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Contents

Bimonthly Volume 9 Number 4 August 28, 2021

EDITORIAL

- 327 Watch and wait in locally advanced rectal cancer: Past, present and future
Alvarez-Aguilera M, Jimenez-Rodriguez RM

MINIREVIEWS

- 333 Fate of root shell after pontic/socket shield techniques, is it better to extract the whole tooth?
Agrawal AA

SYSTEMATIC REVIEWS

- 342 Troponin I biomarker as a strong prognostic factor for predicting COVID-19 mortality: A systematic review
Ashraf H, Soleimani A, Kazemi saeid A, Sadat Naseri A, Majidi F, Peirovi N, Karbalai Saleh S

META-ANALYSIS

- 353 Systematic review with meta-analysis of the epidemiological evidence in Europe, Israel, America and Australasia on smoking and COVID-19
Lee PN, Hamling JS, Coombs KJ
- 377 Systematic review and Meta-analysis of efficacy and safety of dienogest in treatment of endometriosis
Lin SC, Wang XY, Fu XL, Yang WH, Wu H, Bai Y, Shi ZN, Du JP, Wang BJ

SCIENTOMETRICS

- 389 Trends in iron deficiency anemia research 2001-2020: A bibliometric analysis
Frater JL

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Watch and wait in locally advanced rectal cancer: Past, present and future

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Abstract

In rectal cancer, a complete pathological response after neoadjuvant therapy means better rates survival and better rates of local recurrence. Nevertheless, these patients suffer from complications following surgery such as low anterior resection syndrome, sexual dysfunction or colostomy for the rest of their lives. Due to this, several groups are working in an organ preservation strategy when a clinical response is diagnosed. This strategy is known as watch and wait. In this editorial, we review the past, present and future perspectives for this conservative management.

Key Words: Rectal cancer; Watch and wait; Neoadjuvant treatment; Organ preservation; Complete response

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Core Tip: Organ preservation for rectal cancer after neoadjuvant therapy should be considered for selected patients with clinical complete response after neoadjuvant therapy.

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INTRODUCTION

The treatment for rectal cancer has changed in the last years due to technical advances: From the surgical technique, to stage and to pre and postop treatments. Nowadays, the standard treatment includes neoadjuvant therapy followed by total or subtotal mesorectal excision and adjuvant therapy[1] achieving excellent local control rates. Nevertheless, a third of the patients diagnosed with rectal cancer died due to distant metastasis[2].

Moreover, this multimodal treatment still has complications, including those coming from surgery: Infections, permanent ostomies, toxicity from chemo and radiotherapy, neurotoxicity or anterior resection syndrome and in some cases even death[3-5].

All these adverse effects cause a decrease in the quality of life of our patients. Due to this, current trend is to tailor the treatment regarding the tumor, its size, location stage and molecular characteristics as well as the own patient.

An example of this tailored treatment is the PROSPECT trial[6], a phase 2/3 clinical trial proposing to suppress systematic preoperative chemoradiotherapy. The authors describe the administration of 6 cycles of FOLFOX as neoadjuvant therapy followed by re-stage of the tumor and selectively use of radio and chemotherapy regarding the response of the tumor.

Despite the different schemas the final objective of all these preoperative treatments is maximize the number of tumor complete responses because these patients with pathological complete response (pCR) will develop a local recurrence rate of 1% and 95% 5-year survival[7-10]. In addition to this, this patients without viable tumor in the specimen could benefit from a non-surgical management thus if we increase the rate in complete responses we will increase the number of patients which could benefit from a non-operative management.

This non-surgical management or watch and wait is not new. Traditionally it has been attempted in frail and old patients with high risk for surgery and with response to the neoadjuvant therapy. We could name this strategy as a "casual watch and wait" or "watch and wait by necessity".

Recently this strategy has been published as intentional and not casual watch and wait. Habr-Gama *et al*[11] described in their work in 2004 their results after treating with neoadjuvant therapy, 265 patients with rectal cancer. These patients were reassessed 8 wk after the end of the neoadjuvant therapy and those with complete clinical response entered into a watch and wait policy. Those patients without complete clinical response underwent surgery. Disease-free survival rates were 100% and 92% after 57 mo. In this work, authors reported 2 local regrowths who underwent salvage surgery and stayed alive and disease-free at the end of the study.

Habr-Gama *et al*[11] concluded that in association with a careful follow-up, watch and wait for rectal cancer is safe and feasible.

More recent studies show pool analysis cases suggesting that watch and wait (WW) is feasible with similar survival rates to the traditional surgery and regrowth rates lower than 20%[12].

There is a difference between complete clinical response (cCR) and pCR. The first one is the absence of tumor after neoadjuvant therapy and the second one is the absence of viable tumor cells in the specimen after surgery. And sometimes these 2 options do not overlap. Current test cannot distinguish between tumor cells and fibrosis. In fact, up to 38% patients with an incomplete clinical response show after surgery pathological complete response[9]. This is a difficult situation for a patient and for a surgeon who have to choose between planning one or other approach.

There are different ways of increasing clinical complete response with the aim of increasing the number of patients who can benefit from a watch and wait strategy. One strategy is by optimizing preoperative radiotherapy. There are 2 ways of administering radiotherapy: Short course (25 Gy in 5 fractions) or long course (2 Gy fractions for in 2 Gy sessions for a total of 40 Gy to 50.4 Gy). Two prospective randomized trials [13,14] analyzed differences between these 2 modalities. The findings suggest there are no differences regarding local recurrences, survival or toxicity but there are differences regarding the rate of complete response in the specimen (0.7% in the short course modality against 16% in patients receiving long course radiotherapy). Other studies such as the one published by Bujko *et al*[13] and Cummings *et al*[15] studied the results of the short course in elderly population. These studies have a very small population, 30 and 20 cases respectively, and both studies concluded that WW is feasible after short course radiotherapy in elderly patients. Other studies such as the RAPIDO trial [16] randomized all patients to chemoradiotherapy (CRT) followed by surgery and optional adjuvant therapy or to total neoadjuvant therapy including short course

radiotherapy, 6 cycles of CapeOx and followed by surgery will show more information about the role of short course radiotherapy in WW.

As far as increasing tumor radio sensibility, the German study CAO/ARO/AIO-04 [17] demonstrated the benefit of adding oxaliplatin to CRT to maximize the outcomes of neoadjuvant therapy in terms of complete pathological response (17% *vs* 13%). This finding was consolidated after the follow-up with a 76% *vs* 71% 3-year disease-free survival (DFS). Nowadays the RAPIDO trial[16] has shown differences in toxicity in the experimental group (84%) but not in postoperative complications.

Another aspect is increasing waiting time after the end of neoadjuvant therapy. Tumor response to radiotherapy depends on the waiting time and sometimes a complete response could be delayed months. Although tumoral damage is produced during radiotherapy the lysis of the cells occurs days and even weeks after the end of the treatment. Surgery delay could increase the rate of pathological complete response from 0%, right after finishing CRT to 11% when the interval is 11 wk[15]. From that moment the rate of pathological complete response does not increase. Other studies also showed that an increase in complete response rates means a decrease in complication and readmission rates after surgery and similar survival rates. The TiMiSNAR trial[18] included 300 patients divided in 2 groups: Those receiving surgery 8 wk after surgery and those who underwent surgery 12 wk after CRT to determine when we should diagnose a pCR without affecting oncological outcomes.

Another strategy is adding chemotherapy to neoadjuvant therapy like induction or consolidation. There are studies that analyzed the result of induction or consolidation therapies in patients that also receive the classical schema: CRT and surgery. Consolidation therapy[19] has been associated to less toxicity, higher rate of completion and higher rates of pCR (25% *vs* 17%). Current evidence supports consolidation therapy as more favorable to increase the number of pCR and thus, WW. Nevertheless, we are still waiting the results coming from studies like the OPRA trial[20] where patients are randomized to induction or consolidation and surgery or WW.

All these strategies increase the rate of pCR and as consequence higher rates of WW. But once we decide we can offer a WW strategy, what should we do?

The first step is to determine the precise stage. Stage 2 and 3 tumors will benefit from neoadjuvant treatment, will possibly respond and will be candidates for a WW strategy. However, stage 1 tumors can also be included. This stage should be done with rectal exam, endoscopy and magnetic resonance imaging (MRI). Incomplete or complete response will be considered regarding our findings (Table 1).

Patient should be trustable and involved with the follow-up, to detect regrowths and perform surgery if needed. Follow-up should be performed as described in Table 2.

A group of patients will have more options of benefit from a WW strategy, for example those with more distal or smaller tumors requiring ultralow anastomosis or abdominoperineal resections. Bigger and circumferential tumors usually develop concentric scars inside the rectum obstructing the assessment of the tumor response. These patients could not be the ideal candidates for a WW program. Those with a higher risk of tumor progression might not be good candidates for this non-surgical management either. Smith *et al*[5] published a higher risk of distant metastasis in those patients who developed a regrowth (36% *vs* 1%, $P < 0.001$). This author declares the higher rate in the regrowth group could be due to delays in surgery or to more aggressive tumors.

We should begin with neoadjuvant treatment including chemo and radiotherapy and assess after 8-12 wk. At this point, there are different options:

cCR: scar, telangiectasia, and findings in the MRI suggesting cCR. We could suggest follow-up.

Incomplete clinical response: surgery.

Nearly complete clinical complete response: A follow-up could be suggested every 6-8 wk if the tumor still responds. If there is a regrowth, we should recommend surgery.

These recommendations are likely to be modified in the next few months with the information obtained from the different ongoing studies described previously, such as the OPRA[20] trial, that aim to assess the results of consolidation chemotherapy.

As we mentioned before, a certain group of patients might experience tumor regrowth during WW follow-up. A variety of studies claim that this scenario is more likely to show up in the first 2 years after neoadjuvant treatment rather than later on [5]. After carefully analyzing the graphical representation of these regrowth patterns, only a few patients are at risk of suffering this regrowth. Nevertheless, it is certainly hard to determine who will experience this, when it will happen, and which follow-up method may be the most effective one (DNAC, biopsies, imaging, *etc.*).

Table 1 Clinical response criteria regarding findings in rectal exam, endoscopy and magnetic resonance imaging described in OPRA trial[20]

	Clinical complete response	Almost complete response	Incomplete response
Endoscopy	Plain, white scar Telangiectasia Absence of ulceration Absence of nodules	Irregular mucosal layer Minimal nodules or rugosity in the mucosal layer Superficial ulceration Light and persistent scar erythema	Visible tumor
Digital rectal exam	Normal	Smooth induration or light mucosal layer alterations	Palpable nodules
MRI T2W	Dark signal in T2 without intermedial signal and no visible adenopathies	Dark signal in T2 with an intermedial signal And/or Partial regression of the adenopathies	More intermediate-dark signal in T2 No scar in T2 And/or No adenopathies regression
MRI DW	No visible tumor with B800-B1000 signal And/or Absent/low signal in ADC map A linear uniform signal in the tumor wall is a non-pathological sign	Significant regression of the signal in B800-B1000 And/or Minimal/ residual signal in ADC map	Insignificant signal regression in B800-B1000 And/or Clear low signal in ADC map

ADC: Apparent diffusion coefficient; MRI: Magnetic resonance imaging.

Table 2 Recommendations for follow-up for patients under a watch and wait strategy regarding OPRA trial[20]

Follow-up in mo	3-6	9-12	15-18	21-24	30	36	42	48	54	60
PE	√	√	√	√	√	√	√	√	√	√
Endoscopy	√	√	√	√	√	√	√	√	√	√
MRI	√	√	√	√	√	√	√	√	√	√
CT CAP	√	√	√	√	√	√	√	√	√	√
TM	√	√	√	√	√	√	√	√	√	√

CT CAP: Computed tomography chest, abdomen and pelvis; MRI: Magnetic resonance imaging; PE: Positron emission; TM: Tumor markers.

Several authors have published failure rates after a WW trial reporting a wide range of results, from 3% described by Habr-Gama *et al*[11] in his first study up to a 30% in other publications[21], clearly higher numbers when compared to the Brazilian group. It might be due to the exclusion of the first 12 mo of follow-up in the Brazilian group, and consequently the first 12-mo regrowth rate.

More recent studies show locoregional recurrence rate of about a 19%[5,20] as the closest to the real number. This recurrence might occur deep into the mucosal layer and therefore could be difficult to detect before the sphincteric complex is affected. However, in the presence of this scenario, savage surgery can be offered to the patient achieving a similar survival rate as to an initial surgery without a WW first step.

CONCLUSION

Patients with rectal cancer who undergo neoadjuvant therapy could present a complete clinical response. When this happens, these patients might benefit from a

non-surgical strategy associated with an exhaustive follow-up as long as they are aware of the implications of this pathway. In the event of a tumor regrowth, salvage surgery can be offered to them with similar oncological results. Nonetheless, future investigations are in order to elucidate the most proper candidates and follow-up methods for this treatment alternative.

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Fate of root shell after pontic/socket shield techniques, is it better to extract the whole tooth?

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Abstract

A series of changes occur in the remaining alveolar process after whole tooth extraction. The basic question is, why do the bony walls (especially the labial/buccal) get resorbed immediately after the tooth is removed? This could be because, with cementum of the concerned tooth and its periodontal ligament, the supporting bundle bone is dependent on the presence of the tooth. This loss can be compensated using numerous techniques, such as socket grafting using various biomaterials to preserve the alveolar bone and buccal grafting with guided tissue regeneration to increase the thickness of buccal bone or placement of implant immediately. However, none of these techniques prevent the modelling of the alveolar bone post-extraction. Few studies have demonstrated that preservation of the roots in the alveolar process maintains the bone volume and facilitates vertical bone growth. A histological study in animals and humans has shown that the retained root shell does not pose any interference in the osseointegration of the implant (if placed simultaneously). Although various names have been proposed to describe the concept of retaining full or part of the root to prevent the resorption of the ridge, socket-shield and pontic-shield are the two most commonly used terms worldwide. The extraction of the whole tooth might be the choice of therapy when socket-shield or pontic-shield is not possible due to anatomical variations, infections, or lack of clinical expertise. Irrespective of the size, when a whole root or a root fragment (is left *in situ*), it is the dentist's ethical duty to advise/inform the patient and ensure repeated clinical and radiographic follow-up. The present study aimed to highlight the current status of these techniques, their benefits, and possible complications and address whether the paradigm of the teeth extraction methods should be altered.

Key Words: Socket shield technique; Pontic shield technique; Alveolar resorption; Tooth root; Tooth extraction; Ridge preservation; Alveolar resorption

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Core Tip: The phrase ‘prevention is better than cure’ holds very true when it comes to alveolar ridge resorption. A significant bone is lost within 3 mo after extraction of the whole tooth. Socket/pontic shield techniques can preserve the alveolar bone and prevent a lot of surgical and economic burden to the patient in restoring what could have been saved in a very economical and natural way. Although these procedures are technique sensitive, clinicians must expertise in these techniques, since preserving what can be preserved is not only scientifically desirable but also ethically advisable.

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INTRODUCTION

Subsequent to whole tooth extraction, a series of changes occur in the remaining alveolar process. This may prevent or pose difficulty in implant installation at a prosthetically driven position. Also, there is an increasing demand for functional restoration and its aesthetic aspect. This emphasizes the importance of retaining sufficient alveolar ridge volume to deliver a functionally and aesthetically acceptable implant-supported prosthesis.

The basic question is, why do the bony walls (especially the labial/buccal) get resorbed rapidly after the tooth is removed? The answer is that with the cementum of the concerned tooth and its periodontal ligament (PDL), the supporting bundle bone is dependent on the presence of the tooth. The structure of the buccal bony wall of anterior teeth also has the same structure, and it is also tooth-dependent[1]. Interestingly, the bundle bone has the potential to exist in a thinner dimension compared to the alveolar/basal bone because of the PDL that provides the functional, nutritional, and cellular source existence and maintenance.

The majority of the dimensional changes that occur as a part of socket healing are primarily observed in the first 3 mo after extraction. However, the reorganization of the alveolar ridge can continue for almost a year[2], indicating a greater degree of bone modelling in the first 3 mo, followed by remodelling (Figure 1). However, the rate and pattern of socket healing could be attributed to the biological differences among individuals, the size of the socket under consideration, the prominence of root in the arch, and the degree of surgical trauma induced during extraction. In addition, the reflection of mucoperiosteal flap/full-thickness flap might lead to bone resorption of the thin buccal bone walls[3-5]. However, various human clinical and animal studies could not conclude that extraction without reflection of full-thickness flap prevents the resorption of alveolar bone/crest. The studies highlighted that the extraction procedure induces significant surgical trauma that exceeds the effect (if any) of full-thickness flap reflection[6-9]. Since there is more bundle bone at the crest of the buccal bone than the lingual, bone loss is pronounced in the buccal wall.

To compensate for this loss, there are numerous techniques described in the literature. Socket grafting (with various biomaterials) to preserve the alveolar bone (Figure 2C), buccal grafting with guided tissue regeneration (GTR) to increase the thickness of the buccal bone (Figure 2D), or placement of immediate implant (Figure 2E). However, none of these techniques truly prevent the modelling of the alveolar bone post-extraction[10-12]. This could be ascribed to significant alterations after tooth extraction due to the loss of PDL and subsequent trauma to the buccal bone. Thus, it could be hypothesized that root retention (vital/pulpless) may avoid tissue alterations that usually occur after whole tooth extraction. Few studies have demonstrated that preservation of the roots in the alveolar process maintains the existing bone volume and helps vertical bone growth[13]. Eventually, instead of retaining the whole root, retaining only a part of the root in contact with the buccal bone plate could be acceptable as only the buccal bone site is at a major risk of resorption (Figure 2F). These methods, termed as ‘socket shield’ or ‘pontic-shield’ techniques, were examined in an investigation in beagle dogs. The histological results of this study revealed that there was no bone modelling observed on the buccal wall, indicating that no resorption occurred[14]. In this study, we described the pros and

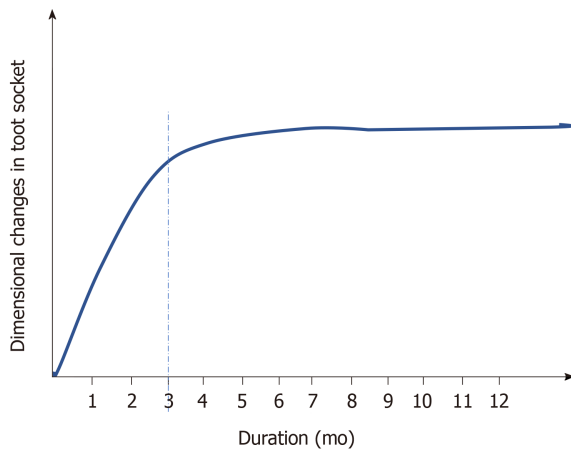


Figure 1 Dimensional changes as a part socket healing. This graph shows that after tooth extraction greater degree of bone modelling occurs in first 3-mo and the remodeling continue later on for a year and beyond.

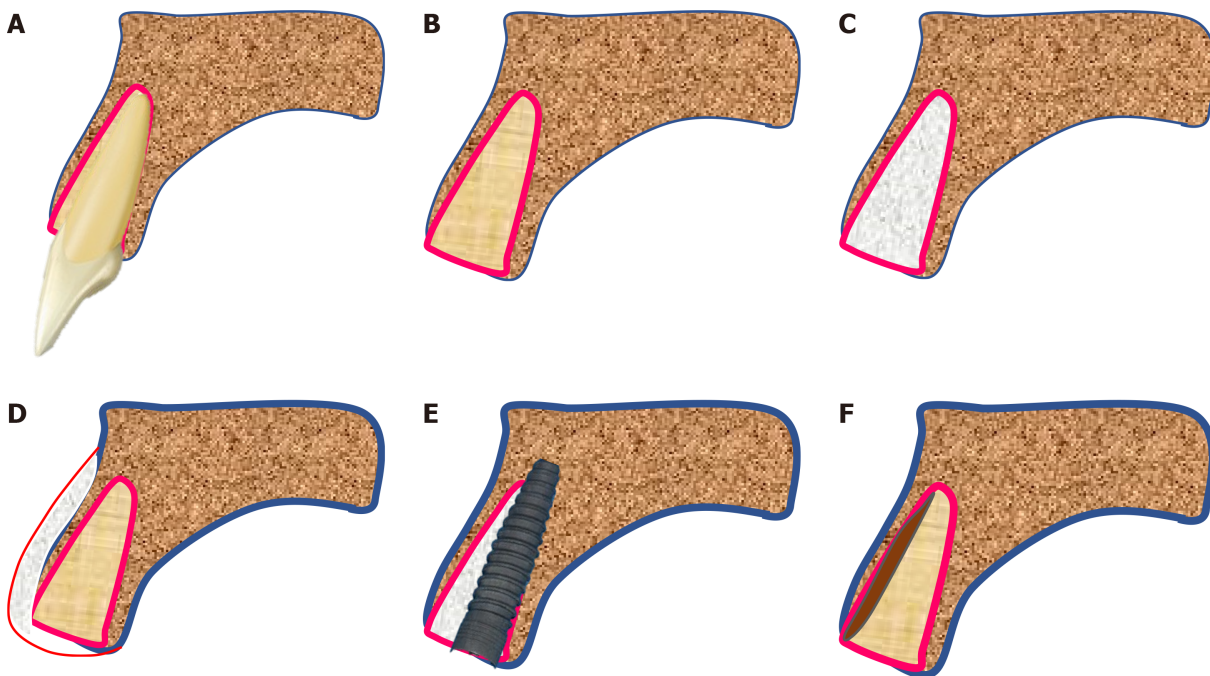


Figure 2 Techniques to compensate for the loss of socket wall post extraction. A: Tooth in socket; B: Empty socket after the tooth is extracted; C: Socket grafting (with lots of different biomaterials) to preserve the alveolar bone; D: Buccal bone grafting with GTR (guided tissue regeneration) to increase the thickness of buccal bone; E: Placement of immediate implant (with/without grafting the jumping space); F: Retaining only a part of root in contact with the buccal bone plate (socket-shield).

cons of leaving the root fragment behind intentionally. Although it might be rational to adopt this technique, whether extracting the whole tooth would be beneficial or leaving a part of the root is justified is yet to be investigated.

NOMENCLATURES AND TECHNICAL TIPS

During extraction, root pieces/root fragments might get retained inadvertently, which is the most common finding on routine radiographs^[15]. Partial extraction therapies (PET) is a wide term that encompasses the different types and modifications of complete and partial root fragment retention. It is one of the earliest attempts of PET, wherein the 'submergence' technique has been successfully demonstrated for the preservation of alveolar ridge post-extraction, as well as the development of pontic sites. The crown of the tooth is sectioned at the bone crest, and the coronal aspect of the remaining root is hollowed out to mimic the future ovate pontic. Primary soft

tissue closure is recommended to encourage healing by primary intention. In a human study, Garver and Fenster[16] demonstrated that the resorption of the alveolar bone is reduced significantly when the root is retained in the alveolar process. Although the concept might be traditional, root submergence is still considered an advantageous method for the development of a pontic-site in clinical practice, wherein the majority of the treatments involve implant prosthesis[17]. Scheuber *et al*[18] published a technique to preserve the alveolar ridge following posttraumatic ankylosis and external root resorption by retaining the de-crowned root parts. Davarpanah *et al*[19] conducted a case series study of unconventional implant treatment and demonstrated that immediate implants in direct contact with ankylosed teeth fragments were successfully preserved without any abnormalities over 2 years.

The socket-shield technique introduced by Hürzeler *et al*[14] involves the facial/buccal root fragment alone to retain the resorption of thin bundle bones. The tooth in concern is sectioned horizontally 1 mm above the bone crest (Figure 3B) and then sectioned longitudinally in facial and palatal halves (Figure 3C). Next, the palatal section was extracted (Figure 3D), and the facial root section is concaved with a long shank dental bur (Figure 3E). It also involves immediate placement of dental implant palatal to the retained root fragment. The jumping space, if any, can be grafted as possible (Figure 3F).

The widespread clinical use of the root-membrane technique started after the outcomes of the first longitudinal study published by Siormpas *et al*[20]. The study claimed that root membrane is an appropriate term as it focuses on the retention of root fragment in the form of a membrane.

A modification of socket-shield technique is termed the pontic shield technique[21]. The surgical procedure is the same as a socket shield, with the only difference being that an immediate implant is not placed. It facilitates space-filling with maximum bone, and then the implant may or may not be placed. Mitsias *et al*[22] advocated that root-membrane techniques, such as socket shield and others, could be termed as 'PDL-mediated ridge preservation for immediate implant placement'. In addition to the preservation of alveolar bone or buccal bone, the proximal socket-shield has been used to preserve the interdental papillae. It is useful when two or more adjacent implants are planned.

TECHNICAL ASPECTS

The partial extraction therapies, socket-shield or pontic-shield or their various modifications, are technique-sensitive. The procedure is associated with the risk of displacement of the retained root fragment or the buccal lamellar bone. In either of these different techniques, no consensus has been achieved with respect to the height or thickness of the root fragment. Glocker *et al*[23] advocated keeping the root fragment at the same level of the buccal alveolar ridge, which prevents the risk of fracture of the root fragment. On the other hand, Mitsias *et al*[22] preferred the root fragment to be at least 1 mm higher than the buccal crest, which would retain more PDL fibers and support more soft tissue at the crest. In an animal study, Tan *et al*[24] demonstrated that the degree of bone resorption is not affected by the height of the root fragment. However, it was positively correlated when the thickness of the root fragment was between 0.5 mm and 1.5 mm, and the bone resorption may decrease significantly. Extremely thick root fragment is stable but occupies more space leaving less for the implant. On the other hand, an overly reduced shield is unstable. Gluckman *et al*[25] recommended reducing the thickness of the retained fragment to approximately half its thickness from the root canal to the tooth's labial limit.

HISTOLOGICAL EVIDENCE OF FATE OF THE RETAINED ROOT FRAGMENT

In a 4-mo histological examination study, O'Neal *et al*[26] submerged 16 endodontically-treated roots. More than 50% of the sectioned surface was covered with bone in about 62.5% of root specimens, and also, complete bone coverage was identified on the cut surfaces in the 2-mo specimen. Guyer[27] submerged vital roots in humans and discovered that the two roots displayed radiographically normal conditions, and the alveolar ridge dimensions were maintained clinically for 27 mo. Plata *et al*[28] conducted a 12-wk histological evaluation of 12 vital submerged roots and reported

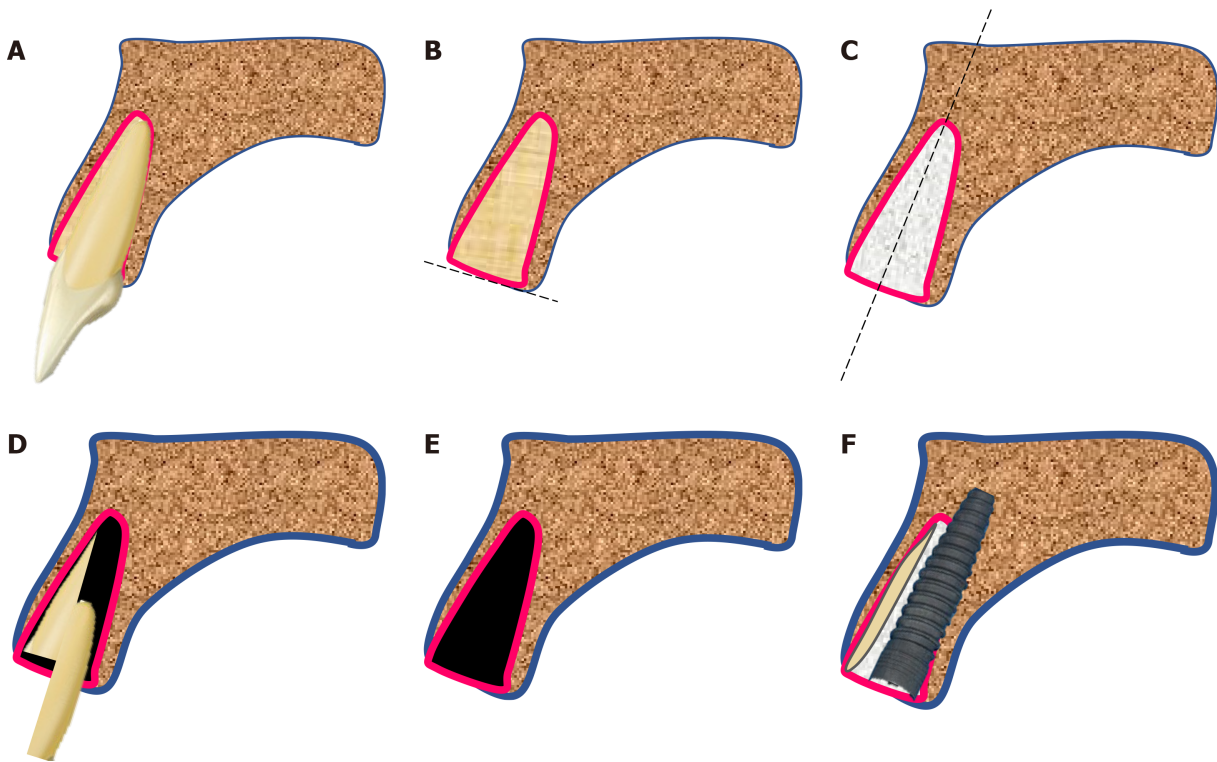


Figure 3 The 'Socket-shield' technique step-by-step. A: Tooth in bony socket; B: The tooth in concern is sectioned horizontally 1 mm above the bone crest; C: Root is sectioned longitudinally in facial and palatal halves; D: The palatal section is extracted; E: The facial root section is concaved with a long shank dental bur; F: Immediate placement of dental implant palatal to the retained root fragment. The jumping space if any can be grafted is possible.

that 8/12 roots had complete bone coverage on the cut surface, and the vitality of all the pulps was retained. In a histological study, Johnson *et al*[29] reported that the root fragments remained vital after 1 year. The study also found some roots achieving complete canal closure due to osteodentine formation.

