179124](#) DOI: [10.1016/j.tmaid.2020.101623](#)]
- 18 **Zhu J**, Ji P, Pang J, Zhong Z, Li H, He C, Zhang J, Zhao C. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. *J Med Virol* 2020; Epub ahead of print [PMID: [32293716](#) DOI: [10.1002/jmv.25884](#)]
- 19 **Li LQ**, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020; **92**: 577-583 [PMID: [32162702](#) DOI: [10.1002/jmv.25757](#)]
- 20 **Arabi S**, Vaseghi G, Heidari Z, Shariati L, Amin B, Rashid H, Javanmard SH. Clinical characteristics of COVID-19 infection in pregnant women: a systematic review and meta-analysis. *MedRxiv* 2020; Preprint [DOI: [10.1101/2020.04.05.20053983](#)]
- 21 **Ebrahimi M**, Malehi AS, Rahim F. Laboratory findings, signs and symptoms, clinical outcomes of Patients with COVID-19 Infection: an updated systematic review and meta-analysis. *MedRxiv* 2020; Preprint [DOI: [10.1101/2020.03.25.20043703v1](#)]
- 22 **Han P**, Han P, Diaio K, Pang T, Huang S, Yang Z. Comparison of clinical features between critically and non-critically ill patients in SARS and COVID-19: a systematic review and meta-analysis. *MedRxiv* 2020; Preprint [DOI: [10.2139/ssrn.3566133](#)]
- 23 **Heydari K**, Rismantab S, Shamsheirani A, Lotfi P, Shadmehri N, Houshmand P, Zahedi M, Shamsheirani D, Bathaiean S, Alizadeh-Navaei R. Clinical and Paraclinical Characteristics of COVID-19 patients: A systematic review and meta-analysis. *MedRxiv* 2020; Preprint [DOI: [10.1101/2020.03.26.20044057v1](#)]
- 24 **Ma C**, Gu J, Hou P, Zhang L, Bai Y, Guo Z, Wu H, Zhang B, Li P, Zhao X. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. *MedRxiv* 2020; Preprint [DOI: [10.1101/2020.03.17.20037572v1](#)]
- 25 **Nasiri MJ**, Haddadi S, Tahvildari A, Farsi Y, Arbabi M, Hasanzadeh S, Jamshidi P, Murthi M, Mirsaedi MS. COVID-19 clinical characteristics, and sex-specific risk of mortality: Systematic Review and Meta-analysis. *MedRxiv* 2020; Preprint [DOI: [10.1101/2020.03.24.20042903v1](#)]
- 26 **Pormohammad A**, Ghorbani S, Khatami A, Farzi R, Baradaran B, Turner DL, Turner RJ, Bahr NC, Idrovo JP. Comparison of confirmed COVID-19 with SARS and MERS cases - Clinical characteristics, laboratory findings, radiographic signs and outcomes: A systematic review and meta-analysis. *Rev Med Virol* 2020; **30**: e2112 [PMID: [32502331](#) DOI: [10.1002/rmv.2112](#)]
- 27 **Xu L**, Mao Y, Chen G. Risk factors for severe corona virus disease 2019 (COVID-19) patients: a systematic review and meta analysis. *MedRxiv* 2020; Preprint [DOI: [10.1101/2020.03.30.20047415v1](#)]
- 28 **Zhang HY**, Jiao F, Wu X, Shang M, Luo Y, Gong Z. Clinical features, treatments and outcomes of severe and critical severe patients infected with COVID-19: A system review and meta-analysis. 2020; Preprint [DOI: [10.21203/rs.3.rs-17307/v1](#)]
- 29 **Carlin JB**. Tutorial in biostatistics. Meta-analysis: formulating, evaluating, combining, and reporting by S-L. T. Normand, Statistics in Medicine, 18, 321-359 (1999). *Stat Med* 2000; **19**: 753-759 [PMID: [10700744](#) DOI: [10.1002/\(sici\)1097-0258\(20000315\)19:5<753::aid-sim427>3.0.co;2-f](#)]
- 30 **Andrews JC**, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013; **66**: 726-735 [PMID: [23570745](#) DOI: [10.1016/j.jclinepi.2013.02.003](#)]
- 31 **Fleming PS**, Koletsi D, Pandis N. Blinded by PRISMA: are systematic reviewers focusing on PRISMA and ignoring other guidelines? *PLoS One* 2014; **9**: e96407 [PMID: [24788774](#) DOI: [10.1371/journal.pone.0096407](#)]
- 32 **van Zuuren EJ**, Fedorowicz Z. Moose on the loose: checklist for meta-analyses of observational studies. *Br J Dermatol* 2016; **175**: 853-854 [PMID: [27790686](#) DOI: [10.1111/bjd.15038](#)]
- 33 **Whiting PF**, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529-536 [PMID: [22007046](#) DOI: [10.7326/0003-4819-155-8-201110180-00009](#)]
- 34 **Kelly J**, Sadeghih T, Adeli K. Peer Review in Scientific Publications: Benefits, Critiques, & A Survival Guide. *EJIFCC* 2014; **25**: 227-243 [PMID: [27683470](#)]
- 35 **Carneiroa CFD**, Queiroza VGS, Moulina TC, Carvalhob C, Haase CB, Rayêf D, Henshallg DE, De-Souzaa EA, Amorima FE, Boosh FZ, Guercioi GD, Costaa IR, Hajdud KL, van Egmondj L, Modrák M, Tanf PB, R.J. A, Burgessm SJ, Guerrad SFS, Bortoluzzie VT, Amarala OB. Comparing quality of reporting between preprints and peer-reviewed articles in the biomedical literature. 2020; Preprint [DOI: [10.1101/581892v3](#)]

Prevalence, awareness and control of hypertension in Malaysia from 1980-2018: A systematic review and meta-analysis

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Abstract

BACKGROUND

Hypertension is a common public health problem worldwide and is a well-known risk factor for increased risk of cardiovascular diseases, contributing to high morbidity and mortality. However, there has been no systematic review and meta-analysis of a multiethnic population such as that of Malaysia.

AIM

To determine the trend in prevalence, awareness and control rate of hypertension in Malaysia.

METHODS

Systematic searches were conducted in six databases (PubMed, Scopus, Ovid, CINAHL, Malaysian Medical Repository and Malaysia Citation Index) for articles

Conflict-of-interest statement: The authors declare that they have no competing interests.

PRISMA 2009 Checklist statement:

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

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published between 1980 and 2018. Two authors reviewed the studies and performed quality assessment and data extraction independently. Pooled estimates of hypertension prevalence, awareness and control rate were calculated using the DerSimonian-Laird random-effects model. Subgroup and sensitivity analyses were performed.

RESULTS

We included 56 studies involving a total of 241796 participants. The overall pooled prevalence of hypertension aged ≥ 18 years was 29.7%. The prevalence of hypertension was the lowest in the 1980s (16.2%, 95% confidence interval (CI): 13.4, 19.0), increasing up to 36.8% (95% CI: 6.1, 67.5) in the 1990s, then decreasing to 28.7% (95% CI: 21.7, 35.8) in the 2000s and 26.8% (95% CI: 21.3, 32.3) in the 2010s. The prevalence of awareness was 51.4% (95% CI: 46.6, 56.3), while 33.3% (95% CI: 28.4, 38.2) of those on treatment had achieved control of their blood pressure.

CONCLUSION

In Malaysia, three in ten adults aged ≥ 18 years have hypertension, while four in ten adults aged ≥ 30 years have hypertension. Five out of ten people are aware of their hypertension status and only one-third of those under treatment achieved control of their hypertension. Concerted efforts by policymakers and healthcare professionals to improve awareness and control of hypertension should be of high priority.

Key Words: Prevalence; Awareness; Control; Hypertension; Blood pressure; Malaysia; Systematic review; Meta-analysis

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Core Tip: This is a systematic review and meta-analysis reporting that the pooled prevalence of hypertension in people aged ≥ 18 years in Malaysia was 29.7%. The pooled prevalence of awareness towards hypertension was 51.4 % and blood pressure control rate was 33.3%.

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INTRODUCTION

Hypertension is a common public health problem over the past several decades^[1,2]. It is one of the major risk factors for cardiovascular diseases such as stroke, heart failure and ischemic heart disease^[3]. In Malaysia, trend analyses have been conducted based on the National Health and Morbidity Surveys, which are nationwide studies that have been performed every 10 years since 1986. The analyses have also shown the trend of hypertension in different genders and ethnicities^[4-7]. Besides the National Health and Morbidity Surveys, several other studies have examined the prevalence, awareness and control of hypertension that differed from that of the National Health and Morbidity Surveys^[8,9]. The prevalence in different settings and in different age groups may present a slightly different picture along with their accompanying set of problems.

The present systematic review aimed to determine the pooled prevalence of hypertension, awareness and control of hypertension in Malaysia from 1980 to 2018 based on a nationwide survey and other important studies that reported the prevalence of hypertension in different settings and specific groups. Heterogeneities among cross-sectional studies and the national survey may conceivably cause different rates of prevalence. Hence, there is a need for a systematic review and meta-analysis to estimate the pooled prevalence of hypertension in Malaysia. We are not only reporting

the trend of hypertension prevalence in Malaysia from 1980 to 2018 but are also providing some important insights into the awareness and control of hypertension among Malaysians.

MATERIALS AND METHODS

Protocol registration

The present review was registered with PROSPERO (2018: CRD42018075369) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines^[10].

Data sources

We searched six databases (PubMed, Ovid, Scopus, CINAHL, Malaysian Medical Repository and Malaysia Citation Index) for the relevant articles and included all relevant citations published before February 28, 2018.

Search strategy

The literature search used the following search terms: (prevalence) and (awareness) and (control) and (hypertension or high blood pressure) and (Malaysia), and a combination of expanded MeSH terms and free-text searches were used for the final search up to February 28, 2018: (Prevalence OR Aware* OR Unaware* OR Undiagnosed OR Control* OR Uncontrol* OR "Achieved target") AND (Hypertension OR "Blood pressure" OR "Systolic blood pressure" OR "Diastolic blood pressure" OR "Raised blood pressure" OR "High blood pressure") AND (Malaysia OR Perlis OR Kedah OR Penang OR "Pulau Pinang" OR Perak OR Johor OR Selangor OR Pahang OR Malacca OR Melaka OR Terengganu OR Kelantan OR "Negeri Sembilan" OR Sabah OR Sarawak OR "Wilayah Persekutuan" OR Putrajaya OR "Kuala Lumpur" OR "Labuan").

Eligibility criteria

Any studies, reports or articles published between January 1, 1980 and February 28, 2018 and fulfilling the following criteria were included in the analysis: (1) Included the general population aged ≥ 18 years; (2) Studied the prevalence of hypertension diagnosed using digital automated or mercury sphygmomanometers; (3) Studied either the prevalence, awareness and control of blood pressure (BP) or hypertension individually or any combination of the three; and (4) In English only. We excluded intervention studies, case studies, pharmacogenetic studies, case series, qualitative data, comments or letters, audits, narrative reviews, conference proceeding, opinion pieces, methodological, editorials, animal studies or any other publications lacking primary data and/or explicit method descriptions. When several publications were derived from the same dataset or cohorts, the article that provided the most updated data was selected. We identified other pertinent studies through reverse-forward citation tracking of relevant articles.

Selection process

We imported relevant articles identified through the databases into EndNote X5 and removed duplicate publications. Two authors (Chow ZY and Tan CH) screened the titles and abstracts independently to search for eligible articles based on the inclusion criteria. If there were discrepancies on including studies, discussions were held and resolved by the senior authors (Ching SM, Hoo FK, Devaraj NK, Salim HS and Cheong AT) for final consensus before the full text of each relevant article was reviewed.

Data collection

One author (Ramachandran V) recorded data from the selected studies into the extraction form using Excel, while the second author (Ching SM) verified the accuracy and completeness of the extracted data.

Data items

The following characteristics of the selected studies were extracted: First author, year of publication, study setting, study design, location of study, geographical area (rural or urban), BP apparatus, sample size and cases with hypertension. The outcome measures extracted were the prevalence of hypertension in terms of the difference of proportion/percent of hypertension, awareness and control in the total patients

examined.

Summary measures

Hypertension was defined as BP $\geq 140/90$ mmHg based on guidelines from the Fifth Joint National Committee. Awareness was defined as knowing one's own hypertension status or having been diagnosed with hypertension previously. Control was defined as achieving a target BP of $< 140/90$ mmHg^[11].

Risk of assessment based on the critical appraisal checklist

Each article underwent quality assessment by two authors (Soo MJ and Lee KW) using a modified critical appraisal checklist (Supplementary material Appendix 1)^[8]. The checklist consisted of 11 items that assessed the components in observational studies. Whenever the information provided was insufficient to assist in the evaluation of a certain item, the two authors agreed to grade that item as "0" indicating absence of the item, "0.5" indicated that the information was incomplete, and "1" indicated that the item was presented clearly. The quality of each article was graded as high if it scored $\geq 7/11$, or low if it scored $< 7/11$ ^[8]. The results of the quality assessment are shown in supplementary material Appendix 2.

Data synthesis

The results from the meta-analysis summarized the data narrative and statistically used a tabulated format. Heterogeneity between studies for the pooled estimates was examined using I^2 ($I^2 < 25\%$, low; $I^2 = 25\%-30\%$, moderate; $I^2 > 50\%$, high), indicating the percent of total discrepancy due to variation in the studies^[12].

Statistical analysis

We used OpenMeta[Analyst] for data analysis (<http://www.cebm.brown.edu/openmeta/index.html>)^[13]. The prevalence estimated from individual studies was pooled using random-effects (DerSimonian-Laird method) meta-analysis and was reported with 95% confidence interval (CI). Subgroup analysis was performed to examine the prevalence, awareness and control of hypertension by age group, sex, ethnicity, study setting, study design, geographical origin and BP tools.

Additional analysis

Publication bias was assessed by sensitivity analysis using the leave-one-out analysis. We also performed sensitivity analyses for the prevalence of hypertension by discarding low-quality studies, removing outlier subpopulations (point estimates $> \pm 3$ standard deviations)^[14] or removing smaller subpopulations (size < 100) or large sample sizes (size > 5000)^[15], where these publication biases are known to have effects on the estimated prevalence. The effect size of interest was the proportion of individuals with hypertension. The secular trend of prevalence was estimated by calculating the point estimates for four separate decades.

RESULTS

Description of included studies

We identified 1493 manuscripts in the initial search (Figure 1). After removal of duplicate records ($n = 251$), 1242 studies were retrieved for further assessment. After careful evaluation of the inclusion/exclusion criteria, 52 studies fulfilled our criteria, and this together with another four studies identified from cross-referencing, a total of 56 studies were included in our meta-analysis.

Characteristics of the included studies

The main characteristics of the included studies are shown in Table 1^[16-71] and supplementary material Appendix 3 in encompassing the prevalence, awareness and control of hypertension of the included studies. A total sample size of 241796 respondents from Malaysia was included in the analysis. Overall, the ethnicity distribution was 56.5% Malay, 24.2% Chinese, 9.7% Indian and 9.5% other ethnicities. Fifty-one studies were conducted in the community setting, four were in a hospital setting and one was in a primary care clinic. Quality assessment using a modified critical appraisal checklist showed that the majority of the studies (52/56) were of good quality with only four having poor quality.

