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APPS
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in annualized severe exacerbations at Week 24 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (*P*=0.0003)[1]

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LIBERTY ASTHMA VENTURE Study Design[2]: 210 patients were randomly assigned with oral glucocorticoid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV_1) before bronchodilator use were also assessed.

LIBERTY ASTHMA QUEST Study Design[3]: 1902 patients who were 12 years of age or older with uncontrolled asthma were randomly assigned in a 2:2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimetre. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid ; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

References: 1. DUPIXENT Summary of Product Characteristics. May 2020. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475-2485. **3.** Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496.

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. Chronic rhinosinusitis with nasal polyposis (CRSwNP): As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control(for 300mg) **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents(12-17y/o): Body weight <60 kg- initial dose of 400 mg (two 200mg injections), followed by 200 mg every other week. Body weight ≥60 kg- same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. AD Children(6-11y/o): Body weight 15Kg~<60 kg- initial dose of 300mg on Day 1 follow by 300mg on Day 15, then 300mg every 4 weeks. Body weight ≥60 kg- same dosage as adults. * The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg ~ < 60 kg based on physician's assessment. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. CRSwNP: for adult patients initial dose of 300 mg followed by 300 mg given every other week. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks. If a dose is missed, administer it asap and thereafter, resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <6 years or <15kg not been established. Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** Most common adverse reactions reported- injection site reactions, conjunctivitis, oral herpes and eosinophilia. Safety profile observed in adolescents consistent with that seen in adults. For other undesirable effects, please refer to the full prescribing information. **Preparation:** 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-22.06

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Contents

Editorial

This journal edition covers three reviews of a very diverse nature but looks at relevant issues that occur here in Asia.

The first review, is a meta-analysis of the use of traditional Chinese medication added to Western medication use for the treatment of patients with mild to moderate COVID-19 infection. Traditional Chinese medication (TCM) use is very rampant in Asia and many patients use it as an adjunct to Western treatments or even wholly for medical treatments for several disease conditions. TCM is perceived to be less harmful to the body compared with Western medications, in part due to the fact that all side effects and drug interactions have to be listed for Western medications, which is usually not the case for TCM medications.

The authors reviewed six randomised controlled trials involving the use of the TCM, Lianhua Qingwen, together with Western medications for the treatment of mild to moderate COVID-19 infections. The studies demonstrated improvement in cough and fatigue and a faster resolution of computed tomography thorax changes but not of fever. When used in mild to moderately severe patients, there was less progression to severe disease (RR = 0.57; 95% CI 0.37–0.86; P = 0.007). The TCM was well tolerated with no difference in adverse event rates compared with the control group not given TCM. The only drawback was that almost all these studies were done in adult patients and were conducted only in China.

The authors postulated a possible mechanism of action for the efficacy of the TCM was due to its anti-inflammatory properties by inhibition of mRNA expression of inflammatory cytokines triggered by the viral infection.

However, the authors also caution against the inappropriate use of the TCM when the infection presents with a "Cold Syndrome" versus a "Heat Syndrome." This TCM medication should be prescribed for patients presenting with the "Heat Syndrome" and not the "Cold Syndrome." It also should be taken only on physician's advice if the patient has liver and renal impairment. This highlights the fact that not all TCM medications can be taken indiscriminately by the public as there can be potential side effects. It also highlights the benefit of using TCM as adjunctive therapy to Western medicine.

The second review article looks at mechanical ventilation and the consequent lung injury. The use of mechanical ventilation has saved the lives of many patients with respiratory failure. However, when used incorrectly, it can result in ventilator-induced lung injury. Lung injury can be due to excessive pressure (barotrauma), high volumes (volutrauma), effects on the alveoli (atelectotrauma), and the inflammatory cytokines (biotrauma) causing stress and strain to occur within the airway and the lung parenchyma.

The alveoli function best in a non-collapsed state for good gas exchange to occur. The alveoli are kept from collapsing through the presence of surfactant and a patent airway. Atelectotrauma occurs when there is a disruption of surfactant production and decreased airway patency caused by mucus plugging.

Volutrauma occurs when high volumes are delivered resulting in overdistension of the lung and alveolar epithelial damage. Infant lungs are more compliant and the use of low tidal volume ventilation (5–6 mL/kg) may reduce lung injury in these infants. The combination of both atelectotrauma and volutrauma due to over-ventilation can result in greater lung injury. Appropriate positive end-expiratory pressure (PEEP) should be applied to keep the alveoli from collapsing.

Barotrauma is due to the use of high peak inspiratory pressures being used. A high plateau pressure of >28 cmH_2O has been found to lead to lung injury. Again, appropriate PEEP should be applied to keep the alveoli from collapsing.

Mechanical ventilation itself can lead to the release of inflammatory cytokines, which can result in biotrauma.

The authors suggest that the majority of ventilator-induced lung injury is due to the unphysiological stress and strain inflicted on the lung. Lung protective strategies include the use of a higher PEEP, low tidal volume, and lower driving pressure <20 cmH_2O with permissive hypercapnia. In addition, prone positioning may be useful to improve oxygenation, decrease atelectasis, and improve the clearance of secretions.

In using mechanical ventilation to save lives, we must also bear in mind the long-term sequelae of ventilator-induced lung injury. Appropriate ventilation strategies to achieve adequate ventilation without inflicting further damage should be adopted.

The third review article looks at the impact of electronic nicotine delivery systems (ENDS) or e-cigarettes on adolescent respiratory health in Hong Kong. Smoking prevalence has decreased from 23.3% in the 1980s to 9.5%

in 2021 but the use of e-cigarettes and tobacco products has risen slightly in the adolescent age group from 0.1% in 2019 to 0.3% in 2021 and from 0.9% in 2019 to 1.1% in 2021, respectively. E-cigarettes were first marketed as a safer alternative to traditional cigarettes and could be used to help cigarette smokers quit smoking. However, the safety of these devices and their efficacy as smoking cessation tools have not been well studied. Recent articles suggest that there can be detrimental effects on the lung with e-cigarettes causing e-cigarette or vaping product use associated lung injury.

A review of the literature finds that the use of ENDS use is associated with increased respiratory impedance and airway resistance. Cigarette smoking decreases exhaled nitric oxide, which may have an impact on defence against respiratory tract infections. Long-term effects of ENDS use can result in hypersensitivity pneumonitis, airway remodelling, and chronic obstructive pulmonary disease. Prolonged use of ENDS also results in nicotine dependence similar to traditional cigarettes.

In Hong Kong, ENDS use is regulated under the smoking (public health) ordinance, which prohibits the sale, distribution, and advertisement of "alternative smoking products." However, the possession of ENDS for personal use is not regulated, making it easy for adolescents to access these products through alternative sources. Given the potential harm that the use of e-cigarettes has, more should be done by the governments to educate the public and in particular the children and adolescents on the ill effects of ENDS use and also to limit accessibility to these products.

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Conflicts of interest
There are no conflicts of interest.

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Traditional Chinese Medicine (Lianhua Qingwen) as an Add-on to Western Medicine for Mild to Moderate COVID-19 Patients: A Meta-analysis

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Abstract

Background: Proprietary traditional Chinese medicine (TCM) such as Lianhua Qingwen (LQ) has been promoted to be an over-the-counter product for treating infectious diseases including COVID-19. This meta-analysis aimed to evaluate the efficacy of LQ in adults with mild or moderate COVID-19 diseases. **Materials and Methods:** The authors conducted the literature search using six electronic databases (Chinese and English) from the inception dates of the different database to October 31, 2022, using search for relevant keywords, that is, "severe acute respiratory syndrome coronavirus 2," "COVID-19," "Lianhuaqingwen," and "Lianhua Qingwen" to identify randomized controlled trials (RCTs). Three reviewers independently identified studies, extracted the data, and assessed study quality. All analyses were conducted on RevMan 5.3. **Results:** A total of 6 RCT studies involving patients with COVID-19 were identified according to the inclusion and exclusion criteria. The quality of included studies was moderate. LQ was effective in improving overall clinical efficacy (RR = 1.25; 95% CI: 1.14–1.36; $P < 0.001$), and relieved three features, that is, cough (WMD = –2.04; 95% CI: –3.92 to –0.17; $P = 0.03$), fatigue (WMD= –2.58; 95% CI: –3.45 to –1.71; $P < 0.001$), and chest CT resolution (RR = 1.21; 95% CI: 1.02–1.43; $P = 0.03$) but not resolution of fever (WMD = –0.46; 95% CI: –1.54 to 0.62; $P = 0.40$) among adults with mild or moderate COVID-19. LQ was also effective in reducing the rate of conversion to severe cases (RR = 0.57; 95% CI: 0.37–0.86; $P = 0.007$). The adverse events rate (RR = 0.74; 95% CI: 0.40–1.37; $P = 0.35$) were similar between LQ group and the control group. **Conclusion:** This meta-analysis of six RCT shows that the Lianhua Qingwe (LQ) as an add-on to Western medicine achieves a higher overall clinical efficacy, faster resolution of cough, fatigue and chest CT changes than Western medicine alone in COVID patients. LQ is also effective in reducing the rate of conversion to severe cases. Further double-blinded placebo-controlled randomized studies are warranted for LQ as a stand-alone treatment for the "heat" subtype of mild to moderate COVID diseases.

Keywords: COVID-19, Lianhua Qingwen, traditional Chinese medicine

Introduction

The coronavirus disease 2019 (COVID-19) pandemic was a global crisis caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] At the time of writing, COVID-19 was the greatest threat to global public health.[2] Like many respiratory viruses, the most common symptoms in patients with COVID-19 were fever, cough, and fatigue affecting both adults and children.[3] In more severe cases, patients may have dyspnea, bilateral lung infiltration, and hemodynamic instability.[1,4]

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Vaccines were now available to prevent more severe complications of COVID and death.[5,6] Specific antiviral drugs were available for treatment of COVID.[7,8] Traditional Chinese medicine (TCM) has been used in the treatment of patients with COVID-19 in China.[9-15] A total of 60,107 confirmed cases used TCM as treatment of COVID-19.[16] Among the TCM, Lianhua Qingwen (LQ) was reported to be efficacious in the treatment of influenza by reducing the severity of illness and the duration of symptoms including fever, cough, sore throat, and fatigue.[17] It is a manufactured product of TCM (Lianqiao, Jinyinhua, Zhimahuang, Chaoxingren, Shigao, Banlangen, Guanzhong, Yuxingcao, Guanghuoxiang, Dahuang, Hongjingtian, Bohenao, and Gancao) that could significantly inhibit proliferation of virus as well as exhibiting anti-inflammatory activity.[18] LQ was reported to be effective in reducing respiratory symptoms, fever, and hospital stay.[18]

Recently, network pharmacology by Xia *et al*. indicated that LQ might target the Akt1 gene with six compounds (beta-carotene, kaempferol, luteolin, naringenin, quercetin, and wogonin) to reduce tissue damage induced by COVID-19.[19] At molecular levels, Li *et al*. showed that LQ inhibited SARS-CoV-2 replication in Vero E6 cells, resulted in abnormal intracellular virion morphology, and reduced the mRNA expression of pro-inflammatory cytokines, that is, mTNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) at a concentration-dependent manner *in vitro*.[20] Meta-analyses concluded that addition of LQ to Western medicine in patients with COVID-19 had higher clinical efficacy than Western medicine alone, with a faster resolution rate of chest computer tomography (CT) abnormalities and a lower rate of progression to severe disease.[21] LQ was also shown to increase the resolution rate of fever, cough, fatigue, muscle pain, sputum, nasal congestion, runny nose, and chest tightness of COVID-19. This meta-analysis sought to investigate the efficacy of LQ in mild or moderate COVID-19. The proper use of LQ in accordance with the principle of TCM was also explained by the authors who are TCM practitioners, HDL, WBF, and CHY.