Gray and Vernino[30] conducted an animal study in baboons to evaluate the effect of unintentional placement of the root form implants into or near retained root fragments. The study found that many implants were placed through the retained roots while others were placed through the PDL of the other root fragments. Histologically they did not find any inflammation at any site. At the locations where the implant was in direct contact with PDL, fibrous encapsulations of the implants were detected, while in some areas, calcified material was deposited on the implant surface.

Buser *et al*[31] and Hürzeler *et al*[14] evaluated the effects of placement of endosseous titanium implant fixture in the presence of retained roots in monkeys and Beagle dogs, respectively. Buser *et al*[31] reported that immediate implant placement over apical portions of the fractured retained roots resulted in cementum apposition between the fractured root and the implant surface. Hürzeler *et al*[14] modified this idea further and intentionally fractured the roots axially preserving the buccal portion of the root and placed an enamel matrix derivative in the socket before placing an implant. Similar results were reported showing that cementum covered the surface of both the retained root fragment and the implant. Bäumer *et al*[32] further evaluated the socket-shield using vertically separated root fragments in beagle dogs (without Emdogain). A new bone was found between the dentine layer and the implant surface; however, converse to the previous study, wherein Emdogain was coated on the root fragment, the present study did not find any cementum formation up to 4-mo follow-up period.

This might lead to the speculation that if one root fragment can prevent the resorption of buccal bone, then it would be beneficial to leave the root-membrane-type wall along all the socket walls and place the implant in the centre. Calvo-Guirado *et al*[33] conducted a histological animal study, wherein 36 implants were inserted in the mandible of 6 American Foxhound dogs using the principle of 'root-t-belt', *i.e.*, the crowns were sliced at the bone crest, and implant beds were prepared in the centre of the roots passing 3 mm apically. At the 3-mo histological evaluation, all fixtures were osseointegrated; however, three samples demonstrated inflammatory reaction, and some radicular fragments were detected in the resorption state.

Mitsias *et al*[34] presented histological evidence for a root-membrane case. The human sample analysis revealed that even after 5 years of post-implant placement, the buccal bone plate was perfectly maintained, and no resorption was evident. The buccal bone was supported and nourished by a healthy, intact PDL. Moreover, the implant showed good osseointegration, with a high amount of compact, mature bone on the surface. At the apical region of the root fragment, where the implant was in direct contact with the root membrane, the authors also noted cementum, which may have migrated from the root to the implant surface[34]. Schwarz *et al*[35] presented histological evidence of the integration of an implant in the dentin of an unintentionally retained root fragment. The authors discovered that subsequent to trauma during implant site preparation, a layer of reparative dentin was formed on the surface of the retained root fragment that bridged the space between the implant and the root fragment. This type of mineralized integration led them to coin the term 'dentointegration', and its pace was equivalent to that of osseointegration seen on the other parts of the implant[35].

Siormpas *et al*[20] presented one of the largest longitudinal studies on the survival of immediate implants placed adjacent to a root fragment. The data from 46 patients concluded that all implants successfully maintained osseointegration till the end of the follow-up period, giving a cumulative survival rate of 100%. Regarding the fate of the root fragment, the authors found only one patient with the apical root resorption, which was also self-arrested and did not interfere with the osseointegration of the dental implant. In addition, Bäumer *et al*[32] also raised a genuine clinical question as to what type of tissue would be formed following resorption of the retained root? A previous study demonstrated that the resultant space would be healed by bone fill. Bäumer *et al*[32] further conducted a study to evaluate whether the socket-shield technique could be successful if the buccal root fragment shows a vertical fracture line. Leaving the fracture line untreated is detrimental to the overall prognosis as it acts like a recess for bacteria, ultimately leading to infection. Therefore, the authors recommended surgical separation of the buccal shield into two halves along the fracture line. At the follow-up visit, the animal histological data showed a higher buccal alveolar crest height with healthy peri-implant soft tissue and no resorption at the apical end of the tooth fragment. The gap between the root fragment and the implant and the vertically drilled space between the two parts of the buccal shield was filled with the bone in the horizontal section[32].

Approximately, 4-wk are required post-extraction to cover the socket with epithelium. It may be assumed that a similar process occurs between the implant and the retained root fragment. Initially, a blood clot is filled between the implant and the buccal root fragment. This clot prevents the epithelium from growing along the internal root surface. Thus, it may seem that the cells from the remaining PDL are capable of colonizing the root surface and regenerating a new periodontal attachment.

COMPLICATIONS AND MANAGEMENT

In the previous root submergence technique, gingival tissue perforation and cyst formation were documented complications. To prevent perforation, the roots should be excised at a position slightly apical to the bony edge and beveled and smoothened to avoid any sharp edges.

The earliest histological finding showed a failed, plasma-sprayed titanium implant in contact with an undetected residual root presented with hypercementosis and no PDL[36]. The study also hypothesized that the unintentionally retained root might be a putative source of pathogenic bacteria from the PDL or the root canal itself, which compromises the osseointegration of the implant. Thus, it can be the potential cause of retrograde peri-implantitis, a term introduced by McAllister *et al*[37]. It is characterized by symptomatic periapical lesions with a healthy coronal bone-implant interface that develops within months of implant fixture placement.

In partial extraction therapy cases, where infection of the root fragment/section is coupled with mobility, removing the root membrane is mandatory. The mobility of the root shield, with or without infection, necessitates its removal. If the implant fails to osseointegrate, but the socket-shield is stable, immobile, and free of infection, the implant can be removed, leaving the shield in-situ for healing as a pontic-shield concept. The subsequent re-evaluation could be conducted to deduce whether an implant should be placed palatal to the shield or used as a pontic site.

FUTURE TRENDS AND ADVANCES

With additional literature that would be published on the success of socket-shield and pontic-shield techniques in the future, the procedure would be deemed an ideal requirement. Thus, there would be no more whole tooth extraction, and if not indicated, such whole tooth extraction would be deemed as an act of negligence.

Furthermore, simple and sophisticated technological advances would make the procedure easy and predictable. Thus, there is a dire need to develop a predictable and reproducible set of protocols for socket-shield and/or pontic-shield procedures.

CONCLUSION

The extraction of a tooth, which for long is regarded as a simple and uncomplicated procedure, should hereon be performed with an understanding that significant ridge resorption will follow. Surgical techniques performed later to compensate for the lost bone (guided bone regeneration/GTR/socket grafting/immediate implant) are not completely effective in preventing the alveolar bone resorption. Previous studies have shown that retaining the root fragment (along with its healthy PDL) is the most economical and successful therapy and should be recommended as required. However, the socket-shield/pontic-shield technique is a sensitive procedure, and its success depends on the operating clinician's expertise. The extraction of the whole tooth might be the choice of therapy when socket-shield or pontic-shield is not possible due to anatomical variations, infections, or lack of clinical expertise. Regardless of the size, whenever it is decided to leave a root fragment (or whole root for that matter) *in situ* (for whatever reasons), it is the dentist's ethical duty to advise/inform the patient and ensure repeated clinical, radiographic follow-up in the future.

Although socket-shield technique offers promising results, supporting clinical data are limited due to the lack of well-designed prospective randomised controlled studies. Thus, according to the review by Blaschke and Schwass[38], at this stage, it is not clear whether the socket-shield/pontic-shield techniques provide a long-term stable clinical outcome.

Further clinical research studies, preferably prospective randomised controlled trials involving power analysis to determine an adequate cohort size for statistical interpretation, would draw reliable conclusions.

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Troponin I biomarker as a strong prognostic factor for predicting COVID-19 mortality: A systematic review

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Abstract

BACKGROUND

The increase in circulating Troponin-I in the blood of patients suffering coronavirus disease 2019 (COVID-19) can be a strong prognostic factor for predicting disease poorer outcome.

AIM

To review the literatures to approve this claim systematically.

METHODS

Two blinded reviewers independently screened the titles and abstracts of the manuscripts using the keywords and deeply searching the databanks including PubMed, Scopus, Google Scholar, and Web of knowledge, followed by profoundly appraisalment of the full texts to assess the inclusion appropriateness.

RESULTS

The manuscripts entered into our final assessment were categorized as the two groups including 10 manuscripts describing and comparing death and disease-related complications between the subgroups of patients with raised serum troponin level and those with normal ranges of this biomarker and 7 manuscripts comparing the mean level of serum troponin concentration across the survived and non-survived groups. Comparing outcome of COVID-19 disease in the groups with raised troponin level and normal level of this markers showed increased the likelihood of death [hazard ratio (HR) = 4.967, $P < 0.001$], acute respiratory distress syndrome (HR = 5.914, $P < 0.001$), acute kidney injury (HR =

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3.849, $P < 0.001$), and intensive care unit (ICU) admission (HR = 3.780, $P < 0.001$) following raise of troponin. The pooled analysis showed significantly higher concentration of this marker in the survived group compared to non-survived group (weighted mean differences of 22.278, 95%CI: 15.647 to 28.927, $P < 0.001$).

CONCLUSION

Raising troponin-I on admission can be linked to the increase risk for in-hospital death, acute respiratory distress syndrome, kidney injury, and ICU admission by 4.9, 5.9, 3.8, and 3.7 times as compared to those with initial normal troponin-I concentration. Thus, raising baseline value of troponin-I can be used as a prognostic factor for poor outcome of COVID-19.

Key Words: Troponin-I; COVID-19; Mortality; Morbidity; Cardiac biomarker; Acute respiratory distress syndrome

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Core Tip: We systematically reviewed the literatures to assess this claim that an increase in troponin-I levels could be a prognostic factor in predicting disease severity and mortality in patients with coronavirus disease 2019. According to our findings, regardless of the history of myocardial injuries or the presence of cardiovascular risk profile, the value of troponin I should be accurately assessed on admission. Raising troponin-I on admission can be linked to the increase risk for in-hospital death, acute respiratory distress syndrome, kidney injury, and intensive care unit admission by 4.9, 5.9, 3.8, and 3.7 times as compared to those with initial normal troponin I concentration.

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INTRODUCTION

The new coronavirus known as coronavirus disease 2019 (COVID-19) has so far (15 February 15) infected more than 108 million people, leading to more than 2 million deaths. About 15 to 20 percent of patients experience a severe illness resulting in 2 to 3 percent mortality. The disease presents with acute respiratory syndrome with fever, dry cough, dyspnea and myalgia[1-4]. To date, there is no confirmed treatment for this disease. Therefore, accurate and early diagnosis and determination of its severity can prevent its further progression.

Along with acute respiratory failure as a prominent and debilitating manifestation of COVID-19, multidimensional organ defects have been also detected in the affected patients certainly resulting from the virus triggering role on pro-inflammatory cytokines activation and secretion, as well as coagulation abnormalities[5,6]. A complex of such events can predispose the patients to cardiovascular ischemic and thromboembolic events[7,8]. Some clinical data have supported the strong link of COVID-19 infection to cardiac and cerebrovascular ischemic events leading to high mortality and disabilities[9]. This infection is now suggested to promote myocardial injuries leading to cardiac arrhythmias, myocardial hypertrophy, acute coronary syndrome and even acute heart failure. We obvious a bidirectional interaction between the cardiovascular system and infection to COVID-19, however, the exact mechanisms responsible for such cardiovascular defects remains elusive. Some molecular-based studies emphasize the central role of pro-inflammatory cascades such as the activation of interleukin-6, interleukin-1beta, and tumor necrosis factor- α as the main flaring factors for such events[10]. Also, the presence of some specific receptors for the virus such as ACE2 as a gateway for the virus to enter tissues such as the myocardium seems necessary for the mentioned injuries[9]. There is also strong evidence on a close

association between the effects of the virus and underlying cardiovascular risk factors such as hypertension and diabetes so that the presence of any of these risk factors increases the risk of ischemic events many times over. The body of evidence highlights the high risk of ischemic heart disease such as myocardial infarction in patients with COVID-19[11,12].

Therefore, one of the relatively prevalent adversity in patients with COVID-19, particularly in the elderly and patients with prior predisposing factors like hypertension or diabetes mellitus is cardiovascular lesions in the form of ischemic heart attacks, arrhythmias, and vascular disorders. In this regard, considering that the increase in the level of cardiac biomarkers such as troponin-I as a marker of myocardial damage has been fully proven[13], it seems that in COVID-19 patients with myocardial and arrhythmic lesions, we see an increase in this marker. The increase in circulating troponin-I in the blood of patients may be also a prognostic factor for predicting the severity of the disease and its mortality[14]. In this study, we systematically reviewed the literature to assess this claim that an increase in troponin-I levels could be a prognostic factor in predicting disease severity and mortality in patients with COVID-19.

MATERIALS AND METHODS

For performing the present systematic review and meta-analysis, the full guideline of the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” was followed[15]. In the first step and after explaining the study’s main question and specific goals, all prospective and retrospective comparative studies that evaluated the link between the serum level of troponin-I and two COVID-19 related parameters including disease severity and mortality were considered to be eligible for primary assessment. In this regard, deeply searching the manuscript databanks including PubMed, Scopus, Google Scholar, and Web of knowledge was planned from inception to October 2020; The main keywords were: ‘covid-19’ OR ‘sars-cov-2’ OR ‘2019-ncov’ AND ‘troponin’ AND ‘mortality’ OR ‘death’. In the searches, the review papers, case presentations, letter to editors, and abstracts without full text access were all excluded. Non-English studies were excluded from the meta-analysis. Also, in cases of lack of access to the full text of the articles, correspondence was made with the author in charge of the articles to obtain the full article, and in case of lack of access to the original article; it was removed from the study. The manuscript reviewing was done by two blinded reviewers, screening the titles and abstracts followed by profound appraisal of the full texts independently to assess the inclusion appropriateness. The presence of any disagreement between them was judged and checked again by another reviewer as the last arbiter. The eligibility and reasons for not including the papers are schematically presented in Figure 1. The bias hazard was blindly assessed by two authors using the Cochrane risk of bias tool, afore finalizing the meta-analysis. The level of bias was qualitatively classified into high, uncertain, or low bias[16]. Accordingly, the following domains are typically used to specify the level of bias: How to select the participants (selection bias), how to perform the measurement of troponin-I along the management of disease-related outcomes including disease severity and in-hospital death, and how to manage confounders and missing data. The permanent effects or random-effects (in case of significant heterogeneity across the data) models were used to obtain pooled relative risk (with 95% confidence interval and corresponding *P*-values) for disease severity and death due to troponin-I raising as well as to obtain pooled dichotomous data using the mean difference (MD) for the level of troponin-I. The incongruity between the studies was evaluated by determining *I*² values. A sensitivity analysis was also performed, in which observational studies at critical risk of bias were excluded from the analysis. Publication bias was also appraised by the rank correlation test and also affirmed by the funnel plot analysis. Reported values were two-tailed, and hypothesis testing results were assumed statistically significant at *P* = 0.05. We used the Comprehensive Meta-Analysis Software (CMA, version 3.0) for statistical analysis.

RESULTS

The study selection process is shown in Figure 1. On the field, 216 articles were prepared by the database searching at the beginning. We removed 137 articles as they were duplicated or unrelated to the subject of the systematic review. At first, 79 articles

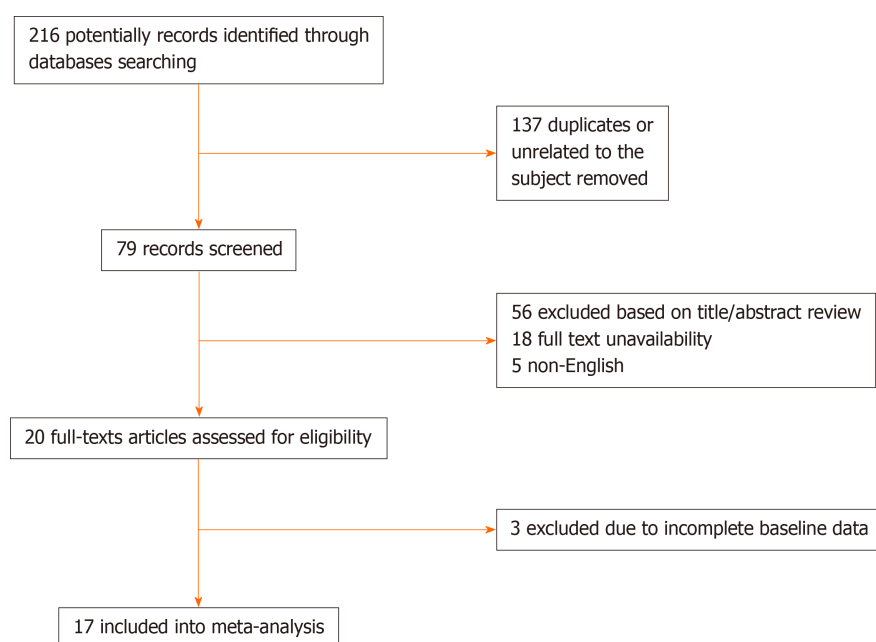


Figure 1 The flowchart of screening the eligible studies.

were initially under-screened. Fifty-nine articles were excluded based on the titles and abstracts. The extant 20 articles were specified for subsequent eligibility. We also excluded 3 more articles because the data and contents were not completed. Eventually, 17 articles were qualified for the final analysis[17-32]. Table 1 describes the baseline characteristics of the included studies. Evaluation of the publication and systematic bias demonstrated that approximately all articles were supposed as low risk or with unclear biases; hence, the obtained results could be considered valid and none of the articles was supposed to have a high risk of bias (Figure 2).

The manuscripts entered into our final assessment were categorized as the two groups including 10 manuscripts describing and comparing death and disease-related complications between the subgroups of patients with raised serum troponin level and those with normal ranges of this biomarker[17-26] and 7 manuscripts comparing the mean level of serum troponin concentration across the survived and non-survived groups[18-33]. The main point concerning the present meta-analysis was to first present the value of troponin with different laboratory units that of course could be matched through unit conversion. However, the different techniques employed for troponin value assessment, the type of study as prospective or retrospective, the different cutoff values considered for defining troponin abnormal raise as well as the time considering for patients' follow-up might lead to high heterogeneity across the two groups that were measured in our meta-analysis.

Overall, 10 studies assessed the early mortality and morbidity in the groups with and without raised serum troponin level (Table 1). In this regard, the outcome of COVID-19 was compared between the group with a normal troponin range ($n = 4566$) and the group with raised troponin level ($n = 1846$). The average age of participants in the two groups was 59.8 years and 71.2 years respectively. First, the overall rate of raising serum troponin level was estimated to be 32.2% (95%CI: 25.0% to 40.5%) in COVID-19 patients admitted to the hospitals. Comparing the outcome of COVID-19 disease in the groups with raised troponin level and normal level of this marker (Table 2) showed an increased likelihood of death [hazard ratio (HR) = 4.967, 95%CI: 2.883 to 8.557, $P < 0.001$], acute respiratory distress syndrome (ARDS) (HR = 5.914, 95%CI: 3.027 to 11.555, $P < 0.001$), acute kidney injury (HR = 3.849, 95%CI: 3.112 to 4.760, $P < 0.001$), and also intensive care unit (ICU) admission (HR = 3.780, 95%CI: 2.405 to 5.943, $P < 0.001$) following raise of troponin and thus the abnormal value of troponin on admission could effectively predict poor outcome in COVID-19 patients (Figure 3). The heterogeneity across the studies in the assessment of disease outcome was relevant with the I^2 values ranged 74.877 to 91.317.

In the second assessment concerning the difference in the value of troponin-I between survived and non-survived patients suffering COVID-19 (Table 3), The pooled analysis showed significantly higher concentration of troponin-I in the survived group compared to non-survived group (weighted MD of 22.278, 95%CI:

Table 1 The baseline details of studies included in our meta-analysis considering the groups with raised and normal values of troponin I

Ref.	Country	Population	Mean age	Male/female	Cutoff for TnI raising
Arcari <i>et al</i> [17]	Italy	Normal TnI: 39	66 ± 17	28/11	14 pg/mL
		Raised TnI: 64	79 ± 13	19/45	
Fan <i>et al</i> [18]	China	Normal TnI: 67	58 ± 15	38/29	0.01 µg/L
		Raised TnI: 22	71 ± 12	11/11	
Guo <i>et al</i> [19]	China	Normal TnI: 135	53 ± 13	57/78	99 th percentile
		Raised TnI: 52	71 ± 9	34/18	
Lala <i>et al</i> [20]	United States	Normal TnI: 2206	66 ± 13	1312/894318/212	0.09 ng/mL
		Raised TnI: 530	68 ± 15		
Lombardi <i>et al</i> [21]	Italy	Normal TnI: 336	64 ± 13	234/102201/77	99 th percentile
		Raised TnI: 278	71 ± 12		
Lorente-Ros <i>et al</i> [22]	Spain	Normal TnI: 560	63 ± 12	367/193	14 ng/L
		Raised TnI: 147	78 ± 14	77/70	
Raad <i>et al</i> [23]	United States	Normal TnI: 630	59 ± 11	280/350	18 ng/L
		Raised TnI: 390	70 ± 13	229/161	
Karbalai Saleh <i>et al</i> [24]	Iran	Normal TnI: 271	57 ± 15	167/104	99 th percentile
		Raised TnI: 115	65 ± 15	69/46	
Shah <i>et al</i> [25]	United States	Raised TnI: 116	59 ± 14	70/123	0.05 ng/ml
		Normal TnI: 193	68 ± 14	62/54	
Singh <i>et al</i> [26]	United States	Normal TnI: 129	53 ± 11	54/75	17 ng/L
		Raised TnI: 132	71 ± 12	70/62	

15.647 to 28.927, $P < 0.001$). The statistical heterogeneity was significant with an I^2 of 99.123. We showed a significant publication bias as evidenced by either funnel plot asymmetry or the Egger test for all comparative analyses.

DISCUSSION

High-sensitive troponin-I has been well known as a strong and even specific cardiac biomarker for diagnosing ischemic cardiac injury as well as predicting its poorer outcome. The observations among critically ill patients who are suffering from COVID-19 especially those who require intensive care also suggested higher levels of this marker on admission as well as within hospitalization. In this regard, recent studies have focused this point that by initially measuring troponin-I in patients hospitalized due to definitive diagnosis of COVID-19, predicting outcomes of disease especially occurring in-hospital death and disease severity may be certainly possible. As shown in our systematic review, assessing the baseline level of troponin-I not only can strongly predict death in COVID-19 patients, but also it can be used as a valuable factor to predict disease sequels including ARDS, kidney injury, and requiring ICU admission. Due to this fact, the appearance of each of these complications are indicators for disease severity (particularly ICU admission). Therefore, raising in troponin-I is a valuable indicator for disease severity. Overall, as well indicated in our meta-analysis, raising troponin-I on admission can be linked to the increased risk for in-hospital death, ARDS, kidney injury, and ICU admission by 4.9, 5.9, 3.8, and 3.7 times as compared to those with initial normal troponin-I concentration. It should be noted that the use of this parameter along with other known predictive parameters can be more valuable to predict non-survived patients or those with disease-related adverse events. Despite demonstrating the value of troponin-I as a strong predictor for COVID-19 poorer outcomes, our results exposed to a high heterogeneity across the findings. Such heterogeneity can be explained by first the difference insignificant

Table 2 The outcome of coronavirus disease 2019 considering the groups with raised and normal values of troponin

Ref.	Raised TnI rate	Death rate	ARDS	Kidney injury	ICU admission
Arcari <i>et al</i> [17]	39/103	Raised TnI: 12 Normal TnI: 7	---	---	---
Fan <i>et al</i> [18]	22/89	---	Raised TnI: 20 Normal TnI: 12	Raised TnI: 9 Normal TnI: 10	---
Guo <i>et al</i> [19]	52/187	Raised TnI: 31 Normal TnI: 12	Raised TnI: 30 Normal TnI: 16	Raised TnI: 14 Normal TnI: 4	Raised TnI: 31 Normal TnI: 14
Lala <i>et al</i> [20]	530/2736	Raised TnI: 223 Normal TnI: 102	---	---	---
Lombardi <i>et al</i> [21]	278/614	Raised TnI: 102 Normal TnI: 43	---	Raised TnI: 41 Normal TnI: 13	---
Lorente-Ros <i>et al</i> [22]	147/707	Raised TnI: 60; Normal TnI: 130	---	---	Raised TnI: 7; Normal TnI: 5
Raad <i>et al</i> [23]	390/1020	Raised TnI: 128 Normal TnI: 52	Raised TnI: 93 Normal TnI: 64	Raised TnI: 224 Normal TnI: 178	Raised TnI: 105 Normal TnI: 93
Karbalai Saleh <i>et al</i> [24]	115/386	Raised TnI: 47 Normal TnI: 30	Raised TnI: 46 Normal TnI: 30	Raised TnI: 35 Normal TnI: 25	Raised TnI: 41 Normal TnI: 38
Shah <i>et al</i> [25]	116/309	Raised TnI: 44 Normal TnI: 22	---	Raised TnI: 13 Normal TnI: 5	Raised TnI: 58 Normal TnI: 52
Singh <i>et al</i> [26]	132/276	Raised TnI: 20 Normal TnI: 5	Raised TnI: 29 Normal TnI: 10	---	Raised TnI: 63 Normal TnI: 25

Table 3 The baseline details of studies included in our meta-analysis considering the survived and non-survived groups

Ref.	Country	Population	Mean age	Male/female	Mean TnI
Aladağ and Atabey[27]	Turkey	Survived: 35	68 ± 14	22/13	Survived: 0.001 ng/mL
		Non-survived: 15	68 ± 15	6/9	Non-survived: 0.010 ng/mL
Deng <i>et al</i> [28]	China	Survived: 212	62 ± 11	97/115	Survived: 0.006 ng/mL
		Non-survived: 52	74 ± 15	33/19	Non-survived: 0.051 ng/mL
Liberati <i>et al</i> [15]	Italy	Survived: 425	61 ± 13	287/138	Survived: 0.006 ng/mL
		Non-survived: 98	76 ± 10	68/30	Non-survived: 0.036 ng/mL
Nie <i>et al</i> [29]	China	Survived: 200	60 ± 11	180/20	Survived: 0.002 ng/mL
		Non-survived: 111	72 ± 12	88/23	Non-survived: 0.032 ng/mL
Rath <i>et al</i> [30]	Germany	Survived: 107	67 ± 15	65/42	Survived: 0.014 ng/mL
		Non-survived: 16	73 ± 16	12/4	Non-survived: 0.024 ng/mL
Shi <i>et al</i> [31]	China	Survived: 609	61 ± 13	287/322	Survived: 0.006 ng/mL
		Non-survived: 62	74 ± 15	35/27	Non-survived: 0.023 ng/mL
Yang <i>et al</i> [32]	China	Survived: 145	57 ± 13	77/68	Survived: 0.004 ng/mL
		Non-survived: 58	67 ± 15	38/20	Non-survived: 0.020 ng/mL

divergent in the cutoff points defined for troponin-I raising, also by the difference in the baseline characteristics of study populations especially with respect to the presence of cardiovascular risk profiles, the sample size of the studies, the time for patients' following-up, as well as the techniques for measuring troponin-I concentration. However, despite such heterogeneities across the studies, this marker should also be considered as an important and strong predictor of disease consequences. In a meta-

Ref.	Patient selection	Index test	Measurement	Managing confounders
Arcari <i>et al</i> ^[17]	+	?	?	+
Fan <i>et al</i> ^[18]	?	?	?	+
Guo <i>et al</i> ^[19]	?	+	+	+
Lala <i>et al</i> ^[20]	+	+	+	+
Lombardi <i>et al</i> ^[21]	?	+	+	+
Lorente <i>et al</i> ^[22]	+	+	+	+
Raad <i>et al</i> ^[23]	+	?	?	+
Saleh <i>et al</i> ^[24]	+	+	+	+
Shah <i>et al</i> ^[25]	+	+	+	+
Singh <i>et al</i> ^[26]	?	?	+	+
Aladağ and Atabey ^[27]	+	+	+	+
Deng <i>et al</i> ^[28]	+	?	+	+
Michela <i>et al</i> ^[15]	+	+	+	+
Nie <i>et al</i> ^[29]	+	+	?	?
Rath <i>et al</i> ^[30]	+	+	?	?
Shi <i>et al</i> ^[31]	+	+	+	+
Yang <i>et al</i> ^[32]	?	?	?	+

+
Low

?
Unclear

-
High

Figure 2 The Assessment of the risk of bias.