Table 1 Prevalence, awareness and control of hypertension in Malaysia

Ref.	Sample size, <i>n</i>	Prevalence of hypertension, %	Prevalence of awareness, %	Prevalence of control, %	Quality of article
Abdul-Razak <i>et al</i> ^[16] , 2016	11288	47.9	52.5	15.9	High
Jinam <i>et al</i> ^[17] , 2008	213	40.4	NA	NA	High
Akter <i>et al</i> ^[18] , 2010	219	35.6	NA	NA	High
Amiri <i>et al</i> ^[19] , 2014	1096	39.3	NA	NA	High
Amplavanar <i>et al</i> ^[20] , 2010	3765	34.2	NA	NA	High
Aniza <i>et al</i> ^[21] , 2015	1107	24.0	NA	NA	High
Aniza <i>et al</i> ^[22] , 2016	1489	39.5	NA	NA	High
Annamalai <i>et al</i> ^[23] , 2011	903	26.9	39.5	15.7	High
Azuwani <i>et al</i> ^[24] , 2013	138	42.0	NA	NA	High
Tan <i>et al</i> ^[25] , 2008	109	33.0	NA	NA	High
Chang <i>et al</i> ^[26] , 2012	260	13.9	NA	NA	High
Cheah <i>et al</i> ^[27] , 2015	218	7.3	NA	NA	High
Chee <i>et al</i> ^[28] , 2002	968	1.8	NA	NA	High
Chin <i>et al</i> ^[29] , 2009	1417	52.4	NA	NA	High
Chow <i>et al</i> ^[30] , 2013	11324	47.0	48.3	12.8	High
Chua <i>et al</i> ^[31] , 2017	482	25.5	NA	NA	High
Gan <i>et al</i> ^[32] , 1993	648	16.2	NA	NA	High
Ghazi <i>et al</i> ^[33] , 2017	410	10.0	41.5	NA	Low
Goh <i>et al</i> ^[34] , 2013	1621	22.1	NA	NA	High
Hasnah <i>et al</i> ^[35] , 2012	125	34.4	NA	NA	High
Hazmi <i>et al</i> ^[36] , 2015	308	14.3	NA	NA	High
Ministry of Health Malaysia ^[37] , 2015	23845	30.3	NA	NA	High
Jamal <i>et al</i> ^[38] , 2015	106527	46.4	NA	NA	High
Khan <i>et al</i> ^[39] , 2008	240	58.3	48.6	51.4	High
Latiffah <i>et al</i> ^[40] , 2008	73	39.7	70.8	40.9	High
Latiffah <i>et al</i> ^[41] , 2008	92	51.1	NA	NA	High
Lee <i>et al</i> ^[42] , 2010	226	12.8	NA	NA	Low
Lian <i>et al</i> ^[43] , 2015	223	25.1	NA	NA	High
Liao <i>et al</i> ^[44] , 2010	206	19.9	NA	NA	High
Lim <i>et al</i> ^[45] , 1991	368	30.4	NA	NA	High
Loh <i>et al</i> ^[46] , 2013	1961	54.9	NA	NA	High
Ministry of Health Malaysia ^[47] , 2010	2572	25.7	NA	NA	High
Mohamed <i>et al</i> ^[48] , 2005	4117	33.0	NA	NA	High
Nazri <i>et al</i> ^[49] , 2008	148	13.5	NA	NA	High
Nazri <i>et al</i> ^[50] , 2008	348	12.6	NA	NA	High
Moy <i>et al</i> ^[51] , 2010	380	20.3	NA	NA	High
Narayan <i>et al</i> ^[52] , 2007	431	33.0	NA	NA	High
Narayan <i>et al</i> ^[53] , 2007	479	33.6	28.0	27.5	High
Nasarudin <i>et al</i> ^[54] , 2016	535	21.1	NA	NA	Low

Nawawi <i>et al</i> ^[55] , 2002	608	30.3	NA	NA	High
Ng <i>et al</i> ^[56] , 1995	427	21.1	NA	NA	Low
Noor Hassim <i>et al</i> ^[57] , 2016	5505	25.2	NA	NA	High
Ong <i>et al</i> ^[58] , 2010	205	36.1	81.1	33.8	High
Ong <i>et al</i> ^[59] , 2013	40400	30.1	NA	NA	High
Raihan <i>et al</i> ^[60] , 2013	251	14.3	NA	NA	High
Rampal <i>et al</i> ^[61] , 2008	454	34.4	64.1	25.0	High
Rashid <i>et al</i> ^[62] , 2011	418	54.6	51.8	NA	High
Rasiah <i>et al</i> ^[63] , 2015	6690	37.4	NA	NA	High
Shahar <i>et al</i> ^[64] , 2011	71	32.4	NA	NA	High
Samsudin <i>et al</i> ^[65] , 2016	1414	42.4	NA	NA	High
Sherina <i>et al</i> ^[66] , 2011	202	12.4	NA	NA	High
Shomad <i>et al</i> ^[67] , 2016	56	4.00	NA	NA	High
Sidik <i>et al</i> ^[68] , 2004	223	22.0	NA	NA	High
Teh <i>et al</i> ^[69] , 2014	3406	35.8	NA	NA	Low
Yusoff <i>et al</i> ^[70] , 2010	289	30.1	NA	NA	High
Zainuddin <i>et al</i> ^[71] , 201	298	37.3	NA	NA	High

NA: Not available.

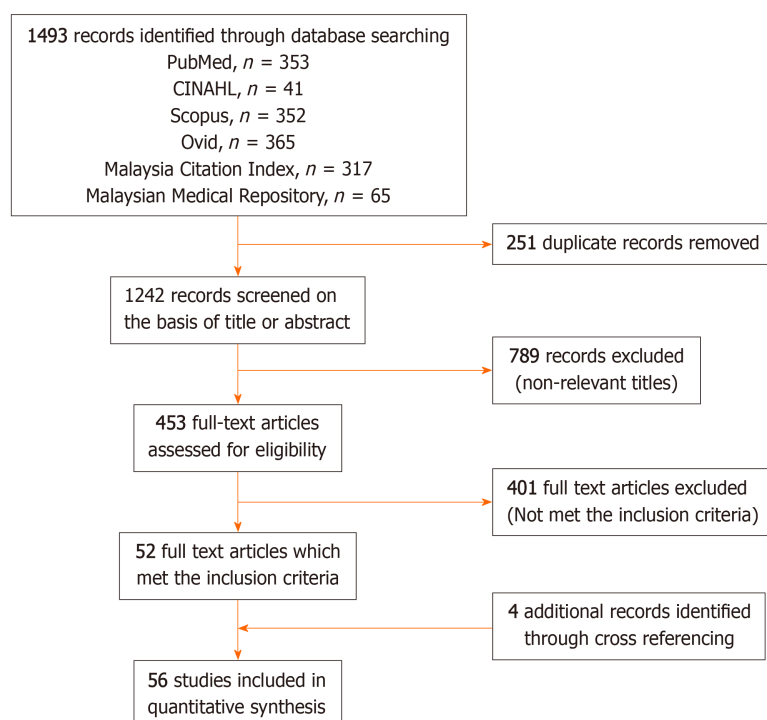


Figure 1 Preferred reporting items for systematic review and meta-analysis flow diagram of the literature screening process. Numbers indicate the article count retained at each step of the process.

Prevalence of hypertension: Overall and subgroup analysis

Table 2 shows the prevalence of hypertension in Malaysia is 29.7% (95%CI: 26.1, 33.3) (Figure 2). The prevalence of hypertension for those aged ≥ 30 years was 40.0% (Figure 3). The pooled prevalence of hypertension increased with age as the prevalence was 8.6% in adults aged 18–29 years as compared to 42.8% in adults aged ≥ 60 years (Figure 4).

Table 2 Pooled prevalence and 95% confidence interval of hypertension and its subgroup analysis

Variable	Number of studies, <i>n</i>	Prevalence, %	95%CI	<i>P</i> value	<i>I</i> ² , %	Figure
Overall prevalence						
Malaysia	56	29.7	26.1, 33.3	< 0.001	99.7	2
30 and above	16	40.0	35.3, 44.8	< 0.001	98.9	3
Mean age, yr						
18–29	4	8.6	5.30, 11.90	0.03	66.9	4
30–39	3	13.5	2.9, 29.9	< 0.001	98.7	
40–49	17	27.9	24.9, 30.9	< 0.001	96.5	
50–59	4	39.4	29.3, 49.4	< 0.001	99.7	
60 and above	6	42.8	30.2, 55.3	< 0.001	95.8	
Gender						
Male	26	31.4	26.5, 36.2	< 0.001	98.1	5A
Female	26	27.8	20.7, 34.9	< 0.001	99.5	5B
Ethnicity						
Malay	17	37.3	32.9, 41.7	< 0.001	98.9	6A
Chinese	8	36.4	31.6, 41.2	< 0.001	96.6	6B
Indian	10	34.8	31.2, 38.4	< 0.001	81.5	6C
Other	9	32.9	25.8, 40.0	< 0.001	98.0	6D
Study setting						
Community	51	30.2	26.4, 34.1	< 0.001	99.7	7
Health care setting	5	24.3	16.6, 32.0	< 0.001	97.5	
Geographical origin						
Rural	19	35.6	29.9, 41.4	< 0.001	98.77	8A
Urban	21	25.4	20.4, 30.4	< 0.001	98.43	8B
Study decade						
1980–1989	1	16.2	13.4, 19.0	NA	NA	9
1990–1999	2	36.8	6.1, 67.5	< 0.001	99.42	
2000–2009	19	28.7	21.7, 35.8	< 0.001	99.9	
2010–2018	9	26.8	21.3, 32.2	< 0.001	98.7	
Blood pressure measurement tools						
Mercury sphygmomanometer	15	33.2	26.4, 40.0	< 0.001	98.8	10
Digital blood pressure device	16	30.8	25.5, 36.0	< 0.001	99.8	

CI: Confidence interval.

Among adults aged ≥ 18 years, the prevalence of hypertension was higher in men compared to women (31.4%, 95%CI: 26.5, 36.2 *vs* 27.8%, 95%CI: 20.7, 34.9) (Figure 5A and 5B). The prevalence of hypertension was highest among Malays (37.3%, 95%CI: 32.9, 41.7), followed by Chinese (36.4%, 95%CI: 31.6, 41.2) and Indians (34.8%, 95%CI: 31.2, 38.4) (Figure 6A–D). The prevalence of hypertension was 24.3% in healthcare setting as compared to 30.2% in community setting (Figure 7). The prevalence of hypertension in rural areas was 35.6% as compared to 25.4% in urban areas (Figure 8A and 8B).

The prevalence of hypertension was 16.2% in the first decade (1980–1989), 36.8% in the second decade (1990–1999), 28.7% in the third decade (2000–2009) and 26.8% in the fourth decade (2010–2018) (Figure 9).

The prevalence of hypertension in studies that used mercury sphygmomanometers

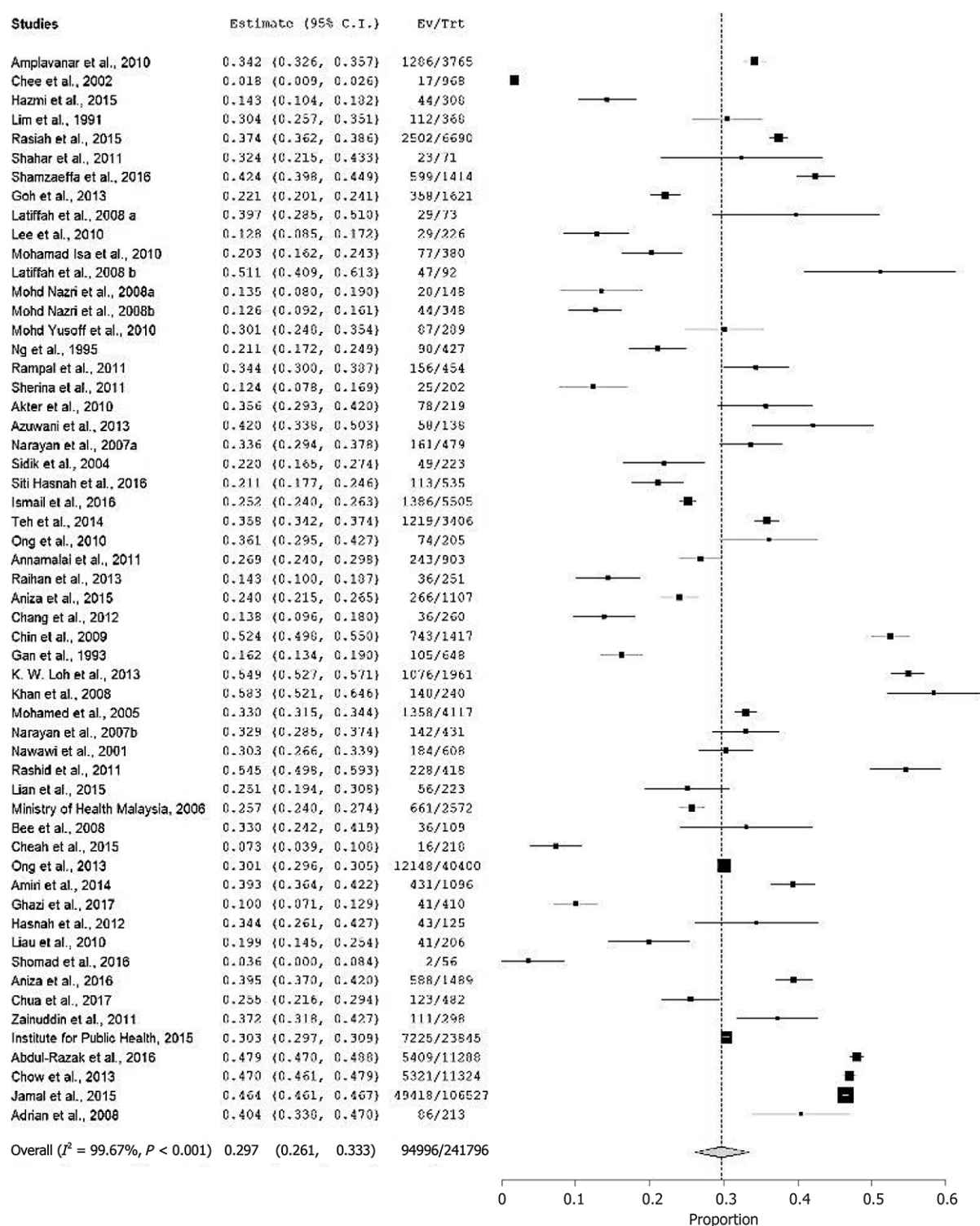


Figure 2 Pooled prevalence of hypertension.

was 33.2% (95%CI: 26.4, 40.0) as compared to 30.8% (95%CI: 25.5, 36.0) in those studies that used a digital BP device (Figure 10). Sensitivity analysis showed that all studies affected the pooled prevalence of hypertension causing it to vary from 25.6% to 30.2%. Therefore, we did not eliminate any studies from the analysis.

Prevalence of awareness towards hypertension

The overall prevalence of awareness towards hypertension in Malaysia was 51.4% (95%CI: 46.6, 56.3) (Table 3 and Figure 11). The prevalence of awareness towards hypertension among male hypertensive patients was 67.8% (Figure 12A), whereas it was 62.7% (Figure 12B) among female hypertensive patients^[52,56]. Hypertension awareness among the Malays was 45.4% (Figure 13A), while that among non-Malay

Table 3 Pooled awareness, pooled control and subgroup analyses

Variable	Number of studies, <i>n</i>	Prevalence, %	95%CI	<i>P</i> value	<i>I</i> ² , %	Figure
Overall awareness	10	51.4	46.6, 56.3	< 0.001	93.4	11
Gender						
Male	3	67.8	42.4, 93.1	< 0.001	97.7	12A
Female	3	62.7	52.8, 72.6	0.046	67.6	12B
Ethnicity						
Malay	3	45.4	29.8, 61.0	< 0.001	96.7	13A
Non-Malay	3	47.9	38.9, 56.8	< 0.001	90.4	13B
Geographical origin						
Rural	4	45.3	34.9, 55.8	< 0.001	93.3	14
Urban	1	54.1	52.2, 56.0	NA	NA	
Overall control	8	33.3	28.4, 38.2	< 0.001	85.2	15
Gender						
Male	3	37.1	26.0, 48.2	< 0.001	59.1	16A
Female	3	30.4	16.0, 44.8	< 0.001	80.7	16B
Ethnicity						
Malay	2	29.3	27.2, 31.5	0.68	0	17A
Non-Malay	3	35.6	29.9, 41.3	0.210	35.9	17B
Geographical origin						
Rural	3	34.1	15.5, 52.7	< 0.001	94.7	18
Urban	1	36.5	33.6, 39.3	NA	NA	

CI: Confidence interval; NA: Not available.

was 47.9% (Figure 13B). The prevalence of awareness towards hypertension among hypertensive patients living in rural areas was 45.3% (Figure 14) as compared to 54.1% in urban areas (Table 3).