Materials and Methods

Literature search

The authors (S.Y.L., Y.T.A., and C.H.Y.) searched Pubmed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) database, Chinese Science and Technology Journals Database (VIP), Wanfang Database from inception of the databases up to October 31, 2022. The key terms of literature search were "severe acute respiratory syndrome coronavirus 2" or "COVID-19" or "SARS-CoV-2" or "2019-nCoV" and "Lianhuaqingwen" or "Lianhua Qingwen" or "lian-hua-qing-wen" (Appendix Tables A1–A6). Three reviewers, S.Y.L., Y.T.A., and C.H.T., independently identified studies, extracted the data, and assessed study quality. In order to avoid omissions, the bibliography of potential articles was also searched manually.

Eligibility criteria

Studies were selected based on the following criteria: (1) Randomized controlled trials (RCTs); (2) participants were diagnosed with mild or moderate COVID-19. The following types of studies were excluded: (1) absence of control arm; (2) retrospective studies; (3) trials with more than one Chinese patent medicine; (4) animal trials.

Outcome measures

(1) Overall clinical efficacy was defined as the proportion of the total number of patients whose clinical symptoms improved with improvement in laboratory results.
(2) Time to recovery of fever was defined time of returning to normal temperature, that is, ≤37.8 °C.
(3) Time to recovery of cough was defined as time of complete remission of cough.
(4) Time to recovery of fatigue was defined as time of complete remission of fatigue.
(5) Chest computed tomographic imaging recovery rate was defined as improvement in chest CT images.
(6) Rate of deterioration to severe COVID.
(7) Adverse reaction rate.

Data extraction

Three researchers (C.H.Y., S.Y.L., and Y.T.A.) independently extracted the following information from the included studies: lead author, year of publication, country of origin, sample size, age, gender, disease severity, interventions, and treatment duration.

Quality assessment

Two researchers (S.Y.L. and C.H.Y.) independently assessed the quality of the included studies by the Cochrane Collaboration risk of the bias assessment tool. The third reviewer WBF was consulted in case of disagreement. Jadad scale was used to assess quality.[22]

Statistics analysis

Continuous and dichotomous outcome measures were extracted from original studies. Continuous variables were represented by weighted mean difference (WMD) and 95% confidence interval (95% CI), while dichotomous variables were represented by risk ratio (RR) and 95% CI. The heterogeneity between studies determined the model (a fixed-effects or a random-effects model) used for the meta-analysis. Heterogeneity of all studies was evaluated through the I^2 test (values of 25%, 50%, and 75% were considered to represent low, medium, and high degrees of

heterogeneity, respectively) and the Q test (heterogeneity was considered statistically significant when $P < 0.1$). If $P > 0.1$ and $I^2 < 50\%$, fixed-effect model was selected, while $P \leq 0.1$ and $I^2 \geq 50\%$, heterogeneity between included studies was identified, random-effect model was applied. Potential publication bias risk was assessed with funnel plots. The meta-analysis was conducted on RevMan 5.3, and a P value < 0.05 was considered to indicate statistical significance.

Results

Study selection

The literature selection process is described in Figure 1 in detail. From the searches on 6 electronic databases, 545 records were identified initially. After removing 244 duplications, screening of the remaining 301 records yielded 44 potentially eligible studies. By screening the full text, 38 studies were excluded because they did not fulfill the inclusion criteria. Finally, 6 studies were included [Figure 1].

Characteristics of included studies

Table 1 presented the characteristics of the included studies. All studies were published between 2020 and 2021.[23-28] The patients recruited had either mild or moderate COVID-19. All 6 included studies were conducted in China and 2 were published in English. All were RCT, and the study durations were 7–21 days. The total sample size was 914 (493 males, 421 females), sample size of studies ranged from 60 to 295. The mean age of patients was between 42.4 and 53.9. One study included children. In these RCT, control groups received Western medicine (such as interferon-α, lopinavir/ ritonavir, arbidol, and other antivirals). While LQ group patients received LQ treatment in addition to Western medicine of the control group. The formulation of LQ included capsules (0.35 g/capsule) and granules (6 g/bag). The duration of treatment varied from 7 to 21 days.

Quality of including studies

The quality of included studies was shown in Table 1. Five studies described the random sequence

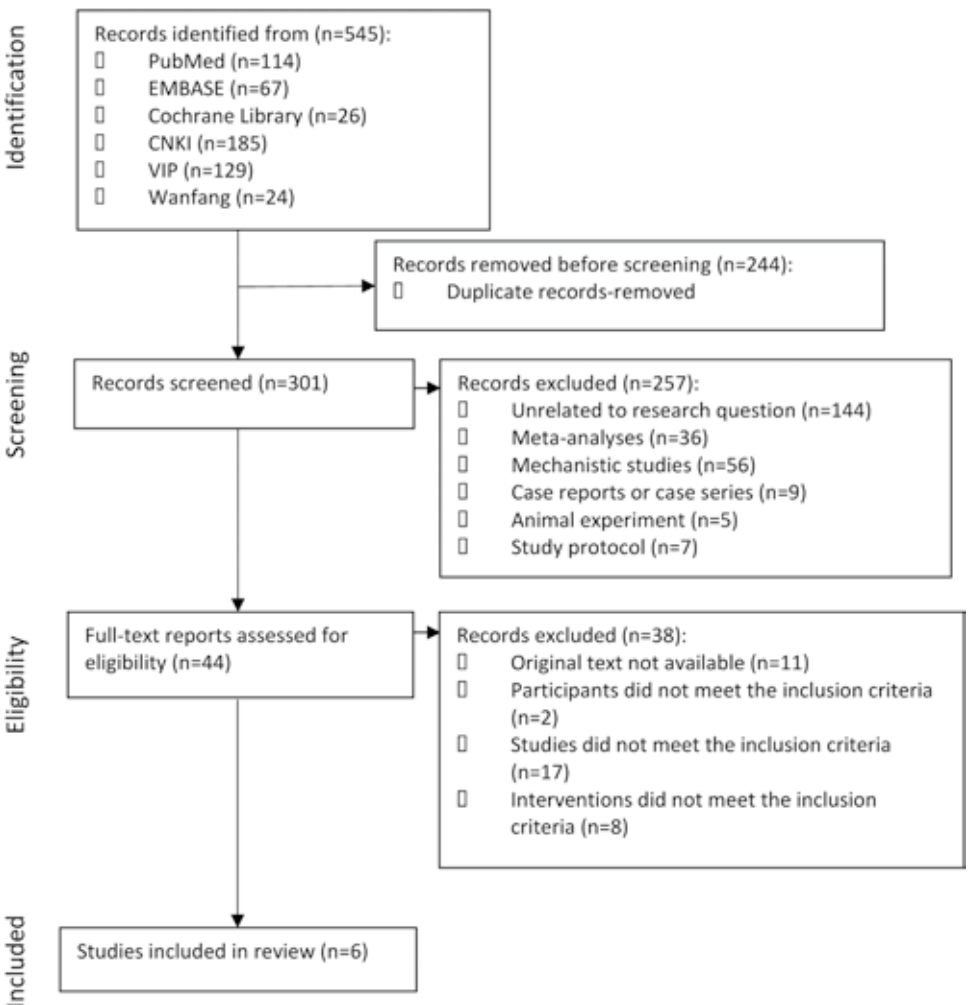

Figure 1: Flow chart of study selection and indentification (from inception to October 31, 2022)

Table 1: Studies included in this review (n = 6)

Authors (year) [ref.]	City	COVID-19 type	Study type	Age range	Age		Treatment	Control	Jadad score
					Treatment group mean ± SD (M:F)	Control group mean ± SD (M:F)			
Chen CW (陈超武) (2021)[23]	Shenzhen	Mild	RCT	19-62	49.5±5.16 (M18:F12)	50.2±5.1 (M17:F13)	Control + LQ capsule, 4 capsules, tid. (0.35 g/capsule) Duration: NA	Recombinant human interferon α2b (5 million U, arm, bid, < 10d); Lopinavir and ritonavir tablets (2 slices/time, oral, bid, < 10d) For patient with clinical improvement: Ribavirin	3/5
Hu K (2020)[24]	Nine provinces throughout mainland China	Ordinary	RCT	>18	50.4±15.2 (M79:F63)	51.8±14.8 (M71:F71)	Control + LQ granules, 4 capsules, tid. (0.35 g/capsule) Duration: 14 days	Antiviral therapy (e.g., oseltamivir), antibacterial therapy, supportive therapy	3/5
Liu W (刘武) (2021)[25]	Wuhan	Mild	RCT	15-80	48.5±4.6 (M16:F28)	48.4±4.5 (M15:F29)	Control + LQ Capsule1.4 g, oral, tid. Pneumonia Agreement 2 1 dose, oral, bid, Duration: 21 day	Arbidol (0.2 g, oral, tid.); Oseltamivir (0.015 g, oral, bid) Duration: 21 day	3/5
Xiao MZ (2020)[26]	Wuhan	Mild	RCT	18-85	52.9±14.0 (M35:F23)	53.9±13.9 (M35:F28)	Control + LQ granules, 1 bag, tid. (6g/bag) Duration: 14 day	Antiviral therapy, antibacterial therapy Duration: 14 day	3/5
Yu P (余平) (2020)[27]	Wuhan	Mild/ moderate	RCT	18-75	48.3±9.6 (M82:F65)	47.3±8.7 (M89:F59)	Control + LQ granules, 6 g, tid. Duration: 7 days	Antiviral therapy (arbidol hydrochloride 0.2 g tid.), antibacterial therapy (moxifloxacin t 0.4 g daily), supportive therapy (ambroxol30 mg tid.)	3/5
Tan D (谭杜勋) (2021)[28]	Guangzhou	Mild/ moderate	RCT	18-60	42.4±0.2 (M19:F14)	42.5±0.1 (M17:F16)	Control + LQ Capsule1.4 g, bd Duration: NA	Interferon Arbidol, Ritonavir, systemic steroid	3/5

Abbreviation: RCT = Randomized control trial; LQ = Lianhua Qingwen

Note: Treatment group = LQ + Western medicine; Control group = Western medicine

generation[23-27] and two studies described the methods used for allocation concealment.[24,26] None of the studies described the blinding of participants, personnel, and outcome assessment. All studies adequately addressed incomplete outcome data,[23-28] and two studies registered the protocol and reported the registration information.[24,26] The Jaded scale is a five-point scale used to evaluate the quality of randomized trial. A score of three points or more indicates high quality.[22] In the current meta-analysis, all included studies had at least a score of three points, therefore, the quality of included studies was high.