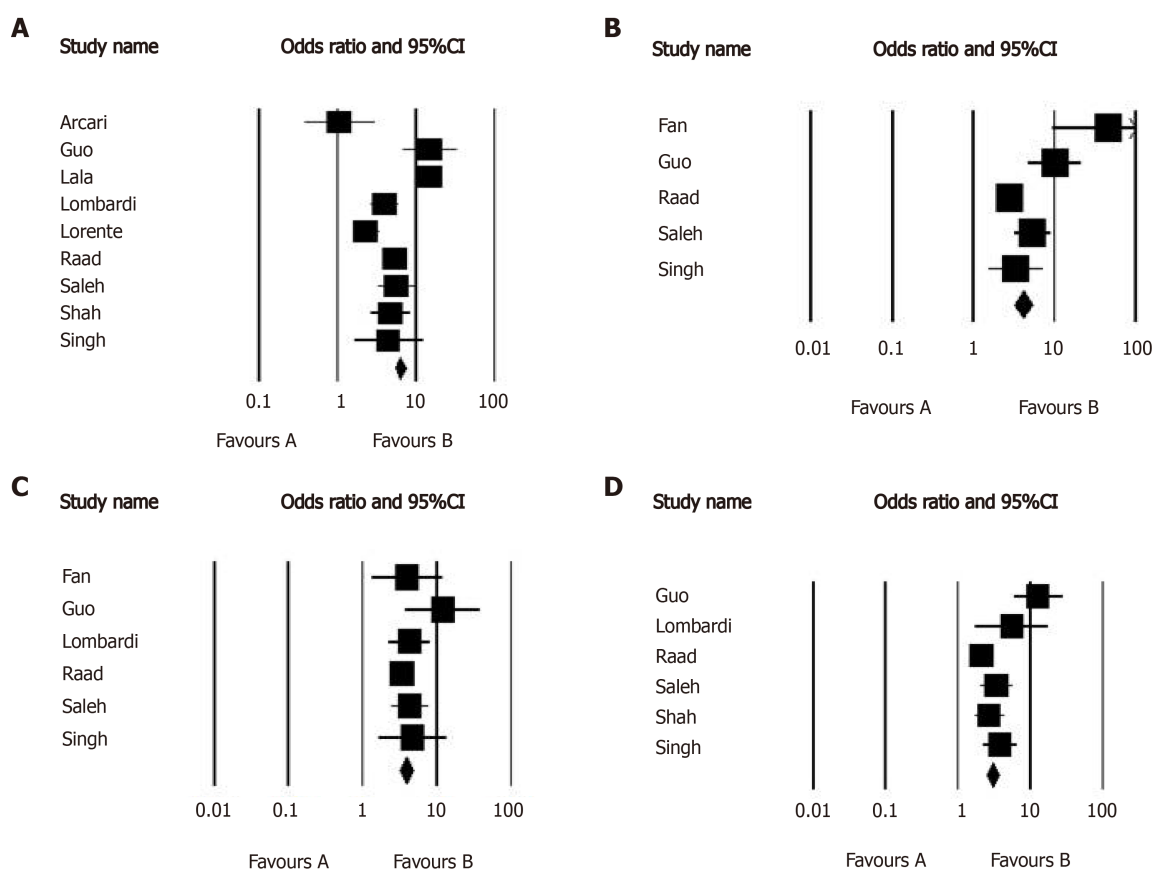


Figure 3 The hazard ratio in coronavirus disease 2019 related death. A: Acute respiratory distress syndrome; B: Acute kidney injury; C: ICU admission; D: In the group with raised troponin as compared to group with normal level of this marker in pooled assessment of the studies.

analysis by Lippi *et al*^[33] demonstrated a significant association between COVID-19 severity and elevated troponin-I level, despite their high heterogeneity.

Regarding the association between the raise of troponin-I and COVID-19 outcome, some probable mechanisms have been delivered. Firstly, it has been revealed that the patients with raised troponin-I level had higher rates of cardiovascular risk factors that

are now shown to be closely linked to the increased risk for death and severity of COVID-19[19]. Also, any severe respiratory viral infections especially when lead to sepsis are also associated with increasing the level of troponin-I. Recently, a quadri-lateral mediator loop is revealed describing the association between raising troponin levels and disease outcome[34,35]. These four loops include: (1) Secretion of pro-inflammatory cytokines that raised favored by ACE2 receptor suppression and induced oxidative stress and endothelial dysfunction; (2) Microangiopathy and prothrombotic states usually stimulated by both oxidative stress and endothelial dysfunction; (3) Myocardial infarction induced directly by viral invasion or by inflammatory cascades activation; and (4) Myocarditis by inflammatory reactions[36].

CONCLUSION

In conclusion, according to our findings, regardless of the history of myocardial injuries or the presence of cardiovascular risk profile, the value of troponin-I should be accurately assessed on admission because of its high predicting value for COVID-19 related mortality and morbidity.

ARTICLE HIGHLIGHTS

Research background

Troponin-I on admission has a high predicting value for coronavirus disease 2019 (COVID-19) related mortality. Troponin-I on admission has a high predicting value for COVID-19 related morbidity. Troponin-I can strongly predict disease sequels including acute respiratory distress syndrome (ARDS), kidney injury, and Intensive care units (ICU) admission requirement.

Research motivation

Accurate and early diagnosis and determination of COVID-19 severity can prevent its further progression. The increase in circulating troponin-I in the blood of patients suffering COVID-19 can be a strong prognostic factor for predicting disease poorer outcome. We systematically reviewed the literatures to approve this claim.

Research objectives

The increase in circulating troponin-I in the blood of patients suffering COVID-19 can be a strong prognostic factor for predicting disease poorer outcome.

Research methods

Deeply searching the manuscript databanks was planned. All studies that evaluated the link between the serum level of troponin-I and two COVID-19 related parameters including disease severity and mortality were considered to be eligible for primary assessment. The review papers, case presentations, letter to editors, non-English studies, and abstracts without full text access were all excluded. The manuscript reviewing was done by two blinded reviewers, screening the titles and abstracts followed by profound appraisal of the full texts independently to assess the inclusion appropriateness. The presence of any disagreement between them was judged and checked again by another reviewer as the last arbiter.

Research results

Comparing outcome of COVID-19 disease in the groups with raised troponin level and normal level of this markers showed increased the likelihood of death [hazard ratio (HR) = 4.967, $P < 0.001$], acute respiratory distress syndrome (HR = 5.914, $P < 0.001$), acute kidney injury (HR = 3.849, $P < 0.001$), and ICU admission (HR = 3.780, $P < 0.001$) following raise of troponin. The pooled analysis showed significantly higher concentration of this marker in the survived group compared to non-survived group (weighted mean differences of 22.278, 95%CI: 15.647 to 28.927, $P < 0.001$).

Research conclusions

In conclusion, according to our findings, regardless of the history of myocardial injuries or the presence of cardiovascular risk profile, the value of troponin-I should be accurately assessed on admission because of its high predicting value for COVID-19

related mortality and morbidity.

Research perspectives

The value of troponin-I should be accurately assessed on admission because of its high predicting value for COVID-19 related mortality and morbidity.

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Systematic review with meta-analysis of the epidemiological evidence in Europe, Israel, America and Australasia on smoking and COVID-19

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Abstract

BACKGROUND

Previous meta-analyses related smoking to death or severe infection from coronavirus disease 2019 (COVID-19) in hospitalized patients, but considered only a few studies, did not adjust for demographics and comorbidities, and inadequately defined smoking.

AIM

To review and meta-analyse epidemiological evidence on smoking and COVID-19, considering a range of endpoints, populations and smoking definitions and the effect of adjustment.

METHODS

Studies were identified from publications in English up to 30 September, 2020 involving at least 100 individuals, carried out in Europe, Israel, America or Australasia, not restricted to those with specific other diseases, and providing information relating smoking to various COVID-related endpoints. Meta-analyses were carried out for combinations of population and endpoint, with variation studied by smoking definition, adjustment level and other factors.

RESULTS

From 96 publications, 74 studies were identified, 37 in the United States, 10 in the United Kingdom, with up to four in the other countries. Three involved over a million individuals, and 37 involved less than a thousand. Adjusted results for smoking were available in 42 studies, with adjustment not considered in 20 studies. Results were considered by endpoint. No significant effect of smoking on COVID-19 positivity was seen in the general population, but there was a reduced

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risk in those tested. Best-adjusted estimates for current (*vs* never) smoking were 0.87 (95% confidence interval: 0.52-1.47) in the general population and 0.52 (0.43-0.64) in those tested. For those hospitalized due to COVID-19, unadjusted rates were significantly increased in current smokers (1.20, 1.01-1.42) and ever smokers (1.64, 1.41-1.91), but those adjusted for comorbidities showed no increase for current (0.82, 0.52-1.30) or ever smokers (1.00, 0.76-1.32). There was little evidence to suggest that smoking was associated with intensive care admission. For those hospitalized with COVID-19, best-adjusted estimates were 0.88 (0.72-1.08) for current smokers and 1.10 (0.99-1.22) for ever smokers. In those hospitalized with COVID-19, smoking was not significantly related to subsequent mechanical ventilation, with best-adjusted estimates of 1.12 (0.60-2.09) for current smokers and 1.05 (0.88-1.25) for ever smokers. For those hospitalized with severe COVID-19, best-adjusted estimates were 0.74 (0.49-1.12) for current smokers and 1.15 (0.87-1.51) for ever smokers; few estimates were adjusted for comorbidities. While smoking was associated with increased mortality in unadjusted analyses, the association disappeared after adjustment for comorbidities. For example, in those hospitalized with COVID-19, the unadjusted estimate for ever smokers of 1.59 (1.37-1.83) reduced to 1.07 (0.82-1.38) when adjusted for comorbidities. Studies on those with severe COVID-19 showed that smoking tended to be associated with worsening of the disease. However, no estimate was adjusted, even for demographics. Estimates did not clearly vary by location or study size, and there was too little evidence to usefully study variations by age, amount smoked or years quit.

CONCLUSION

The increased COVID-19 death rate in smokers seen in unadjusted analyses disappears following adjustment for demographics and comorbidities. Among those tested, smoking is associated with lower COVID-19 infection rates.

Key Words: Smoking; COVID-19; Meta-analyses; Review; Europe; America

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Core Tip: Detailed analyses of 74 studies related smoking to being tested for coronavirus disease 2019 (COVID-19), having COVID-19, or suffering death or severe disease due to COVID-19. Various smoking indices were studied, as were the effects of adjusting for other factors. Although many studies provided limited unreliable results, consistent evidence showed that of those tested, smokers were less likely to have COVID-19. Among those positive for or hospitalized with COVID-19, there was a clear association between smoking and COVID-19 death and severity in unadjusted analyses, which disappeared following adjustment for comorbidities and demographics. Any adverse effects in smokers appear to derive from their poorer prior health status.

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INTRODUCTION

In a previous project commenting on publications on smoking and coronavirus disease 2019 (COVID-19), we considered over 100 papers published up to the end of September 2020. Among these were various meta-analyses falling into two groups.

Eight publications[1-8] considered smoking prevalence in hospitalized patients, generally agreeing it was substantially less than expected from national statistics. This evidence does not necessarily show smoking protects against acquiring COVID-19.

Smoking may be markedly under-reported in studies based on medical records. Also, among those with COVID-19, smokers might be less likely than non-smokers to be hospitalized. These meta-analyses ignored relevant information from studies of those tested for COVID-19, or of the general population, where smoking habits were collected pre-pandemic, as well as more recent studies of hospitalized patients.

The other meta-analyses[3,6,9-28] concerned hospitalized patients, relating smoking to severity, progression or death from COVID-19, mainly from studies in China. While these generally reported positive associations which were often statistically significant, many meta-analysis estimates were unadjusted even for age, with comorbidities present pre-pandemic rarely considered. These meta-analyses also varied on the index of smoking used, which was not always clearly defined.

Here we describe meta-analyses aimed at avoiding the limitations of the early meta-analyses by considering more studies, not limiting attention to hospitalized patients, and paying particular attention to the definition of smoking and the effects of adjustment, as well as the reliability of the smoking data.

To limit the scope of the study and provide timely results various restrictions to the studies were made, as described in the methods section. Notably studies in China and other parts of Asia, except for Israel, were excluded. A recent review[29] classified few studies from Asia as “good” or “fair”, most having much missing data and/or not reliably distinguishing current, former, ever and never smoking status. We were also aware of a large study in Israel[30] without these weaknesses.

Due to the more comprehensive data included, and better quality of the studies considered, the meta-analyses we describe should provide much better insight into the relationships of smoking to various COVID-related outcomes than do the meta-analyses referred to above.

MATERIALS AND METHODS

Full details of the methods used are given in [Supplementary material 1](#) and are summarized below.

Study inclusion and exclusion criteria

Pre-defined criteria stipulated for practical reasons that studies should be described in English and were detected in searches up to September 2020. They should also be conducted in Europe, Israel, America, or Australasia, as discussed above. America here includes all the countries in South and Central America, as well as the United States and Canada. Studies restricted to individuals with specific other diseases were excluded as being less generalizable. Studies of less than 100 individuals were excluded as they provided inadequate power to detect reliable results, and as there were adequate numbers of larger studies. Studies should provide information relating smoking to the probability of one or more of the following relevant endpoints: being tested for COVID-19, having confirmed COVID-19, having self-reported COVID-19, being hospitalized with COVID-19, requiring mechanical ventilation for COVID-19, requiring intensive care for COVID-19, having severe/progressive COVID-19, or dying from COVID-19 or from any cause. The studies may concern various at-risk populations, including the general population, those tested for COVID-19, those positive for COVID-19, those hospitalized with COVID-19, or those with severe COVID-19.

Literature searches

As part of our earlier project, we carried out a first PubMed search on April 7, 2020, and then carried out further daily searches up to September 30, 2020.

Publications identified in our study as being of initial interest were then examined to identify studies satisfying our inclusion/exclusion criteria, and relevant meta-analyses. The meta-analyses were then examined for additional relevant studies meeting our inclusion criteria. Further studies were then sought from meta-analyses identified in further searches, from a further more detailed look at our original searches, and from examining reference lists of publications identified as relevant.

Multiple publications from the same study

To avoid double-counting results from the same study reported in multiple publications, the relevant publications were examined to identify publications from the same study.

Data recorded

Data from each publication were entered onto a study database and a linked effect estimate database. The study database recorded information on: publications considered; study title; study location; sexes, ages and races considered; study dates; study type; nature of population studied; sample size; definition of severe COVID-19 (if relevant); method of COVID-19 diagnosis; whether adjusted effect estimates were available; the confounding variables studied; and whether adjusted results on smoking were reported and, if not, why not (*e.g.*, smoking not significant in the adjusted model). It also recorded information on the smoking index for which results were available (*e.g.*, current *vs* never smoking), the source of the smoking data (*e.g.*, medical records), the extent of missing data, the percentage of smokers in the population studied, and whether dose-response data were available, as well as details of the endpoints and at-risk populations studied.

The effect estimate database included details of each individual effect estimate entered. Effect estimates were entered for every available combination of endpoints within a population, smoking index and level of adjustment (separated into unadjusted (U), adjusted for demographics only (D), adjusted also for comorbidities but not post-infection variables (C), and adjusted also for variables including post-infection responses to COVID-19 (P). Where available, effect estimates were entered by sex, age group and smoking dose (amount, duration, time since quitting). Other factors recorded included the publication the effect estimate was derived from; the population and endpoint considered; the smoking comparison; the type of effect estimate [odds ratio (OR), relative risk (RR) or hazard ratio (HR)]; the adjustment factors considered; the number of cases and at-risk subdivided by the smoking variable; the effect estimate and its lower and upper 95% confidence interval; and whether the estimate was given in the paper or was derived from the data presented. Derivation could be from the 2×2 table of numbers for unadjusted data, or using the method described by Hamling *et al*[31] to derive adjusted estimates for other smoking indices from estimates given in the publication (*e.g.*, ever *vs* never estimates from those for current *vs* never and former *vs* never).

All data were entered by Hamling JS or Coombs KJ and checked by Lee PN, with any disagreements discussed and resolved.

Meta-analyses

For each studied combination of endpoint within a population (*e.g.*, died while hospitalized with COVID-19), meta-analyses were carried out relating the endpoint to each of six indices of smoking; ever *vs* never, current *vs* non-current, current *vs* never, former *vs* never, a combined index most closely approximating to current *vs* never, and a combined index most closely approximating to ever *vs* never. The combined index for current *vs* never smoking includes, from each study reporting the endpoint/population combination, results in the following preference order (most to least preferred) – current *vs* never, current *vs* non-current, smoker (undefined) *vs* non-smoker, tobacco use *vs* none, ever *vs* never, and former *vs* never. The combined index for ever *vs* never smoking uses the preference – ever *vs* never, former *vs* never, smoker (undefined) *vs* non-smoker, tobacco use *vs* none, current *vs* never, and current *vs* non-current.

For each endpoint within a combination of population and smoking index, the results to be meta-analysed were selected using a first preference on level of adjustment and then a second preference on type of effect estimate. For adjustment, the order of preference (first to last) was adjustment for factors including comorbidities, adjustment for demographics only, unadjusted, and adjustment for factors measuring responses to COVID-19 infection (the lowest preference, as this may be a form of over-adjustment). For type of effect estimate, the preference order was HR, then RR, then OR.

Where the numbers of estimates permitted, the meta-analyses compare estimates by level of adjustment, type of estimate, sex, location and study size.

Statistical analysis

Fixed-effect and random-effects meta-analyses were conducted using the method of Fleiss and Gross[32] with heterogeneity quantified by H , the ratio of the heterogeneity chi-squared to its degrees of freedom. H is directly related to the I^2 statistic[33] by the formula $I^2 = 100(H-1)/H$. For all meta-analyses, Egger's test of publication bias[34] was included.

All analyses were carried out using RoeLee release 63, build 52, available from RoeLee Statistics Ltd (www.roelee.co.uk).

RESULTS

Literature searches

Figure 1 summarizes the results of the literature searches, with fuller details, including reasons for rejecting papers (**Supplementary material 2**). Overall, 98 publications met the selection criteria.

Studies and study characteristics

Twelve references represented multiple publications from the same study. Allowing for this, data were entered for 76 separate studies. Subsequently, during data entry, it became apparent that two studies[35,36] provided no data for any of the endpoints considered, and only compared smoking prevalence with published data in the population at large. These studies were not further evaluated.

Supplementary material 3 summarizes the details for the 74 studies, including references. Studies were identified by the six character codes shown there.

Thirty-seven studies were from the United States, 10 from the United Kingdom (including seven restricted to England), four each from France, Israel, Italy, Mexico and Spain, two from Switzerland and one each from Australia, Brazil and Denmark. Also one study was conducted in the United Kingdom and Italy, and one in multiple European countries.

In 31 studies, the population considered was patients hospitalized with COVID-19, with a further four patients admitted to the intensive care unit (ICU). Also 19 studies considered those with a positive COVID-19 test, 11 included those who were tested for COVID-19 and seven included the general population. One study included hospital patients and non-COVID-19 controls, while another included those tested for COVID-19 as well as control groups not tested.

All studies included both sexes, and none selected individuals on race or ethnicity. One study was restricted to adults aged 47-87 years, with a further 41 restricted to adults, generally with a minimum age of 18 years, but sometimes having lower limits ranging from 15 years to 23 years. The remaining 32 studies did not refer to any age restriction. As shown in **Supplementary material 3**, the number of individuals with smoking data varied widely between the studies. The largest was OPENSA in England involving over 16 million individuals, with two other United Kingdom studies over a million, and three others over 100000. In contrast, 37 studies involved less than 1000 individuals.

It is also shown in **Supplementary material 3** that some studies reported analyses for subsets of their populations, and for various endpoints. These endpoints included being tested for COVID-19, having confirmed or having self-reported COVID-19, being hospitalized with COVID-19, requiring intensive care or mechanical ventilation, having severe or progressive COVID-19, and mortality, either from COVID-19 or from all causes combined.

Thirty-six studies allowed calculation of separate effect estimates for current, former and ever smokers. Eight reported results for current smoking only, 19 for smoking history only, and eight for smoking undefined. One (TWIGG) reported results for tobacco use undefined, one (CHAND) had two source papers - one providing results for current smokers only, one for ever smokers only - and another (GUPTA) gave numbers of current or former smokers combined and adjusted results for current *vs* non-current smokers. The smoking data were mainly extracted from medical records, although in some cases the data came from a questionnaire or other sources, with no details given in six studies. Percentages with missing data on smoking were available in 35 studies, with 13 being over 20%.

Adjusted results for smoking were presented for 42 studies. In 12, only predictors other than smoking appeared in the adjusted model, either because smoking was not significant in univariate analyses, so was not considered in multivariate analyses, or because smoking dropped out of the multivariate modelling. In 20 studies, no adjusted results were presented.

In 54 studies, COVID-19 diagnosis was by reverse transcriptase-polymerase chain reaction or simply by polymerase chain reaction, but there were various alternatives, as indicated in **Supplementary material 3**.

Effect estimates available

Effect estimates were available for all but one study (KNIGHT), which stated only that "Ever cigarette smoking was predictive of death ($P < 0.05$)" without providing quantitative detail.

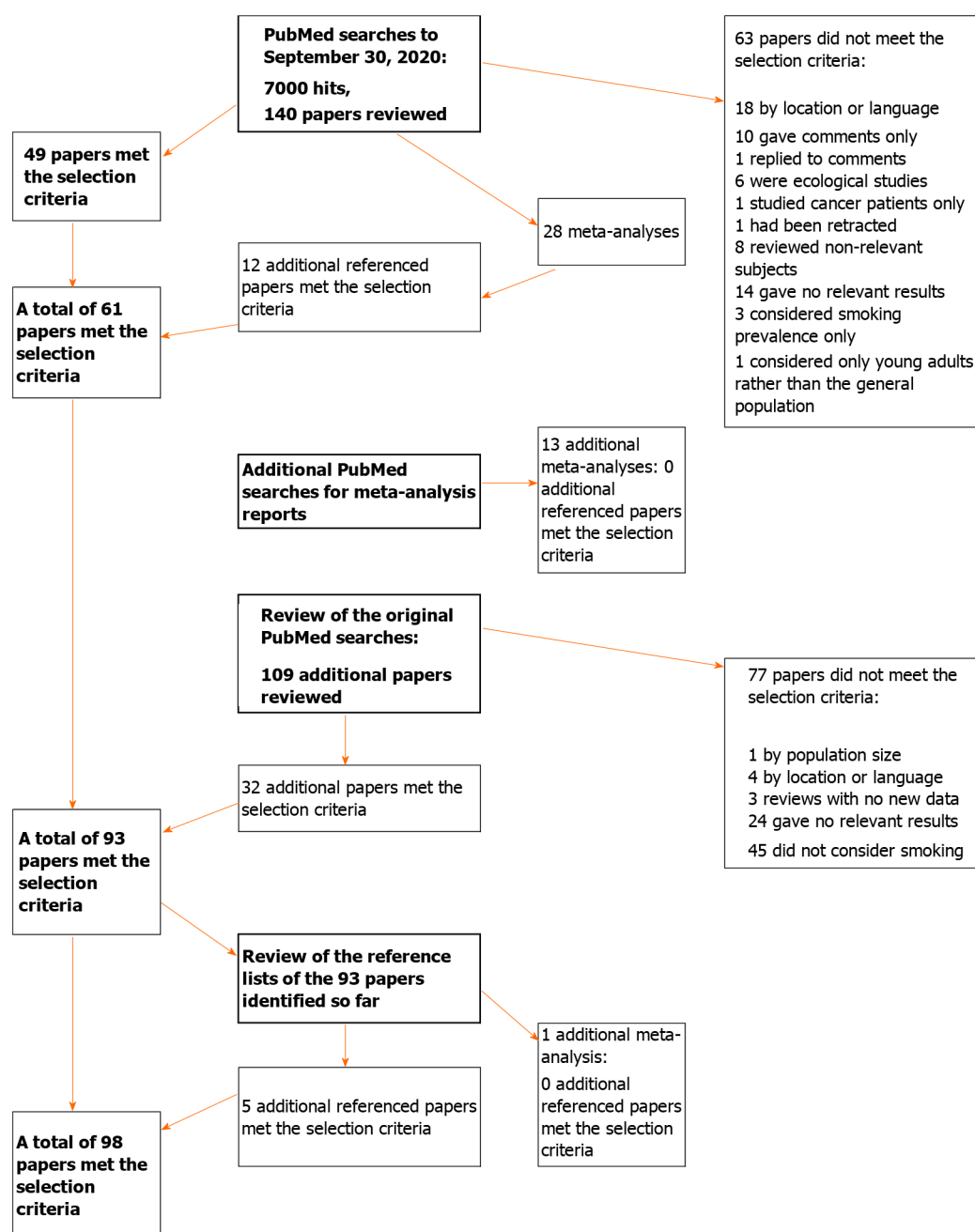


Figure 1 Flowchart of literature search. The flowchart shows, for each of the four stages of the process, the numbers of papers and meta-analyses considered, together with the numbers of papers meeting the selection criteria or rejected, with reasons for rejection shown.

Overall there were 738 effect estimates: 548 ORs, 122 RRs and 68 HRs. The studies providing most estimates were GU (100), BIOBNK (86) and VETERA (52), with 18 other studies providing 10 or more estimates. Fourteen studies provided only one estimate. There were 153 estimates for current *vs* never smoking, 202 for current *vs* non-smoking, 142 for former *vs* never smoking, 223 for ever *vs* never smoking, 16 for smoker *vs* non-smoker not otherwise stated, and two for tobacco *vs* no-tobacco not otherwise stated. One study (HIPPIIS) provided 15 effect estimates by amount smoked, and one (TOOLKI) provided four estimates by years quit. No other study provided dose-response data.

Of the 738 estimates, 432 (58.5%) were unadjusted, 110 (14.9%) adjusted for demographics only, 169 (22.9%) adjusted for variables including co-morbidities but not responses to COVID-19, and 27 (3.7%) adjusted for a list including responses to COVID-19.

One study (YANOVE) provided effect estimates subdivided jointly by sex and age group. Four others (BIOBNK, GDEM, HOPKIN, MIYARA) provided estimates subdivided by sex only, and three others (GDEM, SINAI, VETERA) provided

estimates subdivided by age group only.

The at-risk population was the general population for 155 (21.0%) effect estimates, those tested for COVID-19 for 106 (14.4%), those positive for COVID-19 for 222 (30.1%), those hospitalized with COVID-19 for 188 (25.5%), and those in intensive care for 22 (3.0%). Other populations were considered for 45 (6.1%) effect estimates, with GU providing 36 of these, all based on populations representing a combination of a group considered above (*e.g.*, tested for COVID-19) and unmatched controls. Other such populations included a mixture of those positive for COVID-19 and those untested (two estimates from BIOBNK), those hospitalized but including non-COVID cases (five from MEINI), those tested for COVID-19 but not hospitalized (one from ADORNI) and those hospitalized with COVID-19 but not in ICU (one from PELLAU).

The endpoints considered in the 738 effect estimates were tested for COVID-19 in 41 (5.6%), positive for COVID-19 in 189 (25.6%), hospitalized for COVID-19 in 128 (17.3%), in intensive care in 92 (12.5%), mechanical ventilation in 58 (7.9%), severe COVID-19 (defined variously) in 58 (7.9%), and died in 172 (23.3%).