Prevalence of control rate in hypertension

The control rate of hypertension was indicated in Table 3. Among the patients who were aware they were hypertensive, 33.3% (95%CI: 28.4, 38.2) achieved control of their BP (Figure 15). Our analysis found that men had slightly better control than women (37.1% *vs* 30.4%) (Figure 16A and 16B). We also found that 29.3% of Malays had control of their BP (Figure 17A), while that of non-Malays was 35.6% (Figure 17B). Urbanites had higher hypertension control than those living in rural areas (36.5% *vs* 34.1%) (Figure 18) (Table 3).

Sensitivity analyses

Visual inspection of the funnel plot of the result of overall prevalence of hypertension showed an asymmetrical plot, suggesting some degree of publication bias (Figure 19). The main analysis for the prevalence of hypertension was rerun by removing one subpopulation at a time. The pooled estimates did not vary much from the original analysis during each removal. The removal of five low-quality studies or smaller subpopulations (size < 100) also did not affect the original estimate of hypertension rates (Table 4).

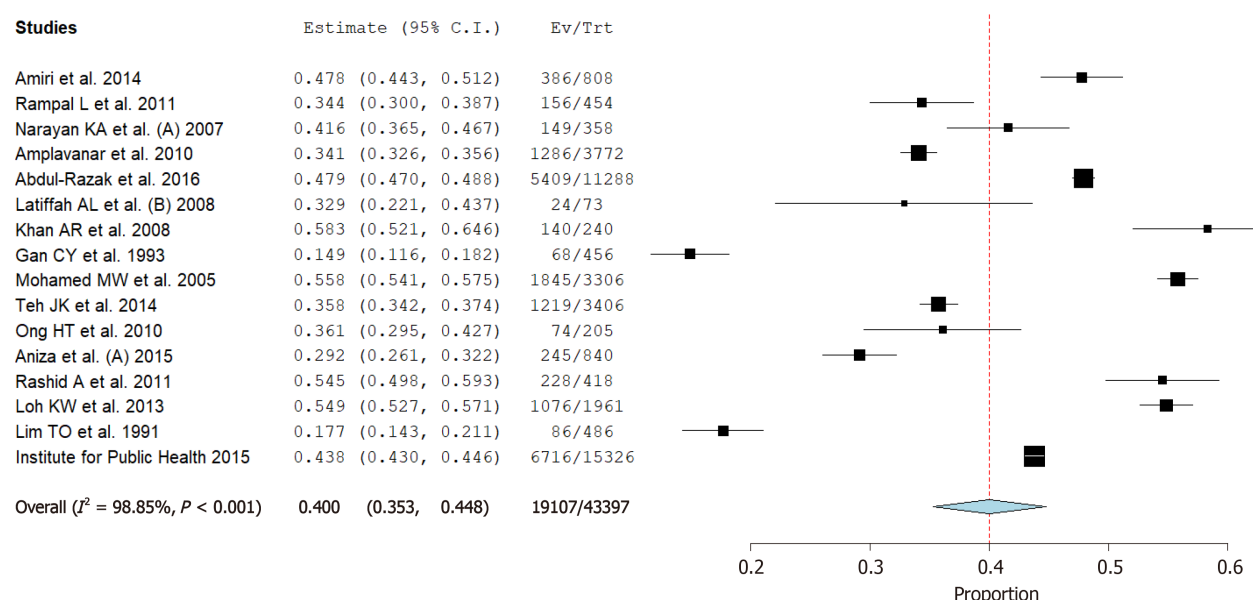
DISCUSSION

To the best of our knowledge, this systematic review is the first in Malaysia to describe the prevalence and its trends over four decades for hypertension awareness and

Table 4 Sensitivity analysis

Variable	Number of studies, <i>n</i>	Total sample size, <i>n</i>	Total hypertensive, <i>n</i>	Prevalence, %	95%CI	<i>P</i> value	<i>I</i> ² , %
Overall prevalence	56	241796	94996	29.7	26.1, 33.3	< 0.001	99.7
Upon removal of studies with poor quality studies	51	237181	93473	28.5	26.0, 31.2	< 0.001	99.4
Upon removal of studies with nonrandom sampling	19	131904	59786	29.7	26.2, 33.4	< 0.001	98.6
Upon removal of studies with sample size < 100	52	131904	59786	28.0	25.6, 30.6	< 0.001	99.3
Upon removal of studies with large sample size > 500	47	28335	8943	28.4	23.3, 33.4	< 0.001	99.2
Upon removal of poor-quality studies, nonrandom studies and studies with sample size < 100	12	46618	16031	26.3	21.6, 31.6	< 0.001	99.2

CI: Confidence interval.

Figure 3 Pooled prevalence of hypertension in adults aged ≥ 30 years.

control. In addition, due to the fact that Malaysia is a multiethnic country, its variation in the prevalence, awareness and control of hypertension is crucial for us to examine in order to plan our policy in managing hypertension on a nationwide scale.

Prevalence

The overall pooled prevalence of hypertension in Malaysia was 29.7%. The overall prevalence of hypertension in Malaysia was within the range of worldwide hypertension prevalence (20%–50%), as described in a systematic review by Kearney *et al*^[72]. Malaysia has a higher prevalence of hypertension as compared to Thailand (24.7%), Singapore (23.5%) and China (25.2%)^[73-75]. A review showed that this prevalence is as high as that in developed countries despite Malaysia being a developing country^[76]. In fact, the prevalence of hypertension in Malaysia is higher than that of the United States by 0.7%^[77].

Trend of hypertension

We noticed a low prevalence of hypertension in the 1980s. This could be due to only having one study that reported the prevalence of hypertension in the 1980s. Furthermore, that study involved the Kadazan and Bajau ethnic groups, which are

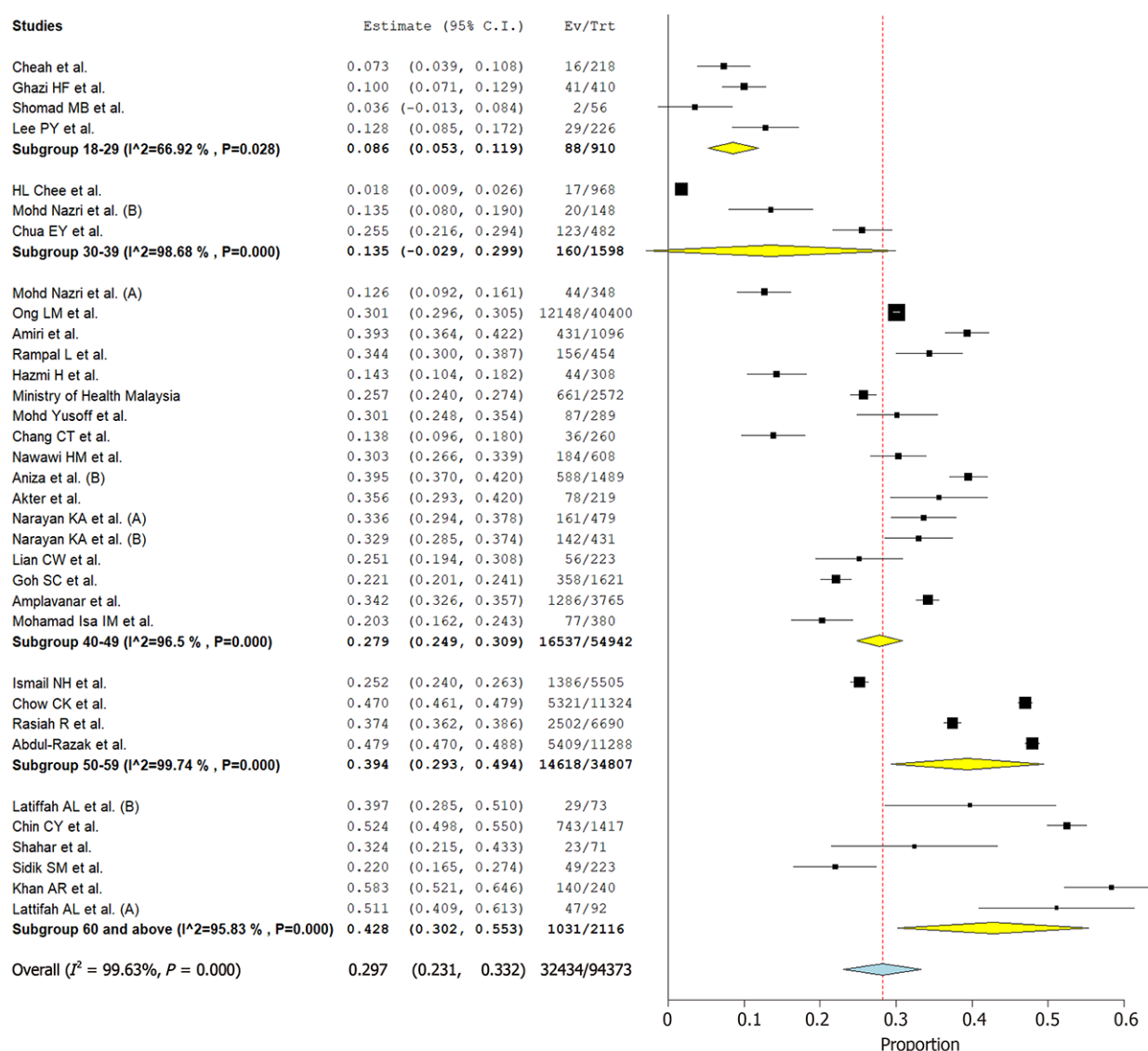


Figure 4 Pooled prevalence of hypertension subanalysis by age groups.

minority groups in a rural part of Sabah^[32]. Hence, it is not surprising that the prevalence was so low. The possible explanations include the fact that the study was not only limited to a rural population, but it was also the era before urbanization whereby unhealthy lifestyles were not practiced commonly reflected strongly by a low prevalence of diabetes of less than 5% in the years 1980-1985 in South East Asia^[78]. Otherwise, we noticed a spike in hypertension prevalence from the 1980s to the 1990s (36.8%). Then, it decreased to 28.7% in the 2000s and further decreased to 26.8% in the 2000s. A possible reason for the increased prevalence in the 1990s could be due to the fact that among the 30 studies that specified their study period, only two studies were conducted in the 1990s. One study, which reported hypertension prevalence of 21.1%, involved three rural communities in Bagan Datoh involving a wide variation of citizens from different age groups^[56], whereas the other study involved three semi-rural areas in Kuala Langat where the study respondents were from the older age groups (range, 55–95 years; mean age, 65.4 years)^[29]. This significantly increases the overall pooled prevalence of hypertension if we only take these two studies with their extreme ends of prevalence into account. In comparison to the trend of prevalence of hypertension in other countries, United States was one of the countries with a consistent prevalence of hypertension of around 29% according to the United States' National Health and Nutrition Examination Survey^[77].

Age and hypertension

Epidemiological studies have shown that the prevalence of hypertension increases with age, which is consistent with our review. Importantly, we also found that

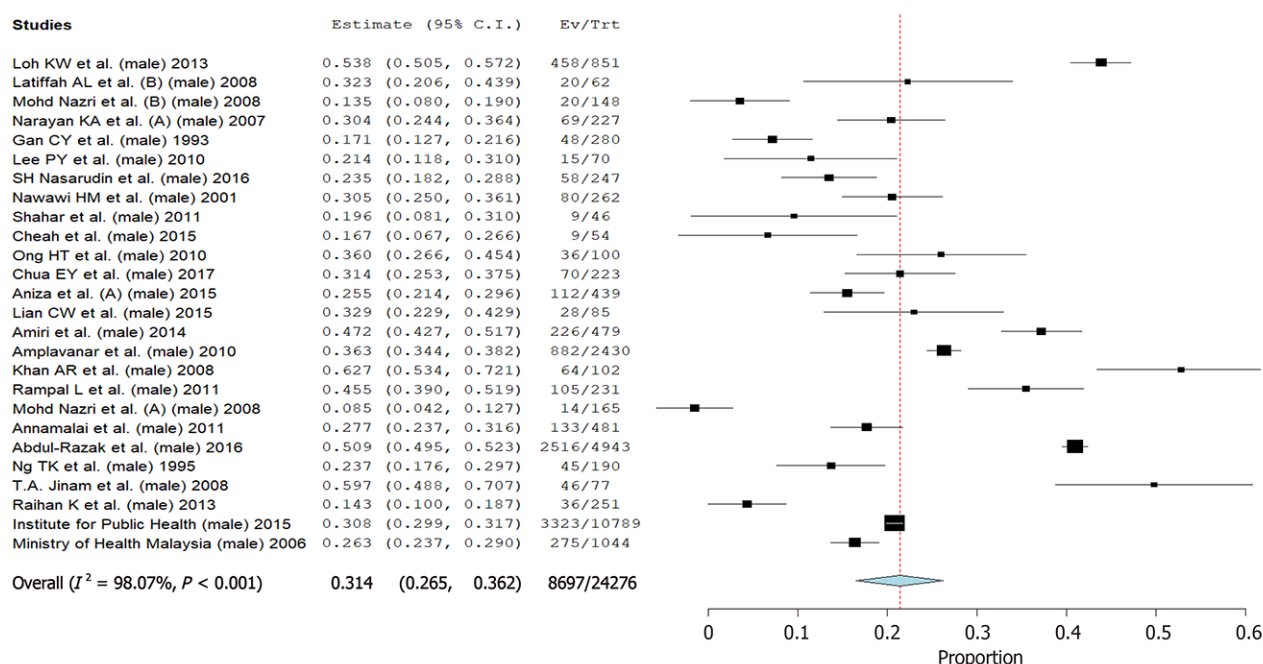
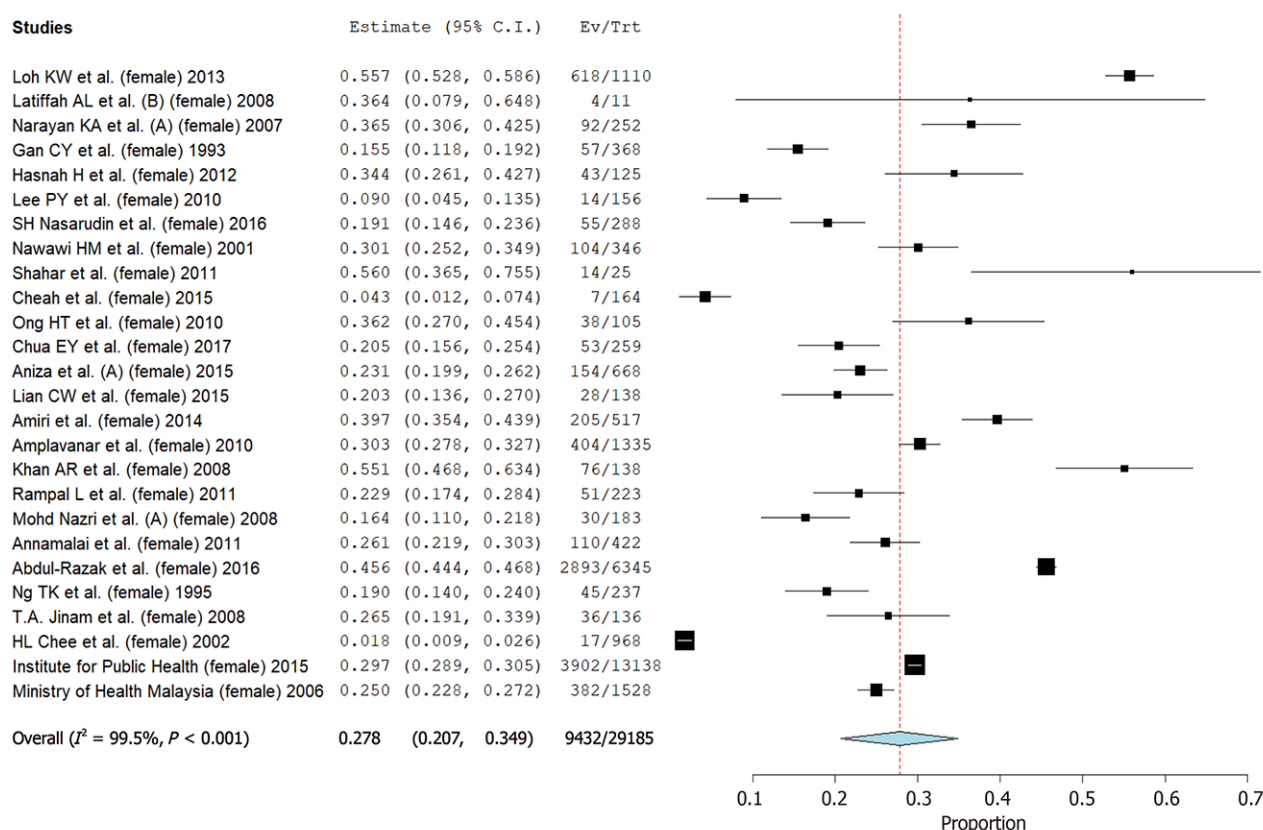
A**B**