Efficacy outcomes

Overall clinical efficacy

Four RCT[24,25,27,28] including 733 patients compared the clinical efficacy between the LQ group and control group, 366 patients in the LQ group and 367 in the control group. There was a low level of heterogeneity (I^2 = 0%, P = 0.68) between studies for clinical efficacy, and a fixed effects model was used for the analyses. The meta-analysis showed that the clinical efficacy in the LQ group was significantly higher than the control group (RR = 1.25; 95% CI: 1.14–1.36; P < 0.001) [Figure 2A].

Time to recovery of fever

Two RCT[23,24] including 341 cases compared the time to resolution of fever in LQ and control groups, with 170 patients in the LQ group and 171 in the control group. There was statistical heterogeneity among the trials (I^2 = 98%, P < 0.001). The meta-analysis showed no significant difference on time of fever resolution between LQ and control group (WMD = –0.46; 95% CI: –1.54 to 0.62; P = 0.40) [Figure 2B].

Time to recovery of cough

Two RCT[23,24] including 341 cases compared the time to recovery of cough in LQ and control groups, with 170 patients in the LQ group and 171 in the control group. There was statistical heterogeneity among the trials (I^2

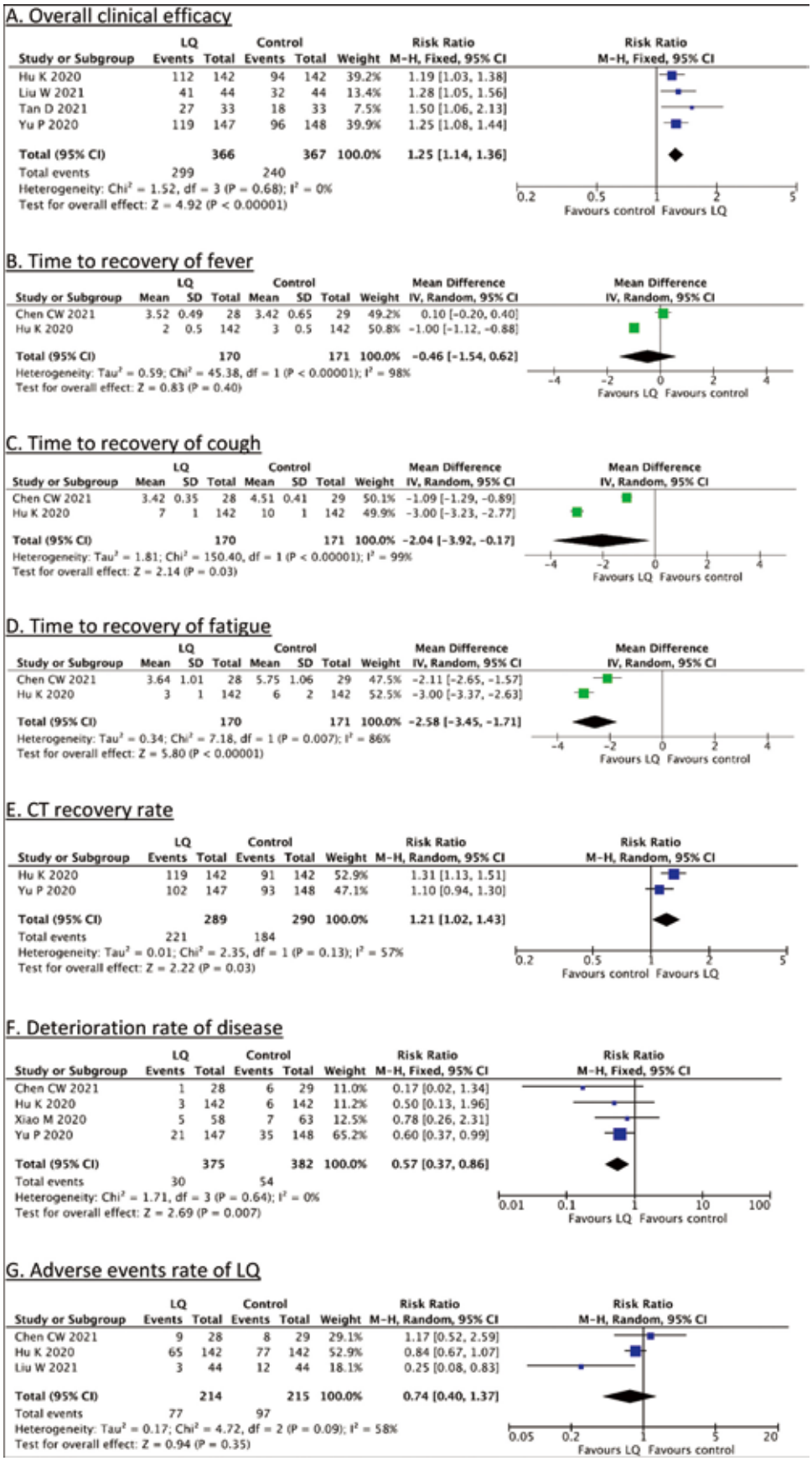

Figure 2: Comparison of outcomes between LQ group and control group. (A) Overall clinical efficacy. (B) Time to recover from fever. (C) Time to recover from cough. (D) Time to recover from fatigue. (E) CT recovery rate. (F) Deterioration rate of disease. (G) Adverse events rate of LQ

= 99%, $P < 0.001$). The meta-analysis showed that LQ group was significantly shorter time of cough than the control group (WMD= –2.04; 95% CI: –3.92 to –0.17; $P = 0.03$) [Figure 2C].

Time to recovery of fatigue

Two RCT[23,24] including 341 cases compared the time to resolution of fatigue in LQ and control groups, with 170 patients in the LQ group and 171 in the control group. There was statistical heterogeneity among the trials (I^2 = 86%, $P = 0.007$). The meta-analysis showed that LQ group was significantly shorter time of fatigue than the control group (WMD = –2.58; 95% CI: –3.45 to –1.71; $P < 0.001$) [Figure 2D].

CT resolution rate

Two RCT[24,27] including 579 cases compared the chest CT resolution rate in LQ and control groups, with 289 patients in the LQ group and 290 in the control group. There was medium level of heterogeneity among the trials (I^2 = 57%, $P = 0.13$). The meta-analysis showed that LQ group was significantly faster chest CT resolution than the control group (RR = 1.21; 95% CI: 1.02–1.43; $P = 0.03$) [Figure 2E].

Deterioration rate of disease

Four RCT[23,24,26,27] including 757 cases compared the deterioration rate in LQ and control groups, with 375 patients in LQ group and 382 in control group. There was no statistical heterogeneity among the trials (I^2 = 0%, $P = 0.64$). The meta-analysis showed that LQ group was significantly reduced the rate of deterioration to severe cases (RR = 0.57; 95% CI: 0.37–0.86, $P = 0.007$) [Figure 2F].

Adverse event rate of LQ

Three RCT[23-25] including 429 cases compared the adverse events rate between LQ and control groups, with 214 patients in the LQ group and 215 in the control group. There was statistical heterogeneity among the trials (I^2 = 58%, $P = 0.09$). The meta-analysis showed that LQ group had similar adverse event rate to the control group (RR = 0.74; 95% CI: 0.40–1.37, $P = 0.35$) [Figure 2G].

Publication bias

We assessed the potential publication bias by using funnel plots. The asymmetry of the funnel plots suggested that the study might have a moderate publication bias, which might be related to the small number of the included studies [Figure 3].

Discussion

LQ was patented in 2003 in China and the formula was approved in 2005 for Phase II clinical trial by US FDA. It was recommended by the National Health Commission for the treatment of COVID-19.[29] The formulation has been used in treating infectious diseases including influenza and COVID-19.[14,17] This meta-analysis of six RCT s showed that the LQ was efficacious in relieving cough and fatigue among patients infected with COVID-19 when added to the Western medicine. Our findings concurred with an earlier meta-analysis which purported to conduct a meta-analysis of two RCT, but the RCT included were in fact not randomized. Their finding also demonstrated the efficacy of LQ in reduction of cough and fatigue.[30] Currently, there was no high-level evidence from RCTs that any herbal drugs targeting SARS-CoV-2 were efficacious.[1,7] Nevertheless, TCM was used at clinics in China and reported to have an increased cure rate in patients with COVID-19.[12,18] Clinical deterioration occurred in more than 50% of older patients (aged ≥65 years) with COVID-19.[31] The current meta-analysis showed that LQ was effective in reducing the rate of deterioration to severe disease when added to Western medicine in mild to moderate COVID. Moreover, the current meta-analysis demonstrated that LQ was safe as the side effects were not higher than that of the Western medicine control arm.

LQ reduced symptom severity in patients with COVID-19.[21] Liu *et al*. reported that LQ combined with Western medicine had a higher overall effective rate (RR = 1.16, 95% CI: 1.04–1.30, $P = 0.01$) for patients with mild to moderate COVID-19 (RR = 0.59, 95% CI: 0.37–0.94, $P = 0.03$).[14] However, the meta-analysis included only three RCTs with other studies being three retrospective case control studies, and two retrospective case series with poor quality, which might affect validity of the results. Another analysis by Hu *et al*. reported that improvements in flu-like symptoms (OR = 3.18, 95% CI: 2.36–4.29, $P < 0.001$), shortness of breath (OR = 10.62, 95% CI: 3.71–30.40, $P < 0.001$) were associated with the LQ treatment. However, it included studies other than RCTs.[32] Zeng *et al*. identified two retrospective studies and reported that the resolution rate of the main clinical symptoms was higher in the LQ group.[30] These results indicated a possible effectiveness of LQ treatment although the results might not be accurate given the poor quality of studies included.

The current study, which included six RCTs with high quality, sought to evaluate the efficacy of LQ in mild to moderate COVID-19. Results of this meta-analysis showed that the LQ as an add-on to Western medicine was significantly better than Western medicine alone in the disappearance of cough and fatigue, CT resolution rate, and deterioration rate.