The effect estimates concerned many different combinations of endpoint within population, the commonest being hospitalized among those positive for COVID-19 (98 effect estimates), positive within those tested (90), died among those hospitalized (82) and positive among the general population (79).

The results below are considered by endpoint and within endpoint by population. Meta-analysis results are shown in the main tables for endpoint/population combinations that have data from at least five studies, with the individual study data summarized in [Supplementary material 4](#) for combinations with data from fewer than five studies. Fuller details, including the individual effect estimates meta-analysed, the extent of heterogeneity between the estimates, and results of tests for publication bias, are provided in [Supplementary material 5](#).

Endpoint: Tested for COVID-19

Four studies provided effect estimates ([Supplementary Table 1](#)). GU compared tested individuals with unmatched controls, and the remaining studies (BIOBNK, ADORNI and HOPKIN) compared those tested and not tested. BIOBNK provided estimates from multiple publications, the results from two being shown in [Supplementary Table 1](#), with the others providing little extra information.

The results presented are somewhat conflicting, with the BIOBNK study reporting estimates above 1.00, generally significant, and tending to decrease with increasing adjustment, while ADORNI and HOPKIN, both only provided unadjusted results, with significant estimates below 1.00. GU shows a reduced probability of testing for current smoking and an increased probability of testing for former and ever smoking, with the estimates reducing with increasing adjustment.

Meta-analysis of this conflicting data was not attempted.

Endpoint: Positive for COVID-19

[Table 1](#) presents the meta-analysis results from six studies where the at-risk population was the general population, and 15 where it was those tested for COVID-19. The “best-adjusted” results are those where, for each study, an effect estimate was selected in the order of preference C, D, U and P for level of adjustment. Results are shown for all the best-adjusted results and for those where C and U were the best-adjusted results available, which form the great majority of the best-adjusted results. The “all estimates U” results give estimates for the totality of unadjusted results, including those not included in the best-adjusted results being superseded by results for the same study with level of adjustment C or D. The results are consistent with no effect of smoking on positivity in the general population, but a reduced risk of positivity, particularly among current smokers, in those tested for COVID-19. No clear effects of adjustment were seen in either analysis.

Four other studies presented results for COVID-19 positivity based on other populations ([Supplementary Table 2](#)). In BIOBNK, COVID-19 positives were compared with the untested population, in ADORNI the population was those non-hospitalized, in MEINI the population was those hospitalized, whether or not from COVID-19, while GU compared tested individuals and unmatched controls. Although the results from BIOBNK suggested smokers were more likely to be positive, those from the other studies did not, the results for current smokers showing a negative association.

Endpoint: Hospitalized for COVID-19

[Table 2](#) shows the meta-analysis results based on 19 studies of those positive for

Table 1 Main results for endpoint: Tested positive for coronavirus disease 2019

Selection of estimates ¹		Statistic ²	Ever vs never	Current vs non-current	Current vs never	Former vs never	Closest to current	Closest to never
Population = general ³								
Best-adjusted	All	EE (95%CI)	1.04 (0.79-1.37)	0.76 (0.56-1.02)	0.87 (0.52-1.47)	1.09 (0.94-1.28)	0.78 (0.57-1.06)	0.89 (0.73-1.09)
		<i>n</i>	5	7	5	5	7	7
	C	EE (95%CI)	1.10 (0.70-1.72)	0.93 (0.43-2.01)	0.96 (0.42-2.17)	1.10 (0.86-1.40)	0.96 (0.42-2.17)	1.10 (0.70-1.72)
		<i>n</i>	3	3	3	3	3	3
	U	EE (95%CI)	0.71 (0.63-0.80)	0.56 (0.43-0.75)	0.45 (0.36-0.55)	0.92 (0.80-1.05)	0.56 (0.42-0.75)	0.65 (0.55-0.77)
		<i>n</i>	1	3	1	1	3	3
All estimates	U	EE (95%CI)	1.04 (0.83-1.29)	0.79 (0.51-1.22)	0.90 (0.46-1.78)	1.13 (0.97-1.31)	0.80 (0.53-1.22)	0.89 (0.74-1.08)
		<i>n</i>	5	7	5	5	7	7
Population = tested for COVID-19 ⁴								
Best-adjusted	All	EE (95%CI)	0.71 (0.60-0.84)	0.61 (0.52-0.71)	0.52 (0.43-0.64)	0.97 (0.86-1.09)	0.55 (0.47-0.65)	0.70 (0.63-0.77)
		<i>n</i>	10	13	8	8	17	17
	C	EE (95%CI)	0.77 (0.56-1.05)	0.60 (0.45-0.79)	0.53 (0.34-0.83)	0.90 (0.76-1.08)	0.58 (0.43-0.80)	0.77 (0.64-0.92)
		<i>n</i>	4	5	4	4	5	5
	U	EE (95%CI)	0.67 (0.52-0.86)	0.62 (0.51-0.75)	0.49 (0.42-0.58)	1.04 (0.85-1.28)	0.55 (0.45-0.67)	0.67 (0.58-0.78)
		<i>n</i>	6	8	4	4	11	11
All estimates	U	EE (95%CI)	0.72 (0.62-0.85)	0.61 (0.50-0.73)	0.53 (0.46-0.61)	0.97 (0.87-1.09)	0.55 (0.46-0.66)	0.71 (0.64-0.79)
		<i>n</i>	10	12	8	8	17	17

¹Best-adjusted = estimates for a study selected in preference order of adjustment (C = comorbidities, D = demographics only, U = unadjusted, P = includes post-coronavirus disease responses).

²EE: Effect estimate from random-effects meta-analysis.

³For population = general, the results are from six studies, one providing sex-specific estimates. Four provided odds ratio (OR)s, one hazard ratios and one relative risk (RR)s and ORs.

⁴For population = tested, the results are from 15 studies, two providing sex-specific estimates, with 13 providing only ORs and two RRs, one of these also providing ORs. COVID-19: Coronavirus disease 2019; CI: Confidence interval.

COVID-19. While the unadjusted estimates show increased hospitalization rates in former and ever smokers, those adjusted for comorbidities show no indication of an increase for any index of smoking.

Supplementary Table 3 shows additional results from three studies. BIOBNK provided results based on the general population, GDEM and GU provided results on those tested for COVID-19, and GU provided results based on those hospitalized and unmatched controls. The results are rather conflicting, with GU showing markedly lower hospitalization rates in current smokers, and the other studies increased rates. In BIOBNK, adjustment tended to reduce the associations, although they remained statistically significant. GDEM reported only results adjusted for demographics and GU reported only unadjusted results.

Endpoint: Admitted to ICU

Table 3 shows the meta-analysis results based on estimates from eight studies of those positive for COVID-19 and 14 of those hospitalized with COVID-19. **Supplementary Table 4** shows the results from one general population study, and one study comparing intensive care patients with unmatched controls. Most estimates considered in **Table 3** are unadjusted, not even for age, and show little evidence of an

Table 2 Main results for endpoint: Hospitalized with coronavirus disease 2019

Selection of estimates ¹	Statistic ²	Ever vs never	Current vs non-current	Current vs never	Former vs never	Closest to current	Closest to ever
Population = positive for COVID-19 ³							
Best-adjusted	All	EE (95%CI)	1.34 (1.13-1.60)	1.00 (0.86-1.16)	1.05 (0.84-1.32)	1.31 (0.93-1.85)	1.31 (1.12-1.54)
		<i>n</i>	19	13	11	11	22
	C	EE (95%CI)	1.00 (0.76-1.32)	0.90 (0.76-1.07)	0.82 (0.52-1.30)	0.87 (0.67-1.12)	0.96 (0.79-1.18)
		<i>n</i>	6	6	4	4	8
	U	EE (95%CI)	1.53 (1.14-2.06)	1.03 (0.75-1.41)	1.13 (0.81-1.59)	1.77 (1.04-3.04)	1.44 (1.03-2.01)
		<i>n</i>	10	6	6	6	11
All estimates	U	EE (95%CI)	1.64 (1.41-1.91)	0.97 (0.71-1.32)	1.20 (1.01-1.42)	1.75 (1.35-2.27)	1.47 (1.21-1.77)
		<i>n</i>	18	13	11	11	21

¹Best-adjusted = estimates for a study selected in preference order of adjustment (C = comorbidities, D = demographics only, U = unadjusted, P = includes post-COVID responses).

²EE = effect estimate from random-effects meta-analysis.

³The results are from 21 studies, one study providing sex-specific estimates. Nineteen studies provide odds ratio (OR)s, one relative risk (RR)s and hazard ratios, and one ORs and RRs. COVID-19: Coronavirus disease 2019; CI: Confidence interval.

association between smoking and ICU admission. Exceptionally, the data in [Supplementary Table 4](#) show reduced admission rates in current smokers, and increased admission rates in former smokers, tending to diminish and become marginally significant after adjustment in the HIPPIIS study.

Endpoint: Mechanically ventilated

Fourteen studies provided results where the population involved patients hospitalized with COVID-19. While the best-adjusted effect estimates in [Table 4](#) were greater than 1.0 for each smoking index, none were statistically significant at $P < 0.05$.

[Supplementary Table 5](#) summarizes the results from three studies where the population was those tested for COVID-19. VETERA, which provided the most detailed results, did not demonstrate any clear association, with estimates for ever and for former smoking significantly increased when unadjusted, but close to 1.0 and non-significant when adjusted for comorbidities. In ESSVRD, a significant unadjusted increase again was non-significant after adjustment for comorbidities. Exceptionally, MUNOZP reported a very high OR for ever smoking after adjustment for comorbidities.

Endpoint: Severe COVID-19

[Table 5](#) shows the meta-analysis results from five studies on those positive for COVID-19 and 10 studies on those hospitalized with COVID-19. As shown in [Table 5](#), definitions of severity varied by study. Few effect estimates were adjusted for comorbidities. The smoking indices were generally associated with a small increase in severity, but this was only significant at $P < 0.05$ in one of the 12 best-adjusted meta-analysis estimates.

Endpoint: Died

[Table 6](#) summarizes the results using data from 25 studies of those hospitalized with COVID-19, and eight studies of those positive for COVID-19 regardless of hospitalization. The estimates adjusted for comorbidities were virtually never statistically significant and usually close to 1.00, but the unadjusted estimates were nearly always elevated and often statistically significant. This was very clearly illustrated by the results for “closest to ever smoking” where about a two-fold increase was seen for the unadjusted results, with little or no increase seen for the comorbidity adjusted results, regardless of the population studied. It is also clear that higher unadjusted estimates were seen for former or ever smoking than for current smoking, perhaps because

Table 3 Main results for endpoint: Admitted to intensive care unit

Selection of estimates ¹		Statistic ²	Ever vs never	Current vs non-current	Current vs never	Former vs never	Closest to current	Closest to ever
Population = positive for COVID-19 ³								
Best-adjusted	All	EE (95%CI)	1.57 (1.14-2.17)	0.87 (0.67-1.12)	0.94 (0.60-1.48)	1.55 (1.00-2.42)	1.13 (0.82-1.54)	1.40 (1.09-1.80)
		<i>n</i>	7	6	5	5	8	8
	C	EE (95%CI)	1.68 (1.15-2.46)	0.85 (0.77-0.94)	0.61 (0.11-3.36)	1.58 (0.97-2.57)	1.14 (0.54-2.41)	1.30 (0.74-2.31)
		<i>n</i>	2	2	1	1	3	3
	U	EE (95%CI)	1.42 (0.94-2.14)	0.94 (0.57-1.57)	0.98 (0.60-1.60)	1.55 (0.91-2.65)	0.98 (0.60-1.60)	1.42(0.94-2.14)
		<i>n</i>	4	4	4	4	4	4
All estimates	U	EE (95%CI)	1.52 (1.04-2.22)	1.03 (0.56-1.88)	0.92 (0.60-1.43)	1.68 (1.05-2.68)	1.11 (0.62-2.00)	1.61 (1.13-2.29)
		<i>n</i>	5	6	5	5	6	6
Population = hospitalized with COVID-19 ⁴								
Best-adjusted	All	EE (95%CI)	1.10 (0.99-1.22)	0.90 (0.72-1.12)	0.88 (0.72-1.08)	1.21 (0.99-1.47)	1.02 (0.87-1.21)	1.11 (0.98-1.25)
		<i>n</i>	9	9	6	6	14	14
	C	EE (95%CI)	1.01 (0.88-1.16)	0.80 (0.61-1.04)	0.81 (0.61-1.07)	1.07 (0.92-1.24)	0.81 (0.61-1.07)	1.01 (0.88-1.16)
		<i>n</i>	1	1	1	1	1	1
	U	EE (95%CI)	1.22 (1.04-1.43)	1.09 (0.93-1.27)	0.96 (0.70-1.31)	1.30 (1.00-1.70)	1.16 (1.05-1.28)	1.19 (1.08-1.30)
		<i>n</i>	8	7	5	5	12	12
All estimates	U	EE (95%CI)	1.20 (1.09-1.32)	1.00 (0.87-1.13)	0.89 (0.74-1.06)	1.28 (1.10-1.48)	1.05 (0.95-1.17)	1.14 (1.04-1.24)
		<i>n</i>	9	9	6	6	14	14

¹Best-adjusted = estimates for a study selected in preference order of adjustment (C = comorbidities, U = unadjusted, P = includes post coronavirus disease responses).

²EE = effect estimate from random-effects meta-analysis.

³For population = positive, the results are from eight studies. Six provided odds ratio (OR)s and two relative risk (RR)s;

⁴For population = hospitalized, the results are from 14 studies. Twelve provided ORs and two RRs. COVID-19: Coronavirus disease 2019; CI: Confidence interval.

former smokers tend to be older than current or never smokers.

Table 6 does not include results where the population studied was those admitted to the ICU, as these form a subset of those reported in Table 7; see the next section.

Results were also available from three studies based on other populations (Supplementary Table 6). OPENSA provided estimates based on the general population, and these seem consistent with the pattern shown in Table 6. For former smoking, for example, an unadjusted estimate of 2.53 [95% confidence interval (CI): 2.43-2.63] reduced to 1.19 (1.14-1.24) after adjustment for comorbidities. Two other studies only reported unadjusted results. PELLAU found no increase in smokers (undefined) when comparing hospitalized patients with and without COVID-19, while GU reported an increased risk of death in former and ever smokers and a decreased risk in current smokers, whether the tested population was considered or whether decedents were compared to unmatched controls.

Not considered above was the KNIGHT study, which provided no effect estimates, merely stating that ever cigarette smoking predicted death from COVID-19.

Other endpoints

As shown in Table 7, nine studies reported results on the endpoint worsened or died, based on those with severe disease. Most estimates relate to death among those in the

Table 4 Main results for endpoint: Mechanically ventilated

Selection of estimates ¹		Statistic ²	Ever vs never	Current vs non-current	Current vs never	Former vs never	Closest to current	Closest to ever
Population = hospitalized for COVID-19 ³								
Best-adjusted	All	EE (95%CI)	1.05 (0.88-1.25)	1.11 (0.72-1.71)	1.12 (0.60-2.09)	1.16 (0.87-1.55)	1.08 (0.86-1.36)	1.11 (0.92-1.35)
		<i>n</i>	12	8	5	5	15	15
	C	EE (95%CI)	1.04 (0.79-1.36)	1.94 (0.40-9.49)	2.77 (0.28-27.2)	2.43 (0.32-18.5)	0.99 (0.77-1.29)	1.04 (0.79-1.36)
		<i>n</i>	7	2	2	2	7	7
	U	EE (95%CI)	1.06 (0.94-1.21)	1.12 (0.60-2.09)	0.76 (0.59-0.98)	1.10 (0.96-1.27)	1.16 (0.80-1.67)	1.24 (0.99-1.54)
		<i>n</i>	5	5	3	3	7	7
All estimates	U	EE (95%CI)	1.07 (0.92-1.26)	1.10 (0.80-1.51)	1.09 (0.60-1.95)	1.12 (0.98-1.28)	1.12 (0.98-1.38)	1.17 (1.00-1.37)
		<i>n</i>	10	8	5	5	13	13

¹Best-adjusted = estimates for a study selected in preference order of adjustment (C = comorbidities, D = demographics only, U = unadjusted, P = includes post-coronavirus disease responses).

²EE = effect estimate from random-effects meta-analysis.

³Fourteen studies provided results, one providing estimates for two age groups. Thirteen studies provided odds ratios and one relative risks. COVID-19: Coronavirus disease 2019; CI: Confidence interval.

ICU or those requiring mechanical ventilation. There was a tendency for smoking to be positively associated with the endpoint. However, each estimate was unadjusted even for demographic variables.

Two studies reported results for endpoints worse than hospitalization among those tested for COVID-19 (see [Supplementary Table 7](#)). Based on estimates adjusted for demographics only, GDEM reported a significant increased risk of pneumonia in current smokers, but no increase in intensive care admissions or need for mechanical ventilation. Similar to the results shown in [Supplementary Table 6](#) for death, and based on unadjusted estimates, GU reported an increased risk of ICU admission in former and ever smokers and a decreased risk in current smokers.

Consistency of results in subgroups

[Table 8](#) compares best-adjusted effect estimates by level of adjustment, effect estimate type, location and study size separately for the indices of smoking closest to current smoking and closest to ever smoking, and for the six combinations of endpoint and population where data were available for at least 10 studies.

For level of adjustment, the results echo those summarized above, with adjustment for comorbidities eliminating unadjusted associations of both current and ever smoking with hospitalization within those COVID-19 positive, and with ICU admission and death within those hospitalized for COVID-19.

Significant variation by type of effect estimate was only seen in two of the 12 analyses, and where it was seen may reflect the fact that the unadjusted estimates were typically ORs.

There is no convincing evidence that effect estimates vary by location.

Large studies, involving 50000 or more individuals, showed no significant increases with smoking in any of the analyses shown. Again, higher effect estimates seen in smaller studies may reflect a greater tendency for such studies to report unadjusted results.

Although meta-analyses were attempted by sex, none of them included sex-specific results from more than two studies, and the results are not shown in [Table 8](#). There were even fewer studies reporting results by age, or by sex and age jointly, so meta-analyses by these factors were not attempted.

Dose-response results

Only one study, HIPPIIS, reported results by amount smoked in current smokers, and only one, TOOLKI, by quit duration in former smokers. Neither study showed a

Table 5 Results for endpoint: Severe coronavirus disease 2019¹

Selection of estimates ²		Statistic ³	Ever vs never	Current vs non-current	Current vs never	Former vs never	Closest to current	Closest to ever
Population = positive ⁴								
Best-adjusted	All	EE (95%CI)	1.39 (1.07-1.80)	1.04 (0.91-1.20)	1.27 (0.82-1.95)	1.20 (0.62-2.32)	1.10 (0.97-1.25)	1.10 (0.97-1.25)
		<i>n</i>	7	5	4	4	8	8
	C	EE (95%CI)	-	1.02 (0.88-1.18)	-	-	1.02 (0.88-1.18)	1.02 (0.88-1.18)
		<i>n</i>	0	1	0	0	1	1
	U	EE (95%CI)	1.30 (0.94-1.79)	1.26 (0.82-1.93)	1.27 (0.82-1.95)	1.20 (0.62-2.32)	1.35 (0.95-1.92)	1.30 (0.94-1.79)
		<i>n</i>	5	4	4	4	5	5
All estimates	U	EE (95%CI)	1.63 (1.27-2.10)	1.17 (1.09-1.25)	1.27 (0.82-1.95)	1.20 (0.62-2.32)	1.48 (1.13-1.94)	1.45 (1.12-1.86)
		<i>n</i>	7	5	4	4	8	8
Population = hospitalized ⁵								
Best-adjusted	All	EE (95%CI)	1.15 (0.87-1.51)	1.05 (0.93-1.18)	0.74 (0.49-1.12)	1.07 (0.87-1.32)	1.08 (0.94-1.25)	1.09 (0.98-1.22)
		<i>n</i>	7	5	2	2	10	10
	C	EE (95%CI)	1.35 (0.66-2.75)	0.76 (0.50-1.15)	0.77 (0.51-1.17)	1.06 (0.86-1.31)	1.23 (0.46-3.27)	1.35 (0.66-2.75)
		<i>n</i>	2	1	1	1	2	2
	U	EE (95%CI)	1.38 (1.04-1.83)	1.12 (1.04-1.21)	0.29 (0.03-2.64)	1.25 (0.56-2.76)	1.17 (0.99-1.37)	1.14 (1.06-1.23)
		<i>n</i>	4	3	1	1	6	6
All estimates	U	EE (95%CI)	1.40 (1.20-1.63)	1.14 (1.04-1.24)	0.89 (0.54-1.46)	1.48 (1.23-1.80)	1.17 (1.08-1.27)	1.21 (1.12-1.29)
		<i>n</i>	6	5	2	2	9	9

¹In most studies the endpoint was severe coronavirus disease 2019 (COVID-19) as defined by the author, but it was admitted to ICU or died in two studies, pneumonia in one, increased oxygen required in one and COVID-19 progressed in one.

²Best-adjusted = estimates for a study selected in preference order of adjustment (C = comorbidities, U = unadjusted, P = includes post-COVID responses).

³EE = effect estimate from random-effects meta-analysis.

⁴For population = positive, the results are from five studies, one study providing four estimates by age and sex. All estimates are odds ratio (OR)s.

⁵For population = hospitalized, the results are from 10 studies, nine providing ORs and one relative risks and hazard ratios. COVID-19: Coronavirus disease 2019; CI: Confidence interval.

significant dose-response relationship for any of the endpoint/population combinations considered (results not shown).

DISCUSSION

Table 9 summarizes the results from the meta-analyses of the 10 endpoint/population combinations shown in Tables 1 to 6. Results for the best estimates are shown, where estimates adjusted for comorbidities (and not responses to COVID-19) were preferred, with those adjusted for demographics preferred to unadjusted estimates, and those adjusted for factors including responses to the infection being least preferred. Results are also presented for comorbidity-adjusted estimates and for unadjusted estimates. The results show no consistent evidence of publication bias.

The clearest result shows that, of those tested for COVID-19, smoking was associated with a reduced risk of positivity (Figures 2 and 3), with less clear evidence of a negative association between smoking and positivity seen among the general population.

Table 6 Main results for endpoint: Died

Selection of estimates ¹		Statistic ²	Ever vs never	Current vs non-current	Current vs never	Former vs never	Closest to current	Closest to ever
Population = hospitalized with COVID-19 ³								
Best-adjusted	All	EE (95%CI)	1.42 (1.19-1.70)	0.99 (0.89-1.10)	1.12 (0.98-1.29)	1.61 (1.34-1.92)	1.27 (1.08-1.49)	1.42 (1.22-1.65)
		<i>n</i>	18	10	10	10	25	25
	C	EE (95%CI)	1.07 (0.82-1.38)	0.64 (0.12-3.35)	1.02 (0.70-1.49)	1.15 (1.02-1.29)	1.09 (0.84-1.40)	1.12 (0.91-1.39)
		<i>n</i>	8	2	3	3	10	10
	U	EE (95%CI)	1.78 (1.40-2.26)	0.95 (0.77-1.16)	1.18 (0.91-1.52)	1.92 (1.48-2.50)	1.52 (1.22-1.91)	1.79 (1.47-2.19)
		<i>n</i>	9	6	6	6	13	13
All estimates	U	EE (95%CI)	1.59 (1.37-1.83)	1.00 (0.88-1.13)	1.12 (0.97-1.29)	1.80 (1.48-2.17)	1.33 (1.18-1.51)	1.58 (1.39-1.78)
		<i>n</i>	15	10	9	9	20	20
Population = with COVID-19 ⁴								
Best-adjusted	All	EE (95%CI)	1.41 (0.93-2.14)	0.96 (0.92-1.01)	0.98 (0.72-1.32)	1.61 (0.79-3.29)	1.08 (0.82-1.42)	1.34 (0.96-1.86)
		<i>n</i>	7	6	5	5	8	8
	C	EE (95%CI)	0.99 (0.87-1.13)	0.96 (0.92-1.01)	0.85 (0.67-1.07)	1.04 (0.91-1.19)	0.96 (0.92-1.01)	0.97 (0.93-1.02)
		<i>n</i>	3	4	3	3	4	4
	U	EE (95%CI)	2.07 (1.12-3.82)	0.93 (0.60-1.46)	1.49 (0.94-2.36)	2.70 (1.11-6.58)	1.59 (1.40-1.80)	2.07 (1.12-3.82)
		<i>n</i>	3	2	2	2	3	3
All estimates	U	EE (95%CI)	2.04 (1.39-3.02)	1.06 (0.39-2.90)	1.07 (0.72-1.58)	2.58 (1.31-5.07)	1.52 (0.89-2.60)	2.22 (1.51-3.27)
		<i>n</i>	5	5	4	4	6	6

¹Best-adjusted = estimates for a study selected in preference order of adjustment [C = comorbidities, D = demographics only, U = unadjusted, P = includes post-coronavirus disease (COVID) responses.

²EE = effect estimate from random-effects meta-analysis.

³For population = hospitalized, the results are from twenty four studies, one providing age-specific estimates. Seventeen provided only odds ratio (OR)s, two only hazard ratio (HR)s, two only relative risk (RR)s, and three RRs and HRs, one of these also providing ORs.

⁴For population = with COVID-19, the results are from eight studies, six providing ORs, one RRs and one HRs and RRs. COVID-19: Coronavirus disease 2019; CI: Confidence interval.

In contrast, all the best estimates for the other eight endpoint/population combinations, each of which relate to adverse events in those positive for, or hospitalized with COVID-19, were greater than 1 (ranging from 1.02 to 1.42), with five of the 16 estimates statistically significant (at $P < 0.05$). However, there was a clear difference between estimates unadjusted for other risk factors, where nine of the 16 estimates were significant, and those adjusted for comorbidities where none were significant and six were below 1.0. This difference is strikingly seen for the most commonly considered endpoint/population combination - died among those hospitalized - where (Figures 4 and 5) unadjusted estimates of 1.52 (95%CI: 1.22-1.91) for the smoking index closest to current smoking and 1.79 (1.47-2.19) for that closest to ever smoking can be contrasted with comorbidity adjusted estimates of, respectively, 1.09 (0.84-1.40) and 1.12 (0.91-1.39).

A major limitation of the available data is that, of the 73 studies which provided effect estimates, adjusted results were available for only 42. In most epidemiological contexts, effect estimates adjusted for age and sex are a basic starting point for analysis, but this was not so here. Given the different age distribution of current, former and never smokers and the strong age relationship to severe COVID-19 and death, unadjusted estimates would seem likely to be biased, as would the analyses

Table 7 Results for endpoint: Worsened or died¹

Selection of estimates ²	Statistic ³	Ever vs never	Current vs non-current	Current vs never	Former vs never	Closest to current	Closest to ever
Unadjusted ⁴	EE (95%CI)	1.34 (1.00-1.79)	1.31 (1.06-1.62)	1.21 (0.35-4.17)	2.01 (0.67-6.09)	1.27 (1.15-1.39)	1.36 (1.15-1.62)
	<i>n</i>	5	5	3	3	9	9

¹Seven studies considered death among those admitted to the intensive care unit (ICU), and one of these and one other considered death among those mechanically ventilated. One considered admission to ICU or death among those hospitalized with severe coronavirus disease 2019.

²All estimates were unadjusted.

³EE = effect estimate from random-effects meta-analysis.

⁴The data are from nine studies, five reporting odds ratio (OR)s, two relative risk (RR)s and two RRs and hazard ratios, one of these also reporting ORs. CI: Confidence interval.

which adjusted for variables representing a response to the virus. The most useful analyses were based on estimates adjusted for demographics only, or those adjusted also for comorbidities. These answer different questions. Analyses adjusted for demographics and comorbidities attempted to answer the question “Is a smoker more at risk of COVID-19 related outcome (such as hospitalization, admission to intensive care, undergoing mechanical ventilation or death) than an otherwise equivalent never smoker of the same age, sex and other relevant demographics and health status pre-pandemic?” This is a valid question and is somewhat equivalent to that investigated in a cohort study where smoking, demographics and health status were recorded at baseline, and smoking was related to an outcome occurring during follow-up. In analyses adjusting for demographics only, any increased risk of COVID-19 related outcomes in smokers may be due to their poorer status of health pre-pandemic. While clear answers to both questions would be nice to have, it must be noted that there are very few studies providing effect estimates adjusted only for demographics. Thus, considering deaths in the hospitalized population, only three out of 25 studies with relevant data provided estimates adjusted for demographics only, and none provided comparable unadjusted, demographic adjusted and comorbidity adjusted effect estimates.