Figure 5 Pooled prevalence of hypertension in male and female adults. A: In male adults; B: In female adults.

hypertension prevalence was doubled in those aged 40–49 years (27.9%) from those aged 30–39 years (13.5%). Comparing our results to that of a developed country, we also found a similar doubling phenomenon in hypertension prevalence, but it only happened in the older age group, which was 63.1% in those aged ≥ 60 years, rising from 33.2% from those aged 40–59 years^[77]. It is expected that aging is closely related to increased rates of hypertension because of the arterial structure alteration and ongoing calcification that leads to increased arterial stiffness^[79]. However, when focusing on the

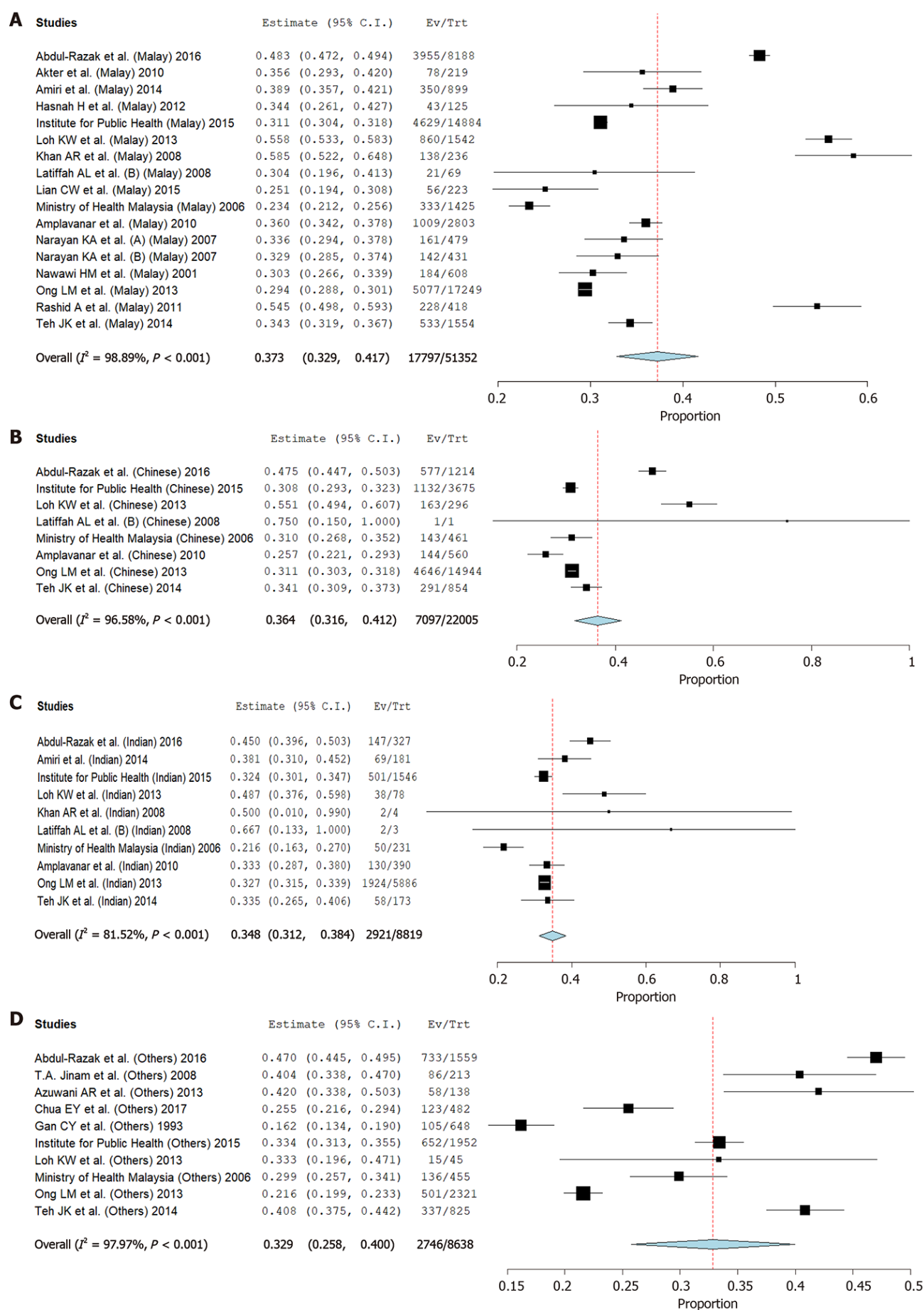


Figure 6 Pooled prevalence of hypertension in Malay, Chinese, Indian and other ethnicity. A: In Malay; B: In Chinese; C: In Indian; D: In other

ethnicity.

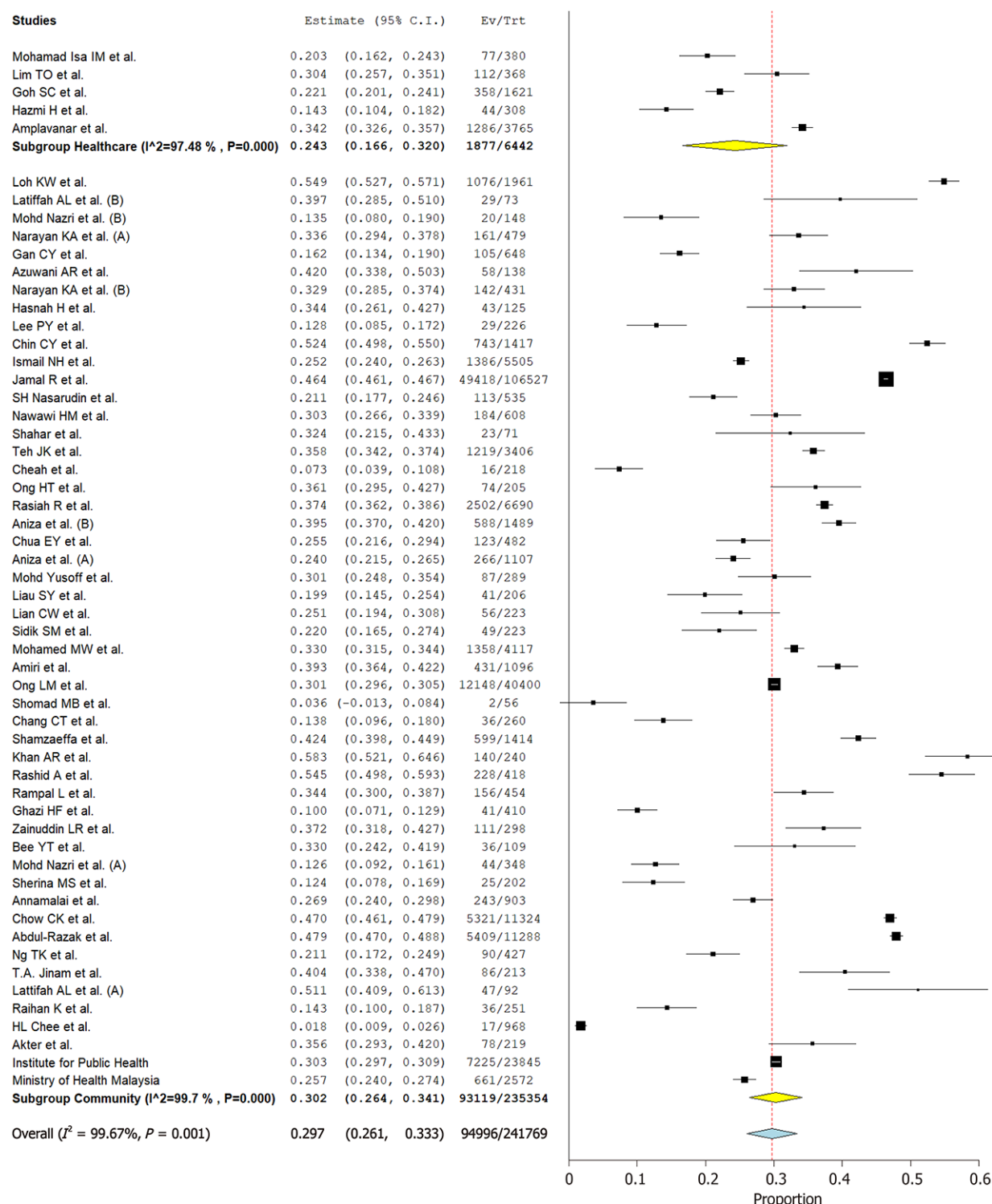


Figure 7 Prevalence of hypertension subanalysis by study setting.

older population aged ≥ 60 years, the prevalence of hypertension in this age group in Malaysia is the lowest among Asian countries such as Singapore (73.9%), Korea (68.7%), India and Bangladesh (65%), Taiwan (60.4%), Thailand (51.5%) and China (48.8%)^[80-85]. However, this could be due to the fact that studies in Malaysia have defined the elderly as people aged ≥ 60 years old compared to the other studies above, which defined the elderly as people aged ≥ 65 years^[80,81,83,85]. In Malaysia, the prevalence of hypertension was 8.6% among those aged 18–29 years and 13.5% among

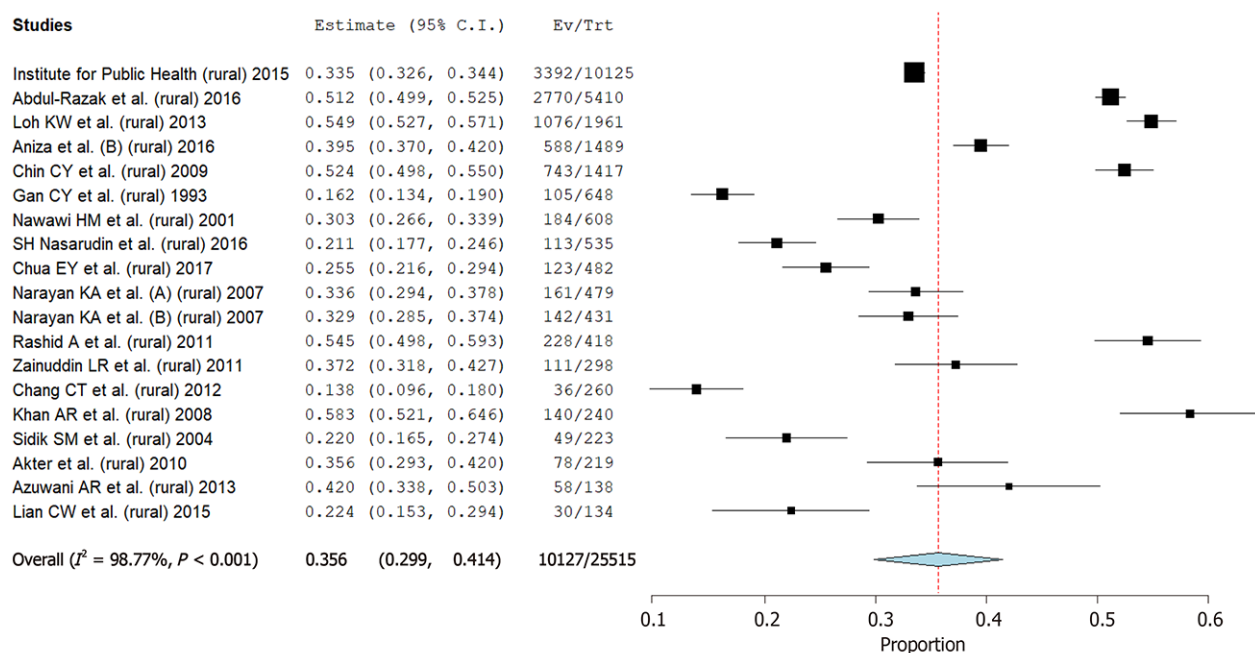
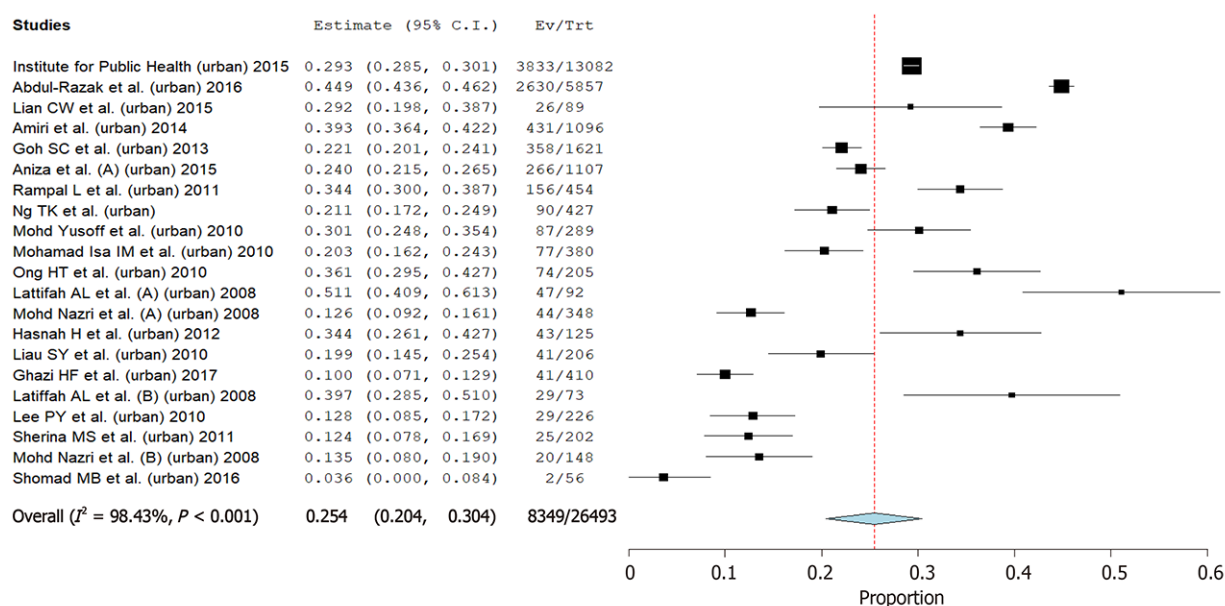
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Figure 8 Pooled prevalence of hypertension in rural and urban area. A: In rural areas; B: In urban areas.

those aged 30–39 years. The prevalence rates are fairly similar to China (18–29 year age group, 9.6%; 30–39 year age group, 13.1%)^[86] but lower compared to India (18–29 year age group, 13%; 30–39 year age group, 23%)^[87].

