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## COVID-19-associated stroke risk: Could nutrition and dietary patterns have a contributing role?

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### Abstract

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has created a life-threatening world pandemic. Unfortunately, this disease can be worse in older patients or individuals with comorbidities, having dangerous consequences, including stroke. COVID-19-associated stroke widely increases the risk of death from COVID-19. In addition to the personal hygiene protocols and preventive policies, it has been proven that immune-compromised, oxidative, and pro-coagulant conditions make a person more susceptible to severe COVID-19 complications, such as stroke; one of the most effective and modifiable risk factors are poor nutritional status. Previous literature has shown that healthy dietary patterns, such as the Mediterranean diet, some food groups, and specific micronutrients, reduce the risk of ischemic and hemorrhagic stroke. In this work, for the first time, we hypothesized that a healthy diet could also be a protective/preventive factor against COVID-19-associated stroke risk. In order to prove this hypothesis, it is required to study nutritional intake and dietary patterns in patients suffering from COVID-19-associated stroke. If this hypothesis is proven, the chronic supportive role of a healthy diet in critical situations will be highlighted once again.

**Key Words:** COVID-19; COVID-19-associated stroke; Nutrition; Dietary patterns; Food

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**Core Tip:** The novel coronavirus disease 2019 (COVID-19) can be worse in older patients or individuals with comorbidities, having dangerous consequences, including stroke. COVID-19-associated stroke widely increases the risk of death from COVID-19. Previous literature has shown that healthy dietary patterns, such as the Mediterranean diet, some food groups, and specific micronutrients, reduce the risk of ischemic and hemorrhagic stroke. Recently, healthy nutrition and certain nutrients or nutraceuticals reported to be effective in common relief functions in stroke and COVID-19 pathways. If growing studies confirm our hypothesis, it means that healthy nutrition could be a protective/preventive factor against COVID-19-associated stroke risk.

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## INTRODUCTION

Due to the significance of the current pandemic, many studies have paid attention to its consequent clinical outcomes. Clinical manifestations can astonishingly vary from asymptomatic to the most life-threatening conditions resulted from cytokine storm<sup>[1,2]</sup>. Currently, the novel coronavirus disease 2019 (COVID-19)-associated stroke is not common and, simultaneously, is one of the most deteriorate consequences of this infection, particularly in those with severe infection<sup>[3,4]</sup>, which is responsible for the mortality of about 40% of affected patients if it occurs<sup>[5,6]</sup>. Stroke, in turn, is the second cause of death and the leading cause of disability<sup>[7]</sup>. Although it is not yet exactly clear COVID-19 to be a culprit in the co-occurrence of stroke in infected patients<sup>[8]</sup>, studies have shown that the incidence of stroke in COVID-19 patients is about 0.9% to 2.7%<sup>[6,8]</sup>. COVID-19-associated stroke is often an acute ischemic stroke, while hemorrhagic stroke also is rarely reported, especially in elderly<sup>[5,9]</sup>. Although some studies have reported stroke in young COVID-19 patients<sup>[10]</sup>, a systematic review and metasummary of the literature have shown a mean age of  $63.4 \pm 13.1$  years and the simultaneous presence of cardiovascular comorbidities<sup>[6]</sup>. Hypertension, diabetes, and inappropriate cholesterol levels are the main comorbidities associated with the severity of COVID-19<sup>[11]</sup>. On the other hand, the available data, indeed, suggest that severe COVID-19 can lead to stroke<sup>[6,9]</sup>. Preventive strategies and available health-promoting protocols based on antiviral therapies, immune modulators, and anticoagulants to reduce the severity of this disease appear to be significant and interesting points to be studied<sup>[12]</sup>. However, lifestyle has always been the most modifiable factor influencing diseases, of which nutrition is a vital part<sup>[13-15]</sup>. The role of healthy nutrition in the prevention and treatment of hypertension, diabetes, high serum levels of cholesterol, all of which predispose a person to stroke, and most non-communicable diseases has also been proven<sup>[16-18]</sup>. Recently, researchers have discussed immune-modulatory properties and other various effects of healthy nutrition on COVID-19 and its complications<sup>[13-15,19-21]</sup>, among which no attention has been paid to COVID-19-associated stroke.

## HYPOTHESIS

A vast body of evidence-based data from the past to the present has shown that healthy eating can prevent hemorrhagic and ischemic stroke<sup>[22-24]</sup>. Protection against hyper-inflammatory and hypercoagulable states and a pleasant change in metabolites derived from intestinal microbiota leading to cardiovascular health are the mainstream mechanisms involved<sup>[25]</sup>. Although there is no study concerning nutrition in COVID-

19-associated stroke yet, there are growing studies addressing the impact of healthy diets, certain food groups, and some specific nutrients on COVID-19<sup>[13-15,19-21]</sup>. In these studies, healthy nutrition and some nutrients or nutraceuticals are considered mitigators of the disease severity and cytokine storm. On the other hand, some data have shown stroke as the worst event following COVID-19, occurring under cytokine storm and hypercoagulable conditions<sup>[26]</sup>. Altogether, the above-mentioned evidence creates the speculation that people who adherence to a healthy diet and lifestyle may be less likely to have a stroke following COVID-19 affliction.

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## EVALUATION OF THE HYPOTHESIS

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To evaluate our hypothesis, we conducted a comprehensive review by searching both pubmed.gov and scholar.google.com to first understand the association between stroke and COVID-19 and second review the studies in which nutrition has been linked to stroke and COVID-19. The former results are shown in [Table 1](#), and the latter in [Table 2](#). We also explain them in detail below.

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## COVID-19-ASSOCIATED STROKE RISK

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection enters the target cell *via* the angiotensin-converting enzyme 2 (ACE2) receptor<sup>[12]</sup>. In addition to the lung, this receptor is present in the endothelial cells, heart, kidney, and intestine<sup>[27]</sup>. This is an underlying cause of beyond respiratory manifestations of COVID-19. Once the virus infects the endothelial cells lining blood vessels beds, inflammatory cells and apoptotic bodies are accumulated; this results in vascular endothelial dysfunction, shifting vascular autoregulation to vasoconstriction, and organ ischemia, tissue edema, and pro-coagulant condition consequently<sup>[27,28]</sup>. On the other hand, immune-mediated recruitment of immune cells elevates the inflammatory responses and hyper-inflammatory states, leading to cytokine storm in severe cases. Cytokine storm plays a key role in the pathogenesis of severe COVID-19 manifestations, including acute ischemic stroke caused by hypercoagulable state<sup>[26]</sup>. Similar to other viral syndromes, SARS-CoV-2 is associated with an increased risk of stroke<sup>[29,30]</sup>. Elevated interleukin-6 (IL-6) levels following cytokine storm cause hyperviscosity<sup>[6]</sup>. Thus, besides the mechanisms, including infection-induced hypercoagulability, viral cardiomyopathy, and a diffuse hyperinflammatory state<sup>[27,28,31]</sup>, proposed so far for the association between COVID-19 and acute ischemic stroke, a mechanical factor as dehydration can also increase stroke risk<sup>[8,32]</sup>. By comparing measured biomarkers in severe COVID-19 patients with moderate cases, a study has shown higher levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein (CRP), ferritin, D-dimer, IL-2R, IL-6, IL-10, and TNF- $\alpha$  in severely infected patients. Furthermore, the total number of T lymphocytes, CD4<sup>+</sup> T cells, and CD8<sup>+</sup> T cells significantly are lower in severe cases than those moderate. Therefore, they have concluded the cytokine storm to be related to disease severity<sup>[33]</sup>. A recently published systematic review further reveals the outstanding presence of raised D-dimer, fibrinogen, and anti-phospholipid antibodies in COVID-19 patients with coincide acute ischemic stroke<sup>[6]</sup>. Thus, the speculate on COVID-19-associated stroke is consistent with previous studies, which have well demonstrated that higher levels of D-dimer significantly associated with older age and pre-existing comorbidities are related to worse complications and death from COVID-19<sup>[9,34]</sup>. According to a report by Ntaios *et al*<sup>[35]</sup>, COVID-19-associated ischemic stroke is more severe with poorer outcomes and higher mortality than ischemic strokes unrelated to COVID-19. Although most studies have discussed ischemic stroke, there is little data to suggest that SARS-CoV-2-induced diffuse endothelial inflammation also could be a mechanism resulting in hemorrhagic stroke<sup>[31]</sup>. On the other hand, as stated, the infection caused by SARS-CoV-2 is mediated by the host cells ACE2 receptors; this, in turn, downregulates the expression of ACE2. Hence, the availability of angiotensin II increases, leading to severe blood pressure fluctuates, especially in patients with a history of hypertension that makes them prone to hemorrhagic stroke<sup>[9]</sup>. Finally, it is hypothesized that therapeutic targeting of protease-activated receptor (PAR), as a protein engaged in the neuroinflammatory toxicity, may be useful in controlling various complications caused by COVID-19<sup>[32]</sup>.

**Table 1 Summary of available evidence-based associations between stroke and coronavirus disease 2019**

Ref.	Study design	Sample/ Aim	The main culprits suggested in the occurrence of stroke result from COVID-19 affliction
Bhaskar <i>et al</i> <sup>[26]</sup>	The REPROGRAM consortium position paper	An overview of cytokine storm and its implications in COVID-19	(1) Cytokine storm; (2) Thromboembolic events; and (3) Large vessel occlusion
Rothstein <i>et al</i> <sup>[31]</sup>	Retrospective, observational study	844 COVID-19 patients, 28 of them had a stroke	(1) Endothelialitis; (2) Diffuse endothelial inflammation; (3) Infection-induced hypercoagulability; (4) Viral cardiomyopathy; and (5) Diffuse hyperinflammatory state
Valderrama <i>et al</i> <sup>[8]</sup>	Case study	A 52-year-old man with co-occurrence of stroke and COVID-19 infection	(1) Inflammation; (2) Injury to the myocardium; (3) Thrombogenesis; (4) Increased D-dimer levels; (5) Increased interleukin-6 levels; (6) Hyperviscosity; (7) Vascular endothelial damage; (8) Intracerebral hemorrhage; (9) Microthrombosis; and (10) Fibrinogen consumption coagulopathy
Tan <i>et al</i> <sup>[6]</sup>	Systematic review and meta-summary of the literature	A total of 39 studies comprising 135 patients, pooled incidence of co-occurrence of stroke and COVID-19 was 1.2 %	(1) Elevated D-dimer; (2) Elevated fibrinogen; and (3) The presence of antiphospholipid antibodies
Wang <i>et al</i> <sup>[9]</sup>	A review article	Summarizing the potential contribution of COVID-19 to hemorrhagic stroke in the elderly and proposing possible mechanisms	(1) Downregulation of ACE2 expression; (2) Increased angiotensin II availability; (3) Severe blood pressure fluctuates; (4) Predisposition to hemorrhagic stroke; (5) Elevated plasma D-dimer levels; (6) Classical inflammatory biomarkers; (7) Viral CNS infections; (8) Cytokine, chemokine, and protease; and (9) Increasing BBB permeability
Ntaios <i>et al</i> <sup>[35]</sup>	Special report	Pooled all patients who were hospitalized with confirmed COVID-19 and AIS in 28 sites from 16 countries	(1) Endotheliopathy; (2) Potentiate the prothrombotic milieu; (3) Immune-mediated platelet activation; (4) Dehydration; and (5) Infection-induced cardiac arrhythmias

COVID-19: Coronavirus disease 2019; ACE2: Angiotensin-converting enzyme 2; CNS: Central nervous system; BBB: Blood-brain barrier; AIS: Acute ischemic stroke.

## DIETARY PATTERNS AND STROKE RISK

According to several national studies, nearly 90% of the stroke burden can be assigned to the modifiable risk factors, including poor diet<sup>[36,37]</sup>. Therefore, a healthy diet is necessary and important as an approved preventive strategy against stroke<sup>[22]</sup>. Many articles are now available, all of which indicate that healthy eating and adherence to the certain dietary patterns, such as the healthy Nordic diet<sup>[23]</sup>, Dietary Approaches to Stop Hypertension (DASH) diet<sup>[22]</sup>, and especially the Mediterranean diet<sup>[24]</sup>, significantly reduce the risk of both ischemic and hemorrhagic strokes. Hansen *et al*<sup>[23]</sup>, in their cohort study with a median follow-up period of 13.5 years identifying 2283 cases of stroke, have found that adherence to a healthy Nordic diet (containing fish, apples, pears, cabbages, root vegetables, rye bread, and oatmeal) has a positive effect on stroke risk so that the higher Healthy Nordic Food Index score is associated with a lower risk of total stroke. Clinical trials have also shown that adherence to a healthy Nordic diet leads to weight loss, decreased blood pressure, and improved serum lipid status<sup>[38-40]</sup>. This diet is rich in potassium and fiber since it contains high amounts of fruits and vegetables associated with decreased blood pressure. Further, high fiber in whole grains is associated with lower total and low-density lipoprotein cholesterol. On the other hand, abundant flavonoids in apples, kale, and broccoli are also related to a reduced risk of stroke<sup>[23]</sup>. The next most examined dietary approach is the DASH diet, which includes a high intake of fruits, vegetables, whole grains, low-fat dairy, legumes, nuts, low sodium intake, sweetened beverages, and red/processed meat<sup>[22]</sup>. A meta-analysis of prospective studies by Feng *et al*<sup>[22]</sup> has shown that every 4 points increase in the score of adherence to the DASH diet reduces the risk of stroke in a dose-response manner by 4%. This is true for both ischemic and hemorrhagic strokes, although less data is available on the latter. Randomized clinical trials have also shown that adherence to this diet, in addition to lowering blood pressure, can reduce the stroke risk by improving lipid profile, controlling body weight, besides reducing the risk of type 2 diabetes and metabolic syndrome, all of which are important in the pathogenesis of stroke<sup>[41-45]</sup>. Another dietary pattern emphasized to be followed to prevent stroke is the Mediterranean diet. The PREDIMED study<sup>[46]</sup> with 7447 participants has found that adherence to the traditional Mediterranean diet characterized by high consumption of olive oil, fruits, nuts, vegetables, and cereals, moderate intake of fish and poultry, low intake of dairy products, red meat, and

**Table 2 Summary of available studies related to dietary patterns, some foods, and micronutrients in context of stroke and/or coronavirus disease 2019**