In addition, this meta-analysis was the first meta-analysis that included only prospective RCTs, in contrast to previous meta-analysis which included nonrandomized studies.[33] COVID-19 was characterized by an increase in pro-inflammatory cytokines production. The presence of an early inflammatory response was hypothesized to

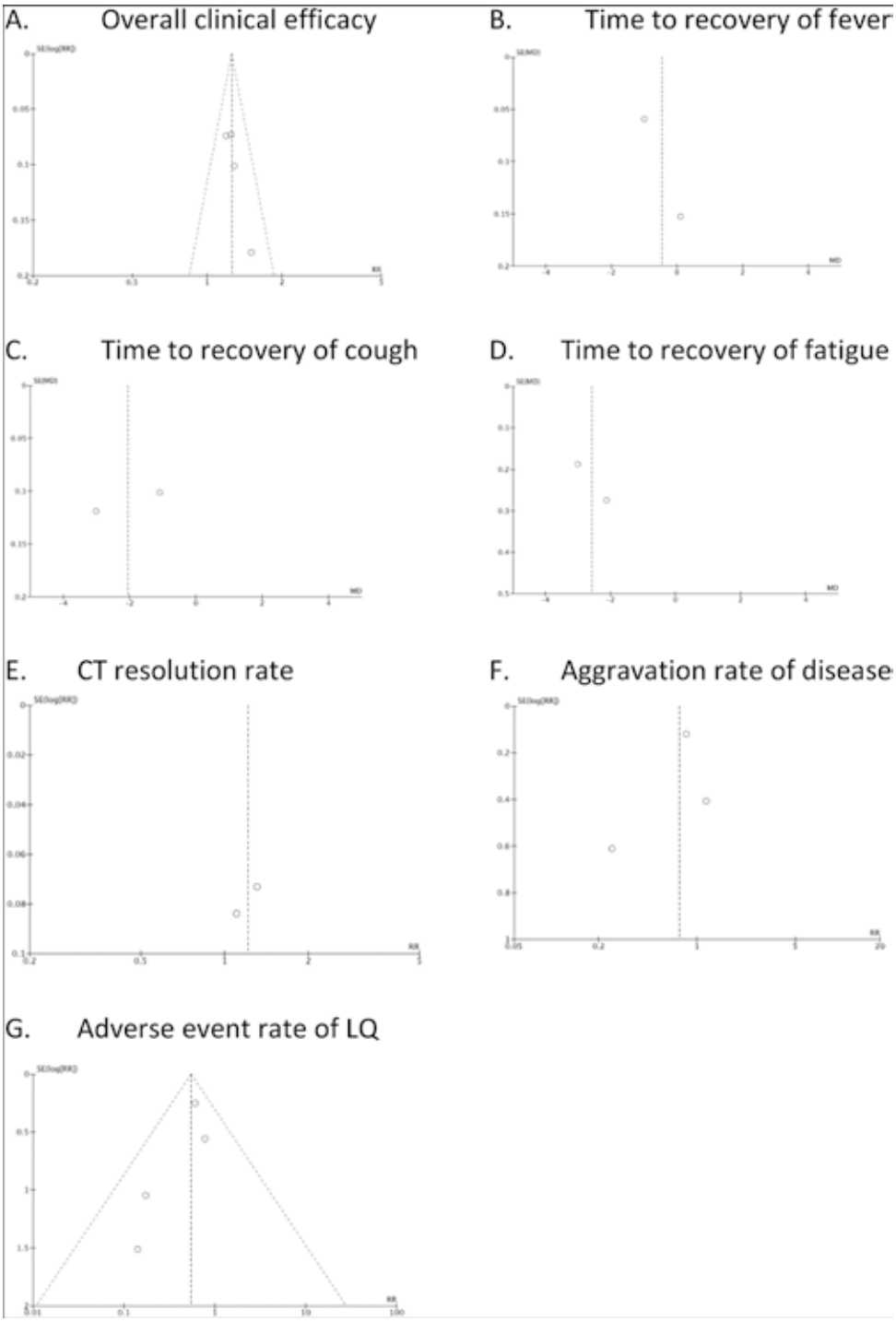

Figure 3: Funnel plots of outcomes. (A) Overall clinical efficacy. (B) Time to recover from fever. © Time to recover from cough. (D) Time to recover from fatigue. (E) CT resolution rate. (F) Aggravation rate of disease. (G) Adverse event rate of LQ

be the underlying mechanism of acute cough in COVID-19 infection.[34] Therefore, we believe that the relief of particular COVID-19 symptoms by LQ may be due to its anti-inflammatory properties. For instance, acute cough can be alleviated quicker because of LQ's ability to effectively diminish the inflammatory effect of the virus. For fatigue in COVID-19, chronic low-grade inflammation and mitochondrial dysfunction were reported to be a potential mechanism.[35] Therefore, the anti-inflammatory impact of LQ may also contribute to the relief of COVID-19-associated fatigue symptoms.

The mechanism of LQ on other respiratory viruses might provide further insight into its mechanism of action in COIVD. Yang *et al.* reported that LQ displayed the effectiveness of antiviral and inhibited the mRNA

expression of inflammatory cytokines against influenza B infection in the mouse model.[36] Ding *et al*. reported that LQ exerted broad-spectrum effects on various influenza viruses by inhibiting viral propagation and impacting immune function.[37] Furthermore, Duan *et al*. reported that LQ, compared with oseltamivir, achieved a similar reduction of the duration of illness and duration of viral shedding in patients with influenza A (H1N1) virus infections.[17] These results indicated that LQ has a broad-spectrum inhibitory effect on influenza viruses by inhibiting viral propagation, impacting immune function, and decreasing inflammatory cytokines. With such antiviral effect on influenza B, it was proposed that LQ might have similar effect on COVID-19.[20]

In 2020, Scotland's COVID-19 disability-adjusted life years (DALYs) were significant enough to be considered the second largest cause of illness and injury, with only ischemic heart disease having a greater impact on population health.[38] In fact, the three most prevalent symptoms of COVID infections were fever (81.2%), cough (58.5%), and fatigue (38.5%).[39] This meta-analysis demonstrated that the addition of LQ to Western medicine was effective in shortening the duration of the two common COVID symptoms. LQ also significantly reduced the rate of deterioration of mild/ moderate COVID-19 to severe cases, hence increasing DALYs by lowering the year of life lost (YLL) and year of life lost due to disability (YLD).

Moreover, the cost of LQ is much lower than conventional COVID-19 antiviral. In Hong Kong, a 5-day course of paxlovid was US$ 529[40] and a 5-day course of molnupiravir cost was US$ 700,[41] compared with a 7-day course of LQ being only US$ 22. Hence, the use of LQ for the treatment of mild to moderate COVID would be a more affordable alternative.

The fundamental therapeutic principle of Chinese medicine is the differentiation and treatment of syndromes; if this rule is ignored, treatment efficacy may be compromised, and adverse effects may potentially manifest. Forsythiae Fructus, Lonicerae Japonicae Flos, Isatidis Radix, Houttuyniae Herba, and Rhei Radix et Rhizoma make up the majority of the medicinal ingredients in LQ. LQ is considered as a heat-clearing medicine and only COVID with this heat subtype would respond to LQ. The current meta-analysis demonstrated that the use of LQ was not associated with a rise in adverse reactions compared to the use of Western medicine alone. This corroborated a meta-analysis on the clinical safety of LQ conducted by Sun *et al*.,[42] which found that the adverse reaction rate of LQ was similar to that of the control group with conventional Western medicine. The most common adverse effect of LQ was gastrointestinal symptoms like nausea, vomiting, abdominal discomfort, diarrhea, stomach discomfort, and appetite loss. This finding was corroborated by a second meta-analysis conducted by Peng *et al*.,[43] which reported that the gastrointestinal side effects of LQ occurred more frequently when the drug was given with an empty stomach. There was no evidence that LQ was associated with deranged liver functions. According to the meta-analysis conducted by Sun *et al*.[42] and Peng *et al*.,[43] liver-related adverse effects of LQ were uncommon (0.01%). In the meantime, Fan *et al*.[44] and Barrera *et al*.[45] reported that COVID-19 patients may present with abnormal liver function.

As LQ was available over-the-counter, the public may not use it properly and it is imperative that the indications for LQ in the management of COVID should be clearly spelled out. Misuse of LQ without comprehending the TCM principle of syndrome differentiation and therapy may lead to an increase in the frequency of adverse reactions. The "Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management"[46] was published by the National Health Commission of the People's Republic of China. In order to promote the use of LQ around the world, the authors presented below a brief note[47] about the appropriate use of LQ in COVID.

LQ is mainly composed of heat-clearing medication, so it is only applicable for the treatment of COVID-19 patients with heat syndrome. Common symptoms of heat syndrome include heat intolerance, dry mouth, sore throat, yellow sputum, sweating, constipation, decreased urine production with dark yellow urine color, red tongue, and yellow tongue fur.[48]

In order to facilitate reader comprehension, the authors developed a rating system to evaluate the application of LQ [Table 2]. If the heat score is equal or greater than 9, LQ may be utilized for COVID-19 therapy. If the heat score was less than 9 points, LQ should only be used after consulting a TCM practitioner. As LQ is a medication for "clearing heat," it cannot be administered to COVID-19 patients presenting with "cold syndrome." Common manifestations of "cold syndrome" include white, thin sputum, loose stools (types 6 and 7 on the Bristol stool scale),[49] and increased, clear urine. If the aforementioned symptoms occur, LQ should not be taken without first consulting a TCM practitioner.

According to the contraindications section of the LQ user guide, people with impaired liver and renal function must use LQ under the supervision of a physician. LQ included Lonicera japonica and Glucose 6 phosphate dehydrogenase deficient (G6PD) patients should not take LQ. Ephedra in LQ, is associated with higher blood pressure, patients with uncontrolled severe hypertension should also avoid taking LQ.

LQ could be used for 3–5 days and discontinued after the symptoms have subsided. LQ should also be stopped if there is loose stool. The adult dose was specified, but the dosage for children was not. Currently, there is limited data on the efficacy and safety of LQ usage in children. According to Fong *et al*.,[50] the LQ dose for children

Table 2: Heat score for COVID-19

Symptoms	Score
Heat intolerance	1
Sweatiness	1
Red tongue[48]	1
	
Dry throat	2
Sore throat	2
Yellow sputum	2
Dry and hard stool[a],[49]	2
Decreased urine production	2
Dark yellow urine	2
Yellow tongue fur[48]	2
	
Total Score (≥ 9: suitable for LQ usage)	

[a]Bristol Stool Scale: TYPE 1&2 Type 1: Separate hard lumps, like nuts. Type 2: Sausage-shaped but lumpy

should be 2 g (under 3 years old), 3 g (3–6 years old), and 6 g (6–14 years old) three times a day. In addition, data on the drug–drug interaction of LQ are limited. Therefore, further studies should be conducted on the drug-drug interaction of LQ.

In all the included paper for the current meta-analysis, COVID-positive patients with mild to moderate symptoms were recruited without subtypes differentiation to heat or cold type. Hence, the unsuitable subtype patients might be included in reported studies and might not respond to LQ. Therefore, the efficacy of LQ in the reduction of symptom duration might have been underestimated. If only the suitable subtypes of patients were included, the efficacy of LQ might be higher.

This study had several limitations. All the RCTs were conducted in the Chinese population so that the results may not be generalizable to other ethnic groups. The details of methodology of some RCTs were unclear and performance bias and detection bias might exist. Due to the urgency of severe public health concerns, open-label research without placebo control was conducted in all the included papers. This may lead to bias on the part of patients and researchers, resulting in inaccurate findings. Future research should be conducted in a double-blind placebo-controlled manner that include only the "heat" subtype of COVID and pediatric study should also be undertaken.

Conclusion

This meta-analysis of 6 RCT studies shows that the LQ formation as an add-on to Western medicine is efficacious in relieving cough, fatigue, and CT scan resolution rate but not fever among patients with mild to moderate COVID-19. LQ is also effective in decreasing the deterioration rate of patients with mild or moderate COVID-19 to severe COVID-19. LQ is also found to be safe. Further research is warranted for the usage of LQ as a stand-alone treatment in COVID patients as well as its use in children as current data in data are sparse. All future studies should only include the heat subtype of mild to moderate COVID.