Gender and hypertension

We found that the prevalence of hypertension was higher in men compared to women. This finding is similar to that of the National Health and Nutrition Examination Survey in the United States^[88], which reported that regardless of race and ethnicity, men in the 20–40 year age group had higher prevalence of hypertension than women^[88]. The sex differences in hypertension are due to both biological and behavioral factors^[89]. Biologically, the female sex hormone, estrogen, serves as a protective factor against hypertension and other cardiovascular-related diseases in women^[90,91]. Unhealthy lifestyle such as smoking was more prevalent among men compared to women^[90-93]. Because smoking is a risk factor for hypertension^[94,95], it is not surprising that the prevalence of hypertension is higher in men.

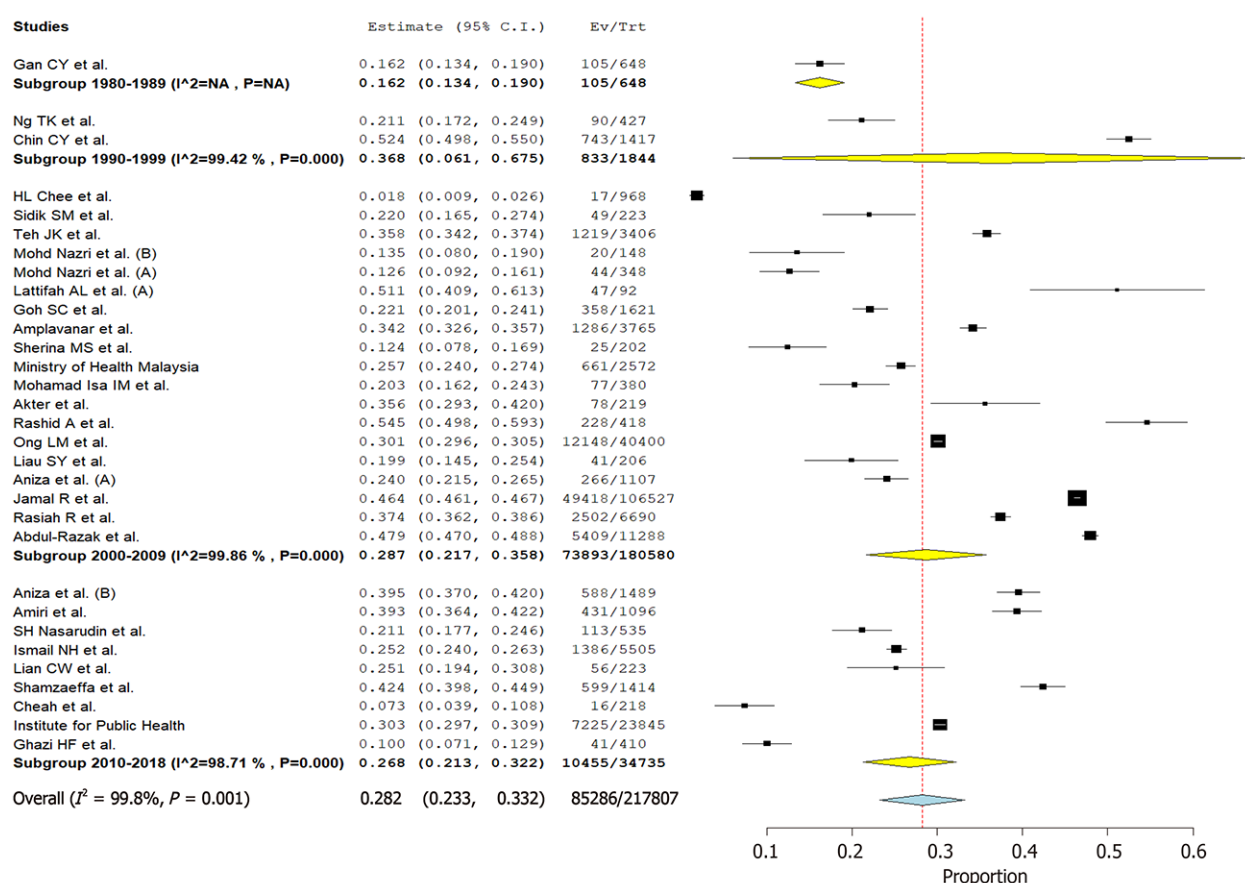


Figure 9 Overall pooled prevalence of hypertension subgroup by study decade.

Awareness

In our review, 51.4% (95%CI: 46.6, 56.3) of the included sample was aware of their hypertension status. This finding is lower than the rates reported in United States (63%)^[96], Singapore (69.7%)^[80] and Korea (91.7%)^[81]. Even though, the awareness of hypertension in Malaysia is higher than that in India (25.1%)^[83] and Indonesia (35.8%)^[73], this finding is still worrying as it indicates one out of two adults remain undetected or untreated for their hypertension. Therefore, various nationwide blood pressure screening campaign is urgently needed. Indeed May Measurement Month was a good move as it was a nationwide blood pressure screening program that was conducted in conjunction with World Hypertension Day under the tutelage of the International Society of Hypertension^[94].

Regarding the higher prevalence of awareness towards hypertension in Malaysia as compared to India^[83] and Indonesia^[73], the possible explanation could be due to the fact that one of the studies was conducted in a residential home with a higher caregiver to resident ratio and frequent supervision. This explained why the residents' awareness of hypertension was high^[58]. On the other hand, another study involved university staff with high education levels, and therefore the awareness of hypertension will certainly be high^[61]. In terms of ethnicity, only one study examined the ethnic differences of hypertension awareness^[16], while the two other studies involved only Malay ethnicity as the study population^[62] and Malay villagers in rural communities, respectively^[70]. Comparison of geographical origin yielded similar results, where only one study examined the difference in awareness^[16] while the three other studies all focused on awareness among the rural communities rather than examining the geographical difference of hypertensive awareness^[46,52,62]. It will be right to assume that there will be much bias and higher heterogeneity, and therefore pooled analyses were not done for these subgroups.

Control

Hypertension control in Malaysia was 33.3%, which is much lower than that of developed countries such as the United States (53%)^[17]. Conversely, it is higher than that of nearby countries such as China (13.8%)^[73,84], Hong Kong (25.8%)^[95] and the

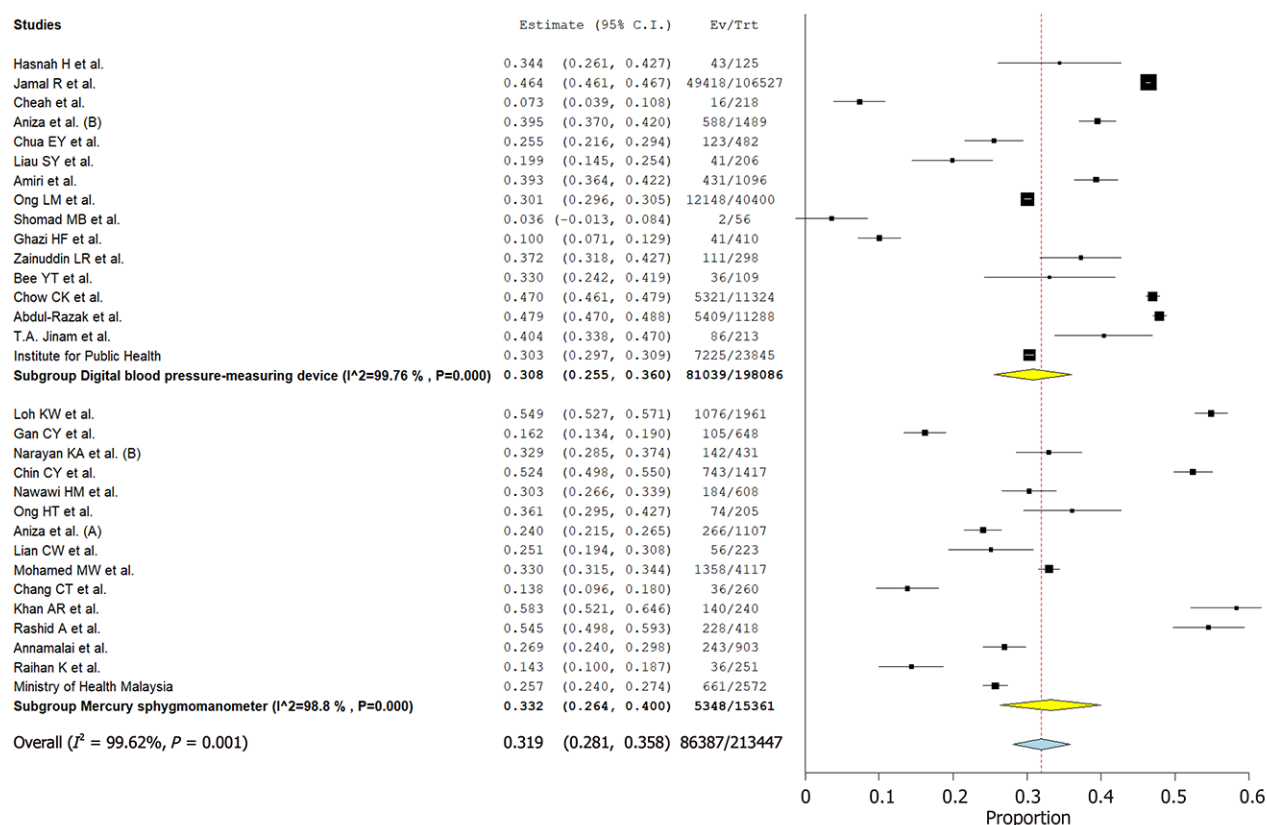


Figure 10 Pooled prevalence of hypertension subanalysis by measurement tools.

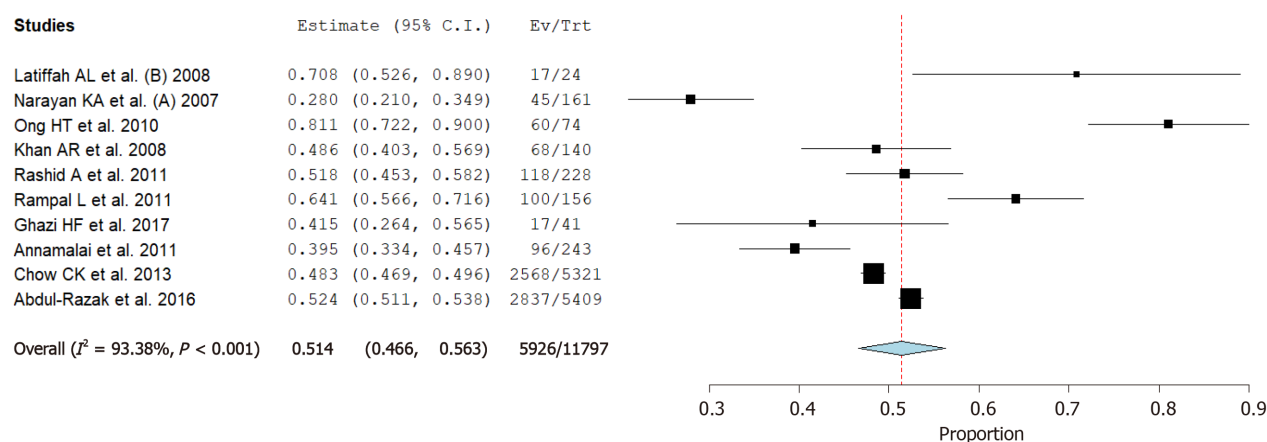


Figure 11 Pooled prevalence of awareness in hypertension.

Philippines (27.0%)^[97]. This could be due to the fact that Malaysia has been improving its quality of healthcare facilities, building more clinics and hospitals and more of the latest drugs are available in these healthcare facilities^[98]. We found that men achieved better BP control than women. This is surprising because the literature reported that women are always more likely to have better health-seeking behavior and expected to have better blood pressure control^[99]. Urban dwellers had better BP control, which correlates with a study in Southern China that reported similar results^[100]. This may be due to limited access to healthcare facilities in rural areas despite the number of rural clinics increasing throughout the past four decades in Malaysia^[98]. It seems likely that a poorer health awareness among those living in rural areas or with lower socioeconomic profiles remains an important barrier to visiting healthcare facilities and thereby receiving proper treatment.

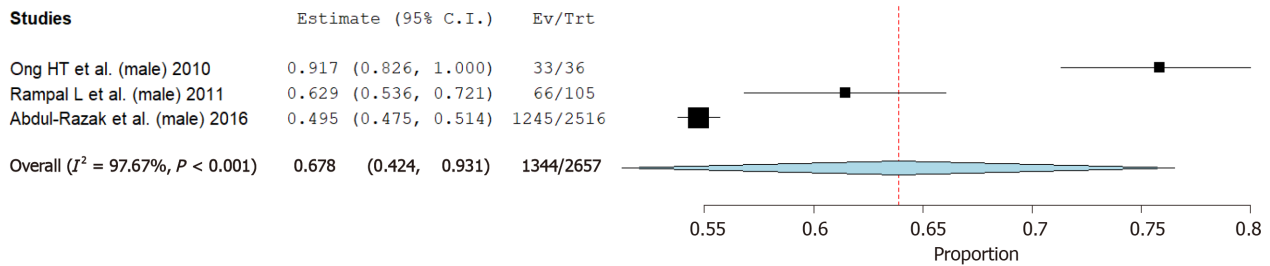
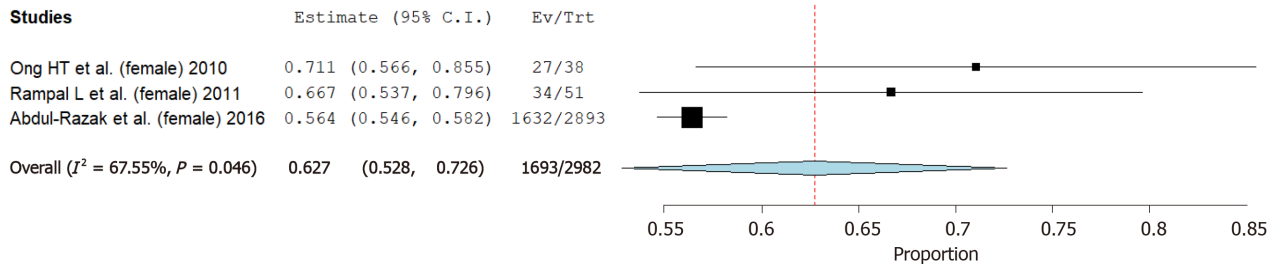
A**B**

Figure 12 Pooled prevalence of awareness in hypertension in male and female. A: In male; B: In female.

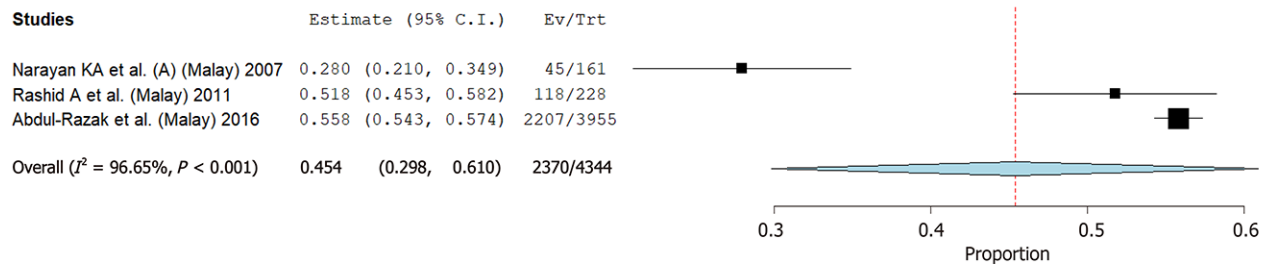
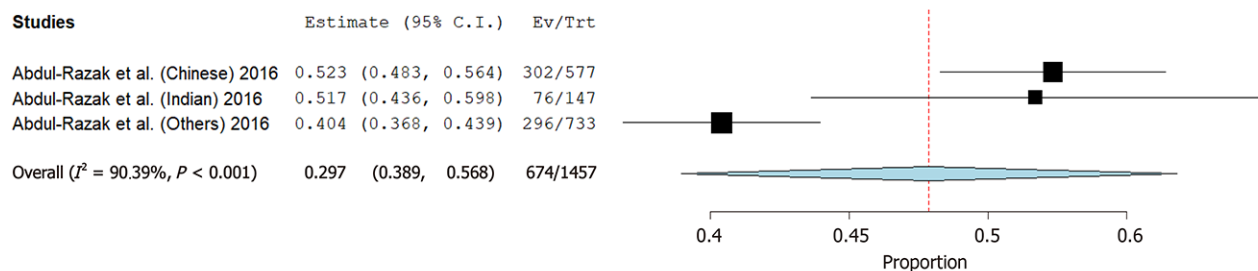
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Figure 13 Pooled prevalence of awareness in hypertension in Malay and non-Malay. A: In Malay; B: In non-Malay.