Another problem is that some studies provided ORs, some RRs and some HRs. Where results for the relevant 2 × 2 table on exposure × outcome were available, and the ORs and RRs were both estimable, we generally used the OR, using the RR only where the source paper had reported adjusted RRs or HRs. Although we could have used an alternative strategy, it is doubtful whether this would have materially affected our results, given the general consistency of the results by type of effect estimate.

Another possible concern is with the mortality data. Much relates to deaths occurring in patients hospitalized with COVID-19, and many publications implicitly assume all those deaths were due to the virus, when some might have been due to other causes. However, given this proportion is small, it seems probable that this would only result in a minor bias.

More concern relates to the quality of the smoking data. There are two issues here. One is the way smoking was recorded and defined, with eight studies reporting results for smoking undefined, and only 36 distinguishing current and former smoking. Also, only one study reported results by amount smoked, and only one reported results by duration of quit. Furthermore, papers generally did not provide details on the smoking questions asked, or when they were asked.

The other issue is that many studies derived their smoking data from medical records, known to be incomplete and inaccurate[37-39]. While many studies gave no information concerning missing data on smoking, 35 did so, and in 13 the proportion with missing data exceeded 20%, giving concern about the validity of their effect estimates. It would not surprise us to find that, in some studies that did not mention missing data, the “non-smokers” included some individuals never actually asked about their smoking.

Recent publications, particularly by Farsalinos *et al*[2-4,6-8], have observed that the prevalence of smoking seen in the studies of hospitalized patients was substantially less than reported in national statistics by a factor of four or so, and have suggested that smokers might be protected against getting COVID-19. While the mean percentage of current and former smokers in the studies of hospitalized patients that we considered (current 7.76%, SE 1.00%; ever 33.24%, SE 2.01%) was clearly less than in the studies of the general population (current 15.14%, SE 1.34%; ever 44.0%, SE

Table 8 Variations in best-adjusted effect estimates by level of adjustment, effect estimate type, location and study size

Factor/level	Endpoint	CP	H	IC	MV	S	M
	Population	T	CP	H	H	H	H
	Estimates	17	22	14	15	10	25
Estimates for closest to current smoking							
Adjustment	U	0.55 (0.45-0.67)	1.44 (1.03-2.01)	1.16 (1.05-1.28)	1.16 (0.80-1.67)	1.17 (0.99-1.37)	1.52 (1.22-1.91)
	D	0.23 (0.09-0.59)	1.52 (1.18-1.95)	0.73 (0.56-0.96)	0.85 (0.67-1.07)	1.02 (0.89-1.16)	1.01 (0.87-1.17)
	C	0.58 (0.43-0.80)	0.96 (0.79-1.18)	0.81 (0.61-1.07)	0.99 (0.77-1.29)	1.23 (0.46-3.27)	1.09 (0.84-1.40)
	PC	-	-	-	-	0.71 (0.41-1.23)	-
	<i>P</i>	NS	< 0.05	< 0.001	NS	NS	< 0.05
Estimate type	OR	0.54 (0.46-0.63)	1.26 (0.97-1.64)	1.07 (0.87-1.32)	1.13 (0.88-1.44)	1.09 (0.93-1.27)	1.35 (1.07-1.70)
	RR	0.64 (0.31-1.34)	1.25 (1.20-1.31)	0.90 (0.71-1.15)	0.73 (0.56-0.95)	-	1.11 (0.87-1.40)
	HR	-	1.10 (0.97-1.24)	-	-	1.02 (0.64-1.63)	1.15 (0.89-1.50)
	<i>P</i>	NS	NS	NS	< 0.05	NS	NS
Location	United States	0.45 (0.37-0.54)	1.27 (1.11-1.46)	1.00 (0.81-1.22)	1.02 (0.83-1.26)	1.06 (0.72-1.56)	1.21 (0.95-1.53)
	Other	0.64 (0.55-0.73)	1.11 (0.48-2.57)	1.08 (0.79-1.49)	1.05 (0.65-1.71)	1.10 (1.02-1.17)	1.34 (1.07-1.69)
	<i>P</i>	< 0.01	NS	NS	NS	NS	NS
Study size	< 500	-	0.99 (0.58-1.69)	1.25 (0.91-1.71)	1.35 (1.02-1.80)	1.02 (0.65-1.59)	1.29 (0.97-1.72)
	500-	0.40 (0.27-0.61)	1.42 (1.17-1.72)	1.07 (0.69-1.65)	0.92 (0.34-2.46)	1.62 (1.14-2.29)	1.57 (1.20-2.05)
	5000-	0.51 (0.39-0.66)	1.43 (0.97-2.10)	0.64 (0.29-1.42)	0.83 (0.70-0.98)	0.81 (0.56-1.19)	1.03 (0.83-1.28)
	50,000+	0.67 (0.51-0.87)	1.00 (0.85-1.18)	0.97 (0.72-1.31)	0.98 (0.61-1.59)	1.09 (0.99-1.19)	0.94 (0.82-1.07)
	<i>P</i>	NS	< 0.05	NS	< 0.05	NS	< 0.01
Estimates for closest to ever smoking							
Adjustment	U	0.67 (0.58-0.78)	1.71 (1.24-2.36)	1.19 (1.08-1.30)	1.24 (0.99-1.54)	1.14 (1.06-1.23)	1.79 (1.47-2.19)
	D	0.23 (0.09-0.59)	1.41 (1.04-1.92)	0.73 (0.56-0.96)	0.85 (0.67-1.07)	1.02 (0.89-1.16)	1.11 (0.81-1.53)
	C	0.77 (0.64-0.92)	0.93 (0.80-1.08)	1.01 (0.88-1.16)	1.04 (0.79-1.36)	1.35 (0.66-2.75)	1.12 (0.91-1.39)
	PC	-	-	-	-	0.71 (0.41-1.23)	-
	<i>P</i>	< 0.05	< 0.001	< 0.01	NS	NS	< 0.01
Estimate type	OR	0.67 (0.59-0.76)	1.39 (1.08-1.79)	1.16 (0.99-1.37)	1.14 (0.91-1.42)	1.10 (0.98-1.24)	1.53 (1.19-1.96)
	RR	0.87 (0.59-1.27)	1.25 (1.20-1.31)	1.01 (0.89-1.15)	1.02 (0.88-1.18)	-	1.16 (1.05-1.29)
	HR	-	1.03 (0.95-1.11)	-	-	1.02 (0.64-1.63)	1.28 (1.14-1.44)
	<i>P</i>	NS	< 0.001	NS	NS	NS	NS
Location	United States	0.65 (0.50-0.84)	1.38 (1.14-1.67)	1.10 (0.99-1.23)	1.08 (0.90-1.30)	1.15 (0.87-1.51)	1.43 (1.11-1.84)
	Other	0.74 (0.66-0.82)	1.31 (0.64-2.71)	1.08 (0.79-1.49)	1.05 (0.65-1.71)	1.10 (1.02-1.17)	1.43 (1.19-1.73)
	<i>P</i>	NS	NS	NS	NS	NS	NS
Study size	< 500	-	1.21 (0.84-1.75)	1.25 (0.93-1.69)	1.29 (0.95-1.76)	1.06 (0.74-1.52)	1.36 (1.05-1.75)
	500-	0.55 (0.37-0.80)	1.32 (0.99-1.76)	1.04 (0.92-1.18)	1.24 (0.77-2.00)	1.62 (1.14-2.29)	1.70 (1.34-2.16)
	5000-	0.64 (0.50-0.81)	1.71 (1.18-2.49)	1.48 (1.10-2.00)	0.83 (0.70-0.98)	1.00 (0.83-1.22)	1.27 (0.96-1.68)
	50000+	0.81 (0.73-0.89)	0.97 (0.88-1.07)	0.97 (0.73-1.28)	1.10 (0.79-1.52)	1.09 (0.99-1.19)	0.94 (0.82-1.07)
	<i>P</i>	< 0.05	< 0.01	NS	< 0.05	NS	< 0.001

The table shows effect estimates with 95% confidence interval. Variation between levels of a factor is coded as $P < 0.001$, $P < 0.01$, $P < 0.05$ or NS ($P \geq 0.05$).
 C: Adjusted for comorbidities; CP: Coronavirus disease 2019 positive; D: Adjusted for demographics only; H: Hospitalized; HR: Hazard ratio; IC: Intensive

care; M: Mortality; MV: Mechanical ventilation; OR: Odds ratio; PC: Adjusted for variables including post-coronavirus disease 2019 responses; RR: Relative risk; S: Severe coronavirus disease 2019; T: Tested for coronavirus disease 2019; U: Unadjusted.

Table 9 Summary of results from meta-analyses¹

Endpoint	Population	Smoking index = closest to current smoking			Smoking index = closest to ever smoking		
		Best estimate ²	Comorbidity adjusted ³	Unadjusted ⁴	Best estimate ²	Comorbidity adjusted ³	Unadjusted ⁴
Positive	General	0.78 (0.57-1.06) ⁵	0.96 (0.42-2.17)	0.56 (0.42-0.75) ⁵	0.89 (0.73-1.09)	1.10 (0.70-1.72)	0.65 (0.55-0.77)
Positive	Tested	0.55 (0.47-0.65)	0.58 (0.43-0.80)	0.55 (0.45-0.67)	0.70 (0.63-0.77)	0.77 (0.64-0.92)	0.67 (0.58-0.78)
Hospitalized	Positive	1.31 (1.12-1.54)	0.96 (0.79-1.18)	1.44 (1.03-2.01)	1.38 (1.17-1.63)	0.93 (0.80-1.08)	1.71 (1.24-2.36)
ICU admission	Positive	1.13 (0.82-1.54)	1.14 (0.54-2.41)	0.98 (0.60-1.60)	1.40 (1.09-1.80) ⁵	1.30 (0.74-2.31)	1.42 (0.94-2.14)
ICU admission	Hospitalized	1.02 (0.87-1.21)	0.81 (0.61-1.07)	1.16 (1.05-1.28)	1.11 (0.98-1.25)	1.01 (0.88-1.16)	1.19 (1.08-1.30)
Mechanically ventilated	Hospitalized	1.08 (0.86-1.36)	0.99 (0.77-1.29) ⁵	1.16 (0.80-1.67)	1.11 (0.92-1.35)	1.04 (0.79-1.36) ⁵	1.24 (0.99-1.54)
Severe	Positive	1.10 (0.97-1.25) ⁵	1.02 (0.88-1.18)	1.35 (0.95-1.92)	1.10 (0.97-1.25) ⁵	1.02 (0.88-1.18)	1.30 (0.94-1.79)
Severe	Hospitalized	1.08 (0.94-1.25)	1.23 (0.46-3.27)	1.17 (0.99-1.37)	1.09 (0.98-1.22)	1.35 (0.66-2.75)	1.14 (1.06-1.23)
Died	Positive	1.08 (0.82-1.42)	0.96 (0.92-1.01)	1.59 (1.40-1.80)	1.34 (0.96-1.86)	0.97 (0.93-1.02)	2.07 (1.12-3.82)
Died	Hospitalized	1.27 (1.08-1.49) ⁵	1.09 (0.84-1.40)	1.52 (1.22-1.91)	1.42 (1.22-1.65)	1.12 (0.91-1.39)	1.79 (1.47-2.19)

¹See also Tables 1 to 6 for further details. Data shown are random-effects estimates with 95% confidence interval.

²Best estimates based on, respectively, 7, 17, 22, 8, 14, 15, 8, 10, 8 and 25 effect estimates (total 134).

³Comorbidity adjusted estimates based on, respectively, 3, 5, 8, 3, 1, 7, 1, 2, 4 and 10 (total 44).

⁴Unadjusted estimates based on, respectively, 3, 11, 11, 4, 12, 7, 5, 6, 3 and 13 (total 75). The unadjusted results shown are based only on those included in the best estimates;

⁵Significant publication bias ($P < 0.05$). ICU: Intensive care unit.

1.75%), the difference was only by a factor of 2 or 1.3 rather than about 4. While we also showed a reduced risk in smokers of COVID-19 positivity in those tested (Table 1), the reduction was again much less than the factor reported by Farsalinos *et al* [6]. Although it is possible that some of the difference between our results and those of Farsalinos *et al* [6] has arisen as we excluded Asian studies, while their results mainly came from Asia, the fact that two out of the three studies on the general population that we considered found no reduced risk of hospitalization in smokers (Supplementary Table 3) suggests to us that the low prevalence of smoking seen in hospitalized patients may largely result from incompleteness of data in hospital records, although it would also be consistent with smokers with COVID-19 tending to be less likely to appear for testing or report to hospital.

As noted in the introduction, there were, by the end of September 2020 (the final date of the searches used to produce these results), quite a number of published meta-analyses which relate smoking to adverse events such as deaths or severity of COVID-19 [3,6,9-28]. These meta-analyses had various limitations, including little attention to possible data inadequacy, limiting attention to studies of hospitalized patients and considering few, if any, studies conducted outside Asia. They also include paying scant attention to the need for adjusting effect estimates for other risk factors. Many of the studies and meta-analyses we considered demonstrated that dying from COVID-19, for example, was strongly related to various factors associated with smoking, including age, obesity, and a history of respiratory, cardiovascular and other diseases, and yet they attempt to draw conclusions for smoking from unadjusted analyses.

By now, we are aware of further meta-analyses that have been conducted, including those that concentrate on smoking [11,19,29,40,41] and those that consider smoking as one of a list of factors considered [16,20,21,42-55]. While some of the reviews considered far more studies than the earlier reviews, including those in non-Asian populations, the weaknesses seen generally persist. Thus, for example, a recent review

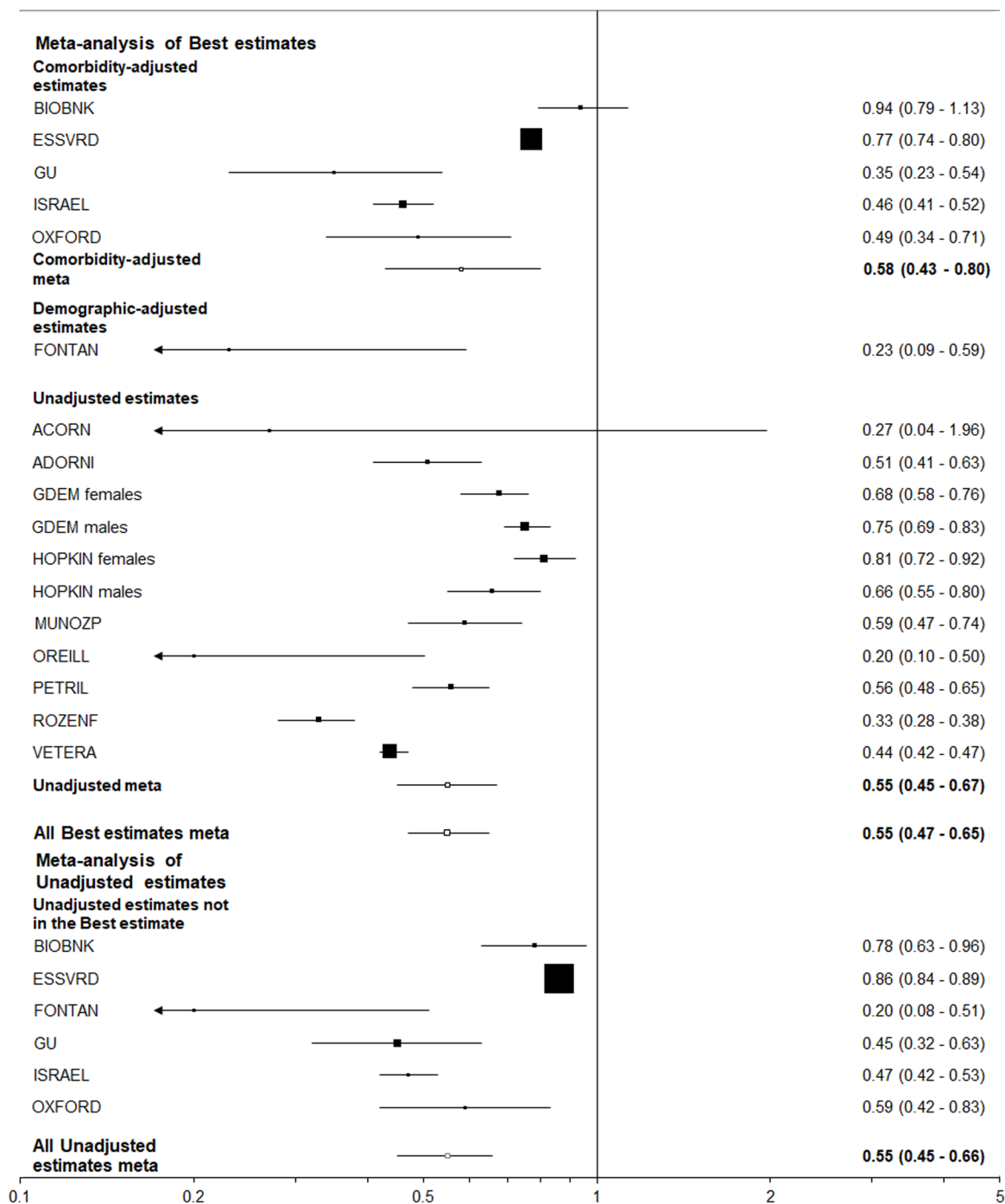


Figure 2 Forest plot of the relationship of the index “closest to current smoking” to positivity for coronavirus disease 2019 among those tested. The individual study effect estimates and random-effects combined effect estimates are shown, both as numbers and as horizontal lines with the weight of the estimate indicated by a box of proportional size. “Best estimates” are selected in the preference order (first to last) comorbidity-adjusted, demographic-adjusted and unadjusted. Estimates from ESSVRD, GDEM and HOPKIN are for current vs non-smokers, from FONTAN and OREILL for smokers (undefined) vs non-smokers, and from MUNOZP and ROZENF for ever vs never smokers, with estimates from the other eight studies being for current vs never smokers.

of 109 studies[41] limited attention to hospitalized patients, considered only unadjusted effect estimates, hardly mentioned lack of adjustment as a possible weakness, and paid very limited attention to the possibility that smoking data from hospital records may be inadequate.

That meta-analysis[41] described the 109 studies included as being all of moderate or high quality and some of the other reviews also attempted to evaluate study quality. We did not attempt classification of study quality, but given so many studies used medical records as the source of smoking data and failed to present results adjusted even for basic demographics, we doubt very much that we would have considered more than a few studies to be of high or even moderate quality. This view aligns with that of a recent meta-analysis[29] which rejected 201 of 233 studies as being

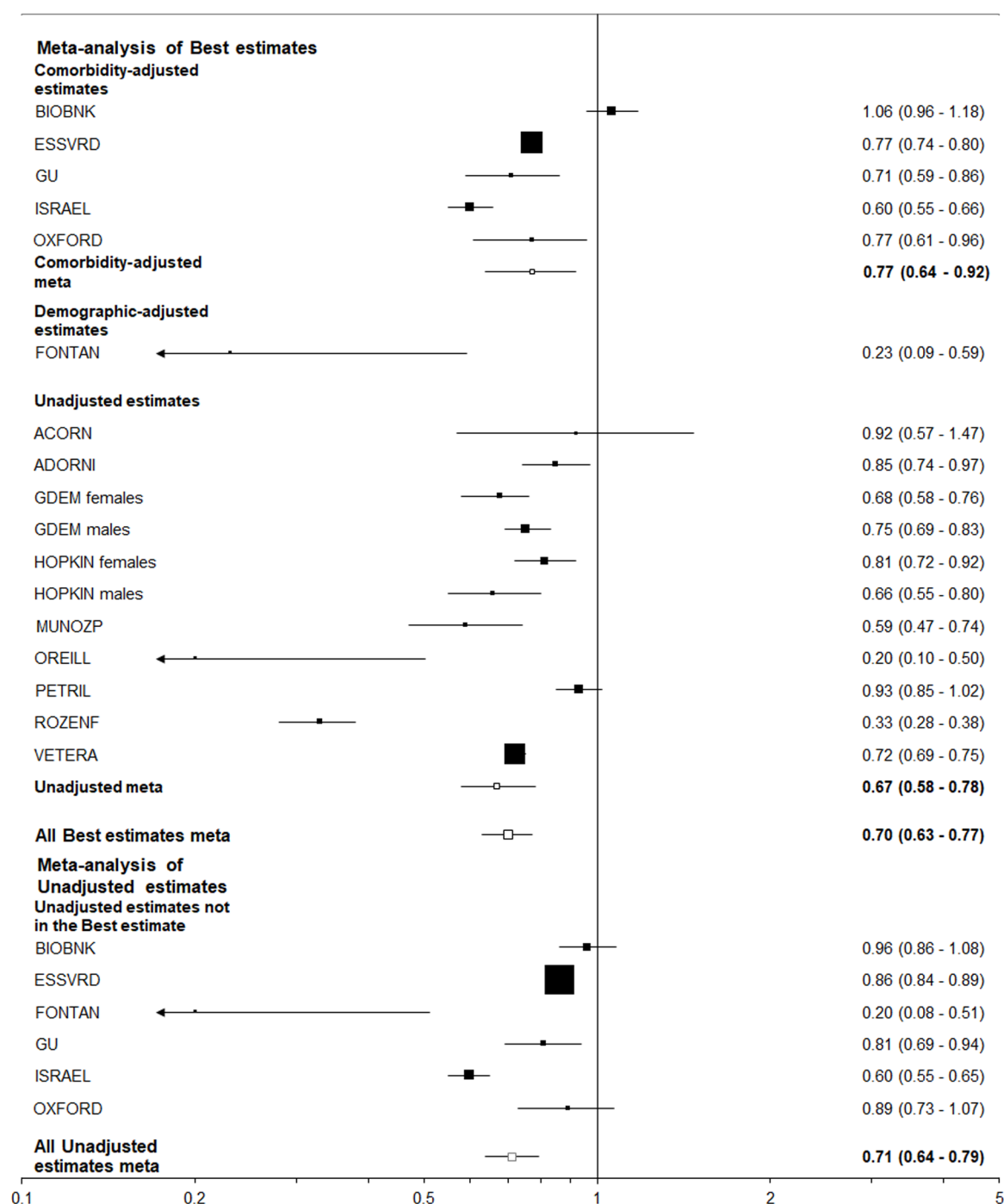


Figure 3 Forest plot of the relationship of the index “closest to ever smoking” to positivity for coronavirus disease 2019 among those tested. This figure is laid out as described for Figure 2. Estimates from ESSVRD, GDEM and HOPKIN are for current vs non-smokers, from FONTAN and OREILL for smokers (undefined) vs non-smokers, with estimates from the other 10 studies being for ever vs never smokers.

of poor quality, with only one of the studies considered in their meta-analyses considered to be of good quality and the rest classified as fair.

Our meta-analyses have various strengths, including giving careful attention to adjustment, considering many combinations of outcome and population at-risk, and including meta-analyses comparing estimates by factors such as location, study size and type of estimate considered. Weaknesses relate mainly to the poor underlying data quality, much from medical records, and many studies failing to provide adjusted estimates. Almost complete lack of data for males and females separately, and by age group is also a limitation, as is the very limited data on amount smoked or quit duration. Other possible limitations relate to the fact that, with the exception of studies from Israel, we did not consider results from other Asian countries; thus, our conclusions may not necessarily apply to all locations. We also did not consider

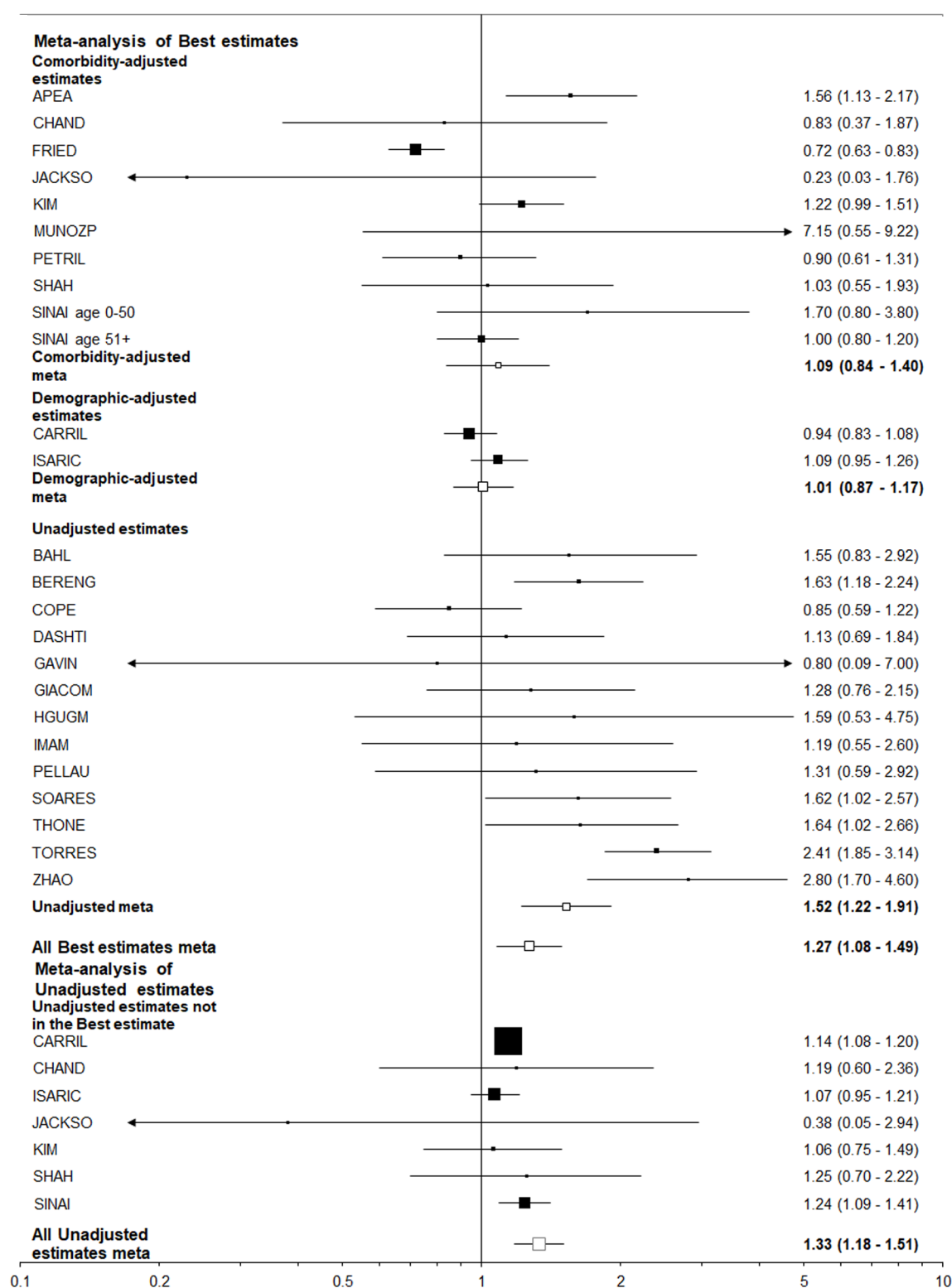


Figure 4 Forest plot of the relationship of the index “closest to current smoking” to death among those hospitalized for coronavirus disease 2019. This figure is laid out as described for Figure 2. Estimates from CARRIL are for current vs non-smokers, from APEA, HGUGM, PELLAU, SOARES and TORRES for smokers (undefined) vs non-smokers, and from CHAND, FRIED, GIACOM, IMAM, MUNOZP, SHAH, SINAI, THONE and ZHAO for ever vs never smokers, with estimates from the other nine studies being for current vs never smokers.

studies involving less than 100 cases as their results would be less reliable, and studies of patients with specific diseases as their results would not be generalizable.

However, we feel that our meta-analysis provides a good insight into the relationship between smoking and a variety of endpoints relevant to COVID-19.