Declaration

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Ethical approval and consent to participate

This is a meta-analysis article and ethical approval or consent is irrelevant.

Human and animal rights

This is a meta-analysis article and human and animal rights are irrelevant.

Consent for publication

This is a meta-analysis article and consents is irrelevant.

Statement of availability of data and materials

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Conflicts of interest

There are no conflicts of interest.

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Appendix

Table A1: Search strategy of Pubmed

Serial No.	Strategy
1	((coronavirus[MeSH Terms]) OR (coronavirus)) OR ("severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [All Fields] OR "COVID-19" [All Fields] OR "COVID 2019" [All Fields] OR "2019-nCoV" [All Fields] OR "2019nCoV" [All Fields] OR "SARS-CoV-2" [All Fields] OR "coronavirus disease-19" [Title/Abstract])
2	"Lianhuaqingwen" [Supplementary Concept] OR "Lianhua Qingwen" [Title/Abstract] OR "Lianhuaqingwen" [Title/Abstract] OR "lian-hua-qing-wen" [Title/Abstract]
3	#1 AND #2

Table A2: Search strategy of Embase

Serial No.	Strategy
1	'coronavirus disease 2019'/exp
2	'covid-19':ab,ti OR 'covid 19':ab,ti OR 'covid-19 virus disease':ab,ti OR 'covid 19 virus disease':ab,ti OR 'covid-19 virus diseases':ab,ti OR 'disease, covid-19 virus':ab,ti OR 'virus disease, covid-19':ab,ti OR 'covid-19 virus infection':ab,ti OR 'covid 19 virus infection':ab,ti OR 'covid-19 virus infections':ab,ti OR 'infection, covid-19 virus':ab,ti OR 'virus infection, covid-19':ab,ti OR '2019-ncov infection':ab,ti OR '2019 ncov infection':ab,ti OR '2019-ncov infections':ab,ti OR 'infection, 2019-ncov':ab,ti OR 'coronavirus disease-19':ab,ti OR 'coronavirus disease 19':ab,ti OR '2019 novel coronavirus disease':ab,ti OR '2019 novel coronavirus infection':ab,ti OR '2019-ncov disease':ab,ti OR '2019 ncov disease':ab,ti OR '2019-ncov diseases':ab,ti OR 'disease, 2019-ncov':ab,ti OR 'covid19':ab,ti OR 'coronavirus disease 2019':ab,ti OR 'disease 2019, coronavirus':ab,ti OR 'sars coronavirus 2 infection':ab,ti OR 'sars-cov-2 infection':ab,ti OR 'infection, sars-cov-2':ab,ti OR 'sars cov 2 infection':ab,ti OR 'sars-cov-2 infections':ab,ti OR 'covid-19 pandemic':ab,ti OR 'covid 19 pandemic':ab,ti OR 'covid-19 pandemics':ab,ti OR 'pandemic, covid-19':ab,ti
3	#1 OR #2
4	'Lianhua Qingwen ':ab,ti OR 'Lianhuaqingwen' ':ab,ti OR 'lian-hua-qing-wen' ':ab,ti
5	3# AND 4#

Table A3: Search strategy of Cochrane Library

Serial No.	Strategy
1	MeSH descriptor: [COVID-19] explode all trees
2	(COVID-19):ti,ab,kw OR (COVID-19 Virus Disease):ti,ab,kw OR (COVID-19 Virus Disease):ti,ab,kw OR (COVID-19 Virus Diseases):ti,ab,kw OR (Disease, COVID-19 Virus):ti,ab,kw OR (Virus Disease, COVID-19):ti,ab,kw OR (COVID-19 Virus Infection):ti,ab,kw OR (COVID-19 Virus Infection):ti,ab,kw OR (COVID-19 Virus Infections):ti,ab,kw OR (Infection, COVID-19 Virus):ti,ab,kw OR (Virus Infection, COVID-19):ti,ab,kw OR (Coronavirus Disease-19):ti,ab,kw OR (Coronavirus Disease 19):ti,ab,kw OR (2019 Novel Coronavirus Disease):ti,ab,kw OR (2019 Novel Coronavirus Infection):ti,ab,kw OR (COVID-19):ti,ab,kw OR (Coronavirus Disease 2019):ti,ab,kw OR (Disease 2019, Coronavirus):ti,ab,kw OR (SARS Coronavirus 2 Infection):ti,ab,kw OR (SARS-CoV-2 Infection):ti,ab,kw OR (Infection, SARS-CoV-2):ti,ab,kw OR (SARS CoV 2 Infection):ti,ab,kw OR (SARS-CoV-2 Infections):ti,ab,kw OR (COVID-19 Pandemic):ti,ab,kw OR (COVID 19 Pandemic):ti,ab,kw OR (COVID-19 Pandemics):ti,ab,kw OR (Pandemic, COVID-19):ti,ab,kw
3	#1 OR #2
4	(Lianhua Qingwen):ti,ab,kw OR (Lianhuaqingwen):ti,ab,kw OR (lian-hua-qing-wen):ti,ab,kw
5	3# AND 4#

Table A4: Search strategy of Chinese National Knowledge Infrastructure database (CNKI)

Serial No.	Strategy
1	主题 = (新冠肺炎 or 新型冠状病毒肺炎or 新冠病毒 or 新型冠状病毒)
2	摘要 = 连花清瘟
3	#1 AND #2

Table A5: Search strategy of Chinese Science and Technology Journals Database (VIP)

Serial No.	Strategy
1	摘要 = (新冠肺炎 OR 新型冠状病毒肺炎 OR 新冠病毒 OR 新型冠状病毒)
2	任何字段 = 连花清瘟
3	#1 AND #2

Table A6: Search strategy of Wanfang database

Serial No.	Strategy
1	主题 = (新冠肺炎 or 新型冠状病毒肺炎or 新冠病毒 or 新型冠状病毒)
2	全部 = 连花清瘟
3	#1 AND #2

Review Article

The Impact of Electronic Nicotine Delivery Systems on Adolescent Respiratory Health: A Review of the HKSAR Situation

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Abstract

Electronic nicotine delivery systems (ENDS) have rapidly gained popularity among adolescents worldwide, leading to concerns about their impact on respiratory health. This review examines evidence on ENDS use among adolescents in the HKSAR (Hong Kong) and its effects on respiratory health, current regulations, and public health implications and strategies. ENDS heat nicotine solutions to produce inhaled aerosols. While marketed as safer alternatives to cigarettes, their safety and efficacy are unestablished. ENDS adoption among Hong Kong adolescents has risen despite reduced smoking prevalence. Studies globally link ENDS to acute respiratory effects like airway inflammation and impairment. Long-term risks include lung irritation, hypersensitivity, and future COPD. ENDS use is associated with more respiratory symptoms versus never-use. Regulation in Hong Kong prohibits ENDS sales and ads, but possession and use is not illegal. Challenges include unclear product sources and public use normalising adolescent uptake. Potential public health strategies include education campaigns, interventions to curb initiation and promote cessation, and expand smoke-free zones. Future research should continue monitoring ENDS use patterns among Hong Kong adolescents and interventions tailored to this population. As ENDS risks likely outweigh benefits for youth, ongoing efforts to reduce uptake are needed to address this major public health concern.

Keywords: Adolescent respiratory health, E-cigarettes, electronic nicotine delivery systems, ENDS

Introduction

Electronic nicotine delivery systems (ENDS), also known as electronic cigarettes, have rapidly gained popularity among adolescents worldwide, leading to concerns about their potential impact on respiratory health, especially in adolescents.[1-3] In the Hong Kong Special Administrative Region (HKSAR), the use of ENDS among adolescents is an emerging public health concern.[4,5] This article aims to review the available evidence on the impact of ENDS use on adolescent respiratory health in the HKSAR context. The article begins with a discussion of the definition and prevalence of ENDS use among adolescents, followed by an examination of the evidence on the harmful effects of ENDS on respiratory health. The article then discusses the current regulatory framework for ENDS in the HKSAR and concludes with a consideration of existing and potential public health strategies to reduce ENDS use among adolescents in the HKSAR.

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Background of Electronic Nicotine Delivery Systems

ENDS are relatively new electronic devices.[3] The basic mechanism of ENDS is that it heats a liquid solution that contains nicotine, propylene glycol, and flavorings, producing an aerosol that users inhale.[6] ENDS have been marketed as a safer alternative to traditional cigarettes and tobacco, but their safety and efficacy as a smoking cessation tool have not been rigorously studied and evaluated.[7,8] ENDS often contain toxicants and carcinogens.[9-12] The rapid adoption of ENDS, adolescents in particular, can

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be explained by many factors, including but not limited to, marketing strategies targeting the younger population, peer influence, easy access, the perception that ENDS are less harmful than traditional cigarettes, and the appeal of flavored e-liquids.[13-15]

Though the overall smoking prevalence rate in the HKSAR has dropped to a single digit of 9.5% in 2021, from 23.3% in the early 1980s, the adoption of ENDS and tobacco products among adolescents has risen from 0.1% in 2019 (~7 200 persons) to 0.3% in 2021 (~17 500 persons), and 0.8% in 2019 to 1.1% in 2021, respectively.[16,17]

Impact of ENDS on adolescent respiratory health

Researchers have begun to investigate the potential impacts of ENDS on adolescent respiratory health. Studies have shown that ENDS use is associated with harmful effects on respiratory health.[18,19] A study by Vardavas *et al*.[20] that looked into the immediate acute effects of ENDS (after a 5-minute use of ENDS) in the population aged between 19 and 56 found that total respiratory impedance ($P = 0.003$), overall peripheral airway resistance ($P = 0.024$) and respiratory resistance ($P < 0.008$) have all significantly increased, while the fraction of exhaled nitric oxide (FENO) decreased significantly ($P = 0.005$), these immediate adverse physiologic effects are also observed in users of tobacco smoking. As cigarette smoking decreases exhaled nitric oxide (NO), it suggests the enzyme NO synthase is inhibited. Research has shown the importance of endogenous NO in various roles, such as defending the respiratory tract against infection, in counteracting bronchoconstriction and vasoconstriction, and in inhibiting platelet aggregation, the observed decrease of exhaled NO may contribute to the increased risks of chronic respiratory and cardiovascular disease in cigarette smokers.[21]

Long-term effects include irritation, inflammation, hypersensitivity pneumonitis, airway remodeling and chronic obstructive pulmonary disease (COPD).[22-24] Moreover, the risk of bronchitic symptoms among ENDS past users (odds ratio (OR) 1.85, 95% confidence interval (CI) 1.37–2.49) and current users (OR 2.02, 95% CI 1.42–2.88) were elevated, when compared to never-users.[25] Respiratory symptoms with ENDS observed in never smokers is similar to those found in adolescent occasional smokers, in addition, the association between use of ENDS and respiratory symptoms was significant (OR 2.13, 95% CI 1.82 – 2.48, $n = 44\ 662$).[26] These long-term effects may only surface and become observable until later in life, adding to the burden of the health care system. Further observational studies are required to accurately note down the long-term effects of using ENDS.