Ref.	Study design	Sample/ Aim	Possible pathways in which nutritional factors may be involved in pathogenesis of stroke and/ or COVID-19-associated stroke
Hansen <i>et al</i> <sup>[23]</sup>	A Danish cohort study	Incident cases of stroke among 55338 men and women	(1) Higher Healthy Nordic Food Index score, was associated with a lower risk of total stroke; (2) Reduction in blood pressure; (3) Improved blood lipids; (4) Induced weight loss; (5) Lower total and low-density lipoprotein cholesterol; and (6) Increased antioxidant and flavonoid levels
Feng <i>et al</i> <sup>[22]</sup>	A meta-analysis of prospective studies	Included 12 prospective cohort studies comprising a total of 548632 participants	(1) Higher adherence to the DASH diet was related to a reduced risk of developing stroke; (2) Blood pressure-lowering effects; (3) Improved lipid profiles and body weight; (4) Decreased the risk of metabolic syndrome; (5) Improved serum inflammatory biomarkers; (6) Reduced oxidative stress; and (7) Anti-inflammatory and antioxidative effects
Estruch <i>et al</i> <sup>[24]</sup>	Randomized clinical trial	A total of 7447 persons randomly assigned to 3 diets: a Med-diet suppl with extra-virgin olive oil, a Med-diet suppl with mixed nuts, or a control diet	(1) A Med-diet suppl with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events; (2) High biologic plausibility; (3) Anti-inflammatory and antioxidative effects; (4) Improved endothelial dysfunction; (5) Resistance to vasoreactivity; (6) Insulin sensitivity; (7) Improved blood lipids
Chiu <i>et al</i> <sup>[47]</sup>	2 Prospective cohort study	Cohort 1, <i>n</i> = 5050; Cohort 2, <i>n</i> = 8302	(1) Taiwanese vegetarian diet is associated with a lower risk of ischemic and hemorrhagic strokes; (2) Shift gut microbial community to reduce the production of trimethylamine N-oxide; and (3) So, decreased platelet hyperreactivity and thrombosis
D'Elia <i>et al</i> <sup>[49]</sup>	A meta-analysis	Pooled analysis of 14 cohorts (overall 333250 participants and 10659 events)	(1) An inverse and significant association between K intake and risk of stroke; and (2) Decreased blood pressure
Zhao <i>et al</i> <sup>[50]</sup>	A systematic review and meta-analysis	18 prospective cohort studies on Mg intake and the incidence of stroke	(1) Increasing Mg intake may be a crucial component of stroke prevention that acts in a dose-dependent manner; and (2) Improved cardiovascular health
Iacoviello <i>et al</i> <sup>[51]</sup>	A systematic review	Prospective studies that focused on primary prevention of stroke by nutrition	Nutrients, food groups and dietary patterns are effective in preventing stroke, such as: (1) Vitamin D, dairy calcium, folate (not supplementation), vitamin C, chocolate, coffee, tea, and the regular and moderate alcohol consumption; (2) Calcium and dairy intake are inversely associated with low-grade systemic inflammation; (3) Low-fat dairy and milk consumption decreased the incidence of hypertension; (4) Vitamin D involved in the modulation of the renin-angiotensin system, endothelial function, vascular smooth muscle proliferation, insulin sensitivity, and systemic inflammation; (5) Vitamin C, beta-carotene, and flavonoids are antioxidant compounds can be reduce blood pressure and improve microvascular function; and (6) Chocolate intake resulted in increased HDL, decreased LDL oxidation, improved endothelial function and reduced blood pressure
Bousquet <i>et al</i> <sup>[52]</sup>	Review article	The role of diet in COVID-19 death rates	(1) Countries where the major daily intake originates from uncooked or fermented kale, cabbages, and fermented dairy products have lower COVID-19 death rates than the others; (2) Mentioned foods known as good sources for anti-ACE activity and rich in antioxidants; and (3) Improving high blood pressure and subsequent hemorrhagic stroke
Kalantar-Zadeh <i>et al</i> <sup>[20]</sup>	Perspective study	The impact of dietary patterns and the commensal microbiome on susceptibility to and severity of COVID-19	(1) A healthy, diverse, and balanced diet based on plants, high fiber, and fermented foods could be a preventative strategy, mitigating harmful effects of SARS-CoV-2; and (2) Probiotics can modulate the immune system, thereby reducing the susceptibility to affliction or morbidity and mortality from COVID-19
Tan <i>et al</i> <sup>[53]</sup>	Prospective observational study	AIS patients ( <i>n</i> = 140), healthy controls ( <i>n</i> = 92)	(1) Gut-brain axis has been brought to attention; (2) Probiotics and beneficial microbes exert pleasant alter on the gut microbiome towards producing more SCFAs; (3) There was dysbiosis (low fecal SCFAs level) in AIS patients; and (4) The SCFAs levels were negatively correlated with stroke severity and prognosis
Zabetakis <i>et al</i> <sup>[14]</sup>	Review article	This review speculates the importance of nutrition as a mitigation strategy to support immune function amid the COVID-19 pandemic	(1) Person's nutritional status and nutrients and foods may exert anti-inflammatory and immunomodulatory effects; (2) Nutrients such as vitamin C, vitamin D, and zinc may hold some promise for the treatment of COVID-19; (3) Nutrients with anti-inflammatory, antithrombotic, and antioxidant properties may prevent or attenuate the inflammatory and vascular manifestations associated with COVID-19; and (4) It is vitally important to maintain a healthy diet and lifestyle during the pandemic
Kanki <i>et al</i> <sup>[56]</sup>	Animal study	Adult male C57BL6N mice included in two group NCD or HFD	(1) Mice with a HFD have higher levels of endogenous thrombin; (2) Thrombin was considered as a stimulator of PAR-1-based signaling; (3) PAR signaling involved in the neuroinflammatory complications; and (4) HFD mice experience larger infarct and worse outcomes after stroke induction
Wallace <i>et al</i> <sup>[21]</sup>	Review article	A summary of clinical and prospective cohort studies assessing the relationship of Mg with IL-6, a prominent drug target for	(1) Nutrition plays an important and safe role in helping mitigate patient morbidity and mortality from COVID-19; (2) Mg participates in the function of many enzymes involved in the severe immune and inflammatory responses that are manifestations of COVID-19; (3) Mg modulates IL-6, nuclear factor-κB, and CRP; (4) Mg enhances vitamin D functionality; (5) Mg is essential in preventing the serious consequences of COVID-19; (6) K restores ACE2

		treating COVID-19	functionality; and (7) Hypokalemia is seen in most patients with severe and critical COVID-19
Rhodes <i>et al</i> <sup>[2]</sup>	Perspective study	To review the evidence relevant to vitamin D and COVID-19	(1) Vitamin D is potential to reduce COVID-19 risk, severity, and mortality; (2) Inflammation and cytokine storm suppression; (3) Inverse modulatory role in the renin-angiotensin system; (4) Downregulating renin and increasing ACE2; and (5) Inverse association between serum level of vitamin D and anti-phospholipid antibodies
Infusino <i>et al</i> <sup>[57]</sup>	A scoping review	Nutraceuticals and supplements studied thus far on COVID-19	(1) Vitamin E, D, C, carotenoids, minerals (Zn, Mn, Cu, and Se), polyphenols, and curcumin have; and (2) Anti-inflammatory, anticoagulant, antioxidant, binding to SARS-CoV-2 target receptor, and antiviral properties

DASH: Dietary approaches to stop hypertension; Med-diet: Mediterranean dietary pattern; suppl: supplemented; K: Potassium; Mg: Magnesium; HDL: High density lipoproteins; LDL: Low density lipoproteins; COVID-19: Coronavirus disease 2019; ACE: Angiotensin-converting enzyme; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; AIS: Acute ischemic stroke; SCFAs: Short-chain fatty acids; NCD: Normal diet; HFD: High fat diet; PAR: Protease-activated receptor; IL-6: Interleukin-6; CRP: C-reactive protein; Zn: Zinc; Mn: Manganese; Cu: Copper; Se: Selenium.

processed/sweetened products, besides moderate consumption of wine, fortified with a mixture of nuts and virgin olive oil for a median of 4.8 years, could reduce the stroke risk by 40% compared to the control. The results of a recent meta-analysis have also shown that any 4 points increase in score of adherence to the Mediterranean dietary pattern in both the Mediterranean and non-Mediterranean populations are significantly associated with a 14% and 17% reduction in the risk of ischemic and hemorrhagic stroke, respectively<sup>[25]</sup>. Although the Mediterranean dietary pattern, similar to the DASH, is not a low sodium diet, following this diet high in potassium can probably lead to a reduction in dietary sodium due to the less consumption of processed foods<sup>[25]</sup>. A newly published cohort study by Chiu *et al*<sup>[47]</sup> has demonstrated that a vegetarian diet reduces the risk of ischemic and hemorrhagic stroke, and higher serum levels of vitamin B12 weaken the relationship. Since a vegetarian diet is a meat and egg free diet, one of the proposed mechanisms is that the adherence to this diet could reduce substrates of intestinal microbiota to produce trimethylamine N-oxide, thus, reduce the platelet hyperactivation and thrombosis functions, and the risk of stroke, consequently<sup>[47]</sup>. In this study, vitamin B12 deficiency is in favor of a decrease in the incidence of stroke, while other studies are the opposite<sup>[48]</sup>.

## SOME STUDIED MICRONUTRIENTS OR FOODS AND STROKE RISK

A meta-analysis study has shown that potassium intake significantly inverses association with stroke risk. It is, therefore, recommended to consume potassium-rich foods to support cardiovascular and prevent stroke<sup>[49]</sup>. The same relationship in a dose-response manner is true for dietary/supplemental magnesium and total stroke<sup>[50]</sup>. Moreover, stroke studies have rigorously recommended the protective effect of vitamin D on stroke incidence<sup>[51]</sup>. Further, other dietary components recommended in the context of stroke incidence have been listed in their work, among which, other than what said thus far, dairy calcium (not supplementation), folate (not supplementation), vitamin C, chocolate, coffee, tea, and the regular and moderate alcohol consumption (not alcohol abuse) are observed<sup>[51]</sup>. Due to controversy and lack of consensus, there is no recommendation for using B12, folate, and B6 to reduce the risk of stroke, and the results are uncertain<sup>[51]</sup>. Hence, more studies are needed in this regard.

## HOW COULD DIETARY PATTERNS BE ATTRIBUTED TO COVID-19-ASSOCIATED STROKE RISK?

A study has found that countries where the major daily intake originates from uncooked or fermented kale, cabbages, and fermented dairy products known as good sources for anti-ACE activity and rich in antioxidants have lower COVID-19 death rates than the others<sup>[52]</sup>. ACE converts angiotensin I to angiotensin II, while ACE2 does the opposite in the renin-angiotensin system<sup>[52]</sup>, in addition to being the entry point for SARS-CoV-2 into host cells as mentioned earlier<sup>[12,52]</sup>. Therefore, in the case of infection with SARS-CoV-2, ACE inhibitors may be effective in improving complications such as high blood pressure and subsequent hemorrhagic stroke<sup>[52]</sup>. The blood levels of ACE respond very quickly to food intake. Hence, dietary patterns can affect this enzyme levels; thus, it is suggested that a diet rich in saturated fatty acids increases ACE levels<sup>[52]</sup>. While many functional foods are listed as the ACE inhibitor and

antioxidant<sup>[53,54]</sup>. A recent study has discussed that a healthy, diverse, and balanced diet based on plants, high fiber, and fermented foods rich in the beneficial probiotics, such as *Bifidobacteria* and *Lactobacilli* species, could be a preventative strategy, mitigating harmful effects of SARS-CoV-2<sup>[20]</sup>. Probiotics can modulate the immune system by controlling the gut microbiota, thereby reducing the susceptibility to affliction or morbidity and mortality from COVID-19<sup>[20]</sup>. Whereas following a high-fat diet and frequent snacks between meals can lead to dysbiosis. Therefore, its frequency should be kept minimum and often include fruits and vegetables<sup>[20]</sup>. In this respect, interestingly, Tan *et al*<sup>[55]</sup> have described that the gut microbiome and the short-chain fatty acids (SCFAs) produced by it could regulate brain functions in the path of the gut-brain axis, thus playing a major role in the prevention of stroke. In the study of 140 acute ischemic stroke patients compared with 92 healthy controls, they have observed dysbiosis and low levels of fecal SCFAs in patients with acute ischemic stroke than in controls, inversely related to stroke severity and prognosis. Therefore, SCFAs are introduced as possible prognostic markers and potential targets for stroke remedy<sup>[55]</sup>. Furthermore, interestingly a few recent studies have discussed the Mediterranean diet and COVID-19<sup>[14]</sup>. This dietary pattern is anti-inflammatory; it is rich in bioactive components with anti-inflammatory and antioxidant properties and a variety of vitamins and trace elements but limited in processed foods<sup>[14]</sup>. Mechanisms involved in reducing stroke following adherence to the Mediterranean diet, which may also be considered for COVID-19-associated stroke, include protection against inflammation, oxidative stress, platelet aggression, endothelial dysfunction, and a pleasant change in metabolites derived from intestinal microbiota that leads to cardiovascular health<sup>[25]</sup>. On the other hand, as one study suggested, therapeutic targeting of PAR could be promising in the management of COVID-19 neuroinflammatory complications<sup>[32]</sup>. In this regard, according to an animal study, mice with a high-fat diet (HFD) have higher levels of endogenous thrombin compared to those with a normal diet, being considered as a model for stimulation of PAR-1-based signaling. Whereas  $\beta$ -arrestin-2, unlike thrombin, has a positive effect on this signaling under ischemic stroke condition. HFD mice experience larger infarct and worse outcomes after stroke induction<sup>[56]</sup>. Therefore, it seems that the role of diet to be also prominent in many signaling pathways related to COVID-19 neuroinflammatory complications. Thus, more human studies in this scope are essential. Apart from nutritional recommendations, due to elevated IL-6 Levels followed by hyperviscosity state<sup>[8]</sup>, it seems necessary to maintain hydration and adequate fluid intake in COVID-19 patients. Altogether, this is important long before and immediately after the COVID-19 pandemic, since long-term and continuous following these healthy dietary patterns, as said, can prevent or reduce comorbidities; this, in turn, may be decrease predisposition to severe COVID-19 and, consequently, its worse complications, such as stroke.

## HOW COULD SOME MICRONUTRIENTS OR FOODS BE ATTRIBUTED TO COVID-19-ASSOCIATED STROKE RISK?

Some studies have shown the importance role of potassium and magnesium in COVID-19. Since hypokalemia has been observed in most patients with severe and critical COVID-19<sup>[21]</sup>, potassium-rich foods might also play a supportive role in these patients. Magnesium is also important since it participates in the function of many enzymes involved in the severe immune and inflammatory responses that are manifestations of COVID-19. It, due to its modulator role in IL-6, nuclear factor- $\kappa$ B, and CRP, besides its ability to activate and enhance the function of vitamin D, is essential in preventing the serious consequences of COVID-19 and reducing its morbidity and mortality<sup>[21]</sup>. In addition to vitamin D, widely discussed due to potential to reduce COVID-19 risk, severity, and mortality *via* mechanisms, including inflammation and cytokine storm suppression, besides the inverse modulatory role in the renin-angiotensin system by downregulating renin and increasing ACE2<sup>[2,21]</sup>, other nutrients, such as vitamins, minerals, and functional foods have been discussed in the context of COVID-19. All of these components have also been studied separately concerning stroke. However, no study has ever considered them all together to discuss their association with stroke as a life-threatening complication of COVID-19. For example, some studies have shown that the prevalence of vitamin D deficiency is about 70% among patients with the anti-phospholipid syndrome with elevated levels of anti-phospholipid antibodies. Furthermore, antibodies titers in healthy controls have been lower in the summer season than in other months of the year<sup>[2]</sup>. This is a fascinating common point in parallel with studies that have shown increased levels of

anti-phospholipid antibodies in COVID-19-associated stroke cases<sup>[6]</sup>. However, the causal relationship between vitamin D levels or supplementation and serum levels of anti-phospholipid antibodies and thrombotic events has not yet been established<sup>[2]</sup>. Some of the main nutraceuticals and supplements studied thus far on COVID-19 include vitamin E, vitamin D, vitamin C, carotenoids, minerals (Zn, Mn, Cu, and Se), polyphenols, and curcumin. Possible mechanisms of their positive effect on COVID-19 pathways have been proposed as anti-inflammatory, anticoagulant, antioxidant, binding to SARS-CoV-2 target receptor, and antiviral properties<sup>[57]</sup>.

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## CONSEQUENCES OF THE HYPOTHESIS

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The present hypothesis stated for the first time in literature proposes a link between a healthy diet and COVID-19-associated stroke risk. Adherence to healthy dietary patterns and more consumption of some foods and nutrients in the recommended daily allowance has always been flagged as a prevention approach in chronic and acute conditions. Here, it is speculated that such a role of healthy nutrition can be highlighted once again in preventing COVID-19-associated stroke too. Since no study to date has proven this, nutritional intake evaluations or food frequency questionnaire-based studies are strongly recommended in order to elicit dietary patterns in COVID-19-associated stroke patients. Also, certain nutrients reported to be effective in common relief functions in stroke and COVID-19 pathways can be prescribed in trials for COVID-19 patients; then, the incidence of stroke in them can be investigated prospectively. If these confirm our hypothesis, it means that healthy nutrition could be a protective/preventive factor against COVID-19-associated stroke risk.

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## CONCLUSION

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Due to the significance of the current pandemic, many studies have paid attention to its consequent clinical outcomes. COVID-19 can be more severe in older patients or individuals with comorbidities, having dangerous consequences, including stroke. Adherence to healthy dietary patterns and more consumption of some foods and nutrients in the recommended daily allowance has always been emphasized as a prevention approach in chronic and acute conditions. However, it should be noted that the present study did not intend to give dietary advice to definite prevention of COVID-19-associated stroke. It only aimed to review the existing literature to evaluate the hypothesis stating that nutrition could be related to COVID-19 and its associated stroke. As far as we know, nutrition cannot be effective in preventing this crisis in the short time, but it can be found that the history of dietary patterns and nutritional intake in patients with stroke or other serious COVID-19-associated complications what is the difference with those in COVID-19 patients without serious complications or even in healthy population by further nutritional intake evaluations or food frequency questionnaire-based studies. If the future studies confirm the present study's hypothesis (*i.e.*, people who adherence to the healthy dietary patterns and habits are less likely to suffer from severe COVID-19-associated complications such as stroke) the chronic supportive role of a healthy diet in critical situations will be highlighted once again.

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## How far has panic buying been studied?

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### Abstract

#### BACKGROUND

Although panic buying (PB) is a ubiquitous behavior, it became prominent during the coronavirus disease 2019 pandemic. However, studies are inadequate to explore the different aspects of it, even though it covers several perspectives of life and academic domains.

#### AIM

To assess the research that have been conducted on PB.

#### METHODS

A search was conducted to identify the articles in PubMed, PubMed Central, Scopus, and Google Scholar using the search term "panic buying" on November 15, 2020. A total of 104 articles was extracted from the initial search. After removing duplicates and initial and full-text screening, 42 articles were included in the study. We only considered peer-reviewed published articles that can be downloaded in a full portable document format. Articles published in other languages and preprints were excluded.

#### RESULTS

Among the 42 articles, 27 were original contributions, 6 were correspondences, 3 were commentaries, 3 were review articles, and there was one each for editorial, opinion, and discussion type of articles. Several domains have been researched

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such as psychology, responsible factors, supply chain, management, disaster preparedness, e-commerce, consumer behavior, marketing, prevention strategies, media, social network, economics, personality, and engineering. Authors from several disciplines, such as psychiatry, management, economics, business, sales and marketing, consumer behavior, public health, communication, information management, sociology, engineering, business administration, psychology, nursing, health economics, food policy, epidemiology, and community health, have been studied it. Definition, causative model, econometric model, controlling strategy, and measuring instrument have been reported. A total of 18 papers had cross-country collaboration, and ten were funded projects. Most of the authors were affiliated with the institutions of Australia, Bangladesh, China, India, Singapore, and the United States.