Strengths and limitations

The strength of this review was the large sample size summarizing prevalence of hypertension in Malaysia across four decades. Furthermore, this is interesting to analyze the prevalence of hypertension according to different subgroups especially when Malaysia is known to have different races with corresponding different cultures and lifestyle. The accompanying underlying problems were different from each other, and it has been addressed in this systematic review.

However, there are several limitations. First, we found that many studies did not report data of prevalence, awareness and control of hypertension in subgroups of gender, ethnicity and geographical origin, whereby these factors could further help

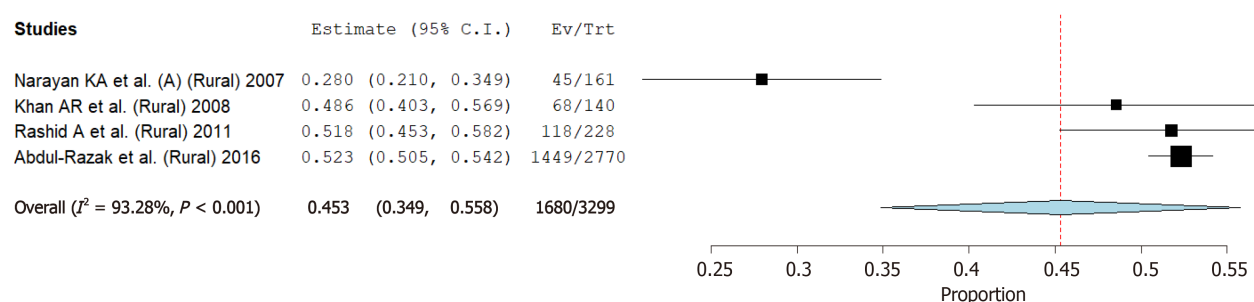


Figure 14 Pooled prevalence of awareness in hypertension in rural areas.

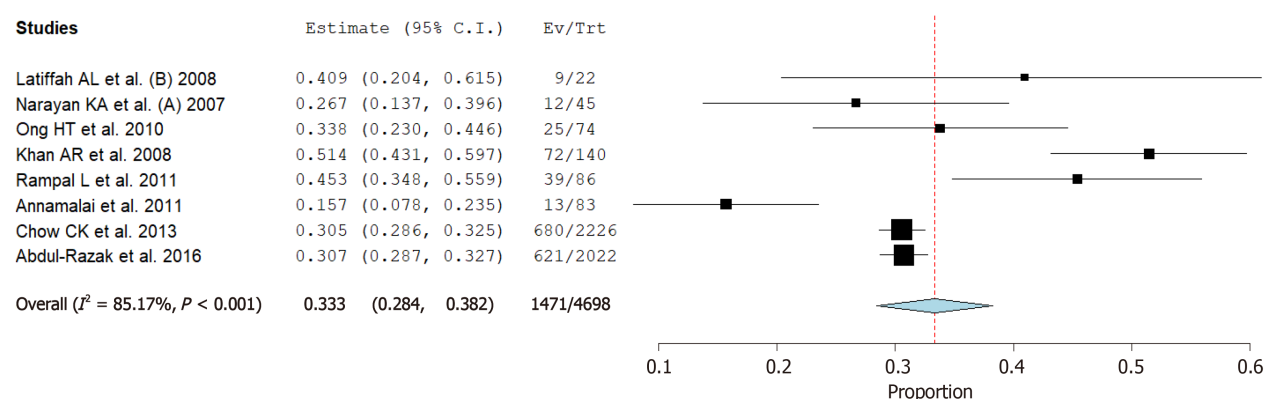
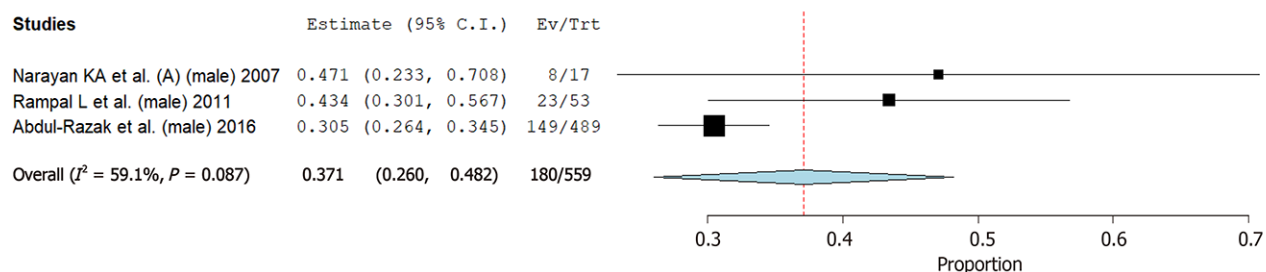


Figure 15 Pooled prevalence of control in hypertension.

A



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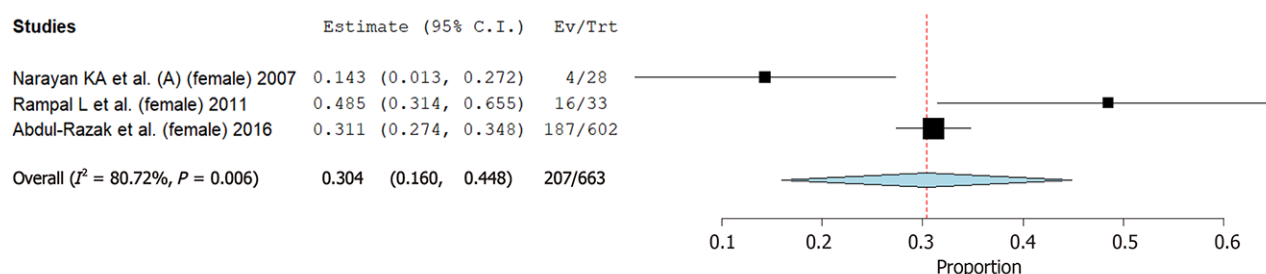


Figure 16 Pooled prevalence of control in hypertension in male and female. A: In male; B: In female.

health care policy makers to configure hypertension screening and awareness campaigns according to these subgroups in regards to hypertension prevalence, poor awareness and lack of control. Secondly, we adopted strict inclusion and exclusion criteria and therefore unpublished data or grey literature were not included in the

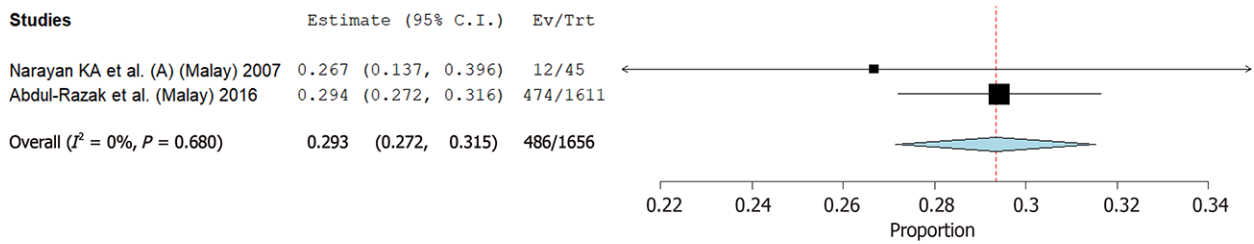
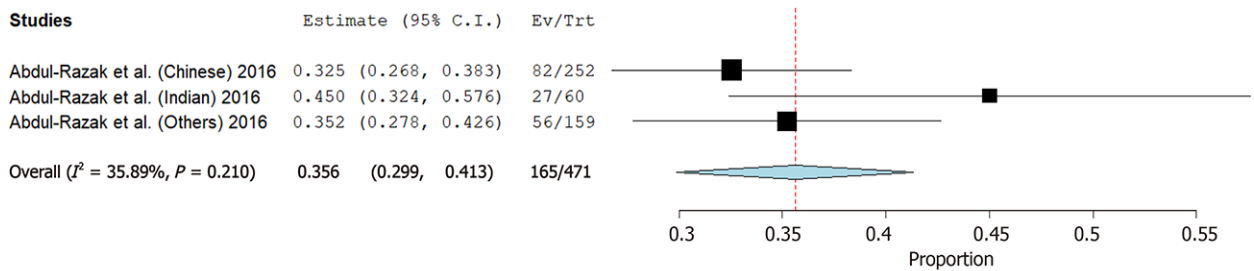
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Figure 17 Pooled prevalence of control in hypertension in Malay and non-Malay. A: In Malay; B: In non-Malay.

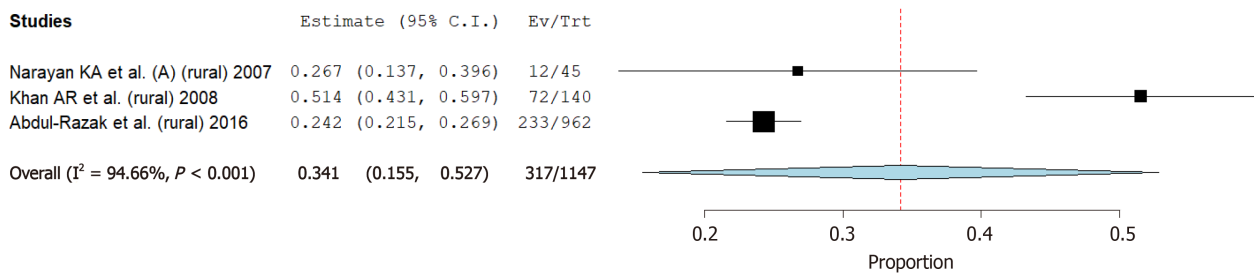


Figure 18 Pooled prevalence of control in hypertension in rural areas.

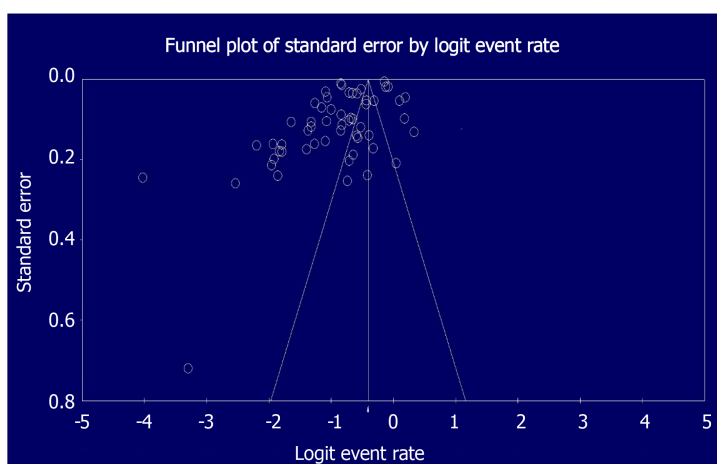


Figure 19 Publication bias assessed using funnel plot.

study. However, based on the sensitivity analysis, prevalence of hypertension after removal of these studies with poor quality, nonrandom sampling and/or extreme sample size were not changed as compared to overall pooled prevalence of hypertension. Thirdly, the estimates for the earlier time periods were based on fewer studies when compared to that for latter periods, which may have caused a paucity of

literature on the topic of interest.

Suggestion for future research

Future studies on the prevalence of hypertension can address some of the issues noted in this research. The prevalence of hypertension according to gender, ethnicity and geographical origin should be studied in more detail. Nonrandom sampling method should be avoided because it would lead to bias in the conducted study. Besides that, future studies should also emphasize on adequate or larger sample size, which is more representative of a population.

CONCLUSION

One-third of Malaysian adults are hypertensive. The prevalence of hypertension is higher in people who reside in rural areas than in those who stay in urban areas. Slightly more than half of the adults are aware of their hypertension status and one-third of these patients achieved target BP control. In view of these findings, urgent steps for improving health promotion and health education need to be undertaken on a larger scale. Although our review shows a decreasing trend of hypertension prevalence throughout the past four decades, hypertension awareness and BP control among Malaysians have yet to improve significantly.

ARTICLE HIGHLIGHTS

Research background

Hypertension is a common public health problem worldwide.

Research motivation

Future studies on the prevalence of hypertension can address some of issues noted in this research. The prevalence of hypertension according to gender, ethnicity and geographical origin should be studied in more detail.

Research objectives

This systematic review aimed to determine the trend in prevalence, awareness and control rate of hypertension in Malaysia.

Research methods

A systematic search was conducted in six databases for articles published between 1980 and 2018. Authors reviewed the studies and performed quality assessment and data extraction independently.

Research results

The overall pooled prevalence of hypertension in Malaysia was 29.7%. The overall prevalence of awareness was 51.4%, and 33.3% of those on treatment had achieved control of their blood pressure.

Research conclusions

In Malaysia, three in ten adults aged ≥ 18 years have hypertension, while four in ten adults aged ≥ 30 years have hypertension. Five out of ten people are aware of their hypertension status and only one-third of those under treatment achieved control of their hypertension.

Research perspectives

Concerted efforts by policymakers and healthcare professionals to improve awareness and control of hypertension should be of high priority.