Other than the vast amount of toxicants and carcinogens found in ENDS, nicotine is also found. Prolonged usage of ENDS may lead to nicotine dependence.[27] Together with the addictive nature of nicotine, it may result in discipline and violence-related issues.[28,29] In addition, exposure to nicotine and other chemicals has been known to negatively impact the development of individuals, resulting in neuropsychiatric effects, cognitive issue and psychiatric comorbidities, including but not limited to depression and drug abuse behaviours.[30-32] Research and review on how nicotine affects the clinical presentation and disease progression of Coronavirus Disease 2019 (COVID-19) was conducted in light of the recent COVID-19 pandemic. It was suggested that, in addition to higher cardiopulmonary vulnerability, nicotine also reduced immune responses, and exposure to nicotine is associated with higher infection rates and severe manifestations.[33-35]

Current Regulation Practices

In the HKSAR, as of April 2022, ENDS are regulated under the Smoking (Public Health) Ordinance (Cap. 371), which prohibits the sale, distribution, and advertisement of "alternative smoking products."[36,37] However, the possession of ENDS for personal use are not regulated, making it relatively easy for adolescents to access ENDS through alternative sources. The local Government's regulatory approach is more restrictive than in some other countries, such as the United States of America (USA) and the United Kingdom, where ENDS are widely available and regulated as consumer products.[38]

One of the challenges in enforcing ENDS regulations in the HKSAR is that the use of "alternative smoking products," including ENDS, is not prohibited and the source of the device used by the smoker is often difficult to track and trace back to. In addition, the lack of regulation on ENDS use in many public spaces may contribute to the normalization of ENDS use among adolescents and undermine efforts to reduce ENDS use in this population.[39-41]

Public Health Policies and their Implications

The potential benefits of ENDS as a harm-reduction tool for adult smokers have been widely debated. In addition to the fact that ENDS contain respiratory irritants and carcinogenic substances, the evidence to support the effectiveness of the ENDS as a cessation tool is limited and inconclusive.[41] Furthermore, others have raised concerns about the potential for ENDS to act as a gateway to traditional cigarette smoking, particularly among young people.[42,43] In the HKSAR context, the risks of ENDS use among adolescents may outweigh the potential benefits, given the relatively low prevalence of traditional cigarette smoking in the population.[16,17]

Moreover, the use of ENDS among adolescents can lead to nicotine addiction and respiratory health problems, which can have long-term implications for their health and well-being. Healthcare professionals have an important role to play in addressing ENDS use among adolescents in the

HKSAR. This includes providing accurate information about the risks of ENDS use, strengthening support for smoking cessation, and advocating for stronger ENDS regulations.[37,44] Strategies for reducing ENDS use among adolescents in the HKSAR may include public education campaigns, the development of evidence-based interventions to prevent ENDS initiation and promote cessation, and expanding smoke-free zones or rather restricting smoking-related behaviours to certain specified areas.[45]

According to a model, if ENDS were unavailable to the population an increase in quality adjusted life years (QALYs) and a decrease in health care costs would result.[46] An upcoming randomized controlled trial would investigate how health interventions would prevent ENDS use among adolescents and estimate QALYs as a result.[47] A modeling study suggested that a smoke-free-generation policy and an aggressive tax rise policy would be most effective as stand-alone policies, while the combination of raising the minimum legal purchase age, moderate tax rises and ENDS on prescription would be most-effective as a bundle.[48]

Governments worldwide have implemented various control measures for ENDS, measures of selected countries and regions have been consolidated in Table 1. As aforementioned, the HKSAR government prohibited the sale, distribution, and advertisement of "alternative smoking products" as of April 2022.[36,37,49] Thus, "Child Safety Packaging", "Clean air", "Health Warning Labeling", "Ingredients/flavor", "Nicotine volume/concentration", "Reporting/notification", "Safety/hygiene", "Tax" and "Trademarks" may not be applicable fields. This information was incorporated into Table 1. Apart from the HKSAR, information of all other regions listed in Table 1 have been extracted from the Institute for Global Tobacco Control. In addition to the control measures, strategies and recommendations aforementioned, the New Zealand "smoke-free generation" tobacco ban is worth mentioning and may be valuable to the HKSAR situation.[50] Though it has been argued that a blanket ban

Table 1: Comparison of control measures of ENDS in selected regions

Policy Domains	Australia	England	HKSAR	Japan	Mainland China	New Zealand	Singapore	Thailand	USA	Republic of Korea
Advertising/promotion/sponsorship	✓	✓	✓	✓		✓			✓	✓
Child safety packaging	✓	✓							✓	
Clean air					✓	✓		✓		✓
Distribution			✓	✓			✓		✓	
Health warning labeling		✓				✓			✓	✓
Importation	✓		✓	✓			✓	✓	✓	
Ingredients/flavors	✓	✓				✓				
Manufacture			✓	✓				✓		
Minimum age		✓			✓	✓			✓	✓
Nicotine volume/concentration	✓	✓								
Reporting/notification		✓		✓		✓			✓	
Safety/hygiene		✓				✓				
Sale	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Tax		✓								✓
Trademarks										

Note: Information for Australia, England, Japan, Mainland China, New Zealand, Singapore, Thailand, USA and Republic of Korea is extracted from the website of the Institute for Global Tobacco Control. The website states that the information "has been verified by in-country experts and/or representatives of the Ministry of Health or other regulatory body in the respective countries."

The data on the website for individual regions have been updated at different time points, the date of last update of each region has been listed in brackets below.

Australia (July 2022)

England (November 2021)

Japan (November 2021)

Mainland China (November 2021)

New Zealand (May 2022)

Singapore (October 2022)

Thailand (November 2021)

USA (November 2021)

Republic of Korea (November 2021)

The definition and explanation of each of the policy domains may be located on the website: https://www.globaltobaccocontrol.org/en/policy-scan/e-cigarettes

or prohibition may result in increasing organized crime and not the desired outcome, it is believed to prevent a large proportion of the younger generation from coming into contact with tobacco products and ENDS.[50-52] The idea has been proposed in the HKSAR but has gained insufficient traction, a similar case with other policies such as raising the tax rate, increasing smoke-free areas and prohibiting the presentation of tobacco products at point-of-sales. Together with the implementation of other policies, with a localized approach, adolescents and the population can be protected from the harms of ENDS and tobacco products.

In July 2023, the HKSAR government published a consultation document on tobacco control strategies, with the aim to achieve a smoking prevalence of 7.8% by 2025.[53] The document proposes a four strategy approach for the coming phase of tobacco control, which includes,

1) Regulate Supply, Suppress Demand;
2) Ban Promotion, Reduce Attractiveness;
3) Expand No Smoking Areas (NSAs), Mitigate Harm; and
4) Enhance Education, Support Cessation.

Some proposed measures that are more relevant to the control of ENDS on adolescents include prohibiting the possession of ENDS, prohibiting the act of smoking while walking and strengthening tobacco prevention education on students.

Conclusion

In conclusion, this review has covered the evidence on the impact of ENDS use on adolescent respiratory health in the HKSAR context. The widespread use of ENDS among adolescents in the HKSAR poses a significant imminent and future public health challenge. ENDS use is associated with harmful effects, acute and chronic, on respiratory health, and the risks of ENDS use among adolescents in the HKSAR outweigh the potential benefits as a harm reduction tool for adult smokers. The current regulatory framework for ENDS in the HKSAR has some limitations, and there is a need for ongoing efforts to reduce ENDS use among adolescents, including the involvement of healthcare professionals and the implementation of evidence-based interventions tailored to adolescents. Future research should continue to monitor the prevalence of ENDS use among adolescents in the HKSAR, as well as the effectiveness of different strategies for addressing this public health concern.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Mechanistic and Protective Approach to Ventilator-Induced Lung Injury: A Narrative Review

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Abstract

Mechanical ventilation is a lifesaving tool in the management of acute hypoxemic respiratory failure and acute respiratory distress syndrome. It is a double-edged sword if not used gently and with lung protective strategies, especially in heterogeneous lung pathology. Ventilator-induced lung injury (VILI) may occur with high airway pressure (barotrauma), improper tidal volume (volutrauma), repeated opening and closing of alveoli (atelectotrauma), and effects of local or systemic inflammatory cytokines on lung architecture (biotrauma). The target lung tissues in VILI are the fibre system, alveolar epithelium, and endothelium of pulmonary capillaries. Stress and strain are the main pathophysiological mechanisms of lung injury. Stress is related to transpulmonary pressure (TPP; the difference between alveolar pressure and pleural pressure) generated to inflate alveoli, and strain is related to the deformation of alveoli from end-inspiration to end-expiration. Junctional alveoli are at maximum risk of stress and strain. Low tidal volume and optimal positive end-expiratory pressure with limiting plateau pressure are the cornerstones of protective lung ventilation. Keeping driving pressure (DP) ≤15 cmH_2O and ventilation in a prone position are shown to have mortality benefits in adults. DP considers total respiratory system compliance and does not differentiate lung compliance from chest wall compliance. TPP measurement aids in eliminating the effect of chest wall elastance on airway pressures. There is an immense need for high-quality prospective or randomised studies to shed light on mechanisms causing VILI and its prevention in children.

Keywords: Lung injury, mechanical ventilation, pediatrics, ventilator-induced lung injury

Introduction

The advent of mechanical ventilation (MV) brought in a revolution in the management of critical patients. However, MV, not being a natural process, incites an inflammatory cascade at the cellular level and leads to lung injury termed as ventilator-induced lung injury (VILI).[1] In the present review, we discuss the various mechanisms, which can precipitate VILI and the strategies to prevent it.

Literature Search

The electronic search was performed on PubMed and Google Scholar platforms. The keywords included were "ventilator-induced lung injury," "mechanical ventilation and lung injury," "lung stress and strain," "driving pressure and lung injury," "lung protective ventilation," and "mechanical power and lung injury." Scientific original studies, retrospective or prospective, review articles, systematic review, and meta-analysis on paediatric and adult studies on VILI in the English language were selected. Animal and human studies on the mechanisms of VILI and studies on the prevention of VILI were chosen. Reference lists of included articles were also screened to identify the potential studies missed by the initial literature search.

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Physiology of Alveoli

The large number of alveoli and the primary site of gas exchange all dependent on each other and this interdependence is an important characteristic of the alveolar physiology. This unique feature results in synchronous inflation and deflation of adjacent alveoli. Alveolar oedema leads to focal collapse, which increases the stress in the surrounding alveoli.[2,3] These surrounding alveoli are called stress risers. With each expiration, there may be collapse of alveolar segments and overdistension of the adjacent alveoli with subsequent opening of the collapsed alveoli during inspiration. This causes cyclical recruitment and de-recruitment. Mechanical interdependence is also seen between the alveoli and the juxtaposed terminal airway. Inflation of alveoli keeps the connected compliant airways patent by tethering them. Similarly, inflation of the terminal airway prevents the adjacent alveoli from collapsing.[3]

Another important alveolar property is their "viscoelasticity." The alveoli are not purely elastic in nature, but rather viscoelastic, which implies that there is a time lag between the application of force and the subsequent inflation and deflation (hysteresis).[2] Alveolar oedema further augments this time gap.