### CONCLUSION

PB is a relatively newer concept to get the attention of the research community. Further robust studies with replication of the findings are warranted to explore, predict, and control during crises.

**Key Words:** Panic buying; Systematic review; COVID-19; Pandemic; Disaster; Supply chain

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**Core Tip:** Panic buying is an under-researched emerging research problem. Although it covers several aspects of human life, there is a dearth of studies. This review was aimed to assess the extent of research that has been done on panic buying. A total of 42 papers were included after a systematic search. Several domains have been researched such as psychology, responsible factors, supply chain, management, disaster preparedness, e-commerce, consumer behavior, marketing, prevention strategies, media, social network, economics, personality, and engineering. Definition, causative model, econometric model, controlling strategy, and measuring instrument have been reported.

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## INTRODUCTION

Panic buying (PB) is an interesting behavioral phenomenon, usually noticed among the public in the face of disasters. The term "panic buying" consists of two words "panic" and "buying," which refer to the affective and behavioral components of this phenomenon. It has some common roots with stockpiling<sup>[1]</sup>. The coronavirus disease 2019 (COVID-19) pandemic has witnessed an increase in PB behavior globally, irrespective of the socioeconomic status of the country<sup>[2,3]</sup>. It has been conceptualized as "the phenomenon of a sudden increase in buying of one or more essential goods in excess of regular need provoked by adversity, usually a disaster or an outbreak resulting in an imbalance between supply and demand"<sup>[4]</sup>. Several intermingled factors interact with each other to influence it, pointed out as primary (provoking stimuli), secondary (media and psychosocial aspects), and tertiary (utility, demand, and price of the goods) factors<sup>[2]</sup>. Multiple psychological explanations have been proposed such as anticipation of shortage and price hike, supply disruption, fear, uncertainty, maladaptive coping, and maintaining control over the environment to attribute it<sup>[2,5-7]</sup>. There are complex interactions between media, environment, rumor, and increased demand and price as these factors can have a bidirectional role with PB<sup>[2,3,6,8]</sup>. It has been traced in response to an adverse stimulus, such as COVID-19, pandemic, war, government's declaration, any policy change, disaster, *etc.*<sup>[2,9]</sup>.

Theoretically, PB shares multiple aspects of human life and several domains of

academia. It is related to behavior, public health, disaster preparedness, mass media, economics, sociology, business, marketing, supply chain, industrial buying and production, e-commerce, and so on<sup>[8]</sup>. However, there is a dearth of studies exploring the different aspects of it. Although studies are recently coming out, the issue is still under-researched. With this background, we aimed to conduct a review to assess the extent of research on PB that has been conducted.

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## MATERIALS AND METHODS

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### **Article search**

A search was done to identify the articles in PubMed, PubMed Central (PMC), Scopus, and Google Scholar (GS) with the search term “panic buying” on November 15, 2020. A total of 104 (PubMed = 19, PMC = 22, Scopus = 30, GS = 33) articles were extracted from the initial search. Subsequently, 44 duplicate articles were removed, and the remainder of the 60 articles were screened. After screening the abstract, another 14 articles were removed as PB was not identified as a study variable. Then, full texts were screened resulting in the removal of four articles because the articles only mentioned PB without discussing its aspects. Finally, 42 articles were included in the study (Figure 1).

### **Inclusion criteria**

We included peer-reviewed published articles that were extracted from the search and downloadable as full portable document format in the study.

### **Exclusion criteria**

Articles published in other languages (for example, Bangla, German, Chinese, and French) and preprints were excluded from the study.

### **Outcome variables**

Type of research, publishing year, applied method, key findings, the geographical distribution of the authors, specialty of authors, collaboration (intracountry or intercountry), a major subject of the journal where the articles published, a principal domain discussed in the article, funding status, and keywords were outcome variables. We considered the first authors' and corresponding authors' affiliated institutions' location to describe the authors' geographical locations.

### **Statistical analysis**

In the current study, we assessed the aspects of PB research, detail statistical analysis was not performed. We did a word cloud of the keywords of the articles to reveal highlighting search terms mentioned in the articles.

### **Ethical statement**

The study was conducted complying with the Declaration of Helsinki (1964). As we analyzed the publicly available media reports, no formal ethical approval was sought.

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## RESULTS

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### **Distribution of the studies**

In this review, we searched articles from PubMed, PMC, Scopus, and GS, and 42 articles were reviewed. The articles were published between 2002 and 2020 whilst 36 papers were published in 2020 (Table 1). Among the selected articles, 27 were original articles, 6 were correspondences, 3 were commentaries, 3 were review articles, and 1 each were editorial, opinion, and discussion type of articles (Table 1).

### **Applied methods**

Nine studies surveyed the target population online or offline, five studies applied cross-sectional data analysis, four papers studied social media, three studies analyzed media reports, and two studies mined data from Google search volume using Google Trends application programming interface (Table 1).

Table 1 Summary of the articles

No.	Ref.	Year	Type	Title	Method applied	Key message
1	Ahmed <i>et al</i> <sup>[10]</sup>	2020	Original	The COVID-19 pandemic and the antecedents for the impulse buying behavior of US citizens	Survey (online and offline)	This study sorted out nine variables from the literature that may influence impulsive buying and tested them by conducting surveys in major United States cities. The variables include fear of complete lockdown, peer buying, the limited supply of essential goods, empty shelves, United States stimulus checks, panic buying, fear appeal, social media fake news, and COVID-19.
2	Alchin <sup>[11]</sup>	2020	Commentary	Gone with the wind		This paper proposes a definition of “panic buying,” with references to literature, philosophy, and contemporary neurobiology. The self-fulfilling prophecy, the contagion model of emotional propagation, the Polyvagal Theory, and Nietzsche’s study of the classical tragedy were discussed in relation to panic buying.
3	Alfa <i>et al</i> <sup>[12]</sup>	2020	Original	Effect of panic buying on individual savings: The COVID-19 lockdown experience	Cross-sectional	The paper assessed the microeconomic effect of PB on the savings of an individual. This study’s findings revealed that price fluctuation, price differential, and spending hurt the individual saving rate.
4	Arafat <i>et al</i> <sup>[2]</sup>	2020	Original	Responsible factors of panic buying: An observation from online media reports	Analysis of media reports	The authors analyzed 784 media reports to find out the reported responsible factors of panic buying. A sense of scarcity, increased demand, importance of the product, and anticipation of the price hike were the major contributing force towards PB, as mentioned in the reports. The authors postulated a causative model of PB.
5	Arafat <i>et al</i> <sup>[3]</sup>	2020	Original	Media portrayal of panic buying: A content analysis of online news portals	Analysis of media reports	This study analyzed content published in media to determine how media is depicting PB during COVID-19. The findings suggested that the media have been portraying more negative aspects of PB. The authors recommended developing media guidelines to censor news that influences impulse buying behavior.
6	Arafat <i>et al</i> <sup>[4]</sup>	2020	Original	Panic buying: An insight from the content analysis of media reports during COVID-19 pandemic	Media report analysis	The authors proposed a definition of PB. This study analyzed information extracted from English media reports to evaluate the nature, extent, and impact of PB.
7	Arafat <i>et al</i> <sup>[5]</sup>	2020	Correspondence	Psychological underpinning of panic buying during pandemic (COVID-19)		The authors studied psychological reasons of PB, which include fear of scarcity, insecurity, losing control over the environment, social learning, and exacerbation of anxiety.
8	Arafat <i>et al</i> <sup>[6]</sup>	2020	Correspondence	Possible controlling measures of panic buying during COVID-19		The authors mentioned possible measures to control PB during a pandemic. The recommendations included positive role-playing by media. Promotion of feeling of kinship and encouraging generosity can reduce it from the public end. Setting a quota policy and subsidiary sales for necessity items could be a potential strategy.
9	Arafat <i>et al</i> <sup>[9]</sup>	2020	Correspondence	Panic buying: Is it really a problem?		The paper mentioned some challenges to study PB in detail to explore its several aspects
10	Benker <sup>[13]</sup>	2020	Original	Stockpiling as resilience: Defending and contextualising extra food procurement during lockdown	Online interview	This study analyzed 19 invited interviews taken online in the United Kingdom. The study found that though food shortages were common for a couple of weeks, food hoarding didn’t make impulsive buying. The United Kingdom households considered food procurement as a single resilience strategy among the taken six strategies.
11	Chen <i>et al</i> <sup>[14]</sup>	2020	Discussion	A discussion of irrational stockpiling behaviour during crisis		The authors discussed the current and long-term impact of PB on the economy, society, and local communities. They think that stopping impulse buying is impossible, but it should be controlled by improving the supply chain and maintaining communication with the stakeholders.
12	Dammeyer <sup>[15]</sup>	2020	Original	An explorative study of the individual differences associated with consumer stockpiling during the early stages of the 2020 Coronavirus outbreak in Europe	Online survey	This study answered whether individual differences influenced PB during crises. The authors found a high tendency of stockpiling on extroversion and neuroticism and a relatively low tendency on conscientiousness and openness.

13	Dickins <i>et al</i> <sup>[16]</sup>	2020	Original	Food shopping under risk and uncertainty	Authors analyzed super market sales data	In this study, the authors showed the importance of food security and suggested optimality models of foraging under risk and uncertainty as foraging correlates to PB.
14	Dulam <i>et al</i> <sup>[17]</sup>	2020	Original	Development of an agent-based model for the analysis of the effect of consumer panic buying on supply chain disruption due to a disaster	Simulation model	This study used an agent-based simulation model to analyze how a supply chain responds to consumer PB caused by a natural disaster. The authors found this model useful in applying a quota policy per person to protect the supply chain from disruption.
15	Du <i>et al</i> <sup>[18]</sup>	2020	Original	COVID-19 increases online searches for emotional and health-related terms	Data mining from Google Trends	This study measured fear-related emotions, protective behaviors, seeking health-related knowledge, and PB due to COVID-19 prevalence in the United States, the United Kingdom, Canada, and Australia using internet search volumes in Google Trends. The results found that the increased prevalence of COVID-19 was associated with panic buying consistently in all four countries.
16	Hall <i>et al</i> <sup>[19]</sup>	2020	Original	Beyond panic buying: consumption displacement and COVID-19	Cross-sectional	The authors analyzed consumer spending data acquired from financial third parties and found instances of PB for grocery, home, hardware, and electrical categories that happened in the Canterbury region of New Zealand before the lockdown that lasted less than a week. The study showed a high consumption displacement in the hospitality and retailing sectors that dominate this area's economy.
17	Hao <i>et al</i> <sup>[20]</sup>	2020	Original	Impact of online grocery shopping on stockpile behavior in COVID-19	Online survey	It investigated how online shops affect the food stockpiling manner among urban consumers in China using bivariate probit models. The authors recommended improved and resilient supply chains that can withstand intense PB phenomena during emergencies.
18	Islam <i>et al</i> <sup>[21]</sup>	2020	Original	Panic buying in the COVID-19 pandemic: A multi-country examination	Online survey	The authors surveyed 1081 people from United States, China, India, and Pakistan to test their conceptual model and hypotheses. The research revealed that stimuli such as Limited Quantity Scarcity and Limited Time Scarcity affect emotional stress, which eventually influences impulse buying. The findings also correlated excessive social media use to PB and discussed some managerial implications.
19	Jeżewska-Zychowicz <i>et al</i> <sup>[22]</sup>	2020	Original	Consumers' fears regarding food availability and purchasing behaviors during the COVID-19 pandemic: The importance of trust and perceived stress	Cross-sectional	It investigated how the public perception of food availability changed based on the trust in the received information from media and friends. The participants showed less trust in media for COVID updates but high trust in media and friends for food availability updates and increased buying more food than usual. The consumers were highly afraid of empty shelves in the market, which also motivated them to stockpile food.
20	Kar <i>et al</i> <sup>[23]</sup>	2020	Correspondence	Online group cognitive behavioral therapy for panic buying: Understanding the usefulness in COVID-19 context		The authors postulated to explain the usefulness of online group CBT in COVID19 context for controlling the PB.
21	Keane <i>et al</i> <sup>[24]</sup>	2020	Original	Consumer panic in the COVID-19 pandemic	Data mining using Google Health Trends API	The authors developed an econometric model of consumer panic using Google search data for 54 countries from January 1 <sup>st</sup> to April 30 <sup>th</sup> , 2020. Findings included limited movement notice announced by local or foreign governments generated a week-long short-run panic. The study found little impact of stimulus offerings and no consumer panic due to travel restrictions.
22	Kostev <i>et al</i> <sup>[25]</sup>	2020	Original	Panic buying, or good adherence? Increased pharmacy purchases of drugs from wholesalers in the last week before Covid-19 lockdown	Retrospective cross-sectional analysis of the IMS RPM <sup>®</sup> (Regional Pharmaceutical Market) Weekly database	The paper assessed the PB of medication during the COVID-19 pandemic in Germany. The study suggested that Germany's lockdown was associated with a sharp increase in purchasing behavior in pharmacies for different markets, including psychotropic, neurological, and cardiovascular drugs.
23	Laato <i>et al</i> <sup>[26]</sup>	2020	Original	Unusual purchasing behavior during the early stages of the COVID-19 pandemic: The stimulus-organism-response approach	Online survey	The authors conducted a web survey with 211 Finnish participants for a week to test a hypothetical research model. The study found a positive link between voluntary self-isolation and unusual purchases. The online information overload caused cyberchondria, which eventually motivated self-isolation followed by PB.
24	Lins <i>et al</i> <sup>[27]</sup>	2020	Original	Development and initial psychometric properties of a panic buying scale during COVID-19 pandemic	Online survey	This study developed the first PB scale that was psychometrically acceptable in the Brazilian context.

25	Loxton <i>et al</i> <sup>[28]</sup>	2020	Review	Consumer behavior during crises: Preliminary research on how coronavirus has manifested consumer panic buying, herd mentality, changing discretionary spending and the role of the media in influencing behaviour	Literature review and cross-sectional data analysis	This study reviewed consumer behavior data, including impulse buying, herd instinct, and prioritization of purchasing decisions of past crises and shock events. The authors then analyzed consumer spending data acquired from data services that confirmed the sorted variables in the COVID-19 context.
26	Martin-Neuninger <i>et al</i> <sup>[29]</sup>	2020	Opinion	What does food retail research tell us about the implications of coronavirus (COVID-19) for grocery purchasing habits?		The paper discussed the consequences of lockdowns on consumer grocery purchasing habits, focusing on New Zealand. In avoidance of PB, the authors suggested few recommendations to the food companies so that people can enjoy visiting supermarkets without compromising safety. They also asked to improve online delivery services to gain trust and customer confidence.
27	Micalizzi <i>et al</i> <sup>[1]</sup>	2020	Original	Stockpiling in the time of COVID-19	Survey	This study aimed to discuss stockpiling behavior during COVID-19 and investigated individual predictors of stockpiling. Those affiliated with conservative politics, worry much about COVID-19, and self-isolated were prone to stockpiling behavior.
28	Naeem <sup>[30]</sup>	2020	Original	Do social media platforms develop consumer panic buying during the fear of Covid-19 pandemic	Telephonic interview	The study revealed how social media aggravated PB by arousing fear appeal. Along with some exacerbating factors like uncertainties, anxiety, persuasive buying, empty shelves, and exert opinion, a huge load of information at users' fingertips made them more anxious about what was to come, leading to panic buying.
29	Prentice <i>et al</i> <sup>[31]</sup>	2020	Original	Timed intervention in COVID-19 and panic buying	Semantic analysis, secondary data and big data analysis	This paper depicted PB as a side effect of the Australian government's timed-intervention policy. The authors supported their findings with real-life evidence.
30	Rosita <sup>[32]</sup>	2020	Review	Panic buying in the COVID-19 pandemic era in Indonesia	Literature review	This paper proposed a definition of PB and extrapolated some underlying reasons for it. It also mentioned the negative impact of impulsive buying and recommended some stakeholders' measures to control it.
31	Shorey <i>et al</i> <sup>[33]</sup>	2020	Original	Perceptions of the public on the COVID-19 outbreak in Singapore: A qualitative content analysis	Qualitative content analysis	This study analyzed 2075 comments made to the 29 published news by local media outlets on their Facebook pages to find common concerns shared by Singapore's public. The five main themes derived from the qualitative thematic analysis were fear and concern, PB and hoarding, reality and expectations about the situation, staying positive amid the 'storm,' and worries about the future. The authors recommended clear communication, timely updates, and support measures from the government to maintain social peace and cohesion.
32	Sim <i>et al</i> <sup>[6]</sup>	2020	Correspondence	The anatomy of panic buying related to the current COVID-19 pandemic		The paper mentioned two episodes of PB in Singapore due to a new alert level set by the local authority and the declaration of COVID-19 as a pandemic by the World Health Organization. The authors found some underlying reasons for PB and suggested some recommendations to facilitate it.
33	Singh <i>et al</i> <sup>[34]</sup>	2020	Commentary	A critical analysis to comprehend panic buying behaviour of Mumbaikar's in COVID-19 era		The authors studied different driving factors of PB and suggested how the retailers should adapt inventory when the supply chain is under disruption. They recommended stopping the panic buying so that others can get the share of the products.
34	Turambi <i>et al</i> <sup>[35]</sup>	2020	Original	Panic buying perception in Waliansatu sub-district, Tomohon City	Online survey	This study analyzed the perception of city dwellers towards PB due to COVID-19. It described different PB episodes that appeared in a city in Indonesia.
35	Yuen <i>et al</i> <sup>[7]</sup>	2020	Review	The psychological causes of panic buying following a health crisis	Systematic review	It was the first systematic review on PB. The authors identified four major themes responsible for PB.
36	Zheng <i>et al</i> <sup>[36]</sup>	2020	Original	Supply disruption management under consumer panic buying and social learning effects	Analytical study	The study analyzed how social learning among customers can influence buying decisions when adequate supply is at risk. When the panic intensity is at a moderate level, social learning can help to adjust the consumer demand, but it will work negatively when the panic intensity is very low or very high. The authors also introduced an optimal inventory ordering strategy for retailers.
37	Tsao <i>et al</i> <sup>[37]</sup>	2019	Original	Product substitution in different weights and brands considering customer segmentation and	Mathematical model	It proposed a mathematical model for managing wholesaler's inventory to maximize the profit during PB. The authors suggested substituting the same products of different weights and brands between high- and