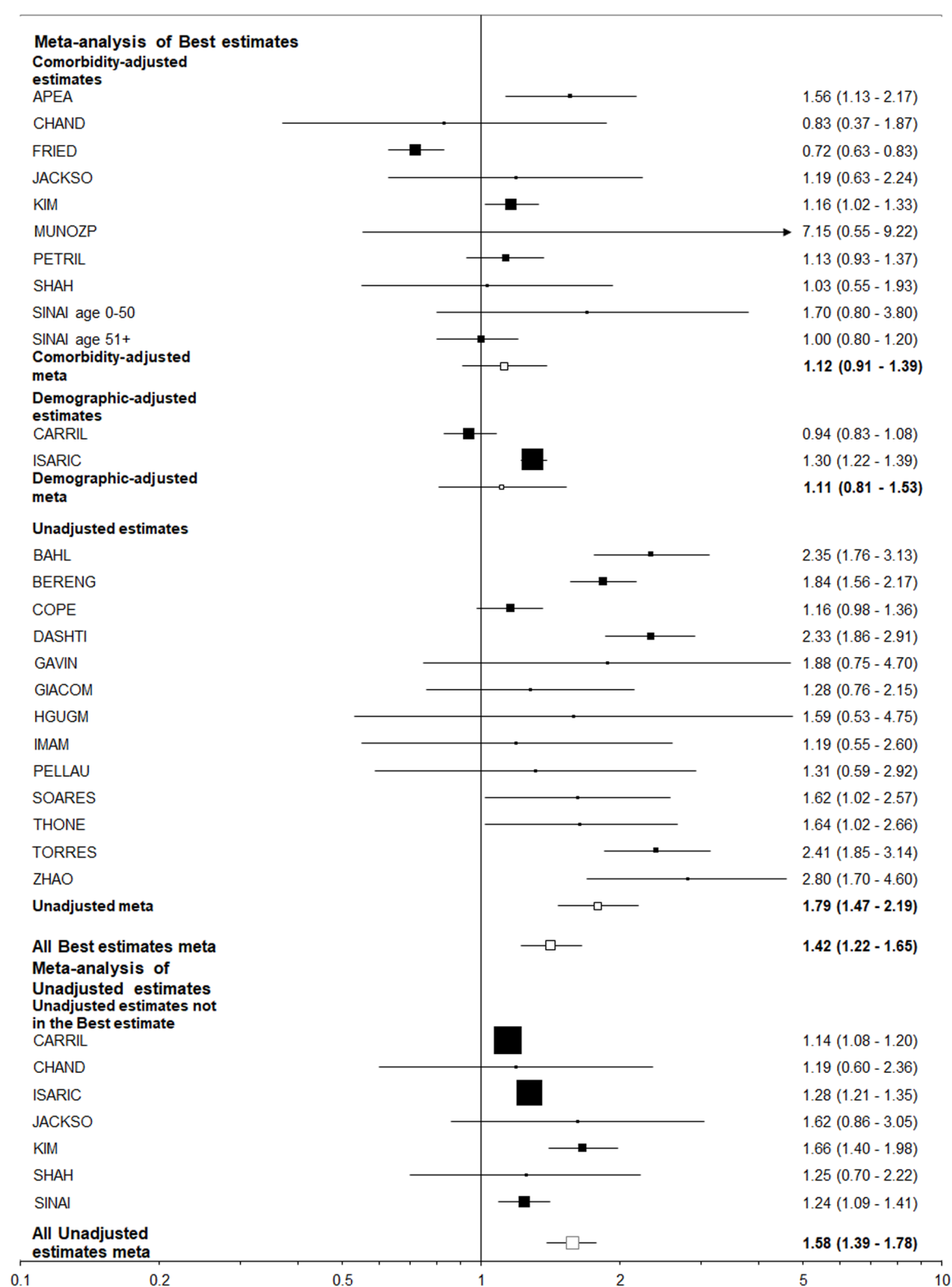


Figure 5 Forest plot of the relationship of the index “closest to ever smoking” to death among those hospitalized for coronavirus disease 2019. This figure is laid out as described for Figure 2. Estimates from CARRIL are for current vs non-smokers, from APEA, HGUGM, PELLAU, SOARES and TORRES for smokers (undefined) vs non-smokers, and from PETRIL for former vs never smokers, with estimates from the other 17 studies being for ever vs never smokers.

CONCLUSION

Based on data from 74 studies conducted in Europe, Israel, America and Australasia, many providing only limited results, there is evidence that, among those tested for COVID-19, smokers are less likely to be positive for the virus. There is also less clear evidence of reduced positivity in smokers in the general population. Among those

who are positive for, or hospitalized with, COVID-19 there is a positive association between smoking and both death and severity of COVID-19. This association is most clearly seen for effect estimates unadjusted for other risk factors, and is not evident for estimates adjusted for comorbidities and demographic variables. This suggests that any apparent adverse effect of smoking is due to the poorer prior health status of smokers and that smokers and non-smokers with equivalent demographics and prior health status have a very similar risk of adverse events linked to COVID-19.

ARTICLE HIGHLIGHTS

Research background

Previous meta-analyses relating smoking to coronavirus disease 2019 (COVID-19) are limited by considering few studies, restricting attention to hospitalized patients, giving limited or no attention to the definition of smoking or the reliability of smoking as recorded, and failing to properly consider the effect of adjustment for demographics and comorbidities.

Research motivation

We wished to gain a detailed insight into the effect of smoking on a variety of endpoints in different populations.

Research objectives

To carry out a systematic review, based on epidemiological studies in Europe, Israel, America and Australasia on the relationship of smoking to being tested for COVID-19, being positive for COVID-19, being hospitalized with COVID-19, having severe disease or dying.

Research methods

Literature searches based on publications in English up to September 30, 2020 identified studies of at least 100 individuals, carried out in Europe, Israel, America and Australasia, and unrestricted to those with specific other diseases, and providing information relating smoking to various COVID-related endpoints. Fixed-effect and random-effects meta-analyses were conducted for combinations of index of smoking, endpoint, population and level of adjustment with heterogeneity studied by level of adjustment, study location, and other factors.

Research results

Data were available from 74 studies of highly variable size: 37 in the United States, 10 in the United Kingdom, and up to four elsewhere, with populations most commonly studied being those hospitalized with COVID-19, positive for COVID-19, tested for COVID-19 and the general population. Only 36 studies distinguished current and former smokers, and adjusted results for smoking were only given in 42 studies. Positivity for COVID-19 was reduced among smokers in those tested, but not in the general population. Apparent increases in risk in smokers of hospitalization for COVID-19 among those positive, and of death among those positive and among those hospitalized disappeared following adjustment for pre-existing comorbidities, and there was little evidence of any relationship of smoking with admission to intensive care, being mechanically ventilated or having severe COVID-19, even in the unadjusted results.

Research conclusions

There is some evidence that smoking is associated with a reduced risk of being COVID-19 positive. Any apparent adverse effects of smoking on hospitalization rates among those positive, and on death rates seem due to the poorer prior health status of smokers.

Research perspectives

Evidence from later studies could consolidate these conclusions, and help to explain why, among those tested for COVID-19, current smokers are less likely to be positive.

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Systematic review and Meta-analysis of efficacy and safety of dienogest in treatment of endometriosis

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Abstract

BACKGROUND

The quality of life of women with endometriosis is substantially adversely affected by the pelvic pain caused by this disease. However, the choice of medication for endometriosis remains controversial, and no drug has been clearly proven to be superior to others.

AIM

To assess the efficacy and safety of dienogest, a synthetic progestin, in the treatment of women with painful symptoms of endometriosis.

METHODS

PubMed, EMBASE, the Cochrane Library, and the Web of Science databases were searched from their inception to January 21, 2020 for randomized controlled trials (RCTs) that compared dienogest with other popular prescription drugs for the treatment of endometriosis. Two reviewers extracted the data. Mean difference (MD) values and risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.

RESULTS

Ultimately, seven RCTs with a total of 1493 participants met the requirements for this review. Dienogest was found to be more effective than placebo in alleviating

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endometriosis-related pain (MD = -32.93, 95%CI: -44.63 to -21.23), but led to a more significant decline in plasma estradiol concentrations than placebo (MD = -44.7, 95%CI: -62.24 to -24.69). Dienogest was superior to gonadotropin-releasing hormone analogues (GnRH-a) in relieving pain (MD = -2.41, 95%CI: -3.58 to -1.24). Moreover, compared with dienogest, GnRH-a were significantly more likely to lead to the loss of bone mineral density (MD = 2.77, 95%CI: 0.16 to 5.37) and were significantly associated with a higher incidence of headaches (RR = 0.68, 95%CI: 0.52 to 0.91) and hot flushes (RR = 0.43, 95%CI: 0.18 to 1.02).

CONCLUSION

This meta-analysis demonstrated that dienogest may be a better pain-relief treatment for endometriosis patients, due to its high efficacy and tolerability.

Key Words: Dienogest; Gonadotrophin-releasing hormone analogues; Meta-analysis; Endometriosis; Medication

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Core Tip: We comprehensively and systematically analyzed the safety and effectiveness of dienogest for the treatment of endometriosis-related pain. Only high-quality randomized controlled trials that compared dienogest with other drugs, such as gonadotrophin-releasing hormone analogues and placebo, were included in the meta-analysis. The results provide guidelines for the standardization of the clinical use of medications for endometriosis and would improve the choice of medications for patients.

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INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma outside of the uterine cavity, and affects about 200 million women worldwide[1-3]. Although the pathogenesis of endometriosis remains unclear, it is generally accepted that its basic feature is the existence of ectopic endometrium. The chronic inflammatory reaction induced by ectopic endometrial lesions is the central process leading to endometriosis-related pain[4,5]. The resulting painful symptoms, such as dysmenorrhea, dyspareunia, and chronic pelvic pain, have a pronounced negative effect on quality of life and are the primary reason for which patients seek treatment[6,7]. Recent studies have emphasized the adverse effect of endometriosis symptoms on sexual function, work productivity, and psychological aspects of life[8]. The physical and mental suffering of patients is possibly due to the absence of sufficiently effective and targeted therapeutic methods.

The management of endometriosis has continuously improved, and a patient's choice of treatment methods, such as medication, surgery, or assisted reproductive technology, usually depends on her age and fertility requirements[4]. Medication is the first-line therapeutic option for women who do not wish to conceive in the immediate future, considering that surgery has a high rate of recurrence and risk of complications and can reduce the ovarian reserve[1]. There are also many widely available pharmacological treatments for endometriosis, such as painkillers, non-steroidal anti-inflammatories (NSAIDs), combined oral contraceptives (COCs), progestins, and gonadotrophin-releasing hormone analogues (GnRH-a)[9,10]. Although each type of drug is widely used worldwide, they also have clear disadvantages. Additionally, no drug has been proven markedly superior to others.

Dienogest, a 19-nortestosterone and progesterone derivative, is a fourth-generation synthetic oral progestin that was designed to treat endometriosis. It binds highly selectively to progesterone receptors, thereby exerting potent progestogenic effects

with little androgenic, mineralocorticoid, or glucocorticoid activity[11]. Crucially, dienogest suppresses the growth of endometrioid tissue and also exerts anti-inflammatory, antiproliferative, and antiangiogenic effects[12-14]. It has also shown good effectiveness and a favorable safety profile in long-term clinical application and follow-up studies. However, it remains uncertain whether dienogest is superior to other drugs.

The aim of this systematic review and Meta-analysis was to evaluate the efficacy and safety of dienogest for the treatment of endometriosis in women of reproductive age. We integrated and Meta-analyzed data from high-quality randomized controlled trials (RCTs) to assess differences between the treatment effects of dienogest and those of other drugs. This revealed strong evidence that dienogest should be the drug of first choice for treating endometriosis.

MATERIALS AND METHODS

Search strategy

To identify all relevant literature, a systematic search of the Cochrane Library, EMBASE, PubMed, and the Web of Science was conducted on January 21, 2020, using combinations of the following search terms: (endometriosis OR adenomyosis OR EMT OR EM OR uterine adenomyosis OR endometrioma) AND dienogest AND (placebo OR blank control OR drug). The search process and determination of eligibility were conducted independently by two investigators (Wang XF and Fu XL). Disagreements about eligibility or search criteria were mitigated through discussion with a third reviewer (Lin SC).

Study selection

We only included trials in which women had signs and symptoms of endometriosis or adenomyosis. Trials that met all of the following criteria were included: (1) Prospective RCTs; (2) English language studies; (3) Patients in the experimental group were treated with dienogest, whereas those in the control group received other medications, such as GnRH-a, placebo, COCs, or NSAIDs; and (4) The primary outcome was an improvement in endometriosis-associated pain, and other outcomes included adverse effects and changes in clinical laboratory parameters.

Meta-analyses, reviews, case reports, conference abstracts, cohort studies, retrospective studies, and trials without available data were excluded. Studies involving adolescent or menopausal women were also excluded.

Data extraction

Two authors (Wang XF and Fu XL) independently extracted the data from the studies that met all of the inclusion criteria and none of the exclusion criteria. The data extracted were the first author's name, the publication year, the study design, the interventions, the number of participants, and the inclusion criteria.

The primary efficacy outcome was a change in the visual analogue scale (VAS) scores of endometriosis-related pain before and after the trial, and the secondary efficacy outcome was a change in the number of analgesics administered. The outcomes used to evaluate safety were changes in bone mineral density (BMD) and estrogen concentration, the incidence of hot flushes and headaches, and the occurrence of other adverse events.

Study quality

To assess the quality of each included study, the Cochrane risk-of-bias assessment tool was used. Each type of risk was graded as low, high, or unclear for the included RCTs. Seven criteria related to the risk of bias were assessed in each study: (1) Random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Two authors (Wang XF and Fu X) independently assessed the risk of bias for each included study. Disagreements were resolved by discussion with a third reviewer (Lin SC).

Statistical analysis

Review Manager (RevMan) 5.3 software was used to conduct the Meta-analysis. Continuous data and dichotomous data are reported as the mean \pm standard deviation (SDs) and the number of outcome events/total number, respectively. We also calcu-

lated the mean difference (MD) and 95% confidence intervals (CIs) of continuous data. Risk ratios (RRs) and 95% CIs were calculated for dichotomous data. Q tests and I^2 statistics were applied to evaluate the heterogeneity in outcomes between studies. If there was no heterogeneity or $I^2 < 50\%$, a fixed-effect model was used to analyze the results. If $I^2 \geq 50\%$, indicating the existence of high heterogeneity between studies, a random-effects model was used. Subgroup analysis was carried out according to the type of intervention. We also conducted a sensitivity analysis to find the source of heterogeneity. A funnel plot was used to assess publication bias. In all analyses, a P -value < 0.05 was considered statistically significant.

RESULTS

Study selection and characteristics

The search strategy identified 1028 trials. Initially, 385 duplicates were excluded, and a further 629 trials were excluded based on the title and/or abstract. The remaining 14 trials were further assessed by reading the full text. Four trials were excluded because randomization was not adopted in the grouping process[15-18]. One dose-ranging study was excluded because it did not compare dienogest with other treatments[19]. One trial's detailed data were not provided, and it was also excluded as the author did not respond to a request for data[20]. One trial investigating the benefits of dienogest treatment before *in vitro* fertilization and embryo transfer was excluded, as it did not measure the specific outcomes analyzed in this meta-analysis[21]. Finally, seven RCTs with a high level of evidence were eligible for the analysis[22-28]. The procedure for study selection is presented in Figure 1.

Table 1 presents the characteristics of the studies included in this meta-analysis. The seven prospective RCTs included a total of 1493 women from ten countries: Germany, Italy, Ukraine, Austria, Spain, Poland, Portugal, Japan, China, and Egypt. Two milligrams of dienogest per day was the dosage in all studies. Efficacy was assessed in terms of changes in VAS scores for endometriosis-related pain and changes in the intake of supportive analgesic medication (SAM). Safety was assessed in terms of changes in BMD and serum estradiol (E2) concentrations, and the incidence of headaches and hot flushes. The results of quality assessment are shown in Figure 2. All eligible trials indicated a low risk of bias.

VAS score for endometriosis-related pain

All seven studies assessed the efficacy of dienogest in comparison with that of other drugs (placebo or GnRH-a) in terms of changes in VAS scores at the end of the treatment period. However, the data of one study were unclearly presented[26]. Our meta-analysis revealed a statistically significant advantage of dienogest, compared with other drugs, in terms of the relief of endometriosis- or adenomyosis-associated pain (MD = -17, 95%CI: -30.19 to -3.80). Considering the rather high heterogeneity between the studies [an I^2 of 97% ($P < 0.00001$)], we conducted a subgroup analysis of the different categories of alternative drugs.

Dienogest was found to be significantly superior to GnRH-a for pain relief (MD = -2.41, 95%CI: -3.58 to -1.24) with a very low heterogeneity ($I^2 = 0.0\%$, $P = 0.57$). Dienogest was also significantly superior to placebo with respect to pain relief [MD = -32.93, 95%CI: -44.63 to -21.23], but with a high heterogeneity ($I^2 = 84\%$, $P = 0.002$) (Figure 3A). Subgroup analysis reduced the heterogeneity within each group but did not eliminate it. Therefore, we performed a sensitivity analysis by excluding each study, and then analyzing the effect of this exclusion. This revealed that the RCT performed by Lang *et al*[25] was the probable source of heterogeneity, as its elimination decreased I^2 from 84% to 0.0%. The combined results of the other two articles also indicated that dienogest was superior to placebo for pain relief (MD = -38.83, 95%CI: -45.17 to -32.49). Visual inspection of the funnel plot of the changes in VAS scores reveals its asymmetry, which suggests that there was some degree of publication bias and that more studies are needed to validate the results (Supplementary Figure 1).

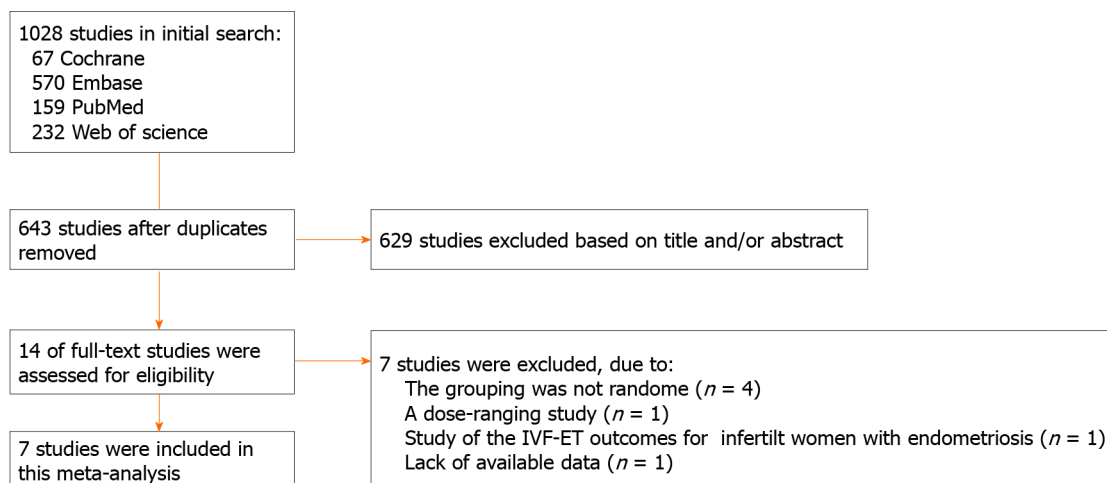
SAM intake

Three studies that compared dienogest with placebo reported the change in the level of SAM intake, and the combined results indicated a significantly larger reduction of SAM intake in the dienogest group than the placebo group (MD = -0.39, 95%CI: -0.75 to -0.03), with an I^2 of 72% ($P = 0.03$) (Figure 3B). Subgroup analyses of two studies (Osuga *et al*[27] and Lang *et al*[25]) demonstrated a high heterogeneity, *i.e.*, a minimum

Table 1 Characteristics of the studies included in the Meta-analysis

Ref.	Study design	Country	Blind	Duration	Intervention	Sample size	Efficacy assessments	Safety assessments
Harada <i>et al</i> [22], 2009	RCT	Japan	Double-blind	24 wk	2 mg/d DNG <i>vs</i> 900 µg/d busarelin	137/134	VAS	BMD change Hot flashes Headache
Strowitzki <i>et al</i> [23], 2010	RCT	Germany Austria Spain Poland Italy Portugal	Open-label	24 wk	2 mg/d DNG <i>vs</i> 3.75 mg/4wk leuprolide	124/128	VAS	Hot flashes Headache
Abdou <i>et al</i> [24], 2018	RCT	Egypt	Open-label	12 wk	2 mg/d DNG <i>vs</i> 3.75 mg/4 wk leuprolide	130/131	VAS	Hot flashes Headache
Lang <i>et al</i> [25], 2018	RCT	China	Double-blind	24 wk	2 mg/d DNG <i>vs</i> placebo	130/132	VAS SAM intake	BMD change E2
Strowitzki <i>et al</i> [26], 2010	RCT	Germany Italy Ukraine	Double-blind	12 wk	2 mg/d DNG <i>vs</i> placebo	102/96	SAM intake	BMD change E2 Headache
Osuga <i>et al</i> [27], 2017	RCT	Japan	Double-blind	16 wk	2 mg/d DNG <i>vs</i> placebo	34/33	VAS SAM intake	E2 Hot flashes
Harada <i>et al</i> [28], 2017	RCT	Japan	DNG: Un-blind Placebo: Blind	24 wk	2 mg/d DNG <i>vs</i> placebo	53/129	VAS	

EM: Endometriosis; AD: Adenomyosis; SAM: Supportive analgesic medication; BMD: Bone mineral density; E2: Serum estradiol.

**Figure 1 Flowchart of study selection process.**

I^2 of 52%. The sensitivity analysis subsequent to removal of either of those studies indicated that the statistical difference between dienogest and placebo was not significant ($P = 0.08$ and 0.24 for Osuga *et al* [27] and Lang *et al* [25], respectively). Thus, additional studies are required to validate this result.

Change in BMD

Three studies investigated the effect of dienogest on BMD, and we found that there was a statistically significant difference between dienogest and the other drugs with respect to changes in BMD. Two studies compared dienogest with GnRH-a, whereas one study compared dienogest with placebo. Therefore, a subgroup analysis was conducted based on the type of drug used as the control. A greater reduction in BMD was observed in the GnRH-a group than in the dienogest group (MD = 2.77, 95%CI: 0.16 to 5.37), but there was a significant heterogeneity between these two trials ($P = 0.02$, $I^2 = 80\%$). Furthermore, a smaller reduction in BMD was observed in the placebo group than in the dienogest group (MD = -0.71, 95%CI: -0.72 to -0.70) (Figure 4A).

Change serum E2 concentrations

Serum E2 concentrations were measured in three studies in which dienogest was

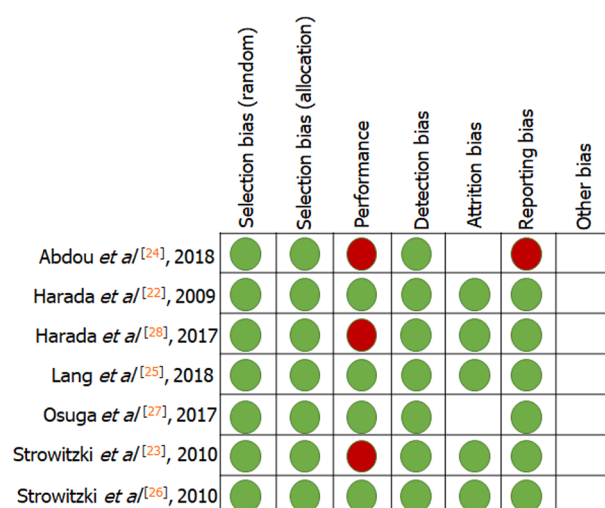


Figure 2 Risk of bias summary of randomized controlled trials.

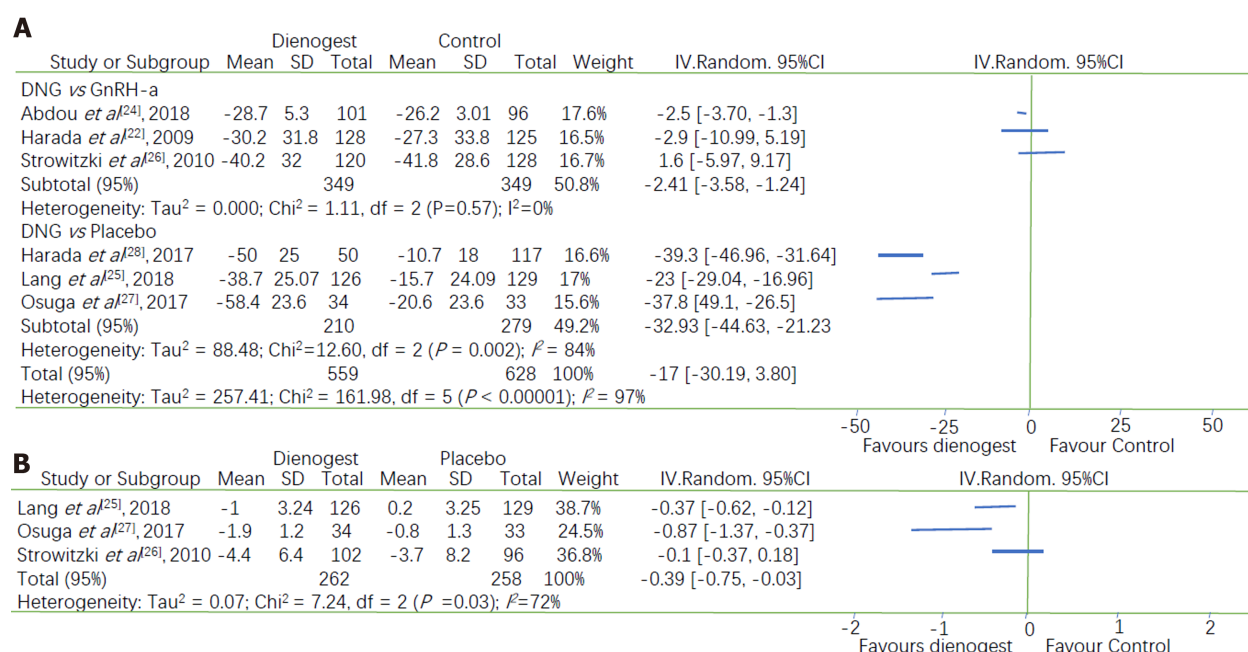


Figure 3 Change in visual analogue scale scores and supportive analgesic medication. A: Forest plot showing dienogest vs other intervention (GnRH-a and placebo) in the outcomes of changes in endometriosis related pain measured on visual analogue scale; B: Forest plot showing dienogest vs placebo in the outcome of supportive analgesic medication intake changes at the end of treatment. CI: Confidence interval.

compared with placebo. The E2 concentrations were lower in the dienogest groups than in the placebo groups. A Meta-analysis of the three studies showed that the decrease in the E2 concentration was -44.47 pg/mL [95%CI: -62.24 to -24.69]. The pooled measures revealed an I^2 value of 0.0% ($P = 0.78$), indicating a homogeneity between studies (Figure 4B).

Headache

Headaches were one of the most common drug-related adverse effects reported during treatment. Four studies reported the incidence of headache after treatment: Three studies comparing dienogest with GnRH-a and one comparing dienogest with placebo. Their I^2 of 31% ($P = 0.23$) indicated that there was a high heterogeneity between these studies. Therefore, the studies were divided into two subgroups according to the type of drug used in the control group. Women in the dienogest group were less likely to experience headaches than those in the GnRH-a group (RR = 0.68, 95%CI: 0.52 to 0.91), with I^2 of 0.0% indicating that there was no heterogeneity between the studies in this group. The only RCT that compared dienogest with a

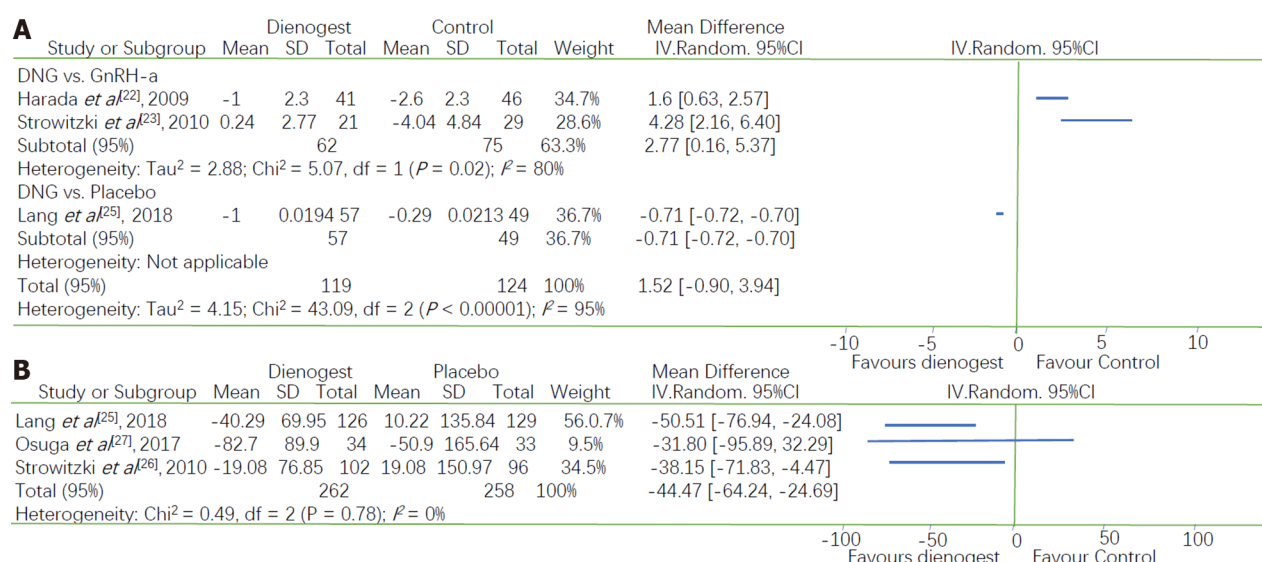


Figure 4 Changes in bone mineral density and serum estradiol. A: Forest plot showing dienogest vs other intervention (GnRH-a and placebo) in the outcomes of percent change in bone mineral density; B: Forest plot showing dienogest vs placebo in the change of serum estradiol at the end of treatment. CI: Confidence interval.

placebo did not show a significant difference in the incidence of headaches (RR = 2.07, 95%CI: 0.75 to 5.74, $P = 0.16$) (Figure 5A).