REFERENCES

- 1 Sengul S, Akpolat T, Erdem Y, Derici U, Arici M, Sindel S, Karatan O, Turgan C, Hasanoglu E, Caglar S, Erturk S; Turkish Society of Hypertension and Renal Diseases. Changes in hypertension prevalence, awareness, treatment, and control rates in Turkey from 2003 to 2012. *J Hypertens* 2016; **34**: 1208-1217

- [PMID: 26991534 DOI: 10.1097/HJH.0000000000000901]
- 2 **Bundy JD**, He J. Hypertension and Related Cardiovascular Disease Burden in China. *Ann Glob Health* 2016; **82**: 227-233 [PMID: 27372527 DOI: 10.1016/j.aogh.2016.02.002]
 - 3 **Ogah OS**, Okpechi I, Chukwuonye II, Akinyemi JO, Onwubere BJ, Falase AO, Stewart S, Sliwa K. Blood pressure, prevalence of hypertension and hypertension related complications in Nigerian Africans: A review. *World J Cardiol* 2012; **4**: 327-340 [PMID: 23272273 DOI: 10.4330/wjc.v4.i12.327]
 - 4 **Ministry of Health Malaysia**. National Health and Morbidity Survey 2. 1996
 - 5 **Ministry of Health Malaysia**. National Health and Morbidity Survey 3. 2006
 - 6 **Ministry of Health Malaysia**. National Health and Morbidity Survey 4 (2011-2014). 2014
 - 7 **Ministry of Health Malaysia**. National Health and Morbidity Survey 5 (2015-2018). 2018
 - 8 **Rizwan SA**, Kumar R, Singh AK, Kusuma YS, Yadav K, Pandav CS. Prevalence of hypertension in Indian tribes: a systematic review and meta-analysis of observational studies. *PLoS One* 2014; **9**: e95896 [PMID: 24797244 DOI: 10.1371/journal.pone.0095896]
 - 9 **Ministry of Health Malaysia**. Summary of NHMS Report on Disease Prevalence: National Prevalence of Noncommunicable Diseases/Risk Factors From NHMS 1996 to 2015. 2017
 - 10 **Moher D**, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**: 1 [PMID: 25554246 DOI: 10.1186/2046-4053-4-1]
 - 11 **Gifford RW Jr**. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: insights and highlights from the chairman. *Cleve Clin J Med* 1993; **60**: 273-277 [PMID: 8339452 DOI: 10.3949/ccjm.60.4.273]
 - 12 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]
 - 13 **Wallace BC**, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw* 2012; **49**: 1-15 [DOI: 10.18637/jss.v049.i05]
 - 14 **Ghosh D**, Vogt A. Outliers: An evaluation of methodologies. *Joint statistical meetings*. San Diego: American Statistical Association 2012; 3455-3460
 - 15 **Sagie A**, Koslowsky M. Detecting moderators with meta-analysis: An evaluation and comparison of techniques. *Pers Psychol* 1993; **46**: 629-640 [DOI: 10.1111/j.1744-6570.1993.tb00888.x]
 - 16 **Abdul-Razak S**, Daher AM, Ramli AS, Ariffin F, Mazapuspavina MY, Ambigga KS, Miskan M, Abdul-Hamid H, Mat-Nasir N, Nor-Ashikin MN, Ng KK, Nawawi H, Yusoff K; REDISCOVER Investigators. Prevalence, awareness, treatment, control and socio demographic determinants of hypertension in Malaysian adults. *BMC Public Health* 2016; **16**: 351 [PMID: 27097542 DOI: 10.1186/s12889-016-3008-y]
 - 17 **Jinam TA**, Phipps ME, Indran M, Kuppusamy UR, Mahmood AA, Hong LC, Edo J. An update of the general health status in the indigenous populations of Malaysia. *Ethn Health* 2008; **13**: 277-287 [PMID: 18568977 DOI: 10.1080/13557850801930478]
 - 18 **Akter SFU**, Fauzi ARM, Nordin MS, Satwi S, Mohamed A, Aznan MA, Samsul D. Prevalence of cardiovascular risk factors in a selected community at Kuantan, Pahang, Malaysia. *Int J Med Med Sci* 2010; **2**: 322-328
 - 19 **Amiri M**, Majid HA, Hairi F, Thangiah N, Bulgiba A, Su TT. Prevalence and determinants of cardiovascular disease risk factors among the residents of urban community housing projects in Malaysia. *BMC Public Health* 2014; **14** Suppl 3: S3 [PMID: 25436515 DOI: 10.1186/1471-2458-14-S3-S3]
 - 20 **Amplavanar NT**, Gurpreet K, Salmiah MS, Odhayakumar N. Prevalence of cardiovascular disease risk factors among attendees of the Batu 9, Cheras Health Centre, Selangor, Malaysia. *Med J Malaysia* 2010; **65**: 173-179 [PMID: 21939163]
 - 21 **Aniza I**, Hayati K, Juhaida M, Taufik JA, Badilla II, Khalib L. Obesity related hypertension-gender specific analysis among adults in Tanjung Karang, Selangor, Malaysia. *Msiian J Public Health Med* 2015; **15**: 41-52
 - 22 **Aniza I**, Nurmawati A, Hanizah Y, Ahmad Taufik J. Modifiable risk factors of cardiovascular disease among adults in rural community of Malaysia: a cross sectional study. *Msiian J Public Health Med* 2016; **16**: 53-61
 - 23 **Annamalai C**, Govindaraja C, Chandramouli C. Prevalence, awareness and control of hypertension in estate workers in Malaysia. *N Am J Med Sci* 2011; **3**: 540-543 [PMID: 22363074 DOI: 10.4297/najms.2011.3540]
 - 24 **Azuwani A**, Noor Khairiah K, Cheong YZ, Kok, CC, Aw NSL, Nadiyah MS, Abdul Rashid K. Body Fat Percentage Distribution of an Orang Asli Group (Aborigines) in Cameron Highlands, Malaysia. *Mal J Nutr* 2013; **19**: 205-214
 - 25 **Tan BY**, Kantilal HK, Singh R. Prevalence of metabolic syndrome among Malaysians using the international diabetes federation, national cholesterol education program and modified World Health Organization definitions. *Mal J Nutr* 2008; **14**: 65-77
 - 26 **Chang CT**, Lee PY, Cheah WL. The prevalence of cardiovascular risk factors in the young and middle-aged rural population in Sarawak, Malaysia. *Malays J Med Sci* 2012; **19**: 27-34 [PMID: 22973135]
 - 27 **Cheah WL**, Hazmi H, Chia HQ, Tindin E, Ahmad Zafri NA, Mohd Shah SH. Hypertension and its association with anthropometric indexes among pre-university students. *Int J Adolesc Med Health* 2016; **28**: 373-379 [PMID: 26215534 DOI: 10.1515/ijamh-2015-0020]
 - 28 **Chee HL**, Rampal KG. Relationship between selected health problems and exposures among women semiconductor workers in Malaysia. *Med J Malaysia* 2003; **58**: 387-398 [PMID: 14750379]
 - 29 **Chin CY**, Pengal S. Cardiovascular disease risk in a semirural community in Malaysia. *Asia Pac J Public Health* 2009; **21**: 410-420 [PMID: 19661103 DOI: 10.1177/1010539509343973]
 - 30 **Chow CK**, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G, Diaz R, Kazmi K, Lanas F, Wei L, Lopez-Jaramillo P, Fanghong L, Ismail NH, Puoane T, Rosengren A, Szuba A, Temizhan A, Wielgosz A, Yusuf R, Yusufali A, McKee M, Liu L, Mony P, Yusuf S; PURE (Prospective Urban Rural Epidemiology) Study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013;

- 310: 959-968 [PMID: 24002282 DOI: 10.1001/jama.2013.184182]
- 31 **Chua EY**, Zalilah MS, Haemamalar K, Norhasmah S, Geeta A. Obesity indices predict hypertension among indigenous adults in Krau Wildlife Reserve, Peninsular Malaysia. *J Health Popul Nutr* 2017; **36**: 24 [PMID: 28545536 DOI: 10.1186/s41043-017-0102-4]
- 32 **Gan CY**, Chan MK. A blood pressure profile of rural Kadazans and Bajaus in Sabah, east Malaysia. *Southeast Asian J Trop Med Public Health* 1993; **24**: 583-589 [PMID: 8160073]
- 33 **Ghazi HF**, Elnajeh M, AbdalQader M, Baobaid MF, Omar AB. Prevalence of Hypertension and its Association with Nutritional Factors Among University Students in Shah Alam, Malaysia. *Pakistan J Nutr* 2017; **16**: 544-549 [DOI: 10.3923/pjn.2017.544.549]
- 34 **Goh SC**, Ho EL, Goh KL. Prevalence and risk factors of non-alcoholic fatty liver disease in a multiracial suburban Asian population in Malaysia. *Hepatol Int* 2013; **7**: 548-554 [PMID: 26201786 DOI: 10.1007/s12072-012-9359-2]
- 35 **Hasnah H**, Amin I, Suzana S. Bone health status and lipid profile among post-menopausal malay women in Cheras, Kuala Lumpur. *Malays J Nutr* 2012; **18**: 161-171 [PMID: 24575664]
- 36 **Hazmi H**, Ishak WR, Jalil RA, Hua GS, Hamid NF, Haron R, Shafei MN, Ibrahim MI, Bebakar WM, Ismail SB, Musa KI. Traditional cardiovascular risk-factors among healthcare workers in Kelantan, Malaysia. *Southeast Asian J Trop Med Public Health* 2015; **46**: 504-511 [PMID: 26521525]
- 37 **Ministry of Health Malaysia**. National Health and Morbidity Survey 2015 (NHMS 2015). Vol. II: Non-Communicable Diseases, Risk Factors Other Health Problems. Available from: https://www.researchgate.net/publication/305213149_National_Health_and_Morbidity_Survey_2015-VOLUME_II_Non-Communicable_Diseases_Risk_Factors_Other_Health_Problems
- 38 **Jamal R**, Syed Zakaria SZ, Kamaruddin MA, Abd Jalal N, Ismail N, Mohd Kamil N, Abdullah N, Baharudin N, Hussin NH, Othman H, Mahadi NM; Malaysian Cohort Study Group. Cohort Profile: The Malaysian Cohort (TMC) project: a prospective study of non-communicable diseases in a multi-ethnic population. *Int J Epidemiol* 2015; **44**: 423-431 [PMID: 24729425 DOI: 10.1093/ije/dyu089]
- 39 **Khan AR**, Narayan K, Ab Manan AH. The prevalence of hypertension among the elderly in fourteen villages in Kedah, Malaysia. *Msian J Med Health Sci* 2008; **4**: 33-39
- 40 **Latiffah A**, Hanachi P. To investigate the relation of hypertension and anthropometric measurement among elderly in Malaysia. *J Appl Psychol* 2008; **8**: 3963-3968 [DOI: 10.3923/jas.2008.3963.3968]
- 41 **Latiffah AL**, Hanachi P, Khandia S. The Association of Hypertension with Major Risks Factors among University Putra Malaysia Retirees. *J Med Sci* 2008; **8**: 254-261 [DOI: 10.3923/jms.2008.254.261]
- 42 **Lee P**, Ong T, Muna S, Syed Alwi S, Kamarudin K. Brief report do university students have high cardiovascular risk? A pilot study from universiti malaysia sarawak (unimas). *Malays Fam Physician* 2010; **5**: 41-43 [PMID: 25606185]
- 43 **Lian CW**, Hazmi H, Thon CC, Muda W. Physical Activity and Cardiovascular Risk Factors Among Malays In Selected Rural and Urban Communities In Sarawak. *Msian J Public Health Med* 2015; **15**: 104-111
- 44 **Liao S**, Mohamed Izham M, Hassali M, Shafie A, Nik Mohamed M, Hamdi M. Outcomes of cardiovascular risk factors screening programme among employees of a Malaysian public university. *J Clin Diagn Res* 2010; **4**: 2208-2216
- 45 **Lim TO**, Ngah BA. The Mentakab Hypertension Study Project. Part III--Detection of hypertension in the outpatient department. *Singapore Med J* 1991; **32**: 338-341 [PMID: 1788580]
- 46 **Loh KW**, Rani F, Chan TC, Loh HY, Ng CW, Moy FM. The association between risk factors and hypertension in perak, malaysia. *Med J Malaysia* 2013; **68**: 291-296 [PMID: 24145254]
- 47 **Ministry of Health Malaysia**. Malaysia STEPS Noncommunicable Disease Risk Factors Survey 2005-2006. Available from: <http://ghdx.healthdata.org/record/malaysia-steps-noncommunicable-disease-risk-factors-survey-2005-2006>
- 48 **Mohamed M**, Winn T, Rampal GL, Abdul Rashid A, Mustaffa B. A Preliminary Result of the Cardiovascular Risk factors Intervention Study (Pikom Study): Diabetes Mellitus, Hypertension and their Associated Factors. *Malays J Med Sci* 2005; **12**: 20-25 [PMID: 22605943]
- 49 **Nazri SM**, Imran MK, Ismail IM, Faris AA. Prevalence of overweight and self-reported chronic diseases among residents in Pulau Kundur, Kelantan, Malaysia. *Southeast Asian J Trop Med Public Health* 2008; **39**: 162-167 [PMID: 18567457]
- 50 **Nazri SM**, Tengku MA, Winn T. The association of shift work and hypertension among male factory workers in Kota Bharu, Kelantan, Malaysia. *Southeast Asian J Trop Med Public Health* 2008; **39**: 176-183 [PMID: 18567459]
- 51 **Moy FM**, Hoe VC, Tan CPL, Rosmawati M. Cardiovascular risks among shift and non-shift workers in a public medical centre in Kuala Lumpur. *J Univ Malaya Medical Cent* 2010; **13**: 45-49
- 52 **Narayan KA**, Khan AR. Blood pressure patterns and prevalence of hypertension and its associated factors in a rural community in northern Malaysia. *Msian J Public Health Med* 2007; **7**: 14-19
- 53 **Narayan K**, Khan AR. Body mass index and nutritional status of adults in two rural villages in Northern Malaysia. *Malays J Nutr* 2007; **13**: 9-17
- 54 **Nasarudin SH**, Ahmad N. Correlation between prehypertension and obesity indices among young adults. *Msian J Public Health Med* 2016; **16**: 235-240
- 55 **Nawawi HM**, Nor IM, Noor IM, Karim NA, Arshad F, Khan R, Yusoff K. Current status of coronary risk factors among rural Malays in Malaysia. *J Cardiovasc Risk* 2002; **9**: 17-23 [PMID: 11984213 DOI: 10.1177/174182670200900103]
- 56 **Ng TK Jr**, Tee ES, Rosman A. Rural communities in nutritional transition: emergence of obesity, hypertension and hypercholesterolemia as public health problems in three kampungs in Bagan Datoh, Perak. *Malays J Nutr* 1995; **1**: 129-139 [PMID: 22692058]
- 57 **Noor Hassim I**, Norazman MR, Diana M, Khairul Hazdi Y, Rosnah I. Cardiovascular risk assessment between urban and rural population in Malaysia. *Med J Malaysia* 2016; **71**: 331-337 [PMID: 28087957]
- 58 **Ong HT**, Oung LS, Ong LM, Tan KP. Hypertension in a residential home for the elderly in Penang, Malaysia. *Med J Malaysia* 2010; **65**: 18-20 [PMID: 21265241]