				panic buying behavior		
38	Wei <i>et al.</i> <sup>[38]</sup>	2011	Original	Research on emergency information management based on the social network analysis – A case analysis of panic buying of salt	Data mining	low-indexed stores during a supply disruption. The model can determine optimal order quantity, the number of substitutable units, leftover units, and the unsated demand to improve the store services.  This research studied how to manage information in an emergency analyzing social network to control PB.
39	Fung <i>et al.</i> <sup>[39]</sup>	2010	Original	Disaster preparedness of families with young children in Hong Kong	Survey	This study surveyed households' heads to explore their perception and preparedness for future disastrous events most likely to occur in Hong Kong. These families experienced PB for necessities during disasters especially for children's items and drugs.
40	Kulemeka <sup>[40]</sup>	2010	Commentary	United States consumers and disaster: Observing "panic buying" during the winter storm and hurricane seasons		This article was an update of ongoing research. This article narrated predisaster shopping and claimed that such shoppers do not go for panic buying rather help each other.
41	Bonneux <i>et al.</i> <sup>[41]</sup>	2006	Correspondence	An iatrogenic pandemic of panic		The authors mentioned humans' overreactions to the perceived threat of a hypothetical pandemic accompanied by clever marketing for the panic buying of antiviral drugs.
42	Thomas <sup>[42]</sup>	2002	Editorial	Panic buying ahead?		The author highlighted the preparedness for future PB influenced by herd instinct in the semiconductor industry.

CBT: Cognitive behavior therapy; COVID-19: Coronavirus disease 2019; PB: Panic buying.

### **Reported aspects of PB**

Definition of PB, causative model, econometric model, media reporting of PB, responsible factors for PB, psychological reasons for PB, controlling strategy, measuring instrument, challenges to explore the problem, and geographical distribution have been identified.

### **Academic domains**

Several domains have been researched such as psychology, supply chain, management, disaster preparedness, e-commerce, consumer behavior, marketing, prevention strategies, media, social network, economics, personality, and engineering (Table 2).

### **Distribution of authors**

Authors from several disciplines, such as psychiatry, management, economics, business, sales and marketing, consumer behavior, public health, communication, information management, sociology, engineering, business administration, psychology, nursing, health economics, food policy, epidemiology, and community health, have been studied it. Most of the authors were affiliated with institutions from Australia, Bangladesh, China, India, Singapore, and the United States (Table 2). Eighteen papers had cross-country collaboration, and ten were funded projects. The average number of authors per paper was 3.3; Arafat SMY has published the maximum number of papers (6) as the first author on the topic.

Table 2 Bibliometric summary of the articles

Ref.	Author No.	Month of publication	Country of the 1 <sup>st</sup> author	Country of the corresponding author	Specialty of the 1 <sup>st</sup> author	Specialty of the corresponding author	Collaboration	Journal	Subject of the journal	Domain of the discussed topic	Funding
Ahmed et al <sup>[10]</sup>	4	Aug 20	Pakistan	Pakistan	Sales and Marketing	Sales and Marketing	Cross-country	<i>J of Competitiveness</i>	Competitiveness	Impulse buying behavior	No info
Alchin <sup>[11]</sup>	1	Jul 20	Australia	Australia	Public health	Public health		<i>Australasian Psychiatry</i>	Psychiatry	Panic buying during disaster	No funding
Alfa et al <sup>[12]</sup>	2	Sep 20	Nigeria	Nigeria	Economics	Economics	Intracountry	<i>Lapai J of Economics</i>	Economics	Economics	No info
Arafat et al <sup>[2]</sup>	7	Nov 20	Bangladesh	Bangladesh	Psychiatry	Psychiatry	Cross-country	<i>Frontiers in Public Health</i>	Public health	Media	No funding
Arafat et al <sup>[3]</sup>	9	Sep 20	Bangladesh	Bangladesh	Psychiatry	Psychiatry	Cross-country	<i>Global Psychiatry</i>	Psychiatry	Media	No funding
Arafat et al <sup>[4]</sup>	9	Jul 20	Bangladesh	Bangladesh	Psychiatry	Psychiatry	Cross-country	<i>Neurology, Psychiatry and Brain Research</i>	Psychiatry	Media	No funding
Arafat et al <sup>[5]</sup>	6	May 20	Bangladesh	Bangladesh	Psychiatry	Psychiatry	Cross-country	<i>Psychiatry Research</i>	Psychiatry	Psychological causes of panic buying	No funding
Arafat et al <sup>[8]</sup>	3	May 20	Bangladesh	Bangladesh	Psychiatry	Psychiatry	Cross-country	<i>Int J of Mental Health and Addiction</i>	Psychiatry	Controlling of panic buying	No funding
Arafat et al <sup>[9]</sup>	3	Sep 20	Bangladesh	India	Psychiatry	Psychiatry	Cross-country	<i>Int J of Social Psychiatry</i>	Psychiatry	Challenges of scientific studying	No funding
Benker <sup>[13]</sup>	1	Oct 20	United Kingdom	United Kingdom	Sociology	Sociology		<i>Appetite</i>	Behavioral science	Emergency preparedness	No funding
Chen et al <sup>[14]</sup>	7	Jun 20	Australia	Australia	Engineering	Engineering	Intracountry	<i>J of Safety Science and Resilience</i>	Disaster	Economics	No funding
Dammeyer <sup>[15]</sup>	1	Jul 20	Denmark	Denmark	Psychology	Psychology		<i>Personality and Individual Differences</i>	Psychology	Individual personality and PB	No funding
Dickins et al <sup>[16]</sup>	2	Oct 20	United Kingdom	United Kingdom	Psychology	Psychology	Intracountry	<i>Learning and Motivation</i>	Psychology	Uncertainty and PB	No funding
Dulam et al <sup>[17]</sup>	3	Apr 20	Japan	Japan	Engineering	Engineering	Intracountry	<i>J of Advanced Simulation in Science and Engineering</i>	Engineering	Technology and PB	No info
Du et al <sup>[18]</sup>	4	Oct 20	China	China	Psychology	Psychology	Intracountry	<i>Applied Psychology: Health and Well-Being</i>	Psychology	Behavioral perspectives	National Natural Science Foundation of China
Hall et al <sup>[19]</sup>	4	Jul 20	New Zealand	New Zealand	Management	Management	Cross-country	<i>J of Service Management</i>	Management	Consumer behavior during a disaster	No info
Hao et al <sup>[20]</sup>	3	Aug 20	China	China	Economics	Economics	Cross-country	<i>China Agricultural</i>	Economics	E-commerce's role	Beijing Municipal

									<i>Economic Review</i>		on food hoarding	Education Commission Social Science
Islam <i>et al</i> <sup>[21]</sup>	7	Oct 20	China	China	Economics and Management	Economics and Management	Cross-country	<i>J of Retailing and Consumer Services</i>	Marketing	Reasons of panic buying	National Social Science Fund of China	
Jeżewska-Zychowicz <i>et al</i> <sup>[22]</sup>	3	Sep 20	Poland	Poland	Business	Business	Intracountry	<i>Nutrients</i>	Human nutrition	Behavioral perspectives	Warsaw university of life sciences	
Kar <i>et al</i> <sup>[23]</sup>	3	Oct 20	India	India	Psychiatry	Psychiatry	Cross-country	<i>Indian J of Psychiatry</i>	Psychiatry	Behavioral perspectives for Controlling of panic buying	No funding	
Keane <i>et al</i> <sup>[24]</sup>	2	Aug 20	Australia	Australia	Health Economics and Marketing	Consumer Behaviour, Econometrics	Intracountry	<i>J of Econometrics</i>	Econometrics	Econometrics model of PB	Australian Research Council grants	
Kostev <i>et al</i> <sup>[25]</sup>	2	Jul 20	Germany	Germany	Epidemiology, public health	Epidemiology, public health	Intracountry	<i>J of Psychiatric Research</i>	Psychiatry	Drug purchasing surge during COVID 19	No funding	
Laato <i>et al</i> <sup>[26]</sup>	4	Jul 20	Finland	Norway	Technologies	Economics and management	Cross-country	<i>J of Retailing and Consumer Services</i>	Marketing	Media and panic buying	No info	
Lins <i>et al</i> <sup>[27]</sup>	2	Sep 20	Portugal	Portugal	Social psychology	Social psychology	Cross-country	<i>Heliyon</i>	Medical sciences	Measurement instrument	No funding	
Loxton <i>et al</i> <sup>[28]</sup>	6	Jul 20	Australia	China	Business	Economics	Cross-country	<i>J of Risk and Financial Management</i>	Finance and Risk	Consumer behavior during disasters	No funding	
Martin-Neuninger <i>et al</i> <sup>[29]</sup>	2	Jun 20	New Zealand	New Zealand	Food Policy and Security	Food Policy and Security	Cross-country	<i>Frontiers in Psychology</i>	Psychology	Consumer behaviour	No funding	
Micalizzi <i>et al</i> <sup>[1]</sup>	3	Oct 20	United States	United States	Behavioral and Social Sciences	Behavioral and Social Sciences	Intracountry	<i>British J of Health Psychology</i>	Psychology	Hoarding during emergency	National Institutes on Drug Abuse	
Naeem <sup>[30]</sup>	1	Sep 20	United Kingdom	United Kingdom	Business administration	Business administration		<i>J of Retailing and Consumer Services</i>	Marketing	Social media and panic buying	No funding	
Prentice <i>et al</i> <sup>[31]</sup>	3	Aug 20	Australia	Australia	Marketing and Consumer Behavior	Marketing and Consumer Behavior	Intracountry	<i>J of Retailing and Consumer Services</i>	Marketing	Government timed-intervention policy and PB	Inspector General Emergency Management Queensland, Australia	
Rosita <sup>[32]</sup>	1	Oct 20	Indonesia	Indonesia	Consumer behavior	Consumer behavior		<i>Int J of Multiscience</i>	All disciplines	Consumer behavior	No info	
Shorey <i>et al</i> <sup>[33]</sup>	4	Jul 20	Singapore	Singapore	Nursing	Nursing	Intracountry	<i>Journal of Public Health</i>	Public health	Responses during emergencies	No funding	

Sim et al <sup>[6]</sup>	4	Apr 20	Singapore	Singapore	Psychiatry	Psychiatry	Cross-country	<i>Psychiatry Research</i>	Psychiatry	Panic buying distribution	No info
Singh et al <sup>[34]</sup>	2	Mar 20	India	India	Arts humanities & communication	Arts humanities & communication	Intracountry	<i>Studies in Indian Place Names</i>	History	Supply chain	No info
Turambi et al <sup>[35]</sup>	2	No info	Indonesia	Indonesia	Economics	Economics	Intracountry	<i>International Journal of Applied Business and International Management</i>	Business	Behavioral perspectives	No info
Yuen et al <sup>[7]</sup>	4	May 20	Singapore	China	Economics and Supply Chain Management	Economics and Supply Chain Management	Cross-country	<i>Int J Environ Res Public Health</i>	Environmental and Public Health	Psychological causes of panic buying	Nanyang Technological University, Singapore
Zheng et al <sup>[36]</sup>	3	Mar 20	China	Hong Kong	Management	Management	Cross-country	<i>Omega</i>	Management	Supply chain	Hongkong & China
Tsao et al <sup>[37]</sup>	3	Feb 19	Taiwan	Taiwan	Industrial management	Industrial management	Intracountry	<i>Industrial Marketing Management</i>	Industrial marketing	Marketing and supply chain	Partially supported by Ministry of Sci and Tech Taiwan
Wei et al <sup>[38]</sup>	3	Sep 11	China	China	Information management	Information management	Intracountry	2011 International Conference on Management Science & Engineering (18 <sup>th</sup> )	Management Science and Engineering	Social network data mining and PB	No info
Fung et al <sup>[39]</sup>	2	Sep 10	Hong Kong	Hong Kong	Family and Community Health	Family and Community Health	Intracountry	<i>Scandinavian J of Public Health</i>	Public health	Disaster preparedness	No funding
Kulemeko <sup>[40]</sup>	1	No info	United States	United States	Business and Economics	Business and Economics		<i>Advances in Consumer Research</i>	Consumer research	Disaster preparedness	No info
Bonneux et al <sup>[41]</sup>	2	Mar 06	Belgium	Belgium	Public health	Public health	Intracountry	<i>BMJ</i>	Medical sciences	Drug stockpiling	No info
Thomas <sup>[42]</sup>	1	Aug 02	No info		Semiconductor			<i>III-Vs Review</i>	Semiconductor industry	Possible pb in semiconductor industry	No info

### Distribution of journals

The maximum number of papers were published in behavioral health (13: Psychiatry 9; psychology 4), followed by business (including marketing and management) (12), public health (4), and economics (3) (Table 2). *Journal of Retailing and Consumer Services* hosted the maximum number of papers on PB (4) followed by *Psychiatry Research* (2).

### Distribution of keywords

A wide spectrum of keywords was found in articles with a prominence of COVID-19, PB, Coronavirus, and pandemic. Figure 2 shows the word cloud analysis of different keywords extracted from research publications on "panic buying." Words with a larger font size refer to the most frequently used keywords and vice versa. Different colors are used to differentiate words from each other. Colors do not have any

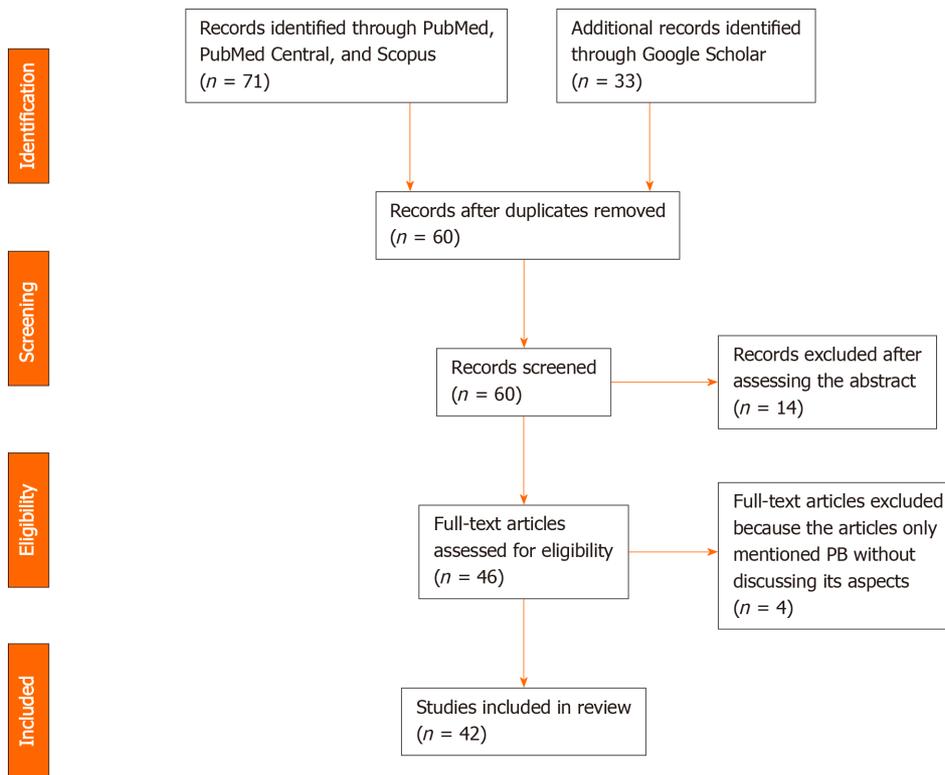


Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.