Types of Lung Injury

The major factors contributing to VILI include atelectrauma, volutrauma, biotrauma, and barotrauma.[4]

Atelectrauma

It is the injury inflicted due to repetitive closing and opening of lung units. The lung parenchyma is protected from atelectrauma by two mechanisms: (i) surfactant, which decreases the surface tension of the fluid lining the alveolus preventing its collapse and (ii) interdependence between the airway and alveoli where alveoli tether the compliant airway keeping it open. In a disease process, proteins leak into the alveoli, which deactivates the surfactant leading to alveolar oedema and cyclical recruitment/de-recruitment. This alveolar fluid even deactivates externally administered surfactant and the damage to type II pneumocytes interrupts further surfactant production.[3] During this tidal atelectasis, there are shear and compressive forces, which act along the alveolar epithelium as the two opposed surfaces are peeled off each other. The former force is tangential to the epithelium of the airway and the passage of a high surface tension interface between air and fluid inflicts injury leading to epithelium necrosis.[5] In addition, surfactant dysfunction results in the formation of liquid plugs in smaller airways.[6] During inspiration, shear forces are produced with distal movement of these plugs in the airways causing epithelial damage and rupture.[3]

Volutrauma

Dreyfuss *et al*.[7] first put forward the concept of volutrauma. Microfractures of extracellular matrix (ECM) and inflammatory cascades are initiated if the lung is ventilated repeatedly at volumes above the total lung capacity causing its overdistension and damage to the alveolar epithelium.[8-10] The concept of baby lung further emphasises the deleterious effects of tidal volume (VT) on normal compliant lungs.[11]

The traditional method for ventilating adults with acute respiratory distress syndrome (ARDS) was to use a higher VT (10–15 mL/kg). The ARDS Net trial (ARMA study) compared the effects of ventilation at higher (12 mL/kg) versus lower (6 mL/kg) VT and showed a significant reduction in mortality (39.8% vs 31%) and more ventilator-free days (VFD) in the low VT group.[9] A meta-analysis showed that the relationship of VT to mortality is "U" shaped. The patients need to be ventilated at an optimal VT and a lower as well as higher VT can lead to higher mortality.[12] Although the use of high frequency oscillation ventilation (HFOV) prevents overdistension by ventilating lungs at very small VT, studies in adults do not show any mortality benefit with HFOV.[13,14]

Atelectrauma + volutrauma

The damage inflicted increases manifold when atelectrauma and volutrauma are present together.[3,15] Though described separately, they are interdependent. While atelectrauma initiates damage to the alveolar epithelium–endothelium barrier, insult is further propagated by overdistensions.[16,17] Application of zero positive end-expiratory pressure (ZEEP) with higher VT on rat lungs causes more damage than ZEEP with modest volumes. The atelectatic areas in dependent lungs suffer more damage and diseased lungs show more epithelial–endothelial changes.[18] It is the repeated atelectrauma coupled with higher volume, which incites the injury.

Barotrauma

This was the first recognised mechanism causing VILI.[19] The incidence of VILI due to barotrauma was around 86%.[20] In 1974, it was shown that ventilating with peak inspiratory pressures (PIP) of 45 cmH_2O without positive end-expiratory pressure (PEEP) led to pulmonary oedema within 30 min, whereas application of PEEP of 10 cmH_2O with the same PIP caused minimal to no lung injury.[21] Application of PEEP avoids complete end-expiratory collapse of alveoli, thus preventing tidal recruitment/de-recruitment. In addition, higher plateau pressures (*P*plat) (>28 cmH_2O) are deleterious and lead to VILI.[22]

Biotrauma

MV leads to the release of inflammatory mediators like interleukin 8 , tumor necrosis factor- alpha, interleukin-6, transcription factor nuclear factor (NF)-kB, and matrix

metalloproteinase-9.[4,23-25] Biotrauma is the result of stress on (a) cell membrane, (b) mechano-sensors, and (c) ion channels. Increased stress and strain, causes the cell membrane to unfold. When damage is severe the healing process is longer as it requires trans-differentiation of type 2 alveolar cells to type 1 cells.[5] There is an associated change in membrane potential causing calcium influx with a resultant increase in intercellular gap. Stimulation of mechano-sensors leads to transcription of IL-8, which recruits neutrophils. However, there are differences in the immune response manifested by paediatric and adult lungs in response to the injury inflicted by MV.[24] Many biomarkers for VILI are currently being studied.[25]

Targets of Injury

Injury at the microscopic level secondary to ventilation is targeted towards three components: (a) the fibre system, (b) the alveoli, and (c) the capillary system.

The pulmonary fibre system comprises elastin and collagen. Elastin acts like coiled springs that bear maximum stress and strain, whereas collagen is like non-expansile folded strings, which act as length-limiting elements. When stress is applied elastin undergoes a change in length, whereas collagen begins to unfold and once the collagen strings are unfolded completely, they limit further expansion of the fibre system. Furthermore, an increase in forces (usually beyond 100 cmH_2O) leads to breakages in collagen, which further increases the stress and strain on other units of fibre systems as the same amount of stress is now applied to fewer elements in the system.[23]

Alveoli have two types of epithelial cells. Type 2 pneumocytes produce surfactant. Type 1 cells share a common basement membrane with the endothelial cells giving rise to mechanical coupling. The epithelium and endothelium are connected to the ECM via the fibre system. The stress applied to the lungs is transmitted via this fibre system to the endothelium and then to the epithelium due to mechanical coupling. Supraphysiological stress leads to breakage in the plasma membrane of the cells, which is called as stress failure. When the strain increases by 12% the macrophages secrete IL-8, which attracts neutrophils and metalloproteinases and causes ECM remodelling.[5,23]

The endothelial cells on the capillary side are exposed to three types of forces: (a) circumferential pressure due to transmural pressure across the capillary wall, (b) surface tension due to fluid lining the alveoli, and (c) longitudinal forces due to the expansion of alveoli. The pulmonary capillaries are unique as they are exposed to cyclical forces associated with respiration.[25] The capillaries are embedded in the fibrous meshwork of the alveolar wall. When the alveolus gets stretched, this meshwork is also stretched, which flattens the capillaries along the alveolar wall while sparing the corner capillaries. In addition, exposure to excess stress induces calcium influx, which contracts the capillary endothelial cells increasing the permeability of capillaries.[23,25]

Pathophysiology of VILI

Various mechanisms are at play in the causation of VILI.

Primary mechanisms include (a) the presence of stress risers and (b) recruitment and de-recruitment of alveoli, whereas secondary mechanisms consist of (a) overdistension and (b) biotrauma.

Stress

It is the force applied per unit area, that is, pressure. During ventilation, the stress at the alveolar level is the pressure applied to keep the alveoli patent, that is, transpulmonary pressure (TPP)

$$\text{Stress} = \text{Force/area} = \text{TPP} = P_{\text{alveolar}} - P_{\text{pleural}}$$

However, measurement of stress is not straightforward because of the following reasons: (a) heterogeneous distribution of stress, (b) not all alveoli are patent and communicating with the airways in pathological states, and (c) there are areas of stress concentrators at the junction of pathological and normal alveoli.[6]

Strain

When stress is applied to any object there is a change in size from the baseline for example, when a pipe is subjected to pressure its length changes from x to $x + y$. In this case, strain is defined as y/x. [Figure 1] In lungs, strain is the ratio of change in the volume of the lungs to its volume in an unstressed state.

In terms of ventilation, strain is change in volume (ΔV)/ functional residual capacity (FRC) where FRC is the volume of lung when no stress (pressure) is applied.

$$\text{Strain} = \Delta V/\text{FRC}$$

FRC corresponds to end-expiratory lung volume (EELV) when no PEEP is applied. [Figure 2] However, on application of PEEP there is addition of PEEP-volume to the baseline FRC. The EELV now corresponds to the volume of lung at the end on tidal expiration, which is FRC + PEEP volume, which is not the volume of unstressed lung. In such cases, ΔV is VT+PEEP volume and strain is (VT+PEEP volume)/FRC.

Specific lung elastance (k) is the TPP at which the FRC doubles.[26] Chiumello *et al.*[26] found that stress varied in

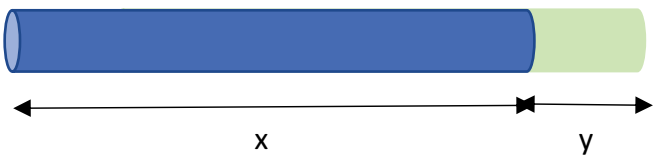

Figure 1: Ratio of change in length of pipe by "y" over resting length "x" represents strain

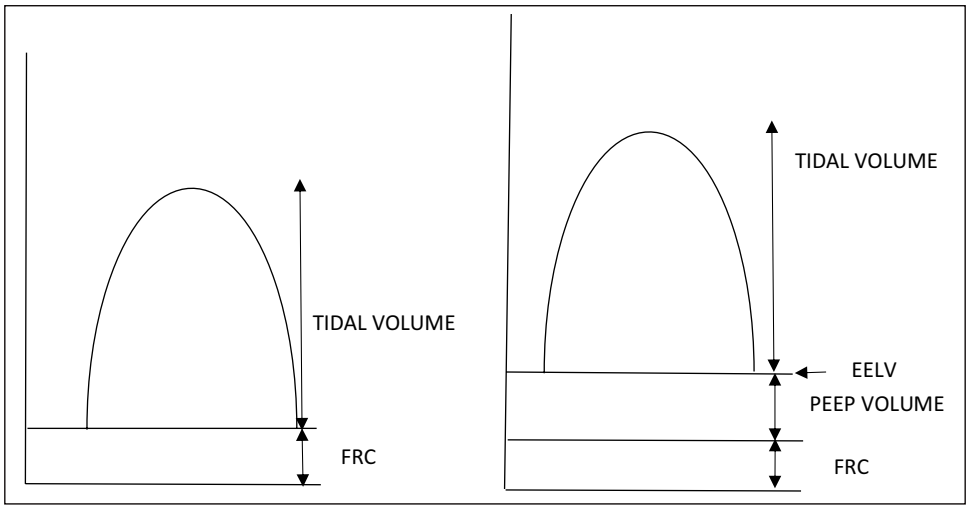

Figure 2: Diagram representing components of lung strain with or without applied positive end-expiratory pressure. FRC, functional residual volume; EELV, end-expiratory lung volume; PEEP, positive end-expiratory pressure

patients exposed to same pressures due to variability in lung compliance and strain in patients subjected to same VT was also highly variable. This showed that different VT can produce same level of stress and strain. However, stress/strain was found to be constant around 13.5±4.1 cmH_2O and was independent of PEEP and VT.

$$\text{Stress} = k \times \text{strain}$$

Usually, the stress in lungs is distributed to the surfactant and fibre system. However, with damage to surfactant in injured lungs, the forces are now concentrated only on the fibre system. The areas, in which alveoli are collapsed experience only stress and not significant strain (as they do not undergo any change in volume). The areas juxtaposed to the collapsed alveoli experience higher stress and strain. According to Mead *et al.*,[27] for an applied pressure of 30 cmH_2O, the pressure exerted in junctional alveoli is around 140 cmH_2O. Hence, there is a greater likelihood of collagen in these areas to snap on account of increased strain. Loss of collagen fibres in these areas, in turn, increases stress on the remaining fibres. This forms a vicious cycle called the vortex of VILI [Figure 3], which leads to progressive loss of the matrix elements.[11] Thus, collapsed alveoli in an area promote damage to the adjacent areas. This is explained by Gaver *et al.*[3] as permeability-originated obstructive response (POOR) and propagation of this in the surrounding stress risers leads to "POOR becoming POORer." If this cycle is not interrupted, it leads to florid VILI. The incidence of VILI in ARDS is high but VILI itself can precipitate ARDS if this vortex is uncontrolled.[25]