- 59 **Ong LM**, Punithavathi N, Thurairatnam D, Zainal H, Beh ML, Morad Z, Lee SY, Bavanandan S, Kok LS. Prevalence and risk factors for proteinuria: the National Kidney Foundation of Malaysia Lifecheck Health Screening programme. *Nephrology (Carlton)* 2013; **18**: 569-575 [PMID: [23782264](#) DOI: [10.1111/nep.12112](#)]
- 60 **Raihan K**, Azmawati M. Cigarette smoking and cardiovascular risk factor among male youth population. *Msiian J Public Health Med* 2013; **13**: 28-36
- 61 **Rampal L**, Rampal S, Azhar MZ, Rahman AR. Prevalence, awareness, treatment and control of hypertension in Malaysia: a national study of 16,440 subjects. *Public Health* 2008; **122**: 11-18 [PMID: [17981310](#) DOI: [10.1016/j.puhe.2007.05.008](#)]
- 62 **Rashid A**, Azizah A. Prevalence of hypertension among the elderly Malays living in rural Malaysia. *Australas Med J* 2011; **4**: 283-290 [PMID: [23386889](#) DOI: [10.4066/AMJ.2011.660](#)]
- 63 **Rasiah R**, Thangiah G, Yusoff K, Manikam R, Chandrasekaran SK, Mustafa R, Bakar NB. The impact of physical activity on cumulative cardiovascular disease risk factors among Malaysian adults. *BMC Public Health* 2015; **15**: 1242 [PMID: [26673166](#) DOI: [10.1186/s12889-015-2577-5](#)]
- 64 **Shahar S**, Hassan J, Sundar VV, Kong AY, Ping Chin S, Ahmad SA, Kuan Lee L. Determinants of depression and insomnia among institutionalized elderly people in Malaysia. *Asian J Psychiatr* 2011; **4**: 188-195 [PMID: [23051116](#) DOI: [10.1016/j.ajp.2011.06.001](#)]
- 65 **Samsudin S**, Abdullah N, Applanaidu SD. The prevalence of diabetes mellitus and hypertension and its effects on healthcare demand among elderly in Malaysia. *Int J Public Health Res* 2016; **6**: 741-749
- 66 **Sherina M**, Rampal L, Hejar A, Rozali A, Yunus AM. Prevalence of Urban Poor and Its Health Related Factors in the State of Selangor, Malaysia. *Malays J Med Health Sci* 2011; **7**: 17-26
- 67 **Shomad MBA**, Rahman NAA, Rahman NIA, Haque M. The prevalence of cardiovascular disease risk factors among students of international Islamic University Malaysia, Kuantan Campus. *J Appl Pharm* 2016; **6**: 051-057 [DOI: [10.7324/JAPS.2016.60309](#)]
- 68 **Sidik SM**, Rampal L, Afifi M. Physical and mental health problems of the elderly in a rural community of sepang, selangor. *Malays J Med Sci* 2004; **11**: 52-59 [PMID: [22977360](#)]
- 69 **Teh JK**, Tey NP, Ng ST. Ethnic and gender differentials in non-communicable diseases and self-rated health in Malaysia. *PLoS One* 2014; **9**: e91328 [PMID: [24603609](#) DOI: [10.1371/journal.pone.0091328](#)]
- 70 **Yusoff MF**, Baki MM, Mohamed N, Mohamed AS, Yunus MR, Ami M, Othman I, Ishak AI. Obstructive sleep apnea among express bus drivers in Malaysia: important indicators for screening. *Traffic Inj Prev* 2010; **11**: 594-599 [PMID: [21128189](#) DOI: [10.1080/15389588.2010.505255](#)]
- 71 **Zainuddin LR**, Isa N, Muda WM, Mohamed HJ. The prevalence of metabolic syndrome according to various definitions and hypertriglyceridemic-waist in malaysian adults. *Int J Prev Med* 2011; **2**: 229-237 [PMID: [22174962](#)]
- 72 **Kearney PM**, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**: 217-223 [PMID: [15652604](#) DOI: [10.1016/S0140-6736\(05\)17741-1](#)]
- 73 **Chia YC**, Buranakitjaroen P, Chen CH, Divinagracia R, Hoshide S, Park S, Shin J, Siddique S, Sison J, Soenarta AA, Sogunuru GP, Tay JC, Turana Y, Wang JG, Wong L, Zhang Y, Kario K; HOPE Asia Network. Current status of home blood pressure monitoring in Asia: Statement from the HOPE Asia Network. *J Clin Hypertens (Greenwich)* 2017; **19**: 1192-1201 [PMID: [28815840](#) DOI: [10.1111/jch.13058](#)]
- 74 **Ministry of Health Singapore**. National Health Survey. 2010
- 75 **Wang HH**, Wang JJ, Wong SY, Wong MC, Li FJ, Wang PX, Zhou ZH, Zhu CY, Griffiths SM, Mercer SW. Epidemiology of multimorbidity in China and implications for the healthcare system: cross-sectional survey among 162,464 community household residents in southern China. *BMC Med* 2014; **12**: 188 [PMID: [25338506](#) DOI: [10.1186/s12916-014-0188-0](#)]
- 76 **Pereira M**, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens* 2009; **27**: 963-975 [PMID: [19402221](#) DOI: [10.1097/hjh.0b013e3283282f65](#)]
- 77 **Fryar CD**, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. *NCHS Data Brief* 2017; **1-8** [PMID: [29155682](#)]
- 78 **NCD Risk Factor Collaboration (NCD-RisC)**. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; **387**: 1513-1530 [PMID: [27061677](#) DOI: [10.1016/S0140-6736\(16\)00618-8](#)]
- 79 **McInnes GT**. Integrated approaches to management of hypertension: promoting treatment acceptance. *Am Heart J* 1999; **138**: 252-255 [PMID: [10467221](#) DOI: [10.1016/s0002-8703\(99\)70318-2](#)]
- 80 **Pinto E**. Blood pressure and ageing. *Postgrad Med J* 2007; **83**: 109-114 [PMID: [17308214](#) DOI: [10.1136/pgmj.2006.048371](#)]
- 81 **Malhotra R**, Chan A, Malhotra C, Østbye T. Prevalence, awareness, treatment and control of hypertension in the elderly population of Singapore. *Hypertens Res* 2010; **33**: 1223-1231 [PMID: [20882026](#) DOI: [10.1038/hr.2010.177](#)]
- 82 **Kim KI**, Chang HJ, Cho YS, Youn TJ, Chung WY, Chae IH, Choi DJ, Kim CH. Current status and characteristics of hypertension control in community resident elderly Korean people: data from a Korean longitudinal study on health and aging (KLoSHA study). *Hypertens Res* 2008; **31**: 97-105 [PMID: [18360024](#) DOI: [10.1291/hypres.31.97](#)]
- 83 **Hypertension Study Group**. Prevalence, awareness, treatment and control of hypertension among the elderly in Bangladesh and India: a multicentre study. *Bull World Health Organ* 2001; **79**: 490-500 [PMID: [11436469](#)]
- 84 **Lu FH**, Tang SJ, Wu JS, Yang YC, Chang CJ. Hypertension in elderly persons: its prevalence and associated cardiovascular risk factors in Tainan City, southern Taiwan. *J Gerontol A Biol Sci Med Sci* 2000; **55**: M463-M468 [PMID: [10952370](#) DOI: [10.1093/gerona/55.8.m463](#)]
- 85 **Chen WW**, Gao RL, Liu LS, Zhu ML, Wang W, Wang YJ, Wu ZS, Li HJ, Gu DF, Yang YJ, Zheng Z, Jiang LX, Hu SS. China cardiovascular diseases report 2015: a summary. *J Geriatr Cardiol* 2017; **14**: 1-10 [PMID: [28270835](#) DOI: [10.11909/j.issn.1671-5411.2017.01.012](#)]
- 86 **Gu D**, Reynolds K, Wu X, Chen J, Duan X, Muntner P, Huang G, Reynolds RF, Su S, Whelton PK, He J;

- InterASIA Collaborative Group. The International Collaborative Study of Cardiovascular Disease in ASIA. Prevalence, awareness, treatment, and control of hypertension in china. *Hypertension* 2002; **40**: 920-927 [PMID: [12468580](#) DOI: [10.1161/01.hyp.0000040263.94619.d5](#)]
- 87 **Liu X**, Xiang Z, Shi X, Schenck H, Yi X, Ni R, Liu C. The Risk Factors of High Blood Pressure among Young Adults in the Tujia-Nationality Settlement of China. *Biomed Res Int* 2017; **2017**: 8315603 [PMID: [28932747](#) DOI: [10.1155/2017/8315603](#)]
- 88 **Zafar K**, Ram V, Kumar M, Gupta M, Kumar S, Verma V. The prevalence of hypertension among young adults in a rural population of North India. *Int J Res Med Sci* 2017; **5**: 4869-4872 [DOI: [10.18203/2320-6012.ijrms20174935](#)]
- 89 **Cutler JA**, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. *Hypertension* 2008; **52**: 818-827 [PMID: [18852389](#) DOI: [10.1161/HYPERTENSIONAHA.108.113357](#)]
- 90 **Everett B**, Zajakova A. Gender differences in hypertension and hypertension awareness among young adults. *Biodemography Soc Biol* 2015; **61**: 1-17 [PMID: [25879259](#) DOI: [10.1080/19485565.2014.929488](#)]
- 91 **Vitale C**, Mendelsohn ME, Rosano GM. Gender differences in the cardiovascular effect of sex hormones. *Nat Rev Cardiol* 2009; **6**: 532-542 [PMID: [19564884](#) DOI: [10.1038/nrcardio.2009.105](#)]
- 92 **Reckelhoff JF**. Gender differences in the regulation of blood pressure. *Hypertension* 2001; **37**: 1199-1208 [PMID: [11358929](#) DOI: [10.1161/01.hyp.37.5.1199](#)]
- 93 **Naing C**, Yeoh PN, Wai VN, Win NN, Kuan LP, Aung K. Hypertension in Malaysia: An Analysis of Trends From the National Surveys 1996 to 2011. *Medicine (Baltimore)* 2016; **95**: e2417 [PMID: [26765422](#) DOI: [10.1097/MD.0000000000002417](#)]
- 94 **Chia YC**, Ching SM, Chew BN, Devaraj NK, Siti Suhaila MY, Tay CL, Kang PS, Verna Lee KM, Kong SZ, Teoh SW, Nurjasmie AJ, Poulter NR, Beaney T, Xia X. May Measurement Month 2017 blood pressure screening: findings from Malaysia-South-East Asia and Australasia. *Eur Heart J Suppl* 2019; **21**: D77-D79 [PMID: [31043885](#) DOI: [10.1093/eurheartj/suz061](#)]
- 95 **Leung GM**, Ni MY, Wong PT, Lee PH, Chan BH, Stewart SM, Schooling CM, Johnston JM, Lam WW, Chan SS, McDowell I, Lam TH, Pang H, Fielding R. Cohort Profile: FAMILY Cohort. *Int J Epidemiol* 2017; **46**: e1 [PMID: [25617647](#) DOI: [10.1093/ije/dyu257](#)]
- 96 **Shahbabu B**, Dasgupta A, Sarkar K, Sahoo SK. Which is More Accurate in Measuring the Blood Pressure? A Digital or an Aneroid Sphygmomanometer. *J Clin Diagn Res* 2016; **10**: LC11-LC14 [PMID: [27134902](#) DOI: [10.7860/JCDR/2016/14351.7458](#)]
- 97 **Sison JA**. Philippine Heart Association—Council on Hypertension Report on Survey of Hypertension (PRESYON 3). A report on prevalence of hypertension, awareness and treatment profile. *Phil J Cardiol* 2013; **41**: 43-48
- 98 **Thomas S**, Beh L, Nordin RB. Health care delivery in Malaysia: changes, challenges and champions. *J Public Health Afr* 2011; **2**: e23 [PMID: [28299064](#) DOI: [10.4081/jphia.2011.e23](#)]
- 99 **Jaafar NI**, Ainin S, Yeong MW. Why bother about health? A study on the factors that influence health information seeking behaviour among Malaysian healthcare consumers. *Int J Med Inform* 2017; **104**: 38-44 [PMID: [28599815](#) DOI: [10.1016/j.ijmedinf.2017.05.002](#)]
- 100 **Ma WJ**, Tang JL, Zhang YH, Xu YJ, Lin JY, Li JS, Lao XQ, Tam WW, Wong MC, Yu IT. Hypertension prevalence, awareness, treatment, control, and associated factors in adults in southern China. *Am J Hypertens* 2012; **25**: 590-596 [PMID: [22337206](#) DOI: [10.1038/ajh.2012.11](#)]



Integrating contextual variables in meta-analyses

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Abstract

Meta-analysis is an important statistical tool, and it is often used to solve clinical problems. However inevitably when conducting a meta-analysis, the included studies often have heterogeneity. This paper suggests the inclusion of relevant background data or contextual variables into the model. The contextual variables are those variables not explicitly measured in the studies included in a meta-analysis; thus, these must be very well-described and justified as parameters for analyses.

Key Words: Covariates; Moderator; Meta-analysis; Contextual; Subgroup analysis; Meta regression

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Core Tip: This letter call for the use of contextual variables, that are typically not in use for covariate analyses. Contextual variables are introduced and defined as variables not immediately/directly measured by the original studies in the meta-analysis but rather can be estimated knowing the background of each study. For example in a meta analysis of clinical trails one might want to adjust for studies from high income vs low income countries or studies that were funded vs independent.

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TO THE EDITOR

Meta-analysis is a statistical procedure for combining data from several studies about a specific problem^[1]. When performing meta-analyses, it is important to determine the

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level of homogeneity between studies^[2]. When effect size is consistent between the studies, meta-analysis approach can be used to identify this common effect by combining all of the studies^[1,2]. However, problems are not always simple and often researchers face the issue of heterogeneity in meta-analysis and therefore employ moderator's analysis techniques. A moderator is an independent variable that conditions the relations between two others variables^[1,3]. Because effect sizes are the relationship between two variables, any variable that predicts the effect sizes is a moderator. When performing a moderator analysis, the moderator data type determines the type of analysis used. For categorical moderators (e.g., males *vs* females) usually a subgroup analysis is performed. For continuous moderators (e.g., age) usually a meta-regression is performed, it must be note here that continuous moderators can be either integer or decimal^[1,3]. Meta-analysis researchers often extract these moderator variables from the studies being reviewed. Available moderator variables might be limited to basic demographics or irrelevant to the core analysis at hand.

The purpose of this paper is to define and describe "contextual variables" and provide reasons for integrating them in meta-analysis studies. Brief section describes a worked example of contextual variables in a moderator analysis. The strengths and limitations of incorporating a contextual variable in moderator analyses are discussed as well as approaches to routinely define and include these variables in future meta-analyses.

A contextual variable is defined as a variable that was not explicitly measured in the studies included in a meta-analysis but rather is inferred or computed for the included studies. Contextual variables are variables that characterize the study setting, methodology or conduct. By adding a contextual variable meta-analysis researcher are encouraged to incorporate other relevant background data into the model. This extends meta-regression to a higher level. These variables would include things like the population sampled, the response rate, the geographical setting, the design, sponsorship *etc*. An example of contextual variable is to include an analysis of therapeutic trials by source of funding (industry, independent, mixed) which has repeatedly shown the presence of publication bias.

To illustrate this, a recent meta-analysis of ours was undertaken to examine the effect of Ramadan intermitting fasting on metabolic syndrome components^[4]. The MetS components analyzed were: Waist circumference (WC), systolic blood pressure (SBP), fasting glucose (FG), triglycerides (TG), and high-density lipoprotein (HDL) cholesterol. We identified 85 studies (4326 participants in total) that were conducted in 23 countries between 1982 and 2019. For illustration purposes, we will use WC. Ramadan fasting induced effect sizes for WC was small ($K = 24$, $N = 1557$) Hedge's $g = -0.312$, 95%CI: -0.387 to -0.236). To better understand the effects of Ramadan fasting on WC we performed moderator analysis for age and sex (proportion of male subjects) in the form of meta-regression. These simple demographic data (age and sex) were available for all of the included 24 studies. Meta-regression results revealed that sex was significant in explaining variation in WC ($\beta = -0.20$, $P = 0.03$), but age was not significant moderator.

As researchers we were also interested in examining the effect of fasting time/day in explaining changes in WC. Unfortunately, the included studies did not include this variable in their results section. However, by having some information about the study e.g. location and year of data collection we were able to use compute the contextual variable of fasting time/day (in minutes) which was defined according to Ramadan as time between sunrise and sunset, see <https://www.sunrise-and-sunset.com/>. Other plausible examples, would be metrological data such as mean temperature or relative humidity which can be obtained easily from historical weather platform available online.

Based on our experience of including contextual variables, this paper proposes the following three conditions to be included in models. First, ensuring that the data available are obtained during the same period of the original included study time. For example, for Ramadan fasting study that was included from Bahrain, 2000 it was crucial that sunrise and sunset were calculated for the same timeframe. Second, Gather data for all of the included studies from the same reliable/trustworthy source. For example, the calculated data on daytime length for a study from Bahrain, 2000 and study from the United Kingdom, 2018 are obtained from <https://www.sunrise-and-sunset.com>. Third, authors need to give detailed descriptions on how contextual variables were computed, summarized and analyzed.

The inclusion of contextual has high potentials in improving the methodology of meta-analysis and the benefits of including contextual variables can be summarized as follow: (1) Increase generalisability of results, as it would be important to demonstrate

that effect size is consistent among variables of interest; (2) Facilitate the identification of iatrogenic effects in subgroups; (3) Modelling improvement, by including meaningful variables that would give scientifically interpretable results; and (4) Have practical and research implications by generating future hypotheses for practice or further studies.

There are few limitations of including contextual variables which include the following: (1) Instability of models due to collinearity *e.g.*, fasting time and country of origin results might yield same results; (2) Difficulty in obtaining some variables with high level of precision; and (3) Interpreting the results might be challenging.

In conclusion, this paper propose that contextual variables are encouraged in meta-analyses to further understand and interpret the data and enrich study findings and inform future studies. These variables must meet a minimum set of conditions before inclusion.

REFERENCES

- 1 **Borenstein M**, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; New Jersey, US 2011
- 2 **Sutton AJ**, Abrams KR, Jones DR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Vol 348: Wiley; Chichester, UK; 2000
- 3 **Borenstein M**, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010; **1**: 97-111 [PMID: [26061376](#) DOI: [10.1002/jrsm.12](#)]
- 4 **Faris MAE**, Jahrami HA, Alsibai J, Obaideen AA. Impact of Ramadan Diurnal Intermittent Fasting on Metabolic Syndrome Components in Healthy, Non-Athletic Muslim People Aged Over 15 Years: A Systematic Review and Meta-Analysis. *Br J Nutr* 2019; 1-51 [PMID: [31581955](#) DOI: [10.1017/S000711451900254X](#)]



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