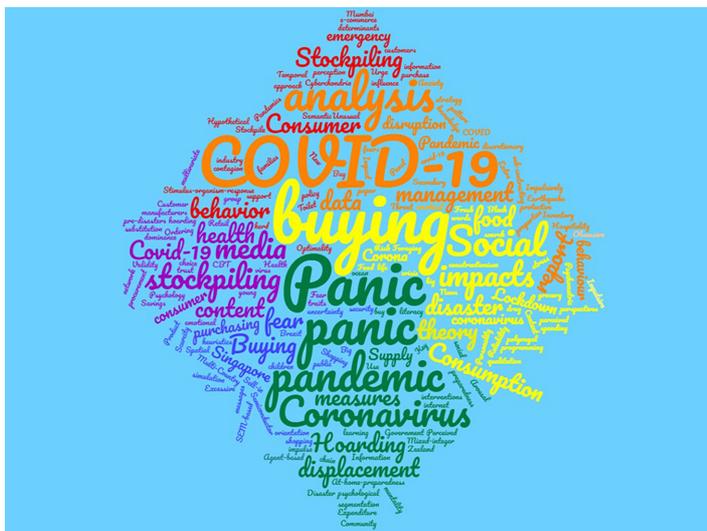


Figure 2 Word cloud analysis of key words. The color of the words does not have any significance.

statistical significance.

## DISCUSSION

We aimed to identify the aspects of PB already explored and research trends. We searched PubMed, PMC, Scopus, and GS with the search term “panic buying” on November 15, 2020. A total of 42 articles were collected and scrutinized (Figure 1). The type of research, publishing year, applied method, key findings, geographical distribution of the authors, specialty of authors, collaboration, subject of the journal, and research funding were assessed (Table 1 and Table 2).

### **Main findings**

The main findings of the review revealed that some aspects of PB have been addressed such as the definition of PB<sup>[4]</sup>, causative model<sup>[2]</sup>, econometric model<sup>[21]</sup>, media reporting of PB<sup>[3]</sup>, responsible factors for PB<sup>[2]</sup>, psychological reasons for PB<sup>[5-7]</sup>, controlling strategy<sup>[8]</sup>, measuring instrument<sup>[27]</sup>, challenges to explore PB<sup>[9]</sup>, and geographical distribution<sup>[2]</sup>. However, the methods were superficial that instigated further studies to replicate the observations.

### **Distribution of the studies**

The study revealed that more than three-quarters (85.71%) of the research output on PB has occurred in the wake of the COVID-19 pandemic. This is an indication of the growing public health relevance of this phenomenon. More than sixty percent (64.28%) of the papers were original contributions indicating that the more empirical studies are coming out gradually (Table 1). Most of the studies applied survey and cross-sectional study design, which may be explained by the pattern of PB as it appears irregularly, episodically, and erratically in response to the adverse stimuli<sup>[2,9]</sup>. However, longitudinal studies are better in order to explore the behavior. Online media reports, social media, and Google Trends were also used, which may be explained by the COVID-19 pandemic, and the lockdown was applied.

### **Responsible factors**

Several studies have looked at the etiological underpinnings of PB, mainly in terms of psychological and social factors that may contribute to the phenomenon<sup>[5-7]</sup>. The results are intuitive and point to the significance of perception of commodity and time scarcity, sense of uncertainty as well as the herd instinct, which has its basis in the social learning theory, as potential contributors to the genesis of PB<sup>[2,5-7]</sup>. Further, perceptions of price differential and price fluctuations have been found to correlate with PB behavior; this has implications from a management perspective and highlights the importance of maintaining supply chains.

### **Controlling measures of PB**

Little empirical evidence is available on the management of PB. One group of authors proposed an online cognitive behavior therapy model for PB, but it was not tested<sup>[23]</sup>. The media should play a central role in curbing PB by spreading awareness about the phenomenon and adopting responsible reporting practices. A collaborative approach between the media, government, and health sector would foster a collective sense of responsibility and bring about sustainable changes in reporting practices, a key strategy to control PB<sup>[3]</sup>.

Drawing upon these insights, it appears that PB can be controlled by adequate, timely, and consistent information on the evolving situation with an additional focus on clarifying misinformation or rumors. To reduce visual cues, big retail stores can encourage online shopping at least for those who are young/internet savvy. This will reduce long queues outside shopping stores, which is a visual signal for other buyers to join, and will reduce the possibility of such images being circulated in the mass media and social media, another important cue for PB<sup>[10]</sup>. Opening fair price shops where commodity prices are tightly regulated may be helpful in curbing panic purchases.

### **Academic domains**

Researchers from several specialties took part in PB research, multiple academic domains have been researched, and articles have been published in several specialty journals such as psychiatry, psychology, business, sales and marketing, public health, supply chain, economics, management, consumer behavior, disaster preparedness, e-commerce, consumer behavior, marketing, prevention strategies, media, social network, economics, communication, information management, sociology, personality, nursing, health economics, food policy, epidemiology, community health, and engineering (Table 2). Consumer behavior patterns have been studied during different situations such as pandemic<sup>[28]</sup> and seasonally recurring disasters<sup>[40]</sup>. Insights from these studies can be used to spread awareness about PB, facilitate the identification of hoarders, and take steps to mitigate supply chain disruptions<sup>[37]</sup>. Reducing conflicting information from different media sources and giving advance information about impending seasonal disasters would assist people in staggering their purchases and reduce eleventh-hour PB. Concordance of information from media sources is likely to promote trust in the media, a key element that has been linked to an increased likelihood of distress purchases<sup>[22]</sup>.

### **Distribution of authors**

Most of the authors were affiliated with institutions from Australia, Bangladesh, China, India, Singapore, and the United States (Table 2). The fact that more than half of the studies reviewed originated from Asia may reflect the proneness of countries in the region for PB, probably due to a combination of structural issues, public mistrust, and lack of adequate governmental action. More than forty percent (42.85%) of the papers had intercountry collaborations signifying the common interest of the research. Among the 10 funded projects, China had the highest funding (3 full; 1 partial); Australia (2), Hong Kong (1 partial), United States (1), Poland (1), Taiwan (1), and Singapore (1).

### **Strengths of the study**

This is the first systematic approach to provide an overview and identify the research gaps on the emerging research topic. Only peer-reviewed published articles were reviewed.

### **Limitations**

The search was done cross-sectionally by a single individual (first author). Only articles published in the English language were included. Preprints were not included.

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## **CONCLUSION**

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PB is a relatively newer concept to get the attention of the research community. The study revealed several important aspects of PB research including research trends, major studied areas, geography, collaboration, and funding of studies. This review would help policymakers, researchers, funders, and other stakeholders to shape their decision while studying PB. Further robust studies with replication of the findings are warranted to fill the research gaps identified in this review.

## **ARTICLE HIGHLIGHTS**

### **Research background**

Panic buying is an under-addressed research entity.

### **Research motivation**

Sporadic evidence is coming out in recent days.

### **Research objectives**

We aimed to see the perspectives of panic buying that have been studied through November 15, 2020.

### **Research methods**

We did a systematic search in PubMed, PubMed Central, Scopus, and Google Scholar and reviewed 42 articles.

### **Research results**

The study identified the distribution of study, aspects of panic buying, academic domain related to panic buying, distribution of authors, the specialty of the authors and journals, funding, and collaborations of the identified articles.

### **Research conclusions**

Although the study identified some important perspectives, further studies are warranted in a systematic manner.

### **Research perspectives**

The review provides a good insight into the different stakeholders to plan further studies and prevent panic buying.

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## Split-dose vs same-day bowel preparation for afternoon colonoscopies: A meta-analysis of randomized controlled trials

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### Abstract

#### BACKGROUND

Quality of bowel preparation in afternoon colonoscopies has been a struggle. Currently, a choice of same-day preparation (SaD) or split-dose preparation (SpD) exists; however, randomized controlled trials' results have varied.

#### AIM

To examine the outcomes of SaD and SpD for afternoon colonoscopies.

#### METHODS

An extensive literature search was conducted using multiple databases. Only randomized controlled trials (RCTs) in adults that compared SaD to SpD with Ottawa bowel preparation score (OBPS) were included. Odds ratio (OR) or mean difference was used to analyze outcomes.

#### RESULTS

Eleven RCTs were included ( $n = 1846$ ). No difference was observed for satisfactory bowel preparation based on OBPS among participants receiving SaD vs SpD (OR 0.77; 95%CI: -0.57-1.03;  $P = 0.07$ ;  $I^2 = 5\%$ ). Subgroup analysis showed no difference in terms of satisfactory bowel preparation based on OBPS between the two groups when receiving same preparation formula (polyethylene glycol) (OR 0.83; 95%CI: 0.51-1.35;  $P = 0.46$ ;  $I^2 = 39\%$ ) as well as receiving same formula

PRISMA guidelines.

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and volume (4 L polyethylene glycol) (OR 1.14; 95%CI: 0.65-2.01;  $P = 0.64$ ;  $I^2 = 0\%$ ).

### CONCLUSION

In patients undergoing afternoon colonoscopies, SaD is comparable with SpD in terms of satisfactory bowel preparation. Further studies are needed to validate these results and determine the optimal formula and dosages.

**Key Words:** Afternoon; Colonoscopy; Preparation; Split-dose; Same-day; Meta-analysis

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**Core Tip:** Afternoon colonoscopies have considerably more inadequate bowel preparations than morning colonoscopies. Different bowel preparation regimens have been tried to help improve preparation quality in afternoon colonoscopies, including split-dose and same-day bowel preparations. Studies have shown conflicting results on which preparation regimen is optimal. Therefore, we conducted a meta-analysis on this subject and found that split-dose bowel preparation shows no difference in satisfactory bowel preparations vs same-day bowel preparation for afternoon colonoscopies. Therefore, either preparation may be utilized.

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### INTRODUCTION

Colorectal cancer (CRC) is a common and devastating disease resulting in significant cancer deaths around the world<sup>[1,2]</sup>. Colonoscopy remains the screening test of choice for CRC and the only method which encompasses both diagnostic and therapeutic potential<sup>[3]</sup>. Afternoon colonoscopies have higher rates of suboptimal bowel preparation<sup>[4]</sup>. Suboptimal bowel preparations are associated with prolonged procedure time, low adenoma detection rate, and increased patient discomfort, complications, and healthcare costs<sup>[5-7]</sup>.

Several studies have suggested that the quality of bowel cleansing for afternoon colonoscopies depends on timing and quantity of the bowel preparation<sup>[8,9]</sup>. Some studies have shown that split-dosing bowel preparations (SpD) is superior to same-day preparation (SaD, the morning of the procedure) with regard to both cleansing efficacy and tolerability, while other studies report that SaD has a better cleansing and tolerability compared with SpD. Currently, the U.S. Multi-Society Task Force on Colorectal Cancer (USMSTF) recommends SaD regimen as an alternative for SpD for colonoscopies in the afternoon<sup>[10]</sup>. This recommendation was made based on the results of one prospective study comparing the SaD regimen with the SpD regimen and two randomized controlled trials (RCTs) using controls with day-prior regimens<sup>[6,11,12]</sup>.

Recently published RCTs on this topic report mixed results. Moreover, data pooling from the RCTs is challenging given varied bowel preparation regimens and bowel preparation scales. Therefore, a meta-analysis of the RCTs to compare the SaD with the SpD regimens for afternoon colonoscopies was performed.

### MATERIALS AND METHODS

#### Literature search and study selection

Literature search was conducted with a three-fold system. First, multiple databases, including EMBASE, Cochrane databases, MEDLINE/PubMed, Google Scholar, CINAHL, and Scopus were searched in November 2019 for afternoon and colonoscopy. Second, major conference proceeding abstracts (Digestive Disease Week,

American College of Gastroenterology, United European Gastroenterology meetings) were searched through November 2019. Third, references from identified studies were searched for any potentially omissions. If data required clarification, we communicated with the authors.

### Data extraction

All RCTs on adults comparing the SaD with SpD regimen for afternoon colonoscopies, using the Ottawa bowel preparation score (OBPS) were included. Exclusion criteria were patients < 18 years old or non-RCTs. To reduce confounding, subgroup analyses were performed for the same formulation and volume of bowel preparation using polyethylene glycol with electrolytes (PEG). Two authors (Parsa NP and Grisham EA) independently reviewed all the studies for inclusion and extracted data using standard forms. Any disagreements on inclusion or data extraction were settled by the senior author (Bechtold ML).

### Quality assessment of studies

The Cochrane's Collaboration Risk of Bias Tool was used to assess the quality of studies<sup>[13-15]</sup>. For each study, a grade, as described as low, moderate, or high, was based on the assessment of limitations, effect magnitude, precision, publication and other forms of bias, and consistency of results<sup>[13-15]</sup>.

### Statistical analysis

A meta-analysis was conducted comparing SaD and SpD for afternoon colonoscopies by calculating pooled estimates of quality of bowel preparation. Outcomes were analyzed using mean difference (MD) or odds ratio (OR) by the DerSimonian and Laird method (the random-effects model). The  $I^2$  measure of inconsistency was used to assess heterogeneity ( $P < 0.10$  or  $I^2 > 50\%$  was deemed significant). If heterogeneity was discovered, researchers used performed a sensitivity analysis to remove the least amount of studies necessary to reach non-significant heterogeneity by comparing results to the original pooled data. RevMan 5.3 (Review Manager, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used for statistical analysis. Funnel plots assessed for publication bias.

## RESULTS

### Article search and quality assessment

Evaluation of titles and abstracts resulted in 663 articles being identified. After review, 21 articles remaining in which 11 satisfied the inclusion criteria ( $n = 1846$ ) with mean age range of 51.6-61.8 years<sup>[16-26]</sup> (Figure 1). Studies were global, including many countries (United States, Spain, Italy, China, Korea, India) (Table 1). Most of the studies were deemed high-quality studies based on quality assessment (Table 2).

### Overall results

Eight RCTs reported the mean OBPS ( $n = 1328$ )<sup>[17-21,23-25]</sup>. Eight studies reported the number of satisfactory bowel preparations ( $n = 1483$ )<sup>[16,19,21-26]</sup>. Of these, 1202 had satisfactory bowel preparations with 578 in the SaD group and 624 in the SpD group. There was no difference between SaD and SpD for the mean OBPS (MD 0.33; 95%CI: -0.09-0.75;  $P = 0.13$ ;  $I^2 = 74\%$ ) (Figure 2A) or the number satisfactory bowel preparations (79.1% vs 83%; OR 0.77; 95%CI: 0.57-1.03;  $P = 0.07$ ;  $I^2 = 5\%$ ) (Figure 2B) despite a trend favoring SpD. Given significant heterogeneity in the mean OBPS analysis, a sensitivity analysis was performed which showed similar results without significant heterogeneity when one study<sup>[23]</sup> was eliminated (OR 0.18; 95%CI: -0.11-0.46;  $P = 0.22$ ;  $I^2 = 36\%$ ).