Hot flushes

Three studies comparing dienogest with GnRH-a and one study comparing dienogest with placebo reported the incidence of hot flushes. Due to the high heterogeneity between these studies ($I^2 = 81\%$), we performed a subgroup analysis based on the type of drug used as the control. Only one study compared dienogest with placebo, reporting that the difference in the incidence of hot flushes was not statistically significant (RR = 4.86, 95%CI: 0.24 to 97.51).

The subgroup analysis showed that the incidence of hot flushes was greater in women treated with GnRH-a than in women treated with dienogest (RR = 0.43, 95%CI: 0.18 to 1.02; $I^2 = 86\%$, $P = 0.0008$) (Figure 5B). After excluding the study by Harada *et al* [22] from the sensitivity analysis, the I^2 decreased from 86% to 39%. However, the combined results of the two remaining studies indicated that the difference between dienogest and GnRH-a with respect to the incidence of hot flushes was not statistically significant ($P = 0.06$). Given these conflicting results, more data are required to clarify the differences between the incidence of this adverse effect resulting from dienogest or GnRH-a treatment.

DISCUSSION

The chronic nature of endometriosis means that lifelong management must be the focus of clinical decision making, for which patients urgently need safer and more effective drugs. To comprehensively evaluate the efficacy and safety of dienogest in the treatment of endometriosis, we performed a Meta-analysis of seven RCTs that included a total of 1493 patients. The results showed that the pain-relieving ability of dienogest was superior to that of placebo and GnRH-a. Dienogest also exhibited significant safety advantages over GnRH-a, due to its low incidence of adverse effects. Taken together, these findings indicate that dienogest should be the first-line treatment for endometriosis.

The superior pain-relieving ability of dienogest may be attributable to the greater decrease in serum E2 concentrations observed in dienogest-treated patients than in those who received other treatments. This is consistent with the fact that a randomized, dose-controlled study indicated that a daily 2-mg dose of dienogest moderately suppresses E2 production and reliably inhibits ovulation[29], and that a moderate decrease in estrogen concentration effectively suppresses the growth of endometrial tissue and does not result in hypoestrogenic adverse effects, in accordance with the threshold theory proposed by Barbieri[30]. The patients' dependence on

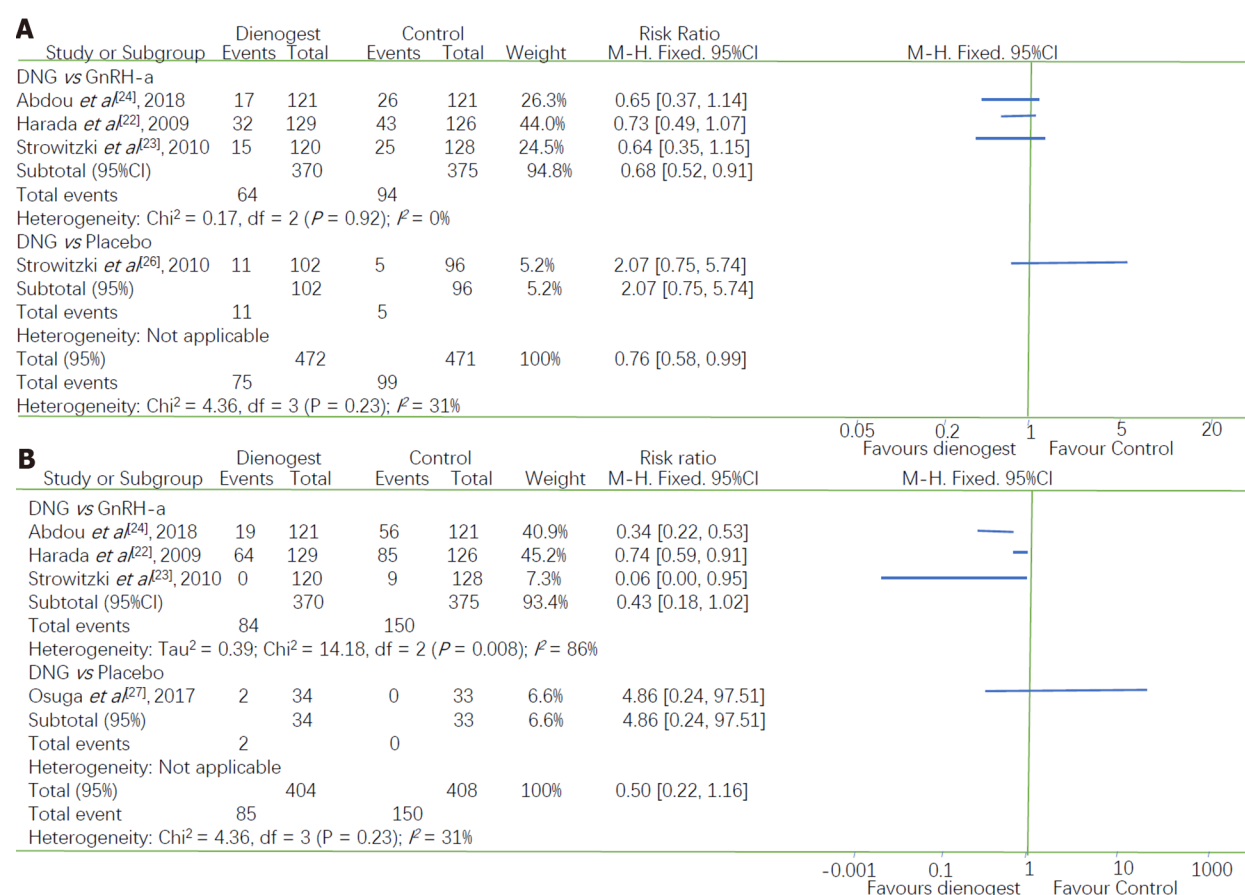


Figure 5 Incidence of headache and hot flushes. A: Forest plot showing dienogest vs other intervention (GnRH-a and placebo) in the incidence of headache; B: Forest plot showing dienogest vs other intervention (GnRH-a and placebo) in the incidence of hot flushes.

supportive analgesics also decreased during treatment with dienogest, providing indirect evidence for the drug's pain-relieving effect. In addition, in the safety analysis, no difference was observed in the incidence of headaches and hot flushes between the two groups. An extended study investigating the effects of dienogest treatment over 53 wk found that it induced a sustained reduction in endometriosis-associated pelvic pain, with low rates of treatment-related adverse events^[31].

The superiority of dienogest over GnRH-a for relieving endometriosis-related pain was also supported by a -2.41 mm difference in VAS pain scores. In concordance with our findings, another meta-analysis concluded that dienogest was superior to GnRH-a in this regard, with a -2.17 mm difference in VAS pain scores^[32]. Gerlinger *et al*^[33] suggested a non-inferiority margin of 10 mm for endometriosis related pain measured using a VAS. Therefore, although the -2.41 mm difference in the VAS pain score is statistically significant, it is less than the suggested minimal clinically significant difference of 10 mm, and thus does not prove that dienogest is superior to GnRH-a in relieving endometriosis-related pain. However, the two drugs appear equivalent in terms of their pain-relieving ability, and more RCTs are required to confirm whether they clinically differ in this ability.

The safety of drugs used for the long-term management of endometriosis must not be overlooked. Dienogest showed significant safety benefits over GnRH-a, as the latter was more likely to lead to decreased BMD and an increased incidence of headaches and hot flushes. GnRH-a are an effective therapy for endometriosis, but they are also associated with hypoestrogenism and decreased BMD if taken for more than 6 mo. Patients are prescribed an add-back therapy to prevent this adverse event^[34]. In contrast, dienogest can be taken for a long term with fewer adverse effects. A pooled analysis from four European RCTs confirmed the favorable safety and tolerability of dienogest in both short- and long-term use^[35]. Thus, dienogest appears a better option for patients who require chronic treatment.

Research on the mechanism by which dienogest relieves the pelvic pain of endometriosis remains exploratory. Some researchers have found that dienogest can inhibit the production of tumor necrosis factor alpha and interleukin 1 beta by agonizing progesterone receptors, and ultimately inhibit the production of nerve growth factor, which

has been shown to be an important factor in the pelvic pain of endometriosis[36-39]. It has also been suggested that the high efficacy of dienogest in relieving endometriosis pain is related to the expression of nuclear factor kappa-B (NF- κ B) and Bcl-2, because dienogest can increase the activity of NF- κ B and thus increase the apoptosis of endometrial mesenchymal cells[13,40]. Accordingly, a fuller understanding of the mechanism of action dienogest is required, as this may optimize its clinical applicability.

The main strength of this meta-analysis is that we only included RCTs with high levels of evidence, which included a total of 1493 patients, most of whom were clearly diagnosed by histology or laparoscopy. Second, our analysis of the safety and effectiveness of dienogest for the treatment of endometriosis was comprehensive and systematic. The results of this meta-analysis demonstrate how the clinical use of medications for endometriosis could be standardized and enhance patients' ability to select the best treatment.

However, there are some limitations of our study. First, the included studies differed in the category of disease, the ethnicity of participants, the types of GnRH-a used for treatment, the administration route, and the duration of treatment, which may account for the heterogeneity between studies that we observed. For example, in analyzing the changes in BMD between the two studies, Gerlinger *et al*[32] attributed the heterogeneity observed between these studies to ethnicity. Moreover, estrogen plays a crucial role in the growth and maintenance of the skeleton, and Asian women have higher blood concentrations of estrogens than Caucasian women[41]. In addition, we conducted subgroup and sensitivity analyses to determine the sources of heterogeneity. Second, although the most frequent drug-related effect of dienogest in all included studies was irregular uterine bleeding (spotting and breakthrough bleeding), our safety assessments did not analyze this side effect. Although patients used daily diaries to record bleeding patterns in four of the included trials, these data cannot be used to accurately estimate the severity of bleeding. As such, an approach that can quantitatively evaluate irregular genital bleeding is needed to investigate this adverse effect. Third, our meta-analysis only included a small number of studies, and none compared dienogest with other therapies, such as compound COCs or levonorgestrel intrauterine devices, which have been proven effective in the treatment of endometriosis and adenomyosis. Finally, more studies are required to evaluate the pharmacoeconomics of drugs that are commonly used to treat endometriosis.

CONCLUSION

This Meta-analysis systematically evaluated the efficacy and safety of dienogest for the treatment of endometriosis. The results showed that dienogest is superior to placebo and GnRH-a in terms of pain relief and is better tolerated than GnRH-a. This demonstrates that dienogest may be the best medication for endometriosis patients seeking pain relief. Further high-quality RCTs are warranted to confirm these findings.

ARTICLE HIGHLIGHTS

Research background

Endometriosis is one of the common gynecological diseases in reproductive women and the concomitant pelvic pain has substantial negative effects on patients' quality of life. In recent years, significant advances have been made in the treatment of endometriosis, and drugs remain the primary treatment option for women of childbearing age. However, there is no agreement on which drugs are most effective and tolerated for the treatment of endometriosis.

Research motivation

Several well-designed randomized controlled trials (RCTs) have demonstrated that dienogest is effective in relieving endometriosis-related pain and has a tolerable adverse-effect profile. However, these RCTs have not unambiguously demonstrated whether dienogest is superior to other drugs.

Research objectives

This study was conducted to evaluate the effectiveness and safety of dienogest compared with other drugs for the treatment of endometriosis.

Research methods

This meta-analysis only included RCTs that compared dienogest with other drugs in the treatment of endometriosis. Review Manager (RevMan) 5.3 software was used to calculate mean difference (MD) values and risk ratios (RRs) with 95% confidence intervals (CIs).

Research results

This study included seven RCTs with 1493 participants and demonstrated that dienogest was more effective than placebo in alleviating endometriosis-related pain (MD = -32.93, 95%CI: -44.63 to -21.23), and led to a more significant decrease in plasma estradiol concentrations than placebo (MD = -44.7, 95%CI: -62.24 to -24.69). The combined results showed that dienogest was superior to GnRH-a in relieving pain (MD = -2.41, 95%CI: -3.58 to -1.24). Furthermore, adverse events were more frequent in patients in the GnRH-a group, including the loss of BMD (MD = 2.77, 95%CI: 0.16 to 5.37), headaches (RR = 0.68, 95%CI: 0.52 to 0.91), and hot flushes (RR = 0.43, 95%CI: 0.18 to 1.02).

Research conclusions

Dienogest is an effective and tolerable therapeutic for the treatment of endometriosis-related pain in women of reproductive age.

Research perspectives

The results of this meta-analysis provide insights on how the clinical use of medications for endometriosis could be standardized and should improve the choice of medications for patients.

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Trends in iron deficiency anemia research 2001-2020: A bibliometric analysis

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Abstract

BACKGROUND

Iron deficiency anemia has a worldwide impact on individual health and national and international economies, with an estimated one-third of the world population being iron deficient.

AIM

To evaluate the iron deficiency literature published between 2001-2020 with an emphasis on: (1) Identification of collaborative research networks most active in this field; (2) Research topics of greatest importance; and (3) Analysis of the most-cited papers published between 2001-2020 and the most cited papers in 5-year intervals during this period to assess for emerging trends in research in this area.

METHODS

A search of Clarivate Analytics World of Science Core Collection was performed for the topic "iron deficiency anemia", limited to document type (article or review), language (English), and time span (2001-2020). The following data were extracted from these articles: Year of publication, journal, study design, country of first author, and number of citations. The metadata derived from the search were used to identify publication trends in iron deficiency anemia research and their distribution in countries/regions and institutions. Network visualization by VOSviewer (Leiden University) was performed to identify international collaborative groups and research hotspots.

RESULTS

The search identified 4828 publications. Three international collaborative networks were identified: United States, Canada, and India; Turkey, China, and Japan; and England and other European countries. Five research areas were hotspots: Epidemiologic aspects of iron deficiency anemia, biochemical aspects of iron deficiency anemia, clinical evaluation of causes of iron deficiency anemia, causes of iron deficiency anemia, and bioavailability of dietary iron. Subset analysis of the top-10 overall cited papers, and the top-10 cited papers for each 5-

and experimental

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year increment beginning in 2001 showed that the largest number of highly cited papers were from the field of epidemiology, the smallest number from the field of bioavailability of dietary iron.

CONCLUSION

The literature on iron deficiency anemia has a high citation rate compared to studies of other topics using similar methodology and is heavily biased toward studies from the United States and epidemiologic studies.

Key Words: Iron deficiency anemia; Bibliometrics; VOSviewer; Trends

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Core Tip: Iron deficiency is a common micronutrient deficiency with a worldwide impact. This bibliometric analysis was performed to analyze the literature on iron deficiency published between 2001-2020. Three international collaborative networks based in North America/India, Europe, and Asia were identified. There are 5 areas of greatest focus: Epidemiologic aspects of iron deficiency anemia, biochemical aspects of iron deficiency anemia, clinical evaluation of iron deficiency anemia, causes of iron deficiency anemia, and bioavailability of dietary iron. Evaluation of the papers published during this period identified epidemiology as the most cited area, and bioavailability of iron as the least cited.

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URL: <https://www.wjgnet.com/2308-3840/full/v9/i4/389.htm>

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INTRODUCTION

Iron deficiency and iron deficiency anemia

Iron deficiency and iron deficiency anemia are health conditions with a worldwide effect on individual health and an impact on national and international economies. An estimated one-third of the world population is affected by iron deficiency, and deficiency of this micronutrient has effects on multiple systems of the body, including the central nervous system and reticuloendothelial systems[1,2]. Health consequences of iron deficiency are widespread and include impaired intellectual function and decreased immunity[3,4].

Anemia is a common consequence of iron deficiency. The degree of severity of anemia is variable, and it is microcytic and hypochromic as demonstrated by routine laboratory testing, which identifies a moderate to severe decrease in red blood cell count, hemoglobin, and hematocrit, accompanied by a moderately decreased mean corpuscular volume and moderate to marked elevation of red blood cell distribution width[1].

The bibliometric method as a research tool

Bibliometric methods are useful to evaluate trends in research activities over time[5]. Bibliometrics take advantage of literature databasing technology, including literature metrology, and is an increasingly important method of providing insight into research in specific fields. This format has been used to evaluate the impact of articles in many areas of study. It is valuable to identify the most cited studies that have influenced the evolution of a given scientific field[6].

Rationale

In this study, the research trends in the field of iron deficiency anemia in the past 20 years were considered. The aims of this study were to: (1) Identify and analyze scientific publications in this field; and (2) Compare the contribution of this research in different countries and institutions. Bibliometric analysis was performed using the functions of the Web of Science Core Collection and further analysis of the metadata

was performed using VOSviewer software (Leiden University). Using the features of VOSviewer, a network visualization of international collaborations and a keyword-based visualization of research fields was performed. This study provides a refined understanding of global trends in iron deficiency anemia research.

MATERIALS AND METHODS

This bibliometric analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) principles (see PRISMA 2009 checklist statement for PRISMA checklist) according to a methodology similar to that described in earlier studies[6-10], which is detailed below.

Data collection and bibliometric analysis

All articles were searched using the Clarivate Analytics World of Science Core Collection (WOSCC) on August 30, 2020. The study used publicly available data, and thus ethical approval was not required. The search criteria were topic ("iron deficiency anemia"), limited to document type (article or review), language (English), and time span (2001-2020). A topic search includes a search of the following fields: The title of the article or review; the abstract, the keywords; and the keywords plus[®], which is a proprietary algorithm using expanded terms from an article's cited references or bibliography. The following data were extracted from these articles: Year of publication, journal, study design, country of first author, and number of citations. The metadata derived from the search were used to identify publication trends in iron deficiency anemia research and their distribution in countries/regions and institutions. This protocol has not been registered.

VOSviewer bibliometric software (Van Eck and Waltman, Leiden University, Leiden, The Netherlands) was used to perform data mining, mapping, and clustering of the retrieved articles[11]. Keywords and countries were labeled with colored circles, the size of which correlated with the occurrence of the keyword or countries in the title and abstract.

Subset analysis of abstracts/full-text

Because of the large number of search results, the title, abstract and full text of the top 200 cited articles were reviewed for appropriateness to the topic. The entire list of retrieved articles was analyzed, and an additional subset analysis of the articles grouped by publication in 5-year increments (2001-2005; 2006-2010; 2011-2015; 2016-2020) was performed. The top 25 keywords identified in the title and abstract of each publication in each time interval was compiled[12]. In addition, the top 10 articles published in each time interval was identified, along with their number of citations.

RESULTS

The search returned 4828 references. Review of the titles, abstracts, and full texts of the top 200 cited papers in this group was performed to assess the quality of the search, and all papers in this group were appropriate to the topic of iron deficiency anemia.

These publications had an h-index of 137 with an average of 25.42 citations *per* item. The number of papers published *per* year in this study has varied from 124 to 402. The year with the largest number of papers published in this study was 2019. The rate of publication of papers in this study has varied from 2.568% to 8.326% (Figure 1).

Of 4163 papers were classified as articles, 695 as reviews. 4569 papers (94.6% of the total) were published in English. Based on WOSCC metadata, the papers were published in 97 different research areas, of which the most common were nutrition and dietetics ($n = 672$, 13.919% of total), gastroenterology ($n = 610$, 12.635%), hematology ($n = 570$, 11.806%), pediatrics ($n = 566$, 11.723%), and general internal medicine ($n = 522$, 10.812%).

Country of publication

In total, publications were contributed by 157 countries, with the top ten publishing countries listed in Figure 2.

The United States has contributed the largest number of the papers. Other nations in the top 5 countries of publication were Turkey, China, Italy, and England. The authors in this study represented 4840 institutions. The institutions contributing the most

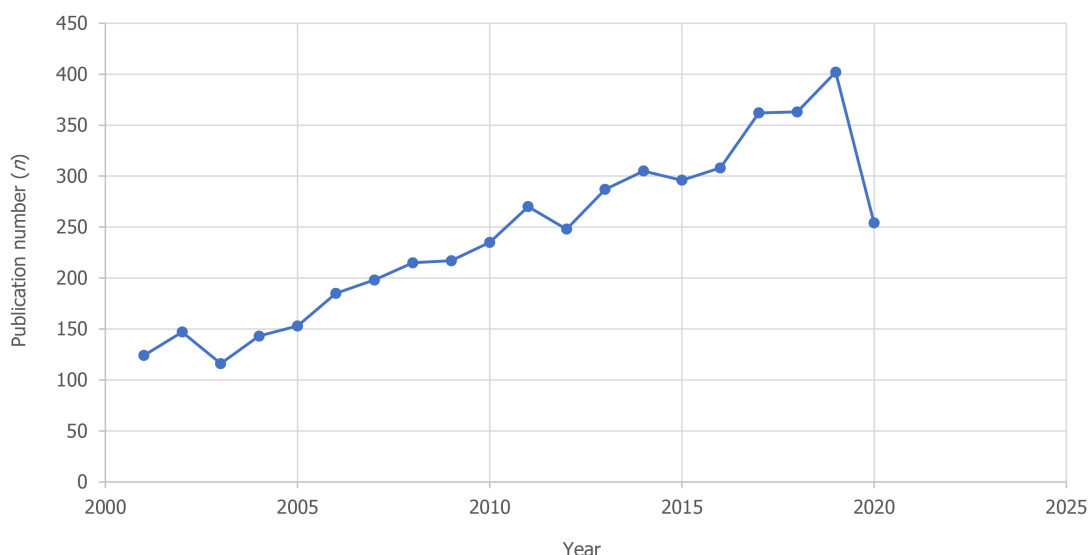


Figure 1 Number of publications (*n*) per year, 2001-2020.

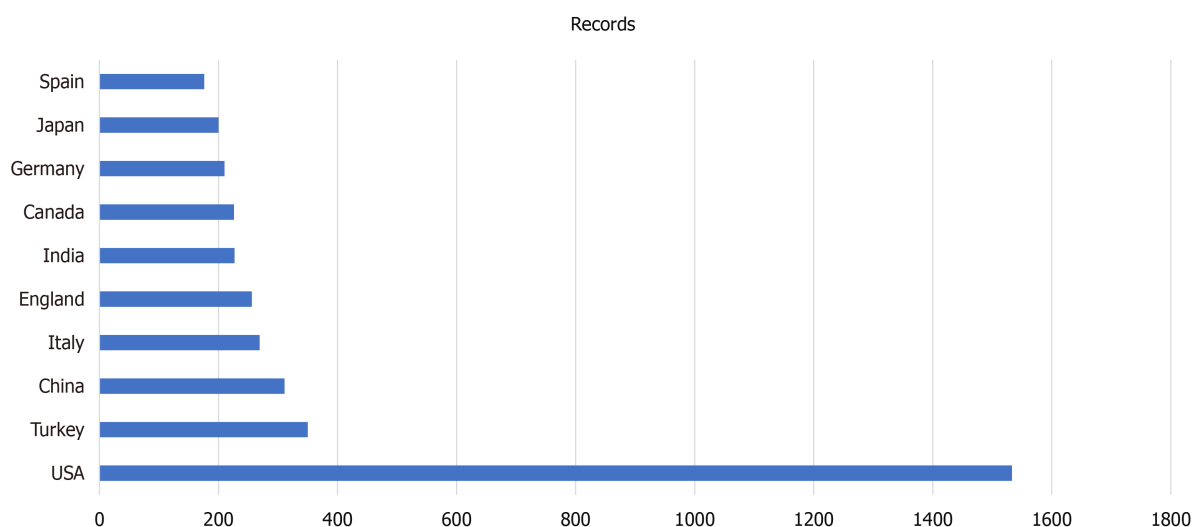


Figure 2 Number of records (*n*) per country for the top 10 countries contributing papers to this study.

papers to this study were the University of California system ($n = 179$ records) and Harvard University ($n = 126$ records). 2411 funding agencies were listed in these publications, of which the largest number of studies were funded by the United States Department of Health and Human Services ($n = 448$), the National Institutes of Health (United States, $n = 431$), and the National Natural Science Foundation of China ($n = 119$).

Collaborations

The collaboration network analysis is illustrated in Figure 3 and includes countries contributing at least 10 papers. Using this criterion, 64 countries are included in the analysis. There are 3 nodes identified using international collaboration data. The largest, illustrated in red, includes the United States, Canada, and India as the largest contributors. The second, illustrated in blue, includes Turkey, China, and Japan as the most prominent contributing members. The third, illustrated in green, includes England and many European countries.

Journals

The papers in this study were published by 1365 journals. 659 journals published ≥ 1 paper; the remaining journals published 1 paper apiece. The top 15 journals, with the number of articles published and the journal's impact factor (IF), drawn from the 2020

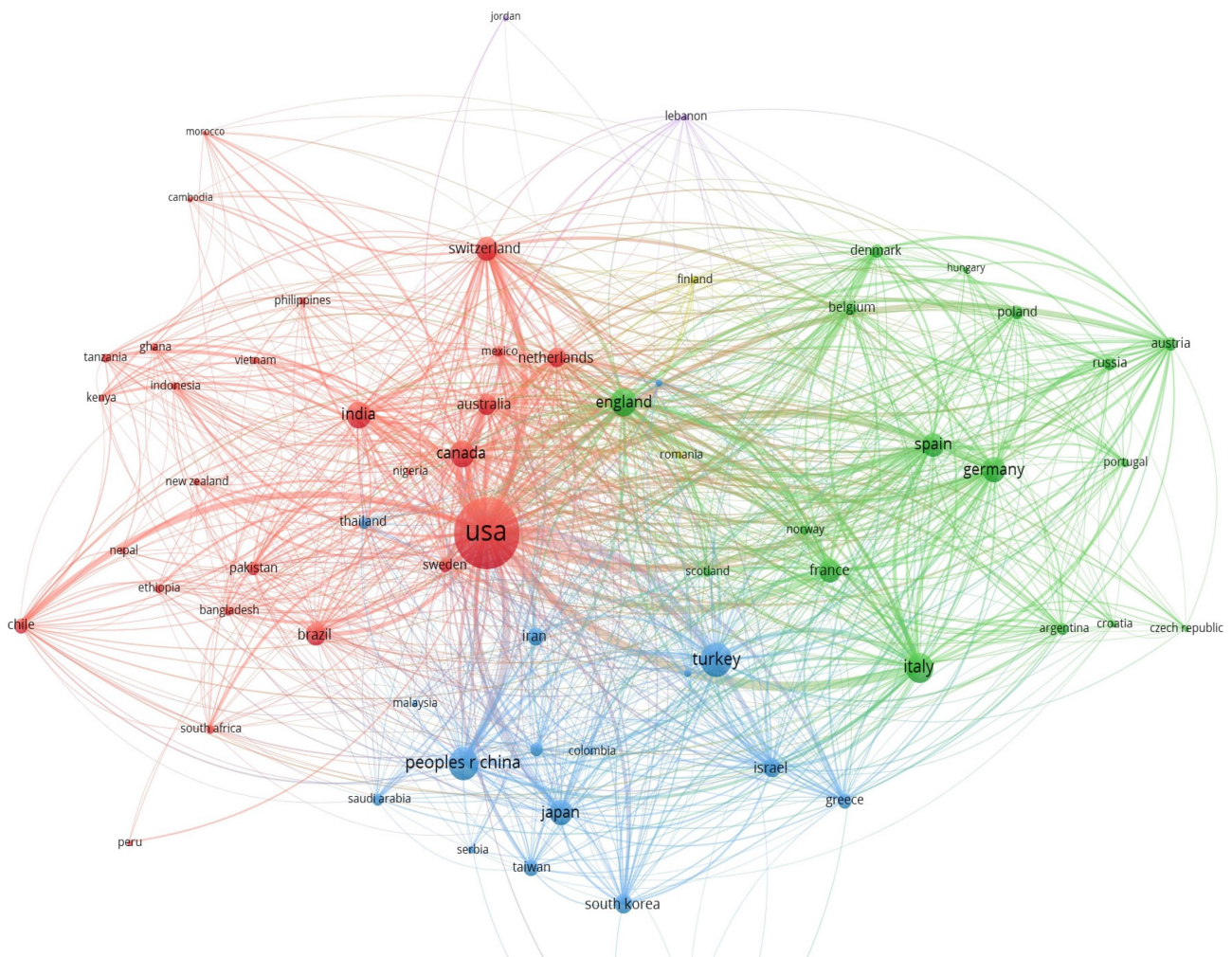


Figure 3 Collaboration network analysis of the 64 countries contributing ≥ 10 papers.