Lung Protective Strategies

Unphysiological stress and strain seem to be the inciting events in the development of VILI.[23] Patients ventilated

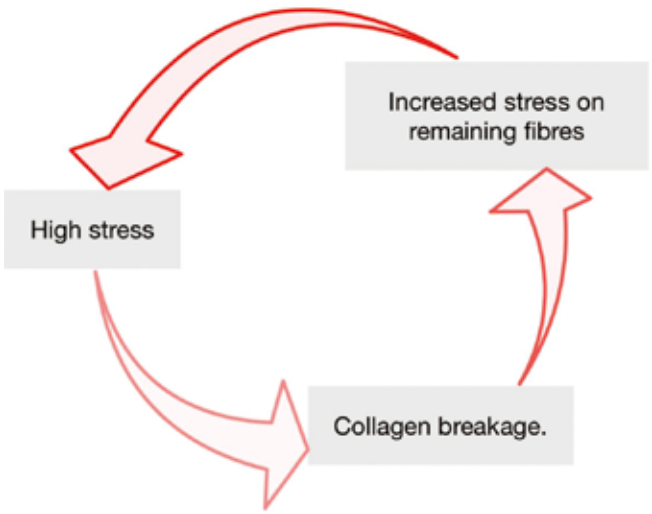

Figure 3: Ventilator-induced lung injury vortex

with higher PEEP, low VT, driving pressure (DP) <20 cmH_2O with permissive hypercapnia with limitation of maximum pressures showed an improved 28-day survival benefit with higher weaning rate and lower incidence of barotrauma [Figure 4].[10]

Low tidal volume

Significantly low mortality, higher VFD, and decrease in IL-6 levels resulted from use of low VT (6 mL/kg vs. 12 mL/kg).[9] This conclusion was supported by Amato *et al.*,[10] where higher survival was seen in those ventilated at lower VT. The *P*plat was much higher in the high VT arm in the ARDS network trial, contradictory to the normal practice of ventilation.[12] However, other studies showed no significant difference in mortality between those ventilated at low versus high VT.[28-30] Lower VTs may lead to atelectasis if too low tidal volumes are used.

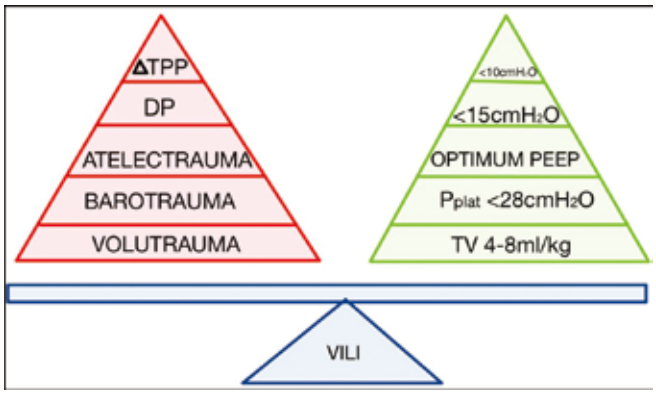

Figure 4: Lung protective ventilation

Low plateau pressure

It has been very well understood that lung injury is proportional to the stress applied.[6] Strain exceeding 2 is considered harmful to the alveoli. With a specific elastance of 13.5 cmH_2O, stress=2×13.5 = 27 cmH_2O.[26] Hence, a *P*plat target of <28 cmH_2O has been suggested.[9] A higher *P*plat leads to positive feedback for the progress of VILI.[11] Hence by targeting lower VT, one can limit the *P*plat and hence DP. Low VT coupled with lower *P*plat results in improved survival in ARDS patients.[9,10]

High PEEP

A major mechanism of VILI is atelectrauma, which can be prevented by the application of optimal PEEP.[27] The advantages of applying adequate PEEP have been studied in animal models.[21] Once recruitment methods are applied to open up the alveoli, PEEP aids in maintaining the patency even during expiration. This eliminates or decreases shunting from the pulmonary bed, thus improving oxygenation.[31] This keeps the collapsed alveoli patent and helps in a more homogeneous distribution of stress and strain, which prevents further atelectasis.[23] Multiple methods for PEEP titration have been proposed. However, the most commonly recommended method for PEEP titration is the use of PEEP/FiO_2 table.[32] Although in children, the evidence does not favour any particular method for setting PEEP, it has been seen that nonadherence to PEEP/FiO_2 table resulted in increased mortality with ARDS.[33] PALICC-2 guidelines for paediatric ARDS have suggested that one may use incremental and decremental PEEP titration for the recruitment of lungs. It also makes a recommendation of maintaining PEEP levels at or above the low PEEP/higher FiO_2 table.[34] PEEP setting below the lower inflection point or above the upper inflection point may worsen VILI. High PEEP reduces cardiac output, increases bronchial vessel resistance, and worsens barotrauma. These adverse effects are more evident in direct parenchymal injury like pneumonia where high PEEP will not recruit the alveoli and instead add to additional stress.[23,31]

Prone position

In ARDS, atelectasis occurs commonly in the dorsal and dependent parts of the lungs in the supine position due to decreased TPP along the vertical axis. Placing a patient in a prone position distributes TPP more uniformly, which allows dorsal alveoli to open up and participate in gas exchange.[31,35] A more homogeneous distribution of stress across the lungs prevents cyclical atelectasis, which minimises VILI.[23] Prone position improves oxygenation in patients with refractory hypoxaemia and with very high *P*plat[11] It also drains secretions more effectively.[33] Mortality benefit was seen in adults with severe ARDS who were treated in the prone position.[36] A meta-analysis demonstrated a decrease in mortality in patients with ARDS who were ventilated with lung protective strategies and in the prone position.[37] However, when the benefits of the prone position were studied in children with acute lung injury it neither showed any increment in VFD, nor in survival.[38] Hence, PALICC-2 does not recommend or refute the use of the prone position in children. Prone positioning may be used in children where hypoxaemia is not responding to conventional therapies.[34] The ongoing PROSpect trial plans to study 800 children from across the world for two forms of ventilation (conventional vs. high frequency) and two forms of position (prone vs. supine).[39]

Driving pressure

DP is defined as distending pressure applied across the airway during VT delivery. It determines the change in alveolar volume as per compliance of the respiratory system (Crs) (DP = VT/Crs).[40] Thus, it is an indirect indicator of functional size of lungs.[41] In baby lungs, the ventilated volume is significantly decreased and hence the alveoli overdistended easily, which subsequently increases DP. Higher the DP, more is the tidal change in volume with each breath.[41] In addition, the resultant DP is higher when the same VT is delivered to a non-homogeneous ARDS lung as compared with a healthy lung. DP is calculated as the difference between *P*plat and PEEP in volume control ventilation and as difference between PIP and PEEP during zero flow state at end on inspiration in pressure control mode.[42,43] In a *post hoc* analysis of 3,652 patients high DP was independently associated with mortality, whereas protective lung strategies with high PEEP and low VT independently did not affect outcome unless accompanied with lower DP.[44] A meta-analysis further confirmed the association of higher DP with mortality and it was suggested to target DP ≤13–15 cmH_2O.[34,45,46] With every increase of 1 cmH_2O of DP, mortality increased by 5%.[34] In children, a cut off of 15 cmH2O was suggested for dynamic DP (PIP-PEEP).[47] Another study of 300 children found that DP <15 cmH_2O was associated with increase in VFD.[48] However, there are many caveats to measuring DP. Measured DP may be erroneous if inspiratory hold applied is too short

or if applied PEEP is used for calculating DP without taking auto-PEEP into consideration.[40] As DP involves compliance of entire respiratory system, it cannot delineate between lung parenchymal and chest wall involvement. In such instances, transpulmonary DP (difference between end-inspiratory TPP and end-expiratory TPP) aids in eliminating the effect of chest wall elastance on airway pressures.[45,49] Targeting transpulmonary DP [$\Delta PL = (Pplat_{rs} - P_{OES,end\text{-}insp}) - (PEEP - P_{OES,end\text{-}exp})$] <10 cmH_2O has been found to have better correlation with outcome as compared with DP of entire respiratory system.[50,51] In addition, same DP can exert different level of stress on the alveoli.[52] The effect of PEEP is not taken into account in pressured, for example, ZEEP and a PEEP of 10 cmH_2O can have the same DP.[53] It is yet not clear if ventilation strategy should target DP. In a secondary analysis of data from observation studies showed that *P*plat was a better predictor of outcome as compared with DP.[54] In another study, where ARDS patients were ventilated with lower VT, application of higher PEEP to reduce DP did not lead to a significant decrease in mortality[55] It has been suggested that DP can be used to titrate the VT and not PEEP in patients with or without ARDS.[47] The use of DP for ventilation of non-ARDS lungs is still a dilemma and may not be associated with mortality benefits.[56,57]

Differences Between Paediatric and Adult VILI

The mechanisms of VILI in children are similar to those reported in adults and experimental studies on animals. Due to a lack of robust data in children, most of the protective lung ventilation measures have been readily adapted from adult studies. There are many structural, physiological, and biological differences between adults and paediatric patients. There was evidence from animal experimental studies that young animals were less susceptible to VILI as compared with adult animals.[58] To date, there are no randomised controlled studies on low VT and the occurrence of VILI in paediatric cases. A retrospective study reported lower mortality with low VT when paediatric data were compared with pre- and post-ARMA studies.[59] However, there are paediatric retrospective and prospective studies showing no effect or higher mortality in low VT group. Higher mortality was also associated with higher PIP.[60,61] Possibly differences in ultramicroscopic structure of lung and biological functions including cellular and immune functions are responsible for differences between adult and paediatric VILI.[24] Presence of higher elastin content in alveolar matrix as compared with collagen in young animals and infants results in improved elastance and altered effects of mechanical forces on lungs.[62] The differences in surfactant kinetics are not only species specific but also age and time-dependent. These differences possibly may explain the differences in the occurrence of VILI in children and adults.[63,64]

Innate and adaptive immune responses are immature and respond differently to triggers in young children and adults and these may have relevance to the development of VILI.[65] Toll-like receptors are well developed in newborns but their functional expression is low.[66] This may result in a lesser proinflammatory response to MV-induced stress. Similarly, TNF-alpha secretion by monocytes is low in infants as compared with adults.[67]

In summary, the current trajectory of medical practice underscores a significant shift towards the adoption of gentle ventilation techniques. While the focus on addressing the root cause of illness is paramount, it is equally quintessential to consider the harm imposed on the body during the course of treatment. As the landscape of patient management evolves, the imperative to safeguard against VILI assumes a central role in clinical decision-making.

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Conflicts of Interest

No conflicts of interest are declared by any of the authors.

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