### Same formulation bowel preparation (PEG)

Five studies reported the mean OBPS ( $n = 877$ )<sup>[17,20,21,23,25]</sup>. There was no difference between SaD and SpD for mean OBPS (MD 0.45; 95%CI: -0.13-1.02;  $P = 0.13$ ;  $I^2 = 78\%$ ) (Figure 3A). Five studies reported the number of satisfactory bowel preparations ( $n = 1045$ )<sup>[21-23,25,26]</sup>. Of these, 862 had satisfactory bowel preparations (82.5%) with 415 in the SaD group and 447 in the SpD group. There was no difference between SaD and SpD for number satisfactory bowel preparations (81% vs 84%; OR 0.83; 95%CI: 0.51-1.35;  $P = 0.46$ ;  $I^2 = 39\%$ ) (Figure 3B). Given significant heterogeneity in the mean OBPS analysis, a sensitivity analysis was performed which showed similar results without

**Table 1** Description of studies included in the meta-analysis

Ref.	Country	Number of patients (n)	Bowel preparation times (dose 1)	Patients per group (n)	Bowel preparation scale	Satisfactory bowel preparations (n)	OBPS (mean score ± SD)
Parra-Blanco <i>et al</i> <sup>[16]</sup> , 2006	Spain	88	Same day PEG 3 L	43	Ottawa	34	ND
			Split-dose NaP 45 mL/45 mL	45	Ottawa	36	ND
Kang <i>et al</i> <sup>[24]</sup> , 2014	South Korea	196	Same day NaP 1/1	97	Ottawa	59	4.05 ± 1.56
			Split-dose PEG 2 L/2 L	99	Ottawa	71	3.8 ± 1.55
Shah <i>et al</i> <sup>[17]</sup> , 2014	India	159	Same day PEG 2 L	80	Ottawa	ND	6.02 ± 1.34
			Split-dose PEG 1 L/1 L	79	Ottawa	ND	5.52 ± 1.23
Cesaro <i>et al</i> <sup>[18]</sup> , 2013	Italy	101	Same day Halflytely 2 L/10-20 mg Bisacodyl	50	Ottawa	ND	2.78 ± 1.95
			Split-dose PEG 3 L/1 L	51	Ottawa	ND	3.41 ± 1.90
de Leone <i>et al</i> <sup>[19]</sup> , 2013	Italy	154	Same day Halflytely 2 L/10-20 mg Bisacodyl	78	Ottawa	70	3.09 ± 2.4
			Split-dose PEG 2 L/2 L	76	Ottawa	70	2.39 ± 2.55
Kim <i>et al</i> <sup>[25]</sup> , 2014	South Korea	100	Same day PEG 4 L	50	Ottawa	41	4.98 ± 1.78
			Split-dose PEG 2 L/2 L	50	Ottawa	42	4.98 ± 1.57
Kotwal <i>et al</i> <sup>[20]</sup> , 2014	United States	103	Same day PEG 3 L	51	Ottawa	ND	7.15 ± 3.58
			Split-dose PEG 2 L/2 L	52	Ottawa	ND	7.38 ± 3.65
Seo <i>et al</i> <sup>[21]</sup> , 2013	South Korea	197	Same day PEG 2 L	97	Ottawa	72	3.76 ± 2.07
			Split-dose PEG 2 L/2 L	100	Ottawa	75	3.67 ± 1.57
Zhang <i>et al</i> <sup>[23]</sup> , 2014	China	318	Same day PEG 2 L	159	Ottawa	126	4.4 ± 2.7
			Split-dose PEG 1 L/2 L	159	Ottawa	143	2.9 ± 2.4
Alkhairi <i>et al</i> <sup>[26]</sup> , 2017	United States	300	Same day PEG 4 L	142	Ottawa	142	ND
			Split-dose PEG 2 L/2 L	158	Ottawa	156	ND
Castro <i>et al</i> <sup>[22]</sup> , 2019	United States	130	Same day PEG 4 L	65	Ottawa	34	ND
			Split-dose PEG 2 L/2 L	65	Ottawa	31	ND

OBPS: Ottawa bowel preparation score; PEG: Polyethylene glycol; ND: Not detected.

significant heterogeneity when one study<sup>[23]</sup> was eliminated (OR 0.26; 95%CI: -0.02-0.54; *P* = 0.07; *I*<sup>2</sup> = 0%).

**Same formulation and volume bowel preparation (4 L PEG)**

Three studies reported the mean OBPS (*n* = 362)<sup>[17,20,25]</sup>. There was no difference between SaD and SpD for mean OBPS (MD 0.30; 95%CI: -0.08-0.68; *P* = 0.12; *I*<sup>2</sup> = 12%) (Figure 4A). Three studies reported the number of satisfactory bowel preparations (*n* = 530)<sup>[22,25,26]</sup>. Of these, 446 had satisfactory bowel preparations with 217 in the SaD group and 229 in the SpD group. There was no difference between SaD and SpD for number satisfactory bowel preparations (84.4% vs 83.9%; OR 1.14; 95%CI: 0.65-2.01; *P* = 0.64; *I*<sup>2</sup> = 0%) (Figure 4B).

**Publication bias**

For any outcome, no significant publication bias was identified (Figure 5).

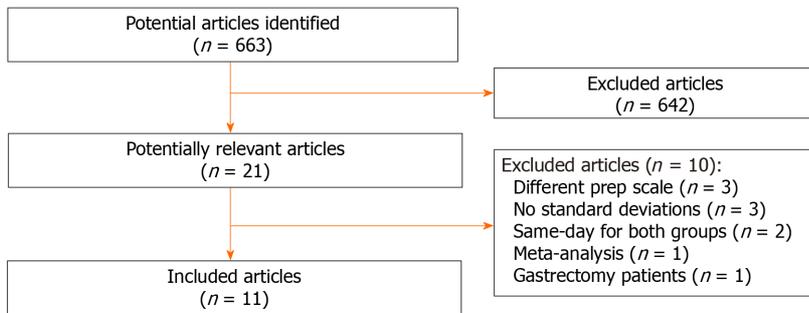
**DISCUSSION**

The USMSTF currently recommends the SaD bowel preparation as an alternative to SpD for afternoon colonoscopies<sup>[10]</sup>. This recommendation, which is based on “high-

**Table 2** Quality assessment of studies included in meta-analysis based upon Cochrane's Collaboration Risk of Bias tool

Ref.	Study design	Random sequence generation	Allocation concealment	Blinding	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Quality assessment
Parra-Blanco <i>et al</i> <sup>[16]</sup> , 2006	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Kang <i>et al</i> <sup>[24]</sup> , 2014	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Shah <i>et al</i> <sup>[17]</sup> , 2014	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Cesaro <i>et al</i> <sup>[18]</sup> , 2013	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
de Leone <i>et al</i> <sup>[19]</sup> , 2013	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Kim <i>et al</i> <sup>[25]</sup> , 2014	RCT	Not described	Adequate	Single-blinded	Adequate	None	None	None	Moderate
Kotwal <i>et al</i> <sup>[20]</sup> , 2014	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Seo <i>et al</i> <sup>[21]</sup> , 2013	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Zhang <i>et al</i> <sup>[23]</sup> , 2014	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Castro <i>et al</i> <sup>[22]</sup> , 2019	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Alkhairi <i>et al</i> <sup>[26]</sup> , 2017	RCT	Not described	Not described	Single-blinded	Adequate	None	None	None	Moderate

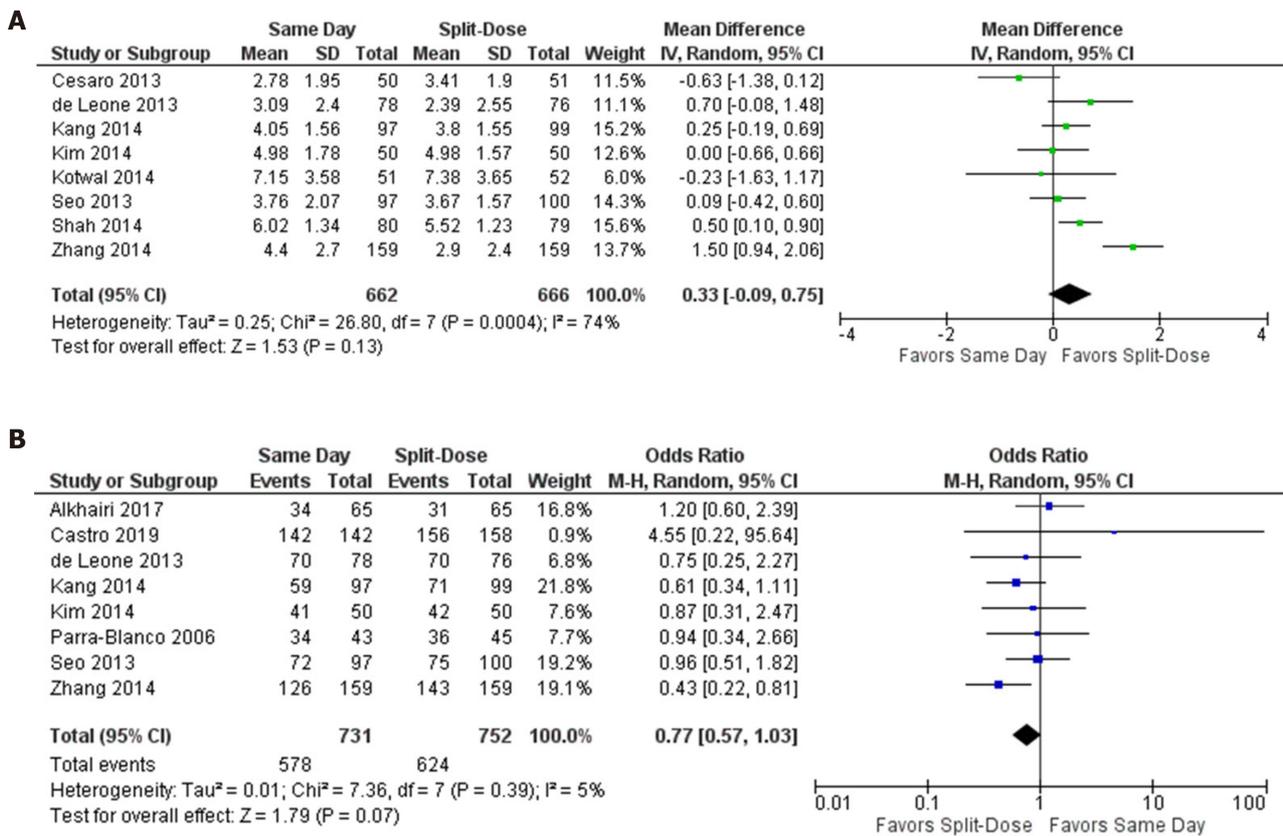
RCT: Randomized controlled trial.



**Figure 1** Details of search algorithm.

quality evidence”, is based on one prospective study and two RCTs that their control groups received a day-prior bowel preparation regimen<sup>[6,11,12]</sup>. Since this recommendation, several high-quality trials have evaluated and compared the efficacy of SaD vs SpD for afternoon colonoscopies, supporting the value of this study.

The practice of SaD bowel preparation was supported by two meta-analyses published in 2017. Both studies concluded the noninferiority of the SaD compared with the SpD regimen with regards to bowel preparation for afternoon colonoscopies, consistent with the findings of our study<sup>[27,28]</sup>. Avalos *et al*<sup>[27]</sup> conducted a meta-analysis on 11 RTCs comparing the efficacy of bowel preparation quality between the SaD and SpD regimens and reported a similar results for the bowel preparation quality, patient willingness to repeat the procedure and adenoma detection rate, although SaD patients reported less bloating and improved quality of sleep. Cheng *et al*<sup>[28]</sup> pooled the results of 14 RTCs and reported comparable results between the SaD and SpD regimens for bowel preparation with substantial heterogeneity ( $I^2 = 60\%$ ), so subgroup

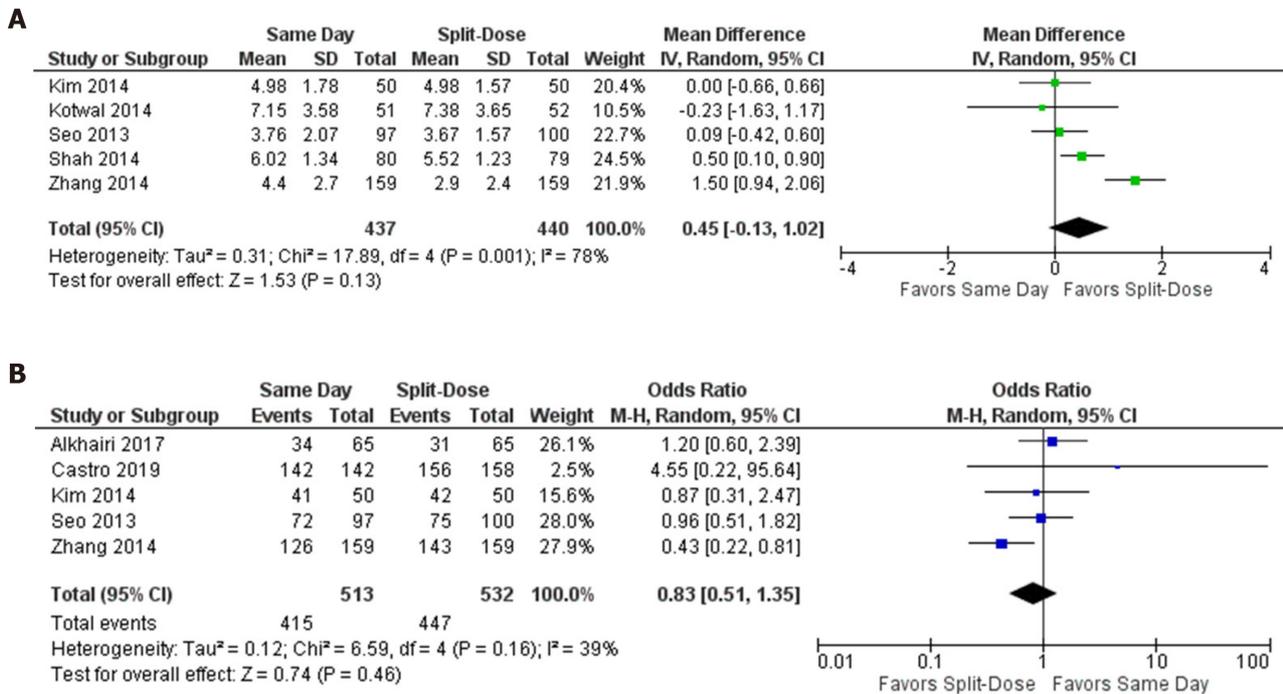


**Figure 2 Forest plot showing overall bowel preparation results between same-day preparation vs split-dose preparation for afternoon colonoscopies. A: Mean Ottawa bowel preparation score; B: Number of satisfactory bowel preparations.**

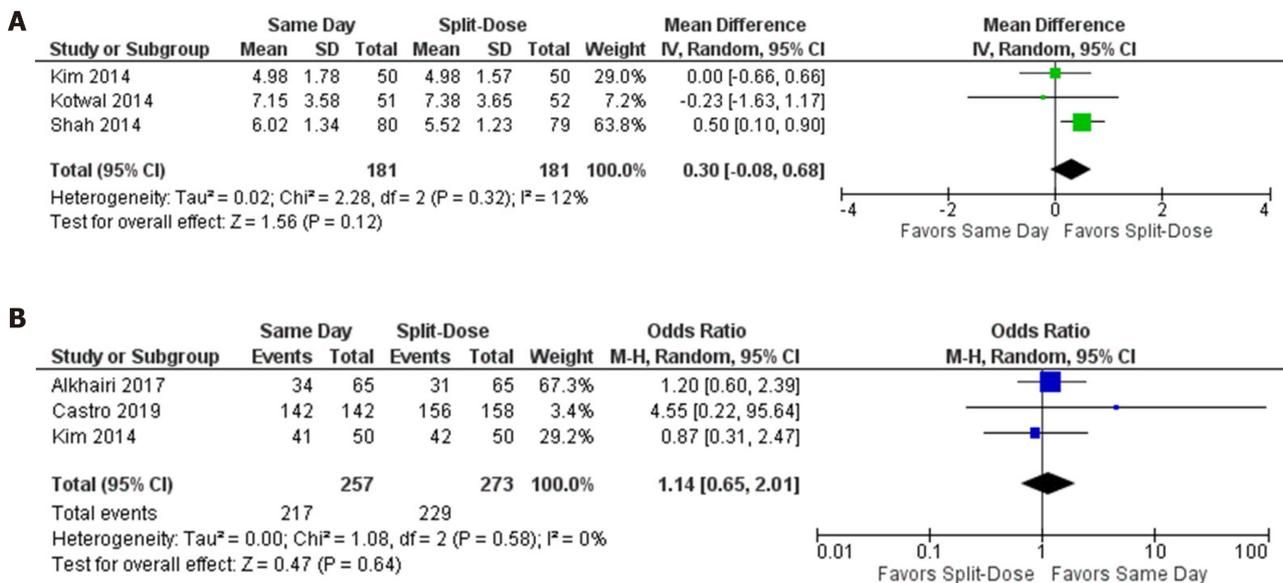
analysis was performed to evaluate the influence of bisacodyl on bowel preparation. Comparing SaDs with bisacodyl to SpDs without it the previous evening showed the results favored SaDs ( $P = 0\%$ ). If both arms eliminated adjuncts, the analysis revealed that patients in the SpD arm had better bowel preparation with no heterogeneity (OR 0.66; 95%CI: 0.49-0.88). Heterogeneity was a significant limitation of these meta-analyses as many studies used varied bowel preparation scales in the study arms. Furthermore, neither compared the SaD and SpD regimens among patients who received same formula and volume bowel preparation.

This meta-analysis is the first comparing SaD *vs* SpD bowel preparation for afternoon colonoscopies that used identical validated scales to evaluate the bowel preparation quality. No significant differences were identified between the SaD and SpD regimens for quality of bowel preparation by total OBPS. Moreover, we performed a comprehensive subgroup analysis in order to minimize potential confounding factors. Further subgroup analyses showed no differences in terms of satisfactory bowel preparation based on OBPS between the two groups when receiving the same preparation formula (PEG) as well as receiving same preparation formula and volume (4 L PEG). Only RCTs in adult patients were evaluated and used in this meta-analysis. Moreover, by using the OBPS, which evaluates the bowel preparation quality before the application of any cleansing maneuvers, the amount of time and adequacy of cleaning was not an issue, thereby limiting confounding variables. Results of our study can help guide clinicians and patients to select the optimal method for bowel preparation. The current guidelines indicate that providers are responsible for maintaining optimal bowel preparations at greater than 85%, which is often affected by inadequate bowel preparation ingestion by patients<sup>[10]</sup>. Given a lack of clinical differences, both SaD and SpD regimens should be offered to patients and their preference should be considered in order to maximize their adherence. This may potentially minimize procedure cancellations and increase the success rates of afternoon colonoscopies.