Journal Citation Reports of Clarivate Analytics) are shown in Table 1. The IF for the journals in this group ranged from 17.543 (*Blood*) to 1.016 (*Journal of Pediatric Hematology Oncology*). The largest number of papers were published by *Journal of Nutrition* ($n = 107$), *PLOS One* ($n = 81$), and *World Journal of Gastroenterology* ($n = 76$).

Co-occurrence of keywords

Overall, 123 terms appeared 50 times or more in the titles or abstracts of the papers in this study (Figure 4). For example, “iron deficiency anemia” appeared 1533 times, “anemia” appeared 1252 times, “children” appeared 726 times, “iron deficiency” appeared 627 times, and “prevalence” appeared 608 times. Based on the VOSviewer keyword mapping, the terms or phrases associated with iron deficiency anemia were divided into 5 clusters, represented by 5 colors (red, green, blue, yellow, and purple). From the results of co-occurrences, current iron deficiency anemia research was shown to be mainly focused on 5 major areas. These are: (1) Epidemiologic aspects of iron deficiency anemia (red); (2) Bioavailability of dietary iron (purple); (3) Clinical evaluation of causes of iron deficiency anemia (blue); (4) Causes of iron deficiency anemia (yellow); and (5) Biochemical aspects of iron deficiency anemia (green). These 5 topics may thus be regarded as the research hotspots in the field of iron deficiency anemia between 2001-2020.

A subset analysis of the top 25 author-selected keywords of each 5-year interval between 2001-2020 and coded to the 5 areas presented in Figure 4 is presented in Table 2[12]. The distribution of keywords was relatively unchanged over the years. The largest number of keywords mapped to the epidemiologic aspects of iron deficiency anemia (red) cluster (11-12 keywords in each interval), with smaller numbers of keywords mapping to the other clusters.

Table 1 Top 15 journals ranked by number of papers published, and corresponding impact factors

Journal	Records	Impact factor
<i>Journal of nutrition</i>	107	4.281
<i>PLoS One</i>	81	2.740
<i>World Journal of Gastroenterology</i>	76	3.665
<i>American Journal of Clinical Nutrition</i>	75	6.766
<i>Nutrients</i>	67	4.546
<i>Pediatrics</i>	50	5.359
<i>Food</i>	48	1.485
<i>Journal of Pediatric Hematology Oncology</i>	48	1.016
<i>Helicobacter</i>	44	4.000
<i>American</i>	39	6.973
<i>Blood</i>	39	17.543
<i>Digestive Diseases and Sciences</i>	35	2.751
<i>Pediatric Hematology and Oncology</i>	34	1.232
<i>Biological</i>	33	2.639
<i>Journal of Pediatric Gastroenterology and Nutrition</i>	33	2.937

Top 10 cited papers

The top 10 cited papers published for the entire period 2001-2020, and the top 10 cited papers published in each 5-year interval are listed in Table 3. The total number of citations *per* paper for the top 10 cited papers published from 2001-2020 ranged from 752 to 4084.

DISCUSSION

This bibliometric analysis was performed to evaluate the research trends in the field of iron deficiency anemia between 2001-2020. The purpose of this study was: (1) To identify and analyze scientific publications in this field; and (2) To compare the contribution of this research in different countries and institutions. The main findings were (1) That the most common topic areas were nutrition and dietetics, gastroenterology, hematology, pediatrics, and general internal medicine; (2) United States-based researchers contributed to the vast majority of papers, although researchers from Turkey, China, Italy, and England also made significant contributions to the literature; (3) Keyword analysis revealed that 5 research areas have developed as current hotspots: Epidemiologic aspects of iron deficiency anemia, biochemical aspects of iron deficiency anemia, clinical evaluation of causes of iron deficiency anemia, causes of iron deficiency anemia, and bioavailability of dietary iron; and (4) Evaluation of the top keywords in 5 year intervals showed that the relative contributions of each research area to the total number of papers has remained static, with the largest contribution to the area of epidemiologic aspects of iron deficiency anemia. The citation rate of the top cited papers in this study is high compared to studies on other research areas using similar methodology[13].

Epidemiologic aspects of iron deficiency anemia

The topic of iron deficiency anemia has been the subject of numerous epidemiologic studies, including the Global Burden of Disease Study, a large-scale observational epidemiologic survey which was published as a 4-paper series[14-17]. This includes the top-cited paper identified in the current study[14]. Approximately a third of the world population is iron-deficient[18], though there are clear disparities in the distribution of iron deficiency. Darmon *et al*[19] established that iron deficiency anemia was more prevalent in individuals from low socioeconomic backgrounds, possibly due to diet quality[19]. Guralnik *et al*[20]'s 2005 paper identified that iron deficiency anemia contributes to a high percentage of cases of anemia in the elderly[20]. Although at-risk

Table 2 Top 25 keywords of each 5-year interval between 2001-2020 color coded to the clusters identified in Figure 4

2001	2006	2011	2016
Iron-deficiency anemia ³	Iron-deficiency anemia ³	Iron-deficiency anemia ³	Iron-deficiency anemia ³
Anemia ¹	Anemia ¹	Anemia ¹	Anemia ¹
Children ¹	Iron deficiency anemia ¹	Iron deficiency anemia ¹	Iron deficiency anemia ¹
Iron deficiency anemia ¹	Children ¹	Children ¹	Prevalence ¹
Iron deficiency ²	Iron deficiency ²	Iron deficiency ²	Children ¹
Iron ⁵	Prevalence ¹	Prevalence ¹	Iron deficiency ²
Prevalence ¹	Diagnosis ³	Iron ⁵	Diagnosis ³
Serum ferritin ⁵	Iron ⁵	Diagnosis ³	Management ³
Ferritin ⁵	Supplementation ¹	Supplementation ¹	Iron ⁵
Supplementation ¹	Infants ¹	Hepcidin ⁵	Supplementation ¹
Diagnosis ³	Serum ferritin ⁵	Management ³	Pregnancy ¹
Absorption ²	Women ¹	Hemoglobin ¹	Hepcidin ⁵
Deficiency ⁵	Hemoglobin ¹	Pregnancy ¹	Hemoglobin ¹
Infants ¹	Absorption ²	Ferritin ⁵	Risk ³
Erythropoietin ⁴	Deficiency ⁵	Intravenous iron ⁴	Intravenous iron ⁴
Pregnancy ¹	Hepcidin ⁵	Women ¹	Women ¹
Women ¹	Therapy ⁴	Deficiency anemia ¹	Ferritin ⁵
Therapy ⁴	Iron-deficiency ¹	Disease ³	Oral iron ⁴
Hemoglobin ¹	Growth ¹	Inflammation ⁵	Health ¹
Eradication ³	Helicobacter pylori ³	Risk ³	Disease ³
Serum transferrin receptor ⁵	Pregnancy ¹	Association ³	Infants ¹
Helicobacter pylori ³	Disease ³	Metabolism ¹	Deficiency ⁵
Iron-deficiency ¹	Risk ³	Infants ¹	Iron-deficiency ¹
Deficiency anemia ¹	Celiac disease ³	Serum ferritin ⁵	Deficiency anemia ¹
Disease ³	Expression ⁵	Deficiency ⁵	Ferric carboxymaltose ⁴
Number of keywords			
Red			
11	12	11	12
Purple			
2	2	1	1
Blue			
5	5	6	5
Yellow			
2	1	1	3
Green			
5	5	6	4
New items in each quartile			
(None)	Serum ferritin ⁵	Management ³	Oral iron ⁴
	Hepcidin ⁵	Intravenous iron ⁴	Health ¹
	Growth ¹	Inflammation ⁵	Ferric carboxymaltose ⁴
	Risk ³	Association ³	

Celiac disease ³	Metabolism ¹
Expression ⁵	Infants ¹

¹Red.²Purple.³Blue.⁴Yellow.⁵Green.

Summary shows the number of keywords in each 5-year quartile by cluster and a list of the keywords appearing for the first time in the top-25 list for each quartile.

populations are particularly prevalent in the developing world[21], residents of industrialized national are also impacted, as noted by Dubé *et al*[22].

Additional highly cited papers in this study addressed the neurologic implications of iron deficiency and iron deficiency anemia. These include Grantham-McGregor *et al* [23]'s review of the long-term effects of iron deficiency on neurological functioning in children[23] and Beard and Connor's seminal paper on iron status and its correlation with neural functioning[24]. The work of Lozoff and colleagues, including their 2006 paper which is highlighted in the current study, detailed that the neurological defects in patients in iron-deficient children may extend into adulthood, even after correction of the underlying nutritional issue[25].

An important consequence of iron deficiency and iron deficiency anemia is decreased work output, which may have long-term impact on affected individuals and has an established societal effect. These features were described in highly-cited work by Haas and Brownlie[2].

Bioavailability of dietary iron

Although iron deficiency is a widespread international public health issue, few high-impact studies have been dedicated to the critical issue of iron bioavailability, as evidenced from the survey of top 10-cited papers. Two review papers have discussed features of iron bioavailability. The first, by Plum *et al*[26], examines the role of zinc in iron metabolism[26]. The second, by Xie *et al*[27], examines the physiologic role of polysaccharides derived from medicinal plants, some of which have been identified as having iron-chelating properties[27].

Biochemical aspects of iron deficiency anemia

Though none of the top-10 cited studies had iron metabolism as a main topic, 4 studies in the quartile analysis were focused on biochemical aspects of iron anemia. Three of these had a particular focus on hepcidin. Hepcidin, a protein produced by the liver and cleared by the kidneys, plays a central role in iron uptake by the duodenum and spleen. Its regulation was described in a highly cited paper identified in this study [28], which showed that hepcidin expression is upregulated in response to anemia and hypoxia and downregulated by increased hematopoiesis. An immunoassay for hepcidin was described by Ganz *et al*[29] and Girelli *et al*[30]. Laboratory testing for serum hepcidin levels can be used to distinguish iron deficiency anemia from anemia of chronic disease (inflammation)[1].

Another important step in iron metabolism highlighted by the current study is the action of ferroreductase, which acts on ferric (3+) iron-containing molecules in the cytoplasm of phagocytes to produce bioavailable ferrous (2+) iron[31,32].

Causes of iron deficiency anemia

Numerous health conditions have been implicated in the etiology of iron deficiency anemia. Among these are chronic inflammatory conditions, chronic gastritis (in particular gastritis secondary to *Helicobacter pylori*), chronic use/abuse of non-steroidal anti-inflammatory drugs (NSAID), and celiac disease. Iron deficiency may also follow gastrointestinal procedures such as bariatric surgery and capsule endoscopy[33]. The role of *Helicobacter pylori* gastritis and celiac disease were the subjects of 2 papers from the overall top 10-cited group[34-36]. In addition, Graham *et al*[37] identified the mucosal lesions in the gastrointestinal tracts of chronic NSAID users, many of whom developed iron deficiency anemia[37]. In patients with chronic kidney disease, decreased renal clearance of hepcidin may result in chronic kidney disease, as described by Levin and Rocco[38].

Table 3 The top 10 cited papers published for the entire period 2001-2020, and the top 10 cited papers published in each 5-year interval within the study period

2001-2020									
Ref.	Title	Journal	Year	Volume	Start page	End page	Times cited	Topic	
Vos <i>et al</i> [14], 2012	Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010	<i>Lancet</i>	2012	380	2163	2196	4084	1	
Malfertheiner <i>et al</i> [34], 2007	Current concepts in the management of <i>Helicobacter pylori</i> infection: the maastricht III consensus report	<i>Gut</i>	2007	56	772	781	1481	3	
Bhutta <i>et al</i> [44], 2008	Maternal and Child Undernutrition 3 - What works? Interventions for maternal and child undernutrition and survival	<i>Lancet</i>	2008	371	417	440	1147	4	
Darmon and Drewnowski[19], 2008	Does social class predict diet quality?	<i>American Journal of Clinical Nutrition</i>	2008	87	1107	1117	1061	1	
Walker <i>et al</i> [45], 2007	Child development in developing countries 2 - Child development: risk factors for adverse outcomes in developing countries	<i>Lancet</i>	2007	369	145	157	1033	4	
Chey and Wong [39], 2007	American college of gastroenterology guideline on the management of <i>Helicobacter pylori</i> infection	<i>American Journal of Gastroenterology</i>	2007	102	1808	1825	830	3	
Guralnik <i>et al</i> [20], 2004	Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia	<i>Blood</i>	2004	104	2263	2268	793	1	
Ludvigsson <i>et al</i> [40], 2013	The Oslo definitions for coeliac disease and related terms	<i>Gut</i>	2013	62	43	52	790	3	
Rubio-Tapia <i>et al</i> [41], 2013	ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease	<i>American Journal of Gastroenterology</i>	2013	108	656	676	788	3	
Hill <i>et al</i> [35], 2005	Guideline for the diagnosis and treatment of celiac disease in children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition	<i>Journal of Pediatric Gastroenterology and Nutrition</i>	2005	40	1	19	752	4	
2001-2005									
Guralnik <i>et al</i> [20], 2004	Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia	<i>Blood</i>	2004	104	2263	2268	793	1	
Hill <i>et al</i> [35], 2005	Guideline for the diagnosis and treatment of celiac disease in children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition	<i>Journal of Pediatric Gastroenterology and Nutrition</i>	2005	40	1	19	752	4	
Grantham-McGregor and Ani[23], 2001	A review of studies on the effect of iron deficiency on cognitive development in children	<i>Journal of Nutrition</i>	2001	131	649S	666S	736	1	
Pennazio <i>et al</i> [33], 2004	Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: Report of 100 consecutive cases	<i>Gastroenterology</i>	2004	126	643	653	688	3	
Nicolas <i>et al</i> [28], 2002	Severe iron deficiency anemia in transgenic mice expressing liver hepcidin	<i>Proceedings of The National Academy of Sciences of The United States of America</i>	2002	99	4596	4601	694	2	
Haas and Brownlie[2], 2001	Iron deficiency and reduced work capacity: A critical review of the research to determine a causal relationship	<i>Journal of nutrition</i>	2001	131	676S	688S	573	1	
Dubé <i>et al</i> [22], 2005	The prevalence of celiac disease in average-risk and at-risk Western European populations: A systematic review	<i>Gastroenterology</i>	2005	128	S57	S67	427	1	
Ohgami <i>et al</i> [31], 2005	Identification of a ferrioreductase required for efficient transferrin-dependent iron uptake in erythroid cells	<i>Nature Genetics</i>	2005	37	1264	1269	394	2	

Beard and Connor[24], 2003	Iron status and neural functioning	<i>Annual Review of Nutrition</i>	2003	23	41	58	383	1
Graham <i>et al</i> [37], 2005	Visible small-intestinal mucosal injury in chronic NSAID users	<i>Clinical Gastroenterology and Hepatology</i>	2005	3	55	59	391	4
2006-2010								
Malfertheiner <i>et al</i> [34], 2007	Current concepts in the management of <i>Helicobacter pylori</i> infection: the maastricht III consensus report	<i>Gut</i>	2007	56	772	781	1481	3
Bhutta <i>et al</i> [44], 2008	Maternal and Child Undernutrition 3 - What works? Interventions for maternal and child undernutrition and survival	<i>Lancet</i>	2008	371	417	440	1147	4
Darmon and Drewnowski[19], 2008	Does social class predict diet quality?	<i>American Journal of Clinical Nutrition</i>	2008	87	1107	1117	1061	1
Walker <i>et al</i> [45], 2007	Child development in developing countries 2 - Child development: risk factors for adverse outcomes in developing countries	<i>Lancet</i>	2007	369	145	157	1033	4
Chey and Wong [39], 2007	American college of gastroenterology guideline on the management of <i>Helicobacter pylori</i> infection	<i>American Journal of Gastroenterology</i>	2007	102	1808	1825	830	3
Levin and Rocco [38], 2006	KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease - Foreword	<i>American Journal of Kidney Diseases</i>	2006	47	S9	S145	565	4
Lozoff <i>et al</i> [25], 2006	Long-lasting neural and behavioral effects of iron deficiency in infancy	<i>Nutrition Reviews</i>	2006	64	S34	S43	532	1
Rostom <i>et al</i> [46], 2006	American Gastroenterological Association (AGA) Institute Technical Review on the Diagnosis and Management of Celiac Disease	<i>Gastroenterology</i>	2006	131	1981	2002	514	3
Ganz <i>et al</i> [29], 2008	Immunoassay for Human Serum Hepcidin	<i>Blood</i>	2008	112	4292	4297	502	2
Plum <i>et al</i> [26], 2010	The Essential Toxin: Impact of Zinc on Human Health	<i>International Journal of Environmental Research and Public Health</i>	2010	7	1342	1365	484	5
2011-2015								
Vos <i>et al</i> [14], 2012	Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010	<i>Lancet</i>	2012	380	2163	2196	4084	1
Ludvigsson <i>et al</i> [40], 2013	The Oslo definitions for coeliac disease and related terms	<i>Gut</i>	2013	62	43	52	790	3
Rubio-Tapia <i>et al</i> [41], 2013	ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease	<i>American Journal of Gastroenterology</i>	2013	108	656	676	788	3
Kassebaum <i>et al</i> [18], 2014	A systematic analysis of global anemia burden from 1990 to 2010	<i>Blood</i>	2014	123	615	624	623	1
Walker <i>et al</i> [47], 2011	Child Development 1 Inequality in early childhood: risk and protective factors for early child development	<i>Lancet</i>	2011	378	1325	1338	621	1
Camaschella[48], 2015	Iron-Deficiency Anemia	<i>New England Journal of Medicine</i>	2015	372	1832	1843	402	Multiple
Chey <i>et al</i> [49], 2015	Irritable Bowel Syndrome A Clinical Review	<i>Jama-journal of The American Medical Association</i>	2015	313	949	958	378	3
Balarajan <i>et al</i> [21], 2011	Anaemia in low-income and middle-income countries	<i>Lancet</i>	2011	378	2123	2135	353	1
Pennazio <i>et al</i> [33], 2004	Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline	<i>Endoscopy</i>	2015	47	352	376	317	3
Goodnough <i>et al</i> [42], 2011	Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines	<i>British Journal of Anaesthesia</i>	2011	106	13	22	303	3

2016-2020									
Chey <i>et al</i> [50], 2017	ACG Clinical Guideline: Treatment of <i>Helicobacter pylori</i> Infection	<i>American Journal of Gastroenterology</i>	2017	112	212	239	324	3	
Amieva and Peek [51], 2016	Pathobiology of <i>Helicobacter pylori</i> -Induced Gastric Cancer	<i>Gastroenterology</i>	2016	150	64	78	224	4	
Kyu <i>et al</i> [52], 2016	Global and National Burden of Diseases and Injuries Among Children and Adolescents Between 1990 and 2013 Findings From the Global Burden of Disease 2013 Study	<i>Jama Pediatrics</i>	2016	170	267	287	214	1	
Girelli <i>et al</i> [30], 2005	Hepcidin in the diagnosis of iron disorders	<i>Blood</i>	2016	127	2809	2813	147	2	
Kassebaum[53], 2016	The Global Burden of Anemia	<i>Hematology-oncology Clinics of North America</i>	2016	30	247	308	141	1	
Trenkwalder <i>et al</i> [54], 2016	Restless legs syndrome associated with major diseases A systematic review and new concept	<i>Neurology</i>	2016	86	1336	1343	117	4	
Xie <i>et al</i> [27], 2016	Advances on Bioactive Polysaccharides from Medicinal Plants	<i>Critical Reviews in Food Science and Nutrition</i>	2016	56	S60	S84	112	5	
Enns <i>et al</i> [55], 2017	Clinical Practice Guidelines for the Use of Video Capsule Endoscopy	<i>Gastroenterology</i>	2017	152	497	514	111	3	
Froessler <i>et al</i> [36], 2018	The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery A Randomized Controlled Trial	<i>Annals of Surgery</i>	2016	264	41	46	98	4	
Vasanawala <i>et al</i> [56], 2016	Safety and technique of ferumoxytol administration for MRI	<i>Magnetic Resonance in Medicine</i>	2016	75	2107	2111	93	3 and 4	

For the Topic column, the following numbers correspond to these topics: (1) Epidemiologic aspects of iron deficiency anemia; (2) Biochemical aspects of iron deficiency anemia; (3) Clinical evaluation of causes of iron deficiency anemia; (4) Causes of iron deficiency anemia; and (5) Bioavailability of dietary iron.

Clinical evaluation and management of causes of iron deficiency anemia

Several of the papers in the current study that detailed the causes of iron deficiency anemia were consensus papers that also recommended protocols for the clinical evaluation of patients. These include the American college of Gastroenterology guidelines and the Maastricht III report, which provided guidance on the management of *Helicobacter pylori* infection[34,39], and the Oslo and American College of Gastroenterology guidelines for celiac disease[40,41]. Presurgical workup of anemias was also a highly-cited topic: An example is the NATA guidelines for the evaluation of anemia in preoperative orthopedic patients[42]. The use of perioperative intravenous iron after abdominal surgery has been an important recent contribution to the list of highly-cited papers[36].

Limitations

Bibliometric analysis, although a potent means for highlighting the research hotspots of a given field, has some limitations. First, the bibliometric data are best accessed using the Web of Science database, and currently are not as widely available in other databases. This may cause problems with the search, since checklists for systematic reviews such as PRISMA generally recommend the use of 2 or more databases for searches[43]. Another limitation is that since the number of citations of a given paper would be expected to increase over time, it would be expected that older papers would have a higher citation rate than more recently published papers. In the current study, dividing the study period into 5-year quartiles was an attempt to identify papers which had a high citation rate within their cohort.

CONCLUSION

This study was a bibliometric analysis of the medical literature on iron deficiency anemia published over the last 20 years. Five research hotspots were identified; the area of epidemiology had the largest number of highly cited papers, and the area of bioavailability of dietary iron had the lowest. These relative contributions have been

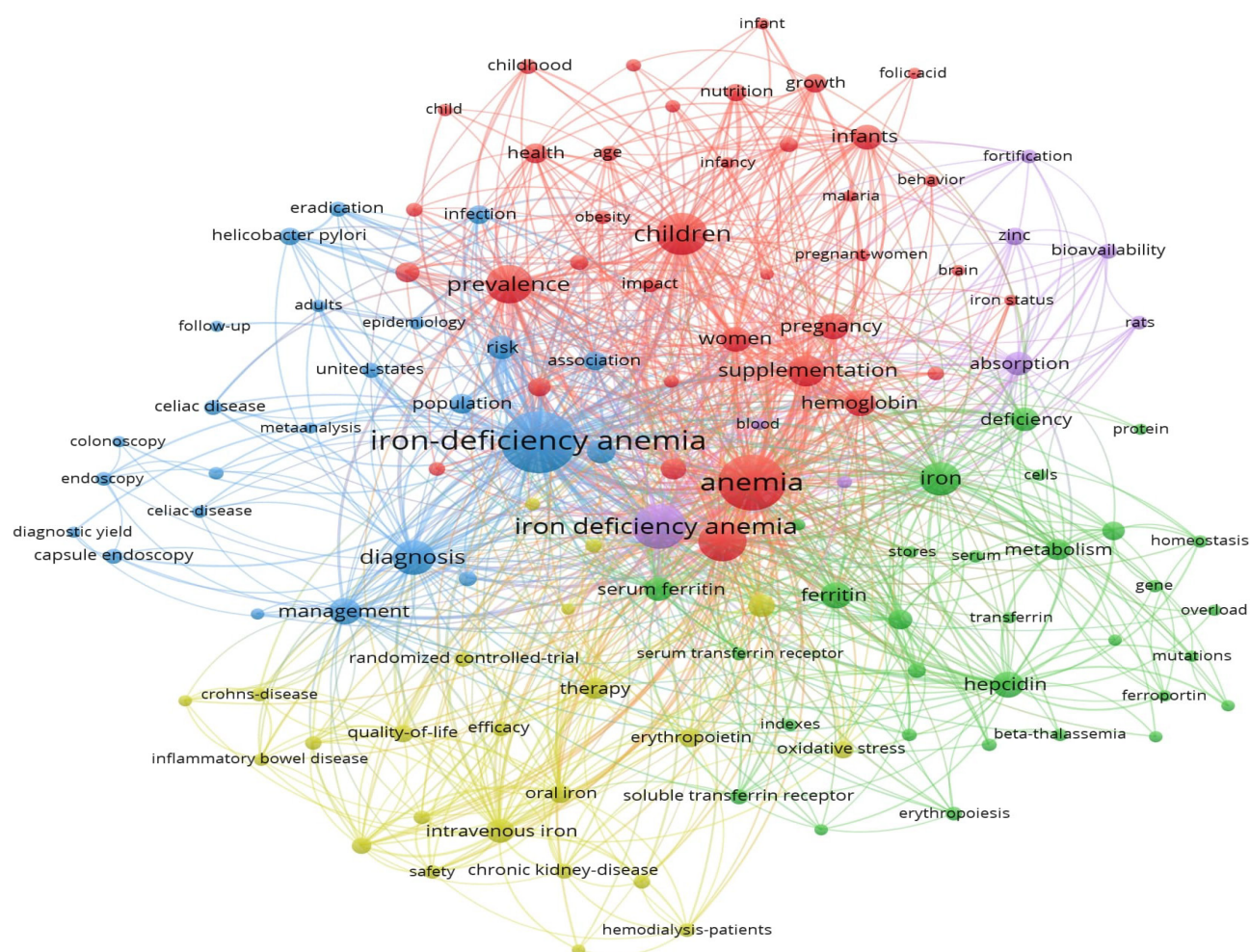


Figure 4 123 terms appearing 50 times or more in the titles or abstracts of the papers in this study.

apparently unchanged over the course of the study period. Although iron deficiency anemia has a worldwide impact, the published research of this period was highly influenced by studies from the United States.

ARTICLE HIGHLIGHTS

Research background

Iron deficiency is the most common micronutrient deficiency and has a worldwide impact. A bibliometric analysis focused on research trends on the topic of iron deficiency anemia has not been performed.

Research motivation

Analyzing the iron deficiency anemia research published between 2001-2020 what collaborative research networks are most active in this field? What subfields are of greatest importance? Are there any emerging research trends in this area?

Research objectives

The objectives of this study were to evaluate the literature published over the last 2 decades, focusing on: (1) The extent of collaborative research networks in this field; (2) The research topics of greatest prominence; and (3) A subset analysis of the most-cited papers published between 2001-2020 and the most-cited papers in 5-year intervals during this period to assess for emerging trends in research in this area.

Research methods

This study was conducted as a bibliometric analysis using Preferred Reporting Items

for Systematic Reviews and Meta-analysis guidelines. A search of the medical literature published between 2001-2020 and related to iron deficiency anemia was performed and data from the search were used to identify publication trends in iron deficiency anemia research. Network visualization by VOSviewer (Leiden University) was performed to identify international collaborative groups and research hotspots in works published during this period.

Research results

Of 4828 publications were included in the study. Network visualization identified 3 international collaborative networks: United States, Canada, and India; Turkey, China, and Japan; and England and other European countries. Five research hotspots were highlighted: (1) Epidemiology of iron deficiency anemia; (2) Biochemistry of iron deficiency anemia; (3) Clinical evaluation of iron deficiency anemia; (4) Causes of iron deficiency anemia; and (5) Bioavailability of iron in the diet. An additional analysis of the top-10 overall cited papers, and the top-10 cited papers for each 5-year increment starting in 2001 showed that the largest number of highly cited papers were from the field of epidemiology, the smallest number from the field of bioavailability of dietary iron.

Research conclusions

Iron deficiency anemia has a high citation rate compared to studies of other topics using similar methodology. Studies from the United States and epidemiologic studies dominate the field.

Research perspectives

Future studies directed from relatively underrepresented areas of the world, and studies directed at less prominently featured areas such as bioavailability of dietary iron may be welcome additions to this already well-developed research area.

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