The strengths of this meta-analysis are abundant. Inclusion of worldwide RCTs in varying populations, including China, Korea, Spain, Italy, India, and United States, allows for generalization to many populations. Second, the quality of RCTs included were moderate-to-high. Given the lack of ability to blind the patient to the bowel



**Figure 3** Forest plot showing same bowel preparation results between same-day preparation vs split-dose preparation for afternoon colonoscopies. A: Mean Ottawa bowel preparation score; B: Number of satisfactory bowel preparations.



**Figure 4** Forest plot showing same bowel preparation (type and volume) results between same-day preparation vs split-dose preparation for afternoon colonoscopies. A: Mean Ottawa bowel preparation score; B: Number of satisfactory bowel preparations.

preparation, the included studies were the highest exceptional quality possible. Third, to minimize confounding factors, extensive subgroup analyses were performed and only studies with the same bowel preparation and the same bowel preparation with same volume were evaluated. This effort limits significant confounding factors. Finally, the OBPS was used which limits confounding variables of cleaning effort and cleaning time since evaluated prior to cleaning. Limitations of this meta-analysis were observed. First, significant heterogeneity was observed in two outcomes. Besides a diversity of bowel preparation across studies, there were slightly varied preparations within study arms. Furthermore, some using SaD or SpD preparations with or without

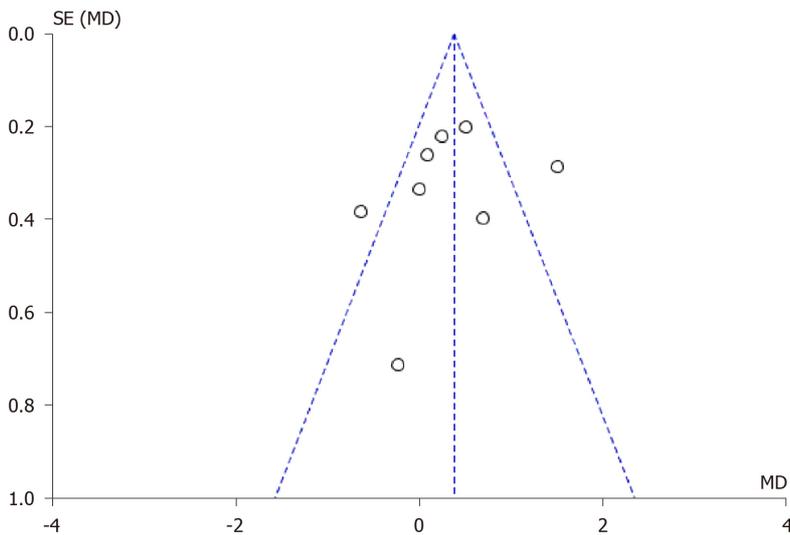


Figure 5 Funnel plot showing no publication bias.

bisacodyl. For those two outcomes with significant heterogeneity, sensitivity analyses were performed with similar results without significant heterogeneity when Zhang *et al.*<sup>[23]</sup> was removed. Second, the type of diet as well as the length of diet restriction during preparation varied among studies and therefore, the influence of diet on bowel preparation could not be further analyzed.

## CONCLUSION

In conclusion, our meta-analysis showed that no difference exists between SaD and SpD bowel preparation for the number of satisfactory bowel preparations in the afternoon colonoscopies. Both options should be offered to patients in order to maximize adherence and increase afternoon colonoscopy success rates.

## ARTICLE HIGHLIGHTS

### Research background

Bowel preparation for afternoon colonoscopies is important for screening for colorectal cancer.

### Research motivation

Bowel preparation for afternoon colonoscopies is controversial. Examining the best approach would be beneficial for patients and those performing colonoscopies.

### Research objectives

This meta-analysis examines the use of same-day preparation (SaD) or split-dose preparation (SpD) for afternoon colonoscopies.

### Research methods

An extensive literature search was conducted using multiple databases. Only randomized controlled trials in adults that compared SaD to SpD with Ottawa bowel preparation score (OBPS) were included. Odds ratio or mean difference was used to analyze outcomes.

### Research results

No differences were observed for satisfactory bowel preparation based on OBPS among participants receiving SaD *vs* SpD overall ( $P = 0.07$ ), when the two groups received the same preparation formula (polyethylene glycol, PEG) ( $P = 0.46$ ), and when the two groups received the same formula and volume (4 L PEG) ( $P = 0.64$ ).

**Research conclusions**

In patients undergoing afternoon colonoscopies, SpD is comparable with SaD in terms of satisfactory bowel preparations.

**Research perspectives**

Patients and proceduralists may be confident in using either SaD or SpD for afternoon colonoscopies.

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# Comparison of hand-assisted laparoscopic radical gastrectomy and laparoscopic-assisted radical gastrectomy: A systematic review and meta-analysis

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## Abstract

### BACKGROUND

Gastrectomy is the optimal treatment for gastric cancer. Laparoscopic-assisted gastrectomy (LAG) has been extensively employed, while hand-assisted laparoscopic gastrectomy (HALG), which is similar to LAG, remains controversial. Although HALG is popular in China, some surgeons do not accept it as a minimal-access technique.

### AIM

To assess the safety and practicability of HALG by comparing the short-term outcomes of HALG and LAG.

### METHODS

The electronic databases of EMBASE, PubMed, China National Knowledge Infrastructure, and Cochrane Library were thoroughly searched, and randomized controlled trials (RCTs) comparing HALG and LAG were included. The study results, including surgery time, blood loss, retrieved lymphatic nodes, incision length, time to first flatus, hospitalization duration, and all postsurgical complications, were compared between the two groups.

### RESULTS

Five RCTs, which included 302 cases with HALG and 298 cases with LAG, were considered eligible for inclusion. Meta-analysis showed that HALG significantly reduced surgery time ( $P < 0.01$ ), hospital duration ( $P < 0.01$ ), and overall postsurgical complications ( $P < 0.01$ ). Additionally, HALG significantly increased the number of retrieved lymphatic nodes ( $P = 0.01$ ) and incision length ( $P < 0.01$ )

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compared with LAG. The blood loss and time to first flatus were similar between the two groups ( $P > 0.05$ ).

## CONCLUSION

Compared with LAG, HALG is a simpler and safer technique. Additionally, HALG should be used as a minimal-access technique, especially in technologically undeveloped areas.

**Key Words:** Gastric cancer; Hand-assisted laparoscopy; Gastrectomy; Laparoscopic-assisted gastrectomy; Meta-analysis; Systematic review

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**Core Tip:** No consensus is available in the literature about which technique is more beneficial to the patients between hand-assisted laparoscopic gastrectomy (HALG) and laparoscopic-assisted gastrectomy (LAG). This is the first systematic review and meta-analysis comparing HALG and LAG. We compared these two techniques in terms of estimated surgery time, blood loss, retrieved lymphatic nodes, incision length, time to first flatus, hospitalization duration, and all postsurgical complications from selected randomized controlled trials. Compared with LAG, HALG is a simpler and safer technique.

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## INTRODUCTION

Gastric cancer is associated with high mortality and morbidity rates in China<sup>[1-3]</sup>. Gastrectomy is the optimal treatment for gastric cancer, but the surgical approach has numerous choices such as traditional open gastrectomy, laparoscopic-assisted gastrectomy (LAG), totally laparoscopic gastrectomy, robot-assisted gastrectomy, and hand-assisted laparoscopic gastrectomy (HALG). Hunter predicted an exciting prospect for hand-assisted laparoscopic surgery (HALS) in gastrectomy<sup>[4]</sup>. HALS combines the advantages of laparoscopic surgery and laparotomy; thus, it is popular in China<sup>[5,6]</sup>.

Compared with laparoscopic-assisted or totally laparoscopic surgery, HALS retains the tactile sensation of the surgeon's hand, which can make the operation faster and safer. Besides, it also has advantages of laparoscopy, such as being minimally invasive and having a zooming surgical field. For young surgeons, it also has the advantage of having a short-learning curve<sup>[7]</sup>. To date, HALG has formed the unique surgical approach called three-step HALG<sup>[8-10]</sup>, which makes gastrectomy more convenient and simpler.

Recently, the number of studies on HALG is increasing. Although certain studies have compared HALG and LAG<sup>[11,12]</sup>, controversy about its useful meaning still exists. Therefore, the present study conducted a systematic review and meta-analysis, with an aim to evaluate the safety and practicability of HALG, and compare the short-term outcomes of HALG and LAG.

## MATERIALS AND METHODS

### Search strategy

EMBASE, PubMed, Cochrane Library, and China National Knowledge Infrastructure were searched for primary studies published up to August 2019. The search terms 'hand-assisted laparoscopic' and 'gastrectomy' and 'gastric cancer' were used in

English and Chinese. Additionally, the references cited in retrieved articles were reviewed in order to select studies that better suit our criteria. Studies with only abstracts or unpublished reports were not included.

### **Inclusion and exclusion criteria**

Two authors (Gan W and Liu LY) independently reviewed the search results. Any studies that met the following criteria were considered: (1) All patients were diagnosed with gastric cancer; (2) The study compared HALG and LAG; (3) It was a randomized controlled trial (RCT); and (4) The endpoints included postsurgical complications. If there were two or more articles by the same authors or research institutions, the one with larger sample size was selected.

To limit heterogeneity across the studies, the following exclusion criteria were used: (1) The study included totally laparoscopic or robotic radical gastrectomy; (2) It did not provide sufficient data to calculate the risk ratio (RR) and its 95% confidence interval (CI) of different procedures for overall postsurgical complications; and (3) The article was an abstract presented at meetings, a case series, a cohort study, a review, or a letter.

### **Data extraction**

Data were extracted independently by two authors, and discrepancies were resolved by consensus. The following details were extracted: Name of the first author, institution, country, study period, publication year, sample size, mean age, gender, tumor stage, surgery time, blood loss, retrieved lymphatic nodes, incision length, time to first flatus, hospitalization duration, and all postsurgical complications.

### **Statistical analysis**

All statistical analyses were performed using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For the meta-analysis, the results were presented as RR for dichotomous variables and weighted mean difference (WMD) for continuous variables. If the  $I^2$  value was  $\leq 50\%$ , a fixed effects model was employed, and if the value was  $> 50\%$ , a random effects model was selected. Two-sided  $P < 0.05$  was considered to indicate a statistically significant difference.  $\chi^2$  test was used to evaluate statistical heterogeneity, and  $I^2$  statistic was calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. To assess the publication bias, a funnel plot was applied.

## **RESULTS**

### **Selected studies**

During the initial search, 126 publications were obtained from electronic databases. A total of 17 articles were reviewed in detail. Two studies derived from the same research institution<sup>[13,14]</sup>; thus, the biggest sample size study was selected<sup>[13]</sup>. Finally, five RCT studies were selected for the meta-analysis<sup>[13,15-18]</sup>. The details of the search strategy are shown in [Figure 1](#).

### **Study characteristics**

The basic characteristics of the included studies are shown in [Table 1](#). Five RCTs were included. A total of 302 patients were included in the HALG group, and 298 patients were included in the LAG group. Five studies were reported from different regions of China.

### **Study quality**

The Jadad scoring system was used to assess the quality of the selected RCT studies. Due to being open-label RCTs, those studies only scored 2 or 3 points ([Table 2](#)). It was known that operation was impossible to blind patients and surgeons. Thus, studies with a score  $\geq 2$  were classified as methodologically sound studies.

### **Intraoperative outcome**

The surgery time, blood loss, incision length, and retrieved lymphatic nodes were evaluated. The HALG group had a shorter surgery time compared with the LAG group (WMD, -23.81 min; 95% CI, -38.80 to -8.81;  $P = 0.002$ ; [Figure 2A](#)). There was no significant difference in blood loss between the two groups (WMD, -8.61 mL; 95% CI, -19.66 to 2.44;  $P = 0.13$ ; [Figure 2B](#)). Only four studies reported the incision length, and

**Table 1 Characteristics of the included studies**

Ref.	Year	Nation	Geographical region	Study period	Sample size		Age, mean (yr)		Gender (M/F)		Tumor stage		Types of operation					
					HALG	LAG	HALG	LAG	HALG	LAG	HALG	LAG	HALG			LAG		
											I/II/III/IV	I/II/III/IV	TG	DG	PG	TG	DG	PG
Gong <i>et al</i> <sup>[13]</sup>	2014	China	Southwest	2008-2013	120	113	58.94	59.29	75/45	82/31	15/19/46/40	9/15/52/37	46	61	13	31	59	23
Wang <sup>[16]</sup>	2015	China	North	2010-2013	61	65	NA	NA	NA	NA	NA	NA	0	61	0	0	60	0
Yang <i>et al</i> <sup>[18]</sup>	2016	China	Southwest	2013-2015	42	42	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Xue <i>et al</i> <sup>[17]</sup>	2018	China	Central	2015-2016	28	28	52.68	52.74	21/7	20/8	3/7/18/0	2/5/21/0	0	28	0	0	28	0
Gao <i>et al</i> <sup>[15]</sup>	2019	China	East	2013-2014	51	50	57.6	58.2	32/19	36/14	10/12/29/0	13/15/22/0	12	39	0	17	33	0

TG: Total gastrectomy; DG: Distal gastrectomy; PG: Proximal gastrectomy; NA: Not reported; HALG: Hand-assisted laparoscopic gastrectomy; LAG: Laparoscopic-assisted gastrectomy.

the value was longer in the HALG group than in the LAG group (WMD, 0.89 cm; 95%CI, 0.45 to 1.33;  $P < 0.01$ ; [Figure 2C](#)). The HALG group had a greater number of retrieved lymphatic nodes compared with the LAG group (WMD, 2.02; 95%CI, 0.40 to 3.64;  $P = 0.01$ ; [Figure 2D](#)).

### Postsurgical outcomes

The time to first flatus and the duration of postsurgical hospitalization were evaluated in the postoperative recovery. There was no significant difference in the time to first flatus between the two groups (WMD, 0.02 d; 95%CI, -0.22 to 0.25;  $P = 0.90$ ; [Figure 2E](#)). The HALG group had shorter hospital duration, compared with the LAG group (WMD, -0.60 d; 95%CI, -0.95 to -0.26;  $P < 0.01$ ; [Figure 2F](#)).

The overall postsurgical complications were evaluated in all the included studies. The pooled result showed that the HALG group had a lower risk of overall postsurgical complications than the LAG group (RR, 0.57; 95%CI, 0.37 to 0.88;  $P < 0.01$ ; [Figure 2G](#)).

### Publication bias

The funnel plot of overall postsurgical complications was used to examine the potential publication bias. Based on the approximate symmetry, there was no evidence of publication bias in this meta-analysis ([Figure 3](#)).

Table 2 Jadad scores of the included randomized controlled trials

Ref.	Randomization	Blind	Withdrawals and dropouts	Total
Gong <i>et al</i> <sup>[13]</sup> , 2014	1	0	1	2
Wang <sup>[16]</sup> , 2015	1	0	1	2
Yang <i>et al</i> <sup>[18]</sup> , 2016	1	0	1	2
Xue <i>et al</i> <sup>[17]</sup> , 2018	2	0	1	3
Gao <i>et al</i> <sup>[15]</sup> , 2019	2	0	1	3

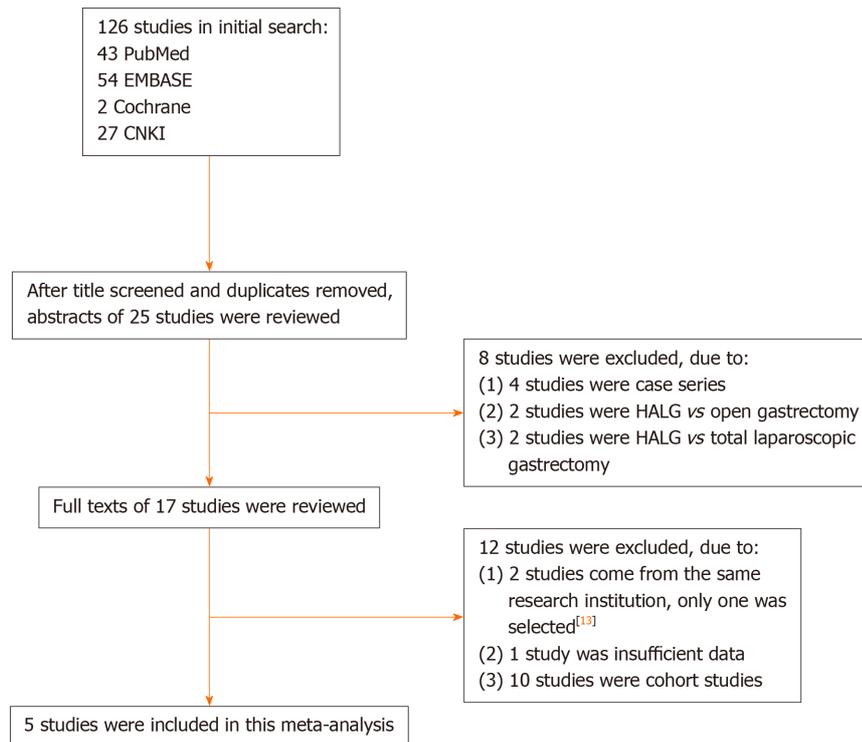


Figure 1 Flowchart of the search strategy. HALG: Hand-assisted laparoscopic gastrectomy.

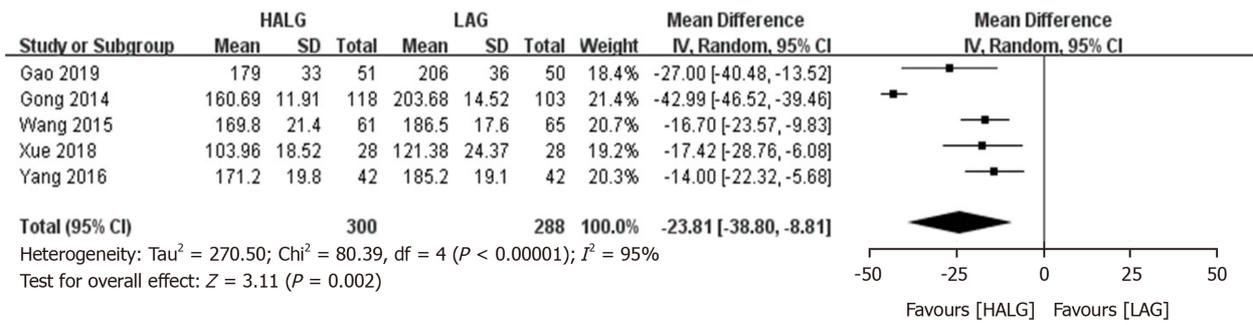
## DISCUSSION

The therapeutic effect of LAG has been confirmed for gastric cancer in previous studies<sup>[19-21]</sup>. Likewise, several studies confirmed the therapeutic effect of HALS on gastrointestinal tumors<sup>[22-24]</sup>. There are numerous similarities between HALG and LAG, such as the use of laparoscopy, a small incision, and digestive reconstruction. However, they also differ in various aspects such as the surgical procedure and the function of incision. 'Three-step HALG' has become the standardized procedure in our hospital<sup>[6,25]</sup>. The application of HALG has been gradually increasing, especially in China. Nevertheless, due to the lack of consistency across different studies, controversy exists on the therapeutic effects and advantages of HALG. In this meta-analysis, in order to improve the reliability, we only included RCTs on HALG and LAG.

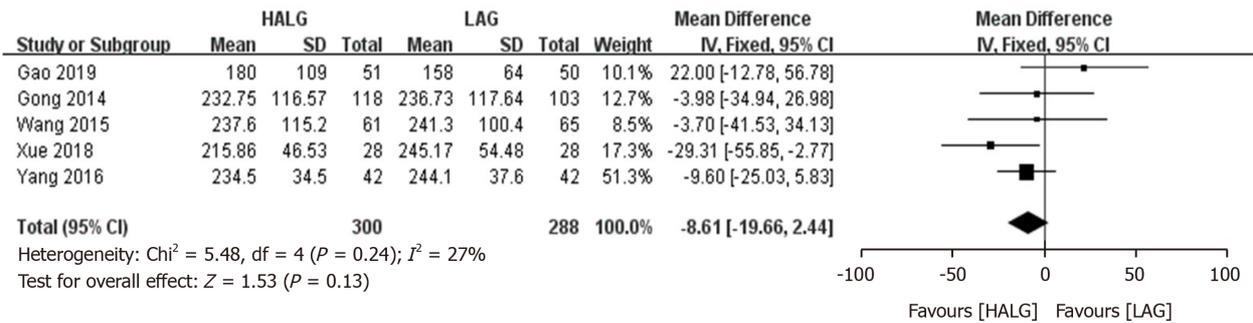
RCTs are the gold standard in study design; however, randomized controlled surgical trials, especially blinding, remain controversial, since the surgeon cannot be blinded to the procedure, and there are practical and ethical barriers to blind patients<sup>[26]</sup>. Due to the absence of blinding, five studies automatically scored poorly on the Jadad score in this meta-analysis. Although the poor-quality RCTs may be biased due to their inherent design limitations, there is no satisfactory program to resolve this issue. In addition, two of the studies did not report the exact value of the groups' baseline<sup>[16,18]</sup>, although they clearly reported that the groups were similar at the baseline in the article.

Previously, HALG has been considered the transitional bridge from traditional open

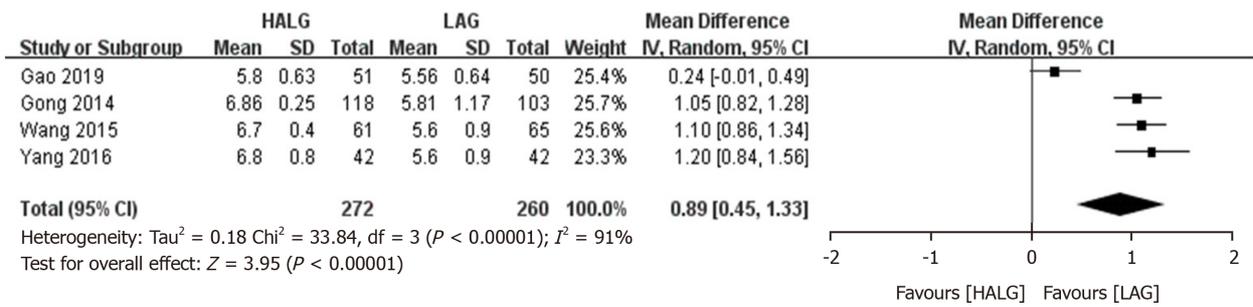
**A**



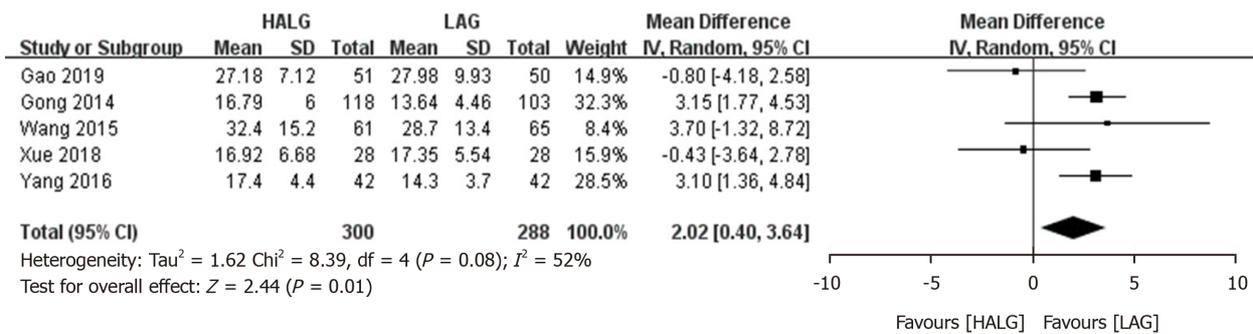
**B**



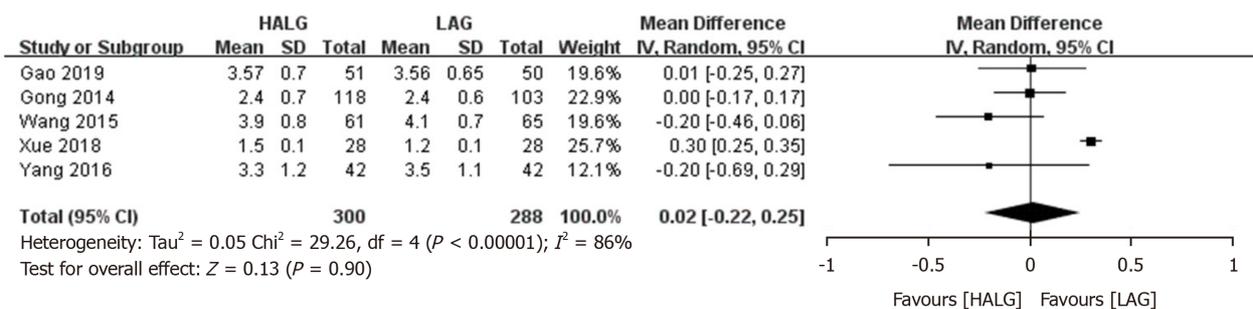
**C**

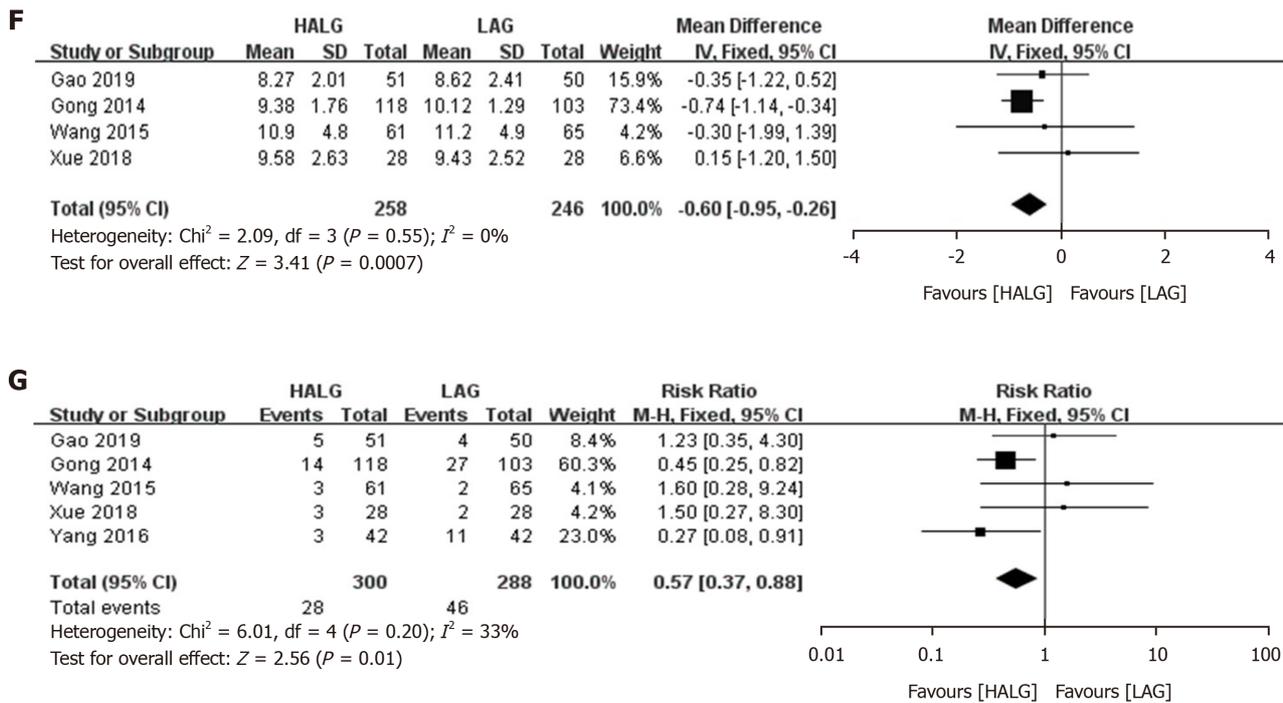


**D**

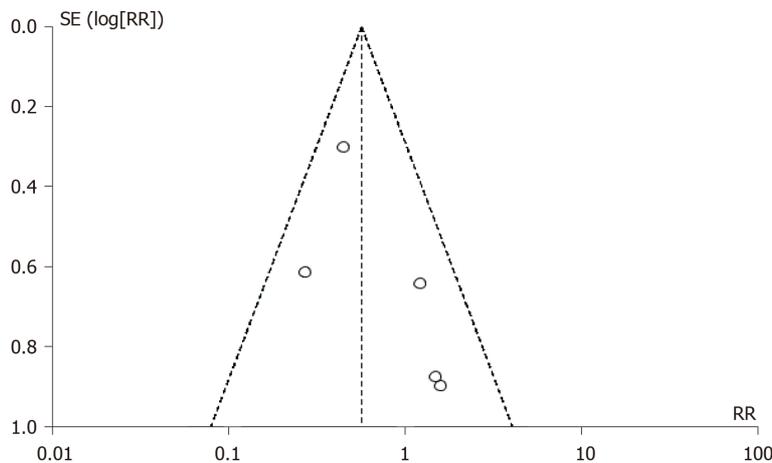


**E**





**Figure 2 Forest plots based on intraoperative and postoperative clinical data.** A: Surgery time; B: Blood loss; C: Incision length; D: Retrieved lymphatic nodes; E: Time to first flatus; F: Postsurgical hospitalization; G: Overall postsurgical complications. HALG: Hand-assisted laparoscopic gastrectomy; LAG: Laparoscopic-assisted gastrectomy.



**Figure 3 Funnel plot of the overall postsurgical complications.** RR: Risk ratio.

surgery to laparoscopic surgery<sup>[27-29]</sup>. Currently, HALG is universally used for gastrointestinal tumors in China. However, most surgeons may prejudice HALG’s minimal invasiveness because of one hand into the abdominal cavity. In fact, several studies have shown that the important prognostic indicators of HALG, with the exception of incision length, are more advantageous than those of LAG<sup>[9,27,30-32]</sup>. Additionally, HALG should not be denied as being minimally invasive just because of slightly longer incision (WMD, 0.89 cm; 95%CI, 0.45 to 1.33). There are several possible reasons for this. First, HALG is simpler for isolating the omentum, and groups 5, 6, and 12 lymph nodes under direct vision through the upper abdomen incision, so that it can greatly reduce the laparoscopic operation time. Second, the surgeon’s left hand is more agile than that of the LAG’s assistant. Third, the initial learning-curve of HALG is shorter; thus, surgeons can better acquire the skill to decrease the operation time. Fourth, the incision length is appropriate for digestive reconstruction.

Severe postsurgical complications could increase the hospitalization duration and affect the prognosis. In this meta-analysis, the rates of all postsurgical complications of HALG were lower than those of LAG, which could be attributed to the following

reasons: First, HALG have a clearer operative field to isolate groups 5, 6, and 12 lymph nodes, and to complete the digestive reconstruction by the comfortable incision. Second, due to the direct hand assistance, the important structures, particularly the splenic lymph node, could more intuitively be revealed *via* the laparoscope. Third, HALG has a lower requirement for pneumoperitoneum pressure, so that it favorably maintains the stability of the internal environment. However, those studies did not evaluate the long-term outcomes. Thus, it is important to evaluate the long-term survival of HALG in the future.

To date, surgeons have multiple options to complete gastrectomy, especially the novel totally laparoscopic gastrectomy and robotic gastrectomy. However, the reconstruction process of totally laparoscopic gastrectomy or robotic gastrectomy is difficult<sup>[33-35]</sup>. Compared with HALG, it also has a longer-learning curve to complete operation<sup>[7]</sup>. The robotic gastrectomy is similar to minimal need for experienced assistance with HALG. However, the robotic approach is not widely used because of its high price<sup>[36,37]</sup>. Compared with the cheap equipment of HALG, many hospitals cannot pay for initial purchasing costs and maintenance costs of robotic procedures, especially in undeveloped areas. Additionally, the high hospitalization costs of robotic gastrectomy also affect the choice of patients. Collectively, we still recommend this ordinary HALG to the undeveloped areas in this analysis.

Nevertheless, this study has certain limitations. First, all the included studies were conducted in China, which limited the universal application of the results. Second, all the studies are RCTs, but there are no uniform criteria and no uniform training of surgeons. Due to the poor-quality RCTs, there is an indeterminate risk of bias. Third, although the present study included all the relevant publications from our search, the sample size is still not sufficient. Fourth, three types of gastrectomy were included in this meta-analysis, and the difference between these types is ignored, which may lead to high heterogeneity.

## CONCLUSION

In conclusion, our meta-analysis suggests that HALG is a simpler and safer technique than LAG. HALG should be used as a minimal-access technique, particularly in technologically undeveloped areas. However, further high-quality RCTs with larger sample size should be conducted in order to evaluate this issue.

## ARTICLE HIGHLIGHTS

### **Research background**

Hand-assisted laparoscopic gastrectomy (HALG) is a popular operation in China, but some surgeons do not accept it as a minimal-access technique.

### **Research motivation**

If the safety and practicability of HALG can be confirmed by comparing with laparoscopic-assisted gastrectomy (LAG), HALG should be used as a minimal-access technique.

### **Research objectives**

This research aimed to assess the safety and practicability of HALG by comparing the short-term outcomes of HALG and LAG.

### **Research methods**

The electronic databases of EMBASE, PubMed, China National Knowledge Infrastructure, and Cochrane Library were thoroughly searched, and only randomized controlled trials (RCTs) comparing HALG and LAG were included.

### **Research results**

This meta-analysis included five RCTs with 600 cases. Compared with LAG, HALG reduced surgery time, hospital duration, and overall postsurgical complications, and increased the number of retrieved lymphatic nodes and incision length.

**Research conclusions**

HALG is simpler and safer technique than LAG. HALG should be used as a minimal-access technique, especially in technologically undeveloped areas.

**Research perspectives**

It is important to evaluate the long-term survival of hand-assisted laparoscopic gastrectomy in the future